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**REPORT OF THE
UNITED NATIONS
SCIENTIFIC COMMITTEE
ON THE
EFFECTS OF ATOMIC RADIATION**

**GENERAL ASSEMBLY
OFFICIAL RECORDS : SEVENTEENTH SESSION
SUPPLEMENT No. 16 (A/5216)**

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UNITED NATIONS
New York, 1962

NOTE

Throughout the present report and the annexes thereto, references to the annexes are indicated by a letter followed by a number : the letter denotes the relevant annex and the number the paragraph therein. Within each annex, references to its scientific bibliography are indicated by numbers.

Symbols of United Nations documents are composed of capital letters combined with figures. Mention of such a symbol indicates a reference to a United Nations document.

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ABBREVIATIONS

FAO	Food and Agriculture Organization of the United Nations
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiological Units and Measurements
WHO	World Health Organization
WMO	World Meteorological Organization

*
* *

CNS	Central nervous system
DNA	Deoxyribonucleic acid
ERG	Electroretinogram
ESR	Electron spin resonance
GI	Gastro-intestinal
LET	Linear energy transfer
OR	Observed ratio
RBE	Relative biological effectiveness
RES	Reticulo-endothelial system
RNA	Ribonucleic acid
TBR	Total body radiation
TNT	Trinitrotoluene

CHAPTER I

INTRODUCTION

Constitution and terms of reference of the Committee

1. The Scientific Committee on the Effects of Atomic Radiation was established by the General Assembly at its tenth session on 3 December 1955, under resolution 913 (X), as a result of debates held in the First Committee from 31 October to 10 November 1955. The terms of reference of the Committee were set out in paragraph 2 of the above-mentioned resolution by which the General Assembly requested the Committee:

"(a) To receive and assemble in an appropriate and useful form the following radiological information furnished by States Members of the United Nations or members of the specialized agencies:

"(i) Reports on observed levels of ionizing radiation and radio-activity in the environment;

"(ii) Reports on scientific observations and experiments relevant to the effects of ionizing radiation upon man and his environment already under way or later undertaken by national scientific bodies or by authorities of national Governments;

"(b) To recommend uniform standards with respect to procedures for sample collection and instrumentation, and radiation counting procedures to be used in analyses of samples;

"(c) To compile and assemble in an integrated manner the various reports, referred to in sub-paragraph (a) (i) above, on observed radiological levels;

"(d) To review and collate national reports, referred to in sub-paragraph (a) (ii) above, evaluating each report to determine its usefulness for the purposes of the Committee;

"(e) To make yearly progress reports and to develop by 1 July 1958, or earlier if the assembled facts warrant, a summary of the reports received on radiation levels and radiation effects on man and his environment together with the evaluations provided for in sub-paragraph (d) above and indications of research projects which might require further study;

"(f) To transmit from time to time, as it deems appropriate, the documents and evaluations referred to above to the Secretary-General for publication and dissemination to States Members of the United Nations or members of the specialized agencies."

2. The Committee consists of Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, France, India, Japan, Mexico, Sweden, the Union of Soviet Socialist Republics, the United Arab Republic, the United Kingdom of Great Britain and Northern Ireland and the United States of America.

Activities of the Committee

FIRST COMPREHENSIVE REPORT

3. In the course of its first four sessions, the Committee prepared a comprehensive report,* which it ap-

* Official Records of the General Assembly, Thirteenth Session, Supplement No. 17 (A/3838).

proved on 13 June 1958 during its fifth session, and which the General Assembly noted with satisfaction during its thirteenth session, on 13 December 1958, under resolution 1347 (XIII). In that resolution the General Assembly: (1) commended the Scientific Committee on the Effects of Atomic Radiation for its work and for the valuable report which it had presented; (2) expressed its appreciation to the United Nations agencies, to the international non-governmental and the national scientific organizations, and to the individual scientists who had assisted the Committee in its work; (3) urged all concerned to take note of the suggestions made and the views expressed in the report of the Committee; (4) decided to request the Committee to continue its useful work, and to report to the General Assembly as appropriate; (5) requested the Committee to consult with the other agencies and organizations concerned on projects within its sphere of activities so as to avoid the duplication of work and ensure effective co-ordination; (6) called upon all concerned to assist the Committee by making available to it reports and studies relating to the short-term and long-term effects of ionizing radiation upon man and his environment and radiological data collected by them, and by pursuing such investigations as might broaden world scientific knowledge in that sphere and by transmitting their results to the Committee; (7) requested the Secretary-General to continue to provide the Committee with the assistance necessary for the conduct of its work.

4. In conformity with this resolution, the Committee continued its technical deliberations, based both on information obtained from the current scientific literature and on data made available to the Committee by Member States and by the specialized agencies, the International Atomic Energy Agency (IAEA) and various non-governmental bodies, in particular the International Commission on Radiological Protection (ICRP) and the International Commission on Radiological Units and Measurements (ICRU). The Committee also pursued its activity in the field of standardization of reference samples of various materials containing strontium-90, which was initiated in 1957.

SECOND COMPREHENSIVE REPORT

5. At its sixth session, the Committee considered its future work within the terms of reference set out by the General Assembly, expressed its intention to submit a further comprehensive report to the General Assembly in 1962 and invited the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), the ICRP and ICRU to undertake, each within its own competence, such specified studies as the Committee felt were relevant to the problem of the effects of radiation on man.

6. The Committee also suggested that a seminar on use of vital and health statistics for genetic and radiation studies be held under the joint sponsorship of the United Nations and WHO. This Seminar was held in Geneva

from 5 to 9 September 1960, and was attended by sixty-five scientists. Its proceedings are being published and the Committee notes with appreciation that WHO, co-sponsor of the Seminar, greatly contributed to its success.

7. At its seventh and eighth sessions, the Committee discussed:

- (a) The physical aspects of fall-out;
- (b) Physical and biological problems concerning the transmission of fission products through food chains;
- (c) The relationships between radiation doses and effects, particularly at low doses;
- (d) Physical and biological problems concerned with carbon-14;
- (e) Genetic problems;
- (f) Dosimetric problems;
- (g) Content and preparation of the Committee's second comprehensive report;
- (h) Results of the Seminar on Use of Vital and Health Statistics for Genetic and Radiation Studies.

In connexion with topic (h) above, the Committee expressed its support of the consensus of the participants in the Seminar, on ways in which greater use might be made of existing information. This consensus was appended to its annual progress report to the General Assembly for 1960 (A/4528).

8. In response to sections I and III of General Assembly resolution 1376 (XIV), the Committee, at its seventh session, requested its Secretary to address a letter to States Members of the United Nations and members of the specialized agencies and of the IAEA, outlining the type of data on environmental contamination needed from certain areas, and mentioning those fields of biological research in which large-scale collaborative investigations are required. In pursuance of the Committee's request a letter, dated 7 April 1960, was sent to the above-mentioned States by the Secretary (see annex K).

9. In further response to sections II and III of resolution 1376 (XIV) of the General Assembly, the Committee also discussed, at the following session, appropriate arrangements for the purpose of stimulating the flow of information and data of the type already contained in its comprehensive report and for encouraging genetic, biological and other studies, including those concerned with carbon-14, that would elucidate the effects of radiation exposure on the health of human populations. The results of its discussions were submitted to the General Assembly in a report which was also appended to the Committee's annual progress report for 1960. The report suggested ways and means whereby the Committee's requests for relevant information could best be channelled, in the respective countries, to the appropriate national scientific organizations and committees, as well as to individual scientists.

10. During its ninth and tenth sessions the Committee considered preliminary drafts of the present report. Between its tenth and eleventh sessions, as requested by the General Assembly in part I of resolution 1629 (XVI), the Committee gave its attention to the possibility of submitting an interim report to the General Assembly but considered that the facts at its disposal did not call for such a report. The Committee did, however, meet the urgency expressed in the resolution by accel-

erating the completion of the present report, which it adopted at its eleventh session on 23 March 1962.

11. In response to a request from the Secretary-General of the World Meteorological Organization (WMO), the Committee at its eleventh session gave consideration to a draft plan proposed by WMO for the implementation of part II of General Assembly resolution 1629 (XVI). The Committee requested its Secretary to transmit to the Secretary-General of WMO a general statement, which it had adopted, in reply to his request for consultation.

12. Since its 1958 report, the Committee, following the recommendation contained in paragraph 2 of resolution 913 (X) and in paragraph 4 of resolution 1347 (XIII) of the General Assembly, has submitted yearly progress reports to the General Assembly.

Sources of information

13. The reports submitted before 10 March 1962 by and through States Members of the United Nations and members of the specialized agencies and of the IAEA, as well as reports of the agencies themselves and of various other non-governmental bodies, are listed in annex J. These reports were supplemented by a number of other reports and publications contributed by various individual scientists and laboratories. The information received or collected was evaluated and interpreted in the context of the current scientific literature.

14. The Committee is gratified that, in response to section IV of General Assembly resolution 1376 (XIV), Governments of a number of Member States, IAEA and WHO informed the Committee that they had made known to other Governments the extent to which they were prepared, at the request of other Governments, to receive and analyse samples in accordance with the programme of the Committee. The offers of assistance which were communicated to the Committee before 10 March 1962 are listed in annex I.

Organization of the work of the Committee

15. The officers serving prior to the sixth session are listed in the first comprehensive report. Dr. R. M. Sievert of Sweden and Dr. V. R. Khanolkar of India served as Chairman and Vice-Chairman, respectively, of the sixth and seventh sessions. Dr. M. Martínez Báez of Mexico and Dr. F. Herčík of Czechoslovakia served as Chairman and Vice-Chairman, respectively, of the eighth and ninth sessions, and Dr. F. Herčík and Dr. K. Tsukamoto of Japan served as Chairman and Vice-Chairman, respectively, at the tenth and eleventh sessions of the Committee. The scientists who have taken part in the preparation of the report as members of national delegations are listed in appendix I. During the eleventh session Dr. D. J. Beninson of Argentina and Dr. M. E. A. El Kharadly of the United Arab Republic were elected Chairman and Vice-Chairman, respectively, of the Committee.

16. As in the past, the Committee set up *ad hoc* groups of specialists to deal with topics falling within their specific competence. The technical discussions and the evaluation of the information submitted to the Committee were informal and no detailed record of these discussions was taken.

Relations with agencies of the United Nations and other international organizations

17. The Committee wishes to acknowledge the valuable contributions made to its deliberations and to the preparation of the present report by the agencies of the United Nations and various non-governmental organizations. In response to an invitation by the Committee, FAO submitted a report on the radio-active contamination of the food chain, WHO a report on questions relating to the hereditary burden of human populations, while ICRP and ICRU prepared, at the request of the Committee, under a special service agreement with the United Nations, a report on the exposure of man to ionizing radiations arising from medical procedures, with special reference to radiation-induced diseases, and WMO organized a panel discussion with a number of leading meteorologists on the factors governing the distribution of nuclear debris in the atmosphere, which was held during the seventh session of the Committee; IAEA submitted a series of reports dealing with the problem of disposal of radio-active wastes.

Scientific staff

18. The Committee was greatly assisted in its work by a scientific staff provided by the Secretariat, which was responsible for presenting to the Committee in a useful form the data submitted by Governments and other bodies, and for seeking relevant information from individual laboratories and scientists. As requested by the Committee at its first session, the scientific staff has been recruited for short-term appointments which both enabled highly qualified scientists actively engaged in research to assist it, and ensured, through rotation of the assignments, a broad geographical distribution among Member States.

19. A number of experts have acted as consultants for shorter periods of time and many scientists have contributed to the work of the Committee on a voluntary basis.

20. While the responsibility for the preparation of the report rests entirely with members of the Committee, they wish to acknowledge the help and advice received from other scientists whose names are listed in appendix II. The Committee's report owes much to their co-operation and goodwill.

Preparation of the report

21. In its first comprehensive report, the Committee emphasized that, as knowledge in its field of inquiry increased, modifications and amplifications of that report would become necessary. Since 1958, new factors have emerged and many experimental results have been obtained. Rather than issue a revised version of the report, the Committee decided, at its eighth session, to prepare an entirely new and self-contained document. At that session, the Committee agreed on the broad outline of the report and requested the Secretariat to prepare first drafts of the annexes of the report under the guidance of groups of delegates nominated by the Committee itself. It also requested the Secretariat to prepare subsequently a first draft of the report, which would be based on the text of the annexes. The ninth and tenth sessions of the Committee were entirely devoted to the consideration of these drafts, the final form of which was adopted at the eleventh session.

Scope of the report

22. The present report is intended to review the current knowledge of the effects of radiation on man and his environment and to emphasize the future investigations that are most urgently needed. Chapter II summarizes the background information in physics, biology and fundamental radio-biology, which is needed to understand the following chapters. Chapters III and IV describe the effects of irradiation on the individual (somatic effects) and on the progeny of irradiated individuals (hereditary effects). The present and foreseeable amounts of irradiation to which human populations are subjected are summarized in chapter V and the doses of radiation from various sources are compared in chapter VI. Chapter VII summarizes the evaluations and conclusions of the Committee on the problems discussed in earlier chapters.

23. As in the first report, the main text of the present one is accompanied by a number of annexes in which technical aspects of the problems with which the Committee is concerned are discussed in greater detail against the background of the current scientific information. The purpose of the annexes is to provide full justification for the statements made in the main text, rather than to cover exhaustively the subjects relevant to the field of study of the Committee.

CHAPTER II

PHYSICAL AND BIOLOGICAL ASPECTS OF THE INTERACTION OF IONIZING RADIATION WITH MATTER

1. Discussion of the effects of radiation on human populations requires an elementary knowledge of physics and biology and of the relevant terminology. The present chapter is intended to meet this requirement as well as to give such a description of the processes induced by radiation in cells as is necessary to make the following chapters understandable.

2. Formal definitions of physical quantities and units are given in annex A and a detailed account of the interactions between radiation and living matter at the cellular and molecular level in annex B.

Physical aspects

TYPES OF IONIZING RADIATIONS

3. Radiation is one way in which energy is emitted and transferred. While the term radiation refers to a wide range of modes of emission, propagation and absorption of energy, this report on the effects of ionizing radiations will be concerned specifically with alpha rays, beta rays, gamma rays, X-rays, neutrons, and all those forms of radiation occurring in cosmic rays.

4. These radiations may be considered jointly as they all give rise, either directly or indirectly, to a common phenomenon, ionization, when they interact with matter. *Ionization* is the removal of electric charges from, or their addition to, electrically neutral atoms and molecules, which then become either negatively or positively charged. In this process molecules may split into separate fragments of either charge. Electrically charged atoms, molecules or fragments of molecules are called *ions*.

5. Despite the common result of their interacting with matter, the radiations considered in this report are sufficiently different in their origin and physical properties to warrant separate description. X- and gamma rays are electro-magnetic waves like light; other radiations consist of streams of individual particles. Alpha, beta and gamma rays and occasionally other radiations are emitted during nuclear disintegration. Unstable nuclei*

* Atomic nuclei are complex structures forming the core of atoms. They are made up of positively charged protons and electrically neutral neutrons which are both elementary particles of approximately the same mass as the hydrogen atom. A *nuclide* is a species of atom characterized by the number of protons and the number of neutrons contained in its nucleus. The positively charged nucleus is surrounded by a number of negatively charged electrons which move in orbits around it. The charge of the electron is the same as that of a proton but of opposite sign so that the number of orbiting electrons in neutral atoms is equal to the number of protons in the nucleus. These orbital electrons participate in the formation of chemical bonds. The number of protons defines the chemical element to which the atom belongs. For a given element, various nuclides with the same chemical properties may be recognized which differ only in the number of neutrons and therefore in the mass of their nucleus. These are called *isotopes* of the element.

are, in one or in a sequence of such disintegrations, converted to stable nuclei. Intermediate nuclides arising in a series of disintegrations are called radio-active *daughters*.

6. Nuclear disintegrations of an unstable isotope do not occur in all atoms at the same time. They are random events occurring with a certain probability per unit time. The time required for 50 per cent of the atoms of a nuclide to disintegrate is a measure of the rate of disintegration and is called the *half-life*. It is constant and characteristic of the nuclide, and it may range from over a thousand million years to a small fraction of a second.

7. The *activity* of a radio-active sample is determined by the number of disintegrations occurring per unit time. The unit by which it is usually expressed is the curie. One curie corresponds to 3.7×10^{10} disintegrations per second. A millicurie, a microcurie and a micromicrocurie (or picocurie) correspond to 3.7×10^7 , 3.7×10^4 and 0.037 disintegrations per second, respectively. It is convenient to remember that one micromicrocurie is approximately two disintegrations per minute. It should also be noted that radio-nuclides of very long half-lives show only a slight radio-activity per unit mass (e.g. one curie of uranium-238 with a half-life of 4.5×10^9 years, has a weight of three tons, whilst one curie of radium-226 with a half-life of 1.63×10^3 years, has a weight of one gram and one curie of iodine-131 with a half-life of 8 days has a weight of 8 micrograms).

8. *Alpha rays* are positively charged particles (helium nuclei) emitted with definite and characteristic kinetic energy by nuclei of some radio-nuclides during disintegration. Alpha rays produce dense ionization in matter but their range, or penetration, is small, usually less than 0.1 mm in water and in living tissues.

9. *Beta rays* are electrons emitted by nuclei of certain radio-active nuclides.† They also produce ionization in the matter through which they pass. The range of beta rays, however, is much greater than that of alpha rays. Few radio-active nuclides emit beta particles of range greater than 2 cm in water and in living tissues, and none of range greater than 8 cm.

10. *Gamma rays* are electro-magnetic radiation emitted by nuclei of some radio-active nuclides; they have definite energies characteristic of the nuclide by which they are emitted. Gamma rays ionize matter indirectly through the ejection of high speed electrons from the material in which they are absorbed. These electrons may be ejected at a considerable depth in matter; each electron then dissipates its energy within a short distance (from less than a millimetre to a few centimetres depending on its energy). No definite range can be given for gamma rays since they penetrate any thickness of matter but with progressively decreasing intensity. The

† In many cases beta rays consist of particles of the same mass as the electrons, but of opposite charge.

thickness of matter required to decrease the gamma-ray intensity by one-half is known as the half-value thickness.

11. *X-rays* are also electro-magnetic radiation and interact with matter and produce biological effects in the same way as gamma rays. They differ from gamma rays only in that emission is extra-nuclear rather than nuclear. In practice, X-rays are usually produced by retardation of high speed electrons in the anode of an X-ray tube. These electrons have been accelerated by the application to the tube of a difference of potential, the magnitude of which determines the maximum energy of the X-rays produced and, therefore, their penetrating power. The X-rays used for diagnostic medical procedures are less energetic and less penetrating than gamma rays from most radio-active nuclei. It is possible, however, using special electron-accelerating machines, to generate X-rays that are more penetrating than gamma rays from any radio-active nuclei.

12. *Neutrons* are constituents of atomic nuclei, from which they are ejected during nuclear processes such as fission (para. 20). Neutrons are uncharged and cannot produce ionization directly.

13. Fast neutrons (of energy greater than 10 keV) lose energy mainly by collision with nuclei of light atoms, especially those of hydrogen. These nuclei recoil and, being charged, produce ions as they dissipate the energy transferred from the neutron. The transmission of energy from fast neutrons to recoil nuclei can take place at a considerable depth in tissue; like X-rays and gamma rays, fast neutrons have no definite range.

14. Slow neutrons have little energy to lose in collision with nuclei. They interact with matter mainly by nuclear reactions that result in emission of charged particles or gamma rays while new nuclides (some of them radio-active) are produced. Matter is ionized by these particles or gamma rays as well as by the radiation emitted during the subsequent disintegration of the induced radio-isotopes.

15. *Cosmic rays*^{B4-5} reach the earth from outer space; they consist of a complex group of heavy particles with different energies, of galactic and solar origin (primary cosmic radiation). The highly energetic fraction of primary radiation interacts with atoms present in the upper atmosphere giving rise to secondary cosmic radiation which is composed of particles and of electro-magnetic radiation. Each component of secondary cosmic radiation produces ionization in its own characteristic manner. The low energy fraction of primary cosmic radiation, trapped by the magnetic field of the earth, becomes part of the inner and outer belts that girdle the globe at two different altitudes.

ENERGY OF RADIATIONS

16. The energy of radiation is normally measured in electron-volts (eV) and its multiples, kiloelectron-volts (keV = 10^3 eV), and million electron-volts (MeV = 10^6 eV). It may be emphasized that the electron volt is a unit that may be used for any kind of energy, radiant, thermal, kinetic, etc., although it is primarily used for ionizing radiation.

EXTERNAL AND INTERNAL IRRADIATION

17. Radiation sources may give rise to external and internal irradiation of living beings. In the former,

radiation reaches the body from sources outside it. In the latter, radiation comes from radio-active materials incorporated within the body after ingestion, inhalation, injection, etc.

18. In external exposure, highly penetrating radiations are generally the most significant although, in certain circumstances, hard beta radiation from outside the body may reach important tissues such as the male gonads or the lenses of the eyes. Alpha and beta radiations are usually more significant in internal exposure, since radio-active substances may enter into the metabolism of the organism and become preferentially deposited in particular organs rather than being uniformly distributed throughout the body. In these circumstances, even short range particles can damage these or adjacent organs. *Critical organs* are those for which the effects of radiation, under any given conditions of exposure, are most likely to cause impairment of essential body functions, because of the radio-sensitivity, the level of radiation exposure, or the importance of such organs in body function.†

NUCLEAR REACTIONS

19. Radio-active materials occur naturally in the environment, but man has recently been adding to this natural radio-activity by artificially producing radio-active atoms on a considerable scale mainly through two reactions, nuclear fission and nuclear fusion.

20. *Fission* is the splitting of a heavy nucleus into two fragments with release of energy. While with a few nuclei fission may occur spontaneously, it may be induced artificially in a range of heavy nuclei by neutron interaction. As a consequence of fission, two lighter nuclei are produced, accompanied by one or more neutrons. Some of these neutrons may in turn be made to interact with neighbouring nuclei to produce further fissions and, under appropriate conditions, a chain reaction may be started. When the chain reaction occurs quasi-instantaneously, a nuclear explosion is produced. In nuclear reactors, however, the chain reaction is controlled, so that the energy released can be used industrially or for research purposes. The release of substantial amounts of energy by the fission process, whether controlled or explosive, is accompanied by the production of large quantities of radio-active fission products.

21. In *fusion* processes two light nuclei are made to react to produce one heavier nucleus. The total amount of energy that may be obtained is high; few radio-active nuclei are directly produced but their formation is usually accompanied by the emission of neutrons.

22. Neutrons emitted in fusion or fission may react with nuclei in the environment, giving rise to the formation of radio-active nuclides (*induced activity*). In particular, when neutrons are released into the atmosphere they are likely to react with nuclei of nitrogen, and give rise to the radio-active nuclide carbon-14.

RADIATION DOSES AND UNITS§

23. *Rad.* When matter, including living matter, is exposed to any ionizing radiation, the resulting effects depend on the energy absorbed in the exposed object. The

† The definition of critical organ given here essentially corresponds with the fuller definitions given by ICRP (report of the Commission, 1958; report of Committee II, 1959).

§ Formal definitions are given in annex A.

amount of radiation received by a given tissue is therefore defined as the energy absorbed per unit mass of the tissue; this is called the *absorbed dose* and is measured in *rad*.

24. *Roentgen*. In some cases, for instance in medical radiology, the quantity of X- or gamma rays is usually measured in terms of the number of ionizations produced by those radiations in a given mass of air under certain conditions. This quantity is called *exposure dose* and its unit is called *roentgen*. In this report, when the term "dose" is used, it shall be understood to refer to "absorbed dose" except where the possibility of confusion makes it necessary to use the complete expression.

25. *Relative biological effectiveness*. Despite the basic similarity of their interaction with living matter, ionizing radiations of different kinds and energies differ in that the dose required to produce a given biological effect (e.g. cell death or lens opacity) may vary. The relative biological effectiveness (RBE) of one radiation with respect to another is defined as the inverse ratio of the respective doses necessary to bring about a given effect. If, for a certain biological system, the RBE of alpha rays is 10, this means that for such system, an alpha-ray dose of 0.1 rad will produce the same biological effect as one rad of the reference radiation. Conventionally, X-rays within a certain energy range are used as the reference radiation. It must be understood that values of RBE strictly apply only to those conditions under which measurements are made, since the RBE for two given radiations can vary with a number of factors, including the effect being observed, the dose level and the dose rate.

26. *Rem*. For purposes of radiation protection, and the calculation of maximum permissible levels, values of RBE have been adopted for various types of radiation to allow for the greater effectiveness of these radiations in causing harmful effects. The dose in rad multiplied by the relevant RBE factor is termed the *RBE dose* and is expressed in *rem*.||

27. A similar method is useful when it is necessary to compare the biological importance of doses of different types of radiation, or to give a biologically relevant dose for a total exposure to which different forms of radiation contribute. In neither case is it strictly appropriate to use the RBE values that are intended for protection purposes and hence are designed to express the maximum likely effectiveness of a radiation in causing any harmful effect under the conditions of exposure relevant to protection work. Since the RBE of a given radiation may vary according to the type of effect considered, as well as with the dose level, dose-rate, species examined, and various other factors, a special value of RBE should ideally be used for each situation. This would be impossible in the present state of knowledge as well as unmanageable in a general account of radiation effects. For purposes of either comparing or summing doses of different types of radiation, therefore, the RBE factors adopted for protection purposes are used in this report. For all other purposes, e.g. when the effect of any one particular form of radiation is reported (as in chapter III and in annex D), it is more appropriate to quote the absorbed dose directly (in rad) since further assumptions as to the effectiveness of one, relative to other types of radiation, are here unnecessary and irrelevant.

28. *Dose-rate*. Since radiation may be delivered over

|| The values of these RBE factors are given in annex A.

a varying and sometimes extended period of time, either the total dose over that period may be considered, or the dose delivered per unit time, which is called the dose-rate. The importance of considering both dose-rates and total doses when dealing with protracted irradiations will become apparent later in this report. Dose-rates are expressed in rad, rem or roentgen per unit time (e.g. per minute, per hour, etc.) depending on the dose unit used.

29. *Distinction between activity and dose*. It is essential to bear in mind the distinction between "activity" measured in curies (para. 7) and dose, measured in rad or rem. Activity is defined in terms of the number of disintegrations occurring in the radio-active material in a given time; such disintegrations may be accompanied by the emission of a variety of radiations of different qualities and energies. Dose, however, is a measure of energy absorbed at some given point in tissue.

Biological aspects

30. Organisms are made of cells, the number of which may range from one (unicellular organisms) to many billions (multicellular organisms). This report deals mainly with multicellular organisms and, unless otherwise stated, the word organism will indicate a multicellular one.

31. In multicellular organisms cells differentiate during embryonic development into tissues, each with a specialized function; different tissues may be assembled to form specific functional and morphological units, systems and organs.

32. While the action of noxious agents affects individual cells, the over-all result of such action has much wider repercussions in complex organisms. These must in fact be viewed as integrated units where each change in any constituent reflects to a lesser or greater extent on the whole.

33. Most cells contain a recognizable nucleus and surrounding cytoplasm. Both nucleus and cytoplasm are highly complex; they contain about 70 per cent water as well as other small molecules such as sodium chloride, and more complex molecules. Threadlike structures—the chromosomes—become apparent in the nucleus during division; their number is fixed for each species. The hereditary factors, the genes, are located linearly along these chromosomes. Chromosomes consist mainly of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) associated with protein to form nucleoproteins. DNA is believed to be the essential constituent of the genes, whereas RNA carries the information from nuclear DNA to the cytoplasmic structures. Among these, mitochondria and ribosomes, which consist mainly of proteins and nucleoproteins, are the site of intense metabolic activity. Their integrated operation is a condition for normal cell function.

34. Individual organisms generally develop from single cells through binary divisions (mitosis). In bisexual species the original cell, called a zygote, is the product of a process of fusion (fertilization) between two cells, called *gametes*, contributed by male and female, respectively, and originating in the gonads (testes and ovaries). After the first few divisions following fertilization the cellular progeny of the zygote differentiates into different lines. One of these lines eventually

gives rise either to male (sperms) or female (eggs) gametes and is called the *germ line*, all other lines being called somatic. Since the zygote originates from the union between gametes, it constitutes a material bridge between successive generations, whereas the somatic cells of an individual are destined to die when the individual has completed its life-course.

35. The inherited characteristics of cells and organisms are determined by *genes*. They are characterized by an inherent stability which ensures that at each duplication two identical genes are produced. The stability is not absolute, however, and changes of a gene, resulting in an alteration in some hereditary characteristic, can occasionally occur. Such changes are called *gene mutations*; their frequency is increased by a number of chemical and physical agents, ionizing radiations being among the most studied mutagens.

36. Cellular division is accompanied by duplication of the chromosomes and their separation into daughter cells. Radiation damage to the chromosomes themselves may also be observed. These are called *chromosome mutations* or *chromosome aberrations* and consist of breaks of chromosomes and their consequences. Chromosome mutations may also result from unequal distribution of chromosomes during cell division.

37. Somatic cells contain two sets of chromosomes, one inherited through the sperm of the father, the other through the egg of the mother. Since the zygote originates from the union of two gametes, the chromosomes, and therefore the genes, would double at each generation if, during their development, cells of the germ line did not undergo a process of reduction. Cells with two sets of genes thus give rise to gametes having only one set through a sequence of two divisions called *meiosis*. As a result of meiosis one chromosome from each pair, irrespective of its paternal or maternal origin, goes to form a gamete.

38. The gametes, which contain one set of chromosomes, are called *haploid* cells, whereas germ-cells prior to meiosis (oögonia and spermatogonia) and somatic cells, contain two sets and are called *diploid*. The *ploidy* of a cell represents the number of haploid sets of chromosomes contained in its nucleus. Polyploids, cells with ploidy higher than two (triploids, tetraploids, etc.) are known in some organisms and tissues. Malignant tissues, as a rule, have some cells with chromosome numbers different from those of normal cells.

39. The distinction between germ cells and somatic cells is important, since injuries produced in somatic cells will be confined to the individual, whereas those affecting germ-cells can be transmitted to the next generations, and may therefore give rise to hereditary effects. Since somatic cells give rise to cellular progenies which can be affected by damage to their genetic material (somatic mutation) and perpetuate such damage within the individual, it is evident that "genetic" effects can be produced in both somatic and germ cells. In the present report the expression "genetic effects" will refer to genic or chromosomal alterations irrespective of their occurring in somatic or in germ cells. The term "hereditary effects" will be limited to those genetic effects that can be transmitted to the next generation.

40. Cells of different organs and tissues differ widely in their morphology, metabolism, and proliferative activity. Cells of the nervous system, which divide during the embryonic life, practically cease to do so after birth, whereas the cells lining the digestive tract are continually replaced.

41. Also rapid is the renewal of the circulating blood-cells, erythrocytes, leukocytes, and platelets, which are continuously supplied by the blood-forming tissue. Unlike the active blood-forming system which is localized in specific organs, red bone-marrow and lymph nodes, another system associated with it, the reticulo-endothelial system, is present throughout most tissues. One of its main functions is to scavenge the tissues of cellular debris and of particulate foreign substances.

Effects of ionizing radiation on cells

42. Comprehension of the action of radiation on living cells is still far from complete and is limited by lack of knowledge of the normal cellular structures and functions likely to be injured. Cellular radio-biology cannot be separated from cellular biology; any progress in either discipline can be expected to be accompanied by advances in the other.

43. The achievements of biochemistry and biophysics in the past few years have meant a remarkable progress in cellular biology and have enabled us to obtain a better picture of the complex chain of events initiated when cells are irradiated. A detailed discussion of these events is given in annex B. Here only those will be mentioned which are necessary to follow the argument of the next chapters of the report. The main end-effects of irradiation in cells will also be briefly described and an account will be given of the factors which may alter the response to radiation.

44. Radiation-induced injuries are largely non-specific; many other agents, both physical and chemical, are able to cause the same effects as those produced by radiation.

45. The first effects of radiation on living matter are physical, in that they affect atoms and molecules irrespective of their arrangement in living structures.^{B 4-9} A result is the splitting of molecules into fragments known as radicals and ions. These fragments are deprived of the chemical stability characteristic of the original molecule.

46. Radicals may interact both between themselves and with unaltered molecules, thus giving rise to new chemical compounds and upsetting the chemical balance of cells.^{B 86-93} Since water constitutes about 70 per cent of the cell, radicals arising from the splitting of water molecules are important in the initial chemical changes induced by radiation.

47. All the essential constituents of cells and in particular complex molecules like proteins^{B 62-78} and nucleoproteins,^{B 83-88} may be affected through the action of radicals. They may also be injured by radiation directly, however, without the intervention of radicals. The respective role of the direct and indirect action of radiation in bringing about cellular lesions is not yet clear; it is probable that in most effects both modes of action operate.^{B 23-26}

48. Radiation damage can also be caused by decay of a radio-active nuclide incorporated into cellular constituents.^{B 216-225} The localization of such a nuclide in cellular structures is therefore important. An example is carbon-14, a nuclide with a very long half-life, which decays, on emission of a beta particle, to the stable nitrogen-14. The beta emission may obviously give rise to radiation effects. However, since carbon is a basic constituent of all essential living structures, it has also been suggested

that the change of carbon-14 into nitrogen will sometimes occur in a key molecular structure; this change may appreciably add to the effects of the radiation released by that nuclide in the form of beta particles. Although direct evidence regarding the effects of transmutation of carbon-14 is still limited, the local effects of disintegrations have been convincingly demonstrated with other isotopes such as phosphorus-32.

49. Depending on the dose of radiation, processes leading to the synthesis of essential cellular constituents are retarded to varying degrees and may even be completely inhibited; this is particularly true for the synthesis of nucleic acids.^{B110-132} The integrity of these synthetic mechanisms is essential for the maintenance of morphological structures and for ensuring growth and division of cells. Inhibition of mitosis is, in fact, one of the earliest effects of irradiation, but probably most cellular functions and structures are to a greater or lesser extent impaired by radiation.^{B168-177} Cellular death is an over-all and ultimate result of irradiation; it can be brought about by different mechanisms, and has in some cases been ascribed to nuclear damage, in the form of chromosome breaks.

50. Chromosome breaks sometimes repair through rejoining of the broken ends shortly after the breakage event; however, a proportion fail to repair. Fragments of chromosomes may be lost if cellular division takes place before healing; then the damage becomes permanent.^{B207-215} Certain rearrangements of chromosome material through union of broken ends in new combinations may likewise cause death at cell division (para. 57).

51. The particular effectiveness of irradiation of the nucleus as compared to that of the cytoplasm might be due to the fact that the nucleus contains the chromosomes, each of which usually occurs only once or twice per nucleus. Cytoplasmic structures on the other hand normally occur in great numbers so that the elimination of one or more of them may be of less consequence. The role of cytoplasmic damage should however not be discounted, since such damage can be held responsible for some cases of cellular death. It is, however, much more difficult to prove, as only exceptionally do radiation-induced morphological changes in the cytoplasm become apparent. Yet, the mere fact that metabolic processes are always affected by radiation, and that most of these processes take place in the cytoplasm, suggests that cytoplasm may have more critical importance than suspected.

52. Extensive quantitative work has been done on the dependence of the frequency of cellular death on dose.^{B10-80} When a cell population is exposed to radiation, a fraction only of the cells becomes unable to reproduce, the size of the fraction depending on dose. It is not predictable whether an individual cell will fail to reproduce, but the proportion of deaths reflects the probability that individual cells may be killed. At low doses proportionality between dose and fraction of cells killed is frequently seen, but sometimes more complex situations arise. In any case, however, the proportion of affected cells increases with increasing doses.

53. The relationship between dose and effect is being studied at lower and lower doses for a number of radiation effects. Since the frequency or the degree of any effect is directly related to the dose, effects at very low doses are very small and may be demonstrated only when very large numbers of cells are irradiated. The possibility of detecting effects at the lowest doses has therefore practical limitations determined by the size of the

experiment that would be necessary to reveal them. The detectability decreases with the dose, since at very low doses the frequency or the degree of any effect becomes so small as to require unmanageably large numbers of cells to become apparent. Radiation-induced lysogenesis (the release of bacterial viruses from bacteria which do not normally release them) is detectable at doses as low as 0.3 rad.

54. The dose of radiation necessary to produce a given effect in a given fraction of different cellular populations is inversely related to their relative sensitivity. When the effect investigated is cellular death, the nature of the cells (protozoa and bacteria are more resistant than mammalian cells), the size of the nucleus (in the case of plant cells sensitivity is related to the volume of the nucleus) and ploidy (haploid cells have a sensitivity different from diploid cells) are among the various cellular factors which affect sensitivity.^{B178-185}

55. Sensitivity is also related to physiological conditions of the cells. Thus, bacteria grown in complex nutritionally rich media are often more sensitive than cells grown in simple media.

56. Various factors influencing the development of radiation effects are known.^{B94-210} Cell sensitivity varies with the temperature and moisture content of the cell; it is also modified by a number of chemical factors that may raise or decrease sensitivity. Among those which reduce sensitivity, lack of oxygen is the best known. Most radiation effects arising at higher doses or becoming less pronounced when cells are poorly oxygenated. Certain chemical compounds, on the other hand, when applied before or during irradiation, are able to some extent to protect cells from radiation damage. These chemicals may act by reducing the amount of oxygen available to cells or by competing with radicals produced by the irradiation. Their study is important since it may lead to methods of reducing radiation injury in man.

57. One of the major effects of radiation is the production of genetic damage.^{B186-225} This can be caused by two different mutational mechanisms, chromosome mutation and gene mutation. The former is the consequence of chromosome breaks. When two or more breaks are produced in the same or in different chromosomes, the unions which may occur frequently involve alterations of the original sequence of genes. Alteration of the gene sequence as well as loss of parts of chromosomes or even of whole chromosomes often leads to cellular death. In some cases, however, the chromosomal damage is transmitted to daughter cells.

58. The nature of gene mutations has been greatly clarified by studies on bacteria and viruses. Nucleic acids, along which genes are arranged within chromosomes, consist of a sequence of elementary units in various specific permutations. Changes in the sequence of these units result in mutation.

59. The mechanism of mutation is, however, far from being understood. Studies in lower organisms have shown that mutation is a complex process going through a first stage in which the damage may, at least to a limited extent, be repairable and only after a certain time become irreversible.

60. Like all radio-biological effects, the induction of mutations is dose dependent and is proportional to the dose down to the lowest levels investigated so far. The proportionality factor, however, has been shown to vary with the dose-rate in a number of species, as will be discussed in chapter IV.

CHAPTER III

SOMATIC EFFECTS

1. This chapter discusses the effects of partial and whole-body irradiation on man. Since observations in man are few, they will be supported by, and interpreted in the light of, information from animal experiments.

2. Owing to interrelationships between parts of the organism, damage to an individual organ may induce effects in other organs or even in the whole organism. Repair mechanisms may play a major role, replacing damaged cells or tissues through regeneration of surviving cells, but complete recovery may be only apparent and residual injury may emerge long after irradiation.

3. The somatic effects of ionizing radiations in man and in animals are mainly determined by physical factors such as the nature of the radiation, the absorbed dose, its distribution in time (instantaneous irradiation, fractionated, protracted for shorter or longer periods) and its spatial distribution, in particular the extent to which the body is exposed.^{D 1-11}

4. In assessing susceptibilities various end points can be used; and the apparent radio-sensitivity of a tissue or organ depends on the method of observation. Sensitivity depends on age at the time of exposure, children being more susceptible than adults.^{D 25-28}

5. The initial effects produced by radiation may lead to clinical effects expressed promptly or months or years after irradiation depending not only on the nature and extent of the initial radiation injury, but also on secondary factors, such as hormonal influences, exposure to other carcinogens, nutritional and other host factors. Animal experiments suggest that even viruses may be such co-factors in carcinogenesis, but no human cancer has thus far been linked to a virus.

6. It is not possible to distinguish sharply between early and late effects since effects observed soon after irradiation may persist. Nevertheless, it is convenient to consider as *early*, such effects as are observable within a few weeks after exposure. *Late* effects are those that appear many months or years later and are not always obviously related to the early effects.^{D 12-14}

Early effects

7. All organs and systems in man and animals can be temporarily or permanently affected by irradiation. Injury to blood and blood-forming organs, to the alimentary tract and to the nervous system are the most critical in determining the possibly fatal outcome of total body irradiation.

8. The clinical course of acute radiation injury in man is well known from observations on individuals exposed to large doses of radiation. Evidence from the irradiated populations in Hiroshima and Nagasaki and in the Marshall Islands, from subjects irradiated therapeutically or in the course of laboratory accidents with critical assemblies, as well as animal data indicate that

the best estimate of the median lethal dose (LD 50) for man is 300 to 500 rad (short-term total body radiation; the actual value depends on the type and distribution of the radiation). This does not mean that man can tolerate this amount of radiation, since all individuals exposed to this level would have serious symptoms and 50 per cent would die. It must be stressed that the results of exposure to 200 rad short-term total body radiation may sometimes cause death.

9. When individuals are exposed for a short period of time to high doses of penetrating radiation the injury to the organism may take three different forms, depending on the dose received. With doses of several thousand rad, the outcome is fatal within hours and the clinical picture is predominantly neurological.^{D 199}

10. Between 500 and 2,000 rad of total body radiation, gastro-intestinal symptoms predominate.^{D 200} They usually develop within a few hours, may then subside for a few days and then recur suddenly, leading to death within about one week.

11. With doses between 100 and 500 rad given within a short time, gastro-intestinal symptoms may develop within a few hours, followed by apparent recovery. Conditions worsen, however, within a period of about three weeks, when the first signs of injury to the blood-forming organs begin.^{D 202} Damage to the blood-forming organs may cause bleeding and increase susceptibility to infection. When appropriately treated with general supportive therapy, patients may recover.

12. Other organs and systems are always involved concomitantly with those whose damage is or may be conducive to death. Not all observed changes are morphological; functional effects also occur, e.g. modification of conditioned reflexes in animals given local doses to the head as low as 5 rad.^{D 200}

13. The radiation pathology of individual tissues and organs was dealt with extensively in the 1958 report and is again reviewed in annex D of the present report. No detailed account will therefore be given in this chapter.

Late effects

14. The difficulties in the study of the late effects of radiation are in part due to the long interval of time that may elapse between irradiation and clinical manifestations, sometimes making it difficult to establish the connexion between the effect and its cause. They are also due to the lack of specificity of the effects.

15. The late effects are, in fact, usually indistinguishable from diseases induced by other causes, and radiation only increases their incidence in the population. The causal relationship between irradiation and a possible late effect in man can only be established in individual cases from circumstantial evidence together with evidence derived from the observed induction by irradiation

of similar effects in experimental animals. Large-scale human surveys may confirm in man the association between given late effects and irradiation.

16. Such surveys must be carried out on sufficiently large irradiated populations to ensure that the observed, and always small, number of individuals showing the effect under study is high in a control, untreated but otherwise similar, population where the incidence of that effect may vary owing to chance alone. When the increase in incidence of the effect in the irradiated population is higher than can be accounted for by chance fluctuations, the increase is said to be statistically significant.

17. In considering populations irradiated for medical reasons, difficult problems may arise in excluding the possibility that the disease which has prompted the irradiation is by itself responsible for an increased incidence of the effect, in which case the association between the effect and the irradiation could be misleading.

18. The main late effects comprise:

- (a) Many types of neoplasms, including leukaemia;
- (b) Local effects on tissues;
- (c) Changes in the life-span;
- (d) Effects on growth and development.

INCIDENCE OF LEUKAEMIA AFTER RADIATION^{D 241-286}

19. In all countries for which mortality data are available, the recorded death-rates from the various forms of leukaemia (malignant proliferation of some of the blood-forming cells) have been rising since the turn of the century. Recent statistics, however, show a perceptible and consistent decline in the rate of increase of these diseases in the United States since 1940. If this trend were to persist, the incidence could eventually stabilize or even decline. A similar trend has been noted in Japan, but at later time periods. It will be necessary to verify the uniformity of this phenomenon by data from other countries.

20. While the cause of the increased incidence of leukaemias is unknown, the recent reduction in the rate of increase appears to discredit the hypothesis that the growing exposure of human populations to radiation is the major factor responsible for the increase.

21. The relationship between external irradiation and the occurrence of leukaemia in man, first suspected when its increased incidence among radiologists was noticed, is now established by two continuing studies: the incidence of leukaemia among survivors of the atom bombs in Hiroshima and Nagasaki and among ankylosing spondylitis patients given X-ray therapy. Very few data are yet available on the induction of leukaemia by internal irradiation in man even at high doses, but this phenomenon has also been described in experimental animals.

22. Two major and closely related questions are: what is the relationship between dose and incidence? Is there a dose of radiation (threshold dose) below which leukaemia will not be induced?

23. The studies on the irradiated populations in Hiroshima and Nagasaki^{D 248-253} are particularly important because the populations involved are very large and are not selected on the basis of age, physiological conditions, incidence of previous diseases or occupational habits.

24. Since the first report of the Committee, a number of new cases of leukaemia have occurred among these

populations. It now seems that the incidence, after having remained fairly constant for a number of years, is declining.

25. Despite continued investigation, the doses received can only be inferred from the distance of the survivors from the hypocentre of the bombs. The doses, therefore, are highly uncertain, and this uncertainty reflects on the dose-effect relationship. The data are not inconsistent with the hypothesis of simple proportionality (linearity) between dose and incidence. However, because of the small number of cases occurring at doses below 100 rad, various other hypotheses can be envisaged.

26. The investigation of the incidence of leukaemia among irradiated patients treated for ankylosing spondylitis^{D 254-262} also shows a clear dependence on dose, and the data are not incompatible with a linear relationship between dose and effect. The validity of these results is limited, however, both by the limited number of observed leukaemias and by the fact that the probability of developing leukaemia after irradiation among spondylitis may not be the same as for the general population. In any case, this study does not provide evidence of an increase in the incidence of leukaemia following doses below 500 rad.

27. Neither investigation, therefore, can definitely answer the question as to the nature of the dose-effect relationship; nor can they answer the further question as to whether the association between radiation and leukaemia occurs below a certain dose. Whatever the dose-response curve at higher doses, it is impossible either to establish or to exclude the possibility that a critical dose might be required before irradiation brings about the morphological and functional cell derangements responsible for inducing leukaemia.

28. In the ankylosing spondylitis as well as in the Hiroshima and Nagasaki surveys, no statistically significant difference can be shown between the observed incidence of leukaemia at the lowest doses investigated and what would be expected if the incidence was the same as in the general population. This cannot be construed as evidence for the existence of a threshold, since the absence of difference may only reflect the fact that the increase in the incidence of leukaemias at low doses is too small to be detected.

29. Experiments to provide critical information concerning dose-response relationships, mechanisms of radiation carcinogenesis and protection against radiation in whole organisms can only be done with animals, but their usefulness is limited by the difficulty of making valid extrapolations from one species to another, particularly to man from animals with a much shorter life-span. Extrapolations should, in any case, be made only from a species in which meaningful data can be obtained. Each type of mouse leukaemia, for instance, should be considered as a specific disease, and inferences and data drawn only from those truly analogous to diseases in man.

30. Since so little is known about the effects of low dose-rates, great care must be exercised in inferring from the available experimental, or human data, the effects to be expected from irradiation due to those artificial nuclides that are being released into the environment. While the importance of the very low dose-rate to which they give rise may be great, it is difficult to evaluate, since their effect cannot be studied experimentally.

owing to the unmanageably large numbers of animals required.

31. An increase in leukaemia and other forms of malignant disease has been reported in children irradiated *in utero*, as a result of pelvic X-ray examination during the mother's pregnancy.^{D277-286} The dose of radiation may have been ~ 1 -10 rad. These results and those of several other studies are equivocal. Results obtained from a different type of study have shown that the incidence of leukaemia in children born of 40,000 mothers irradiated during pregnancy was no greater than that expected among children in the population in general. Although the question remains open, it is a possibility that embryonic and foetal tissue is more susceptible than adult tissue to the induction of leukaemia following irradiation.

OTHER MALIGNANCIES

32. Data from irradiated animals and man indicate that malignant tumours may be induced by radiation in most tissues, provided the dose is sufficiently high.

33. Radiation-induced tumours often take long to develop, and need not be preceded by observable morphological changes in the cells at the site of origin of the cancer. Radiation can also induce malignant disease through indirect mechanisms. Pituitary tumours, for instance, can be observed in mice not as a result of irradiation of the hypophysis but as a consequence of radiological destruction of the thyroid.^{D149} The role of indirect mechanisms has also been shown in the induction of ovarian and thymic tumours in mice.

34. Most animal experiments, usually performed with relatively homogenous populations, have shown that there are dose levels where no increase in incidence of certain neoplasms can be detected. As in the case of leukaemia, this cannot be interpreted as evidence for the existence of a threshold. On the other hand, in the induction of at least one type of tumour in rats, minimal effective dose-levels are extremely low, so that there may be practically no threshold for the induction of tumours. In some of these experiments, the dose-effect relationship seems to permit extrapolation to zero. A difficulty with short-lived laboratory animals is that at low doses the average period required for manifestation of the tumour may exceed the life-span and hence no effect may be seen.

35. Most of the data on the induction of neoplasms by radiation in man have involved extremely high doses. Thus, skin cancers have appeared with low incidence in man after local irradiation in the range of 1,000 rad per year after prolonged latent periods of fifteen years or more.

36. Since the first report, preliminary data on the Japanese survivors of the atom bomb have become available,^{D287-288} indicating an incidence of some forms of cancer other than leukaemia higher than in the non-exposed population. The increase is highest among those who were closest to the explosions. Because the latent periods of induction of most tumours are long, data are not yet available that would indicate whether this increase in the incidence of malignancies will persist, rise further or decline.

37. Data on the induction by radiation of bone tumours in man—chiefly osteogenic sarcoma, probably originating from those bone-forming cells that line bone surfaces—have been obtained from occupationally irra-

diated radium dial painters, patients treated with radium salts for therapeutic purposes, and patients given X-ray treatment of bones, particularly for benign or inflammatory lesions. Again, the latent periods for tumour induction are long and the dose, where known, is high, the local doses being of the order of hundreds of rad or more.

38. Assessment of the risk of carcinogenesis, including leukaemia, at low doses of radiation requires a consideration of possible mechanisms of carcinogenesis.^{D148-158} In the present stage of our knowledge, nothing can, however, be said about the mechanism of radiation carcinogenesis without indulging in speculation. Various hypotheses may be formulated to account for the induction of tumours by radiation. Somatic (gene or chromosome) mutation, the action of latent viruses, differentiation anomalies, are among the possible mechanisms through which radiation could give rise to malignancies. To show how different hypotheses might lead to different dose-effect relationships at low doses while giving similar responses at higher doses, two hypothetical mechanisms of induction of tumours by radiation will be discussed. These have no particular merit in themselves but are described for their simplicity and because they point out the possible fallacies involved in applying to low doses dose-effect relationships observed at higher doses.

39. If radiation induced tumours through somatic mutation, it would be reasonable to expect proportionality between doses and corresponding incidence of tumours down to the lowest doses (no threshold). It is further conceivable that the number of tumours per unit dose may be less than anticipated at low doses, if the mutated cells are too few to develop into a tumour. But it is also conceivable that with such a mechanism low doses might give a higher incidence of tumours per unit dose, since higher doses might kill the majority of mutated cells. Alternatively, it could be assumed that irradiation first involves general tissue damage and that the tumour only arises in the secondary stage of tissue repair. Again, there is the possibility that the production of tumour cells is due to somatic gene mutation, arising indirectly as a result of the increased proliferation that accompanies the repair process. There might thus be a critical level of radiation below which the damage would be too limited to stimulate, during the repair stage, proliferation of such an extent as to give an opportunity for the occurrence of a mutation.

LENS OPACITY^{D289-307}

40. Exposure of the optic lens to radiation may be followed by lens opacities. Normally, doses greater than 500 rad of X-rays are required to produce clinically significant cataract, but lens opacities have been reported after as low as 200 rad of mixed gamma and neutron irradiation. In most cases, lens opacities developed after a latent period which showed little relation to dose and duration of treatment. Radiation-induced lens opacities are slowly progressive for a long time, but they may remain stationary at any stage, or regress. For chronic irradiation, neutrons seem to be much more cataractogenic than X- or gamma rays.

INDUCTION OF STERILITY^{D308-315}

41. The effects of irradiation on gonadal tissue are now fairly well known both in experimental animals—mice, dogs and monkeys—and in man. In all species, the

effects are basically similar but differences are observed, due to the differences in the transformations that germ cells undergo during maturation in different species.

42. Gonadal doses causing sterility are similar for both sexes. Single local doses around 150 rad may induce brief lowering of fertility, doses around 250 rad induce temporary sterility for one or two years; at about 500 rad permanent sterility is obtained in many individuals and prolonged temporary sterility in others. At 800 rad recovery of fertility is extremely unlikely.

43. The data on which these estimates were made are rather limited. They are confirmed by observations on individuals exposed to radiation from atom bomb explosions in Japan and from certain radiation accidents. These observations show that whole-body irradiation in the range between 400 and 600 rad does not have a permanent effect on fertility.

LONGEVITY^{D 118-140, 282-289}

44. Animals having survived substantial or nearly lethal doses of radiation have an average lifetime shorter than controls, the life-shortening depending on the kind and amount of tissue irradiated (for partial body exposure) as well as on the dose. Under continuous irradiation at dose-rates as high as 0.5 rad per day, no difference in life-span between irradiated and control animals is, however, detectable with experiments of the size used so far.

45. Irradiated animals develop some of the diseases prevalent in their species earlier than non-irradiated ones and deteriorate sooner, showing physiological and histopathological changes suggestive of early senescence. The radiation-induced shortening of life-span is conditioned by several factors. Some species are more likely to show the effects than others; within a species, strains with different genetic constitutions have their life-span decreased in various amounts.

46. It is not yet clear how much of the reduction in longevity is due to an increased incidence of radiation-induced diseases and how much is accounted for by premature aging. The difficulty arises both from the lack of rigorous definitions of senescence and its progress, and from the necessity of observing animals for the duration of their lives.

47. Information on life-shortening effects in man is still inadequate. Mortality rates of United States radiologists are slightly higher than in the general male population, but the difference is not supported by the analysis of mortality of British radiologists. These differences may be due to different radiological practices. The survivors of Hiroshima and Nagasaki have so far shown no detectable shortening of the life-span, but it may be that not enough time has elapsed since the exposure as compared to the normal human lifetime.

48. Attempts to assess the risk of life-shortening by low doses in man meet the same difficulties and necessitate the same considerations as those entailed in the assessment of possible carcinogenic effects from low doses. The problem of extrapolation of animal life-shortening data to man is difficult because of the lack of data on life-shortening for large animals with life-spans intermediate between man and rodents. Life-shortening in man as a consequence of short-term irradiation of the whole body at doses higher than 200 rad would not be surprising, but the effects of long-term, low-level irradiation on the human life-span cannot be predicted.

EFFECTS ON EMBRYOS AND FOETUSES^{D 170-192}

49. The effects of radiation on embryonic tissues are especially important because even a minor irreversible injury in an embryo may be amplified in the course of development and thus give rise to major anomalies. Susceptibility of embryonic tissue to radiation is high but probably not higher than that of actively dividing adult tissues. When mouse embryos are irradiated at a dose as low as 25 rad, 40 per cent of the embryos are killed. Irradiation of experimental animals may, at a later stage, be followed by the development of malformations. Similar observations have been reported in man; the most frequent defects involve the central nervous system, the eye and the skeleton.

50. The possibility of inducing somatic effects in foetuses at doses within the ranges of X-ray pelvic examinations (several rad) is shown by the recent observation of an increased incidence of anomalous distribution of pigment in the iris of children which had been irradiated *in utero* during such examinations of their mothers. This harmless anomaly may perhaps be attributed to a somatic mutation—either genic or chromosomal—occurring early in the embryonic development.

Conclusions

51. Since 1958, no new data have emerged which would warrant substantial modification of the view expressed in the last report. The new data have not disproved the assumed proportionality between dose and effect that was used for estimating risks at low doses but they have in fact made it apparent that such a relationship may not hold at doses lower than those which have been investigated. It is also now more fully realized that somatic effects are less likely to occur at low dose rates than at the high dose-rates employed in many experiments.

52. Short of obtaining adequate data on the frequency at low doses of such deleterious effects of radiation as leukaemia and other malignancies—and this will involve extensive human surveys and animal experiments—the use of any relationship to predict effects at low doses will, in fact, imply assumptions on the mechanisms through which specific radiation injuries are brought about.

53. In the present state of our knowledge, any such assumption would be largely speculative. The only justifications for applying to low doses relationships observed at higher doses, therefore assuming that there is no threshold for the induction of malignancies, are the expediency of the procedure and the consistency of the assumptions regarding mechanisms in both dose ranges. We do not know, however, whether in so doing the risk is underrated or overrated.

54. Although more information is required before firm conclusions can be drawn, there is evidence indicating that embryos are more susceptible to radiation injuries than adults and that even low doses may induce both developmental disorders and malignant changes in embryos. Further studies on the effects of radiation on foetuses exposed *in utero* are therefore crucial.

55. Search should be intensified for carcinogenic agents in the environment besides radiation. To assess the importance of radiation in carcinogenesis, radiation hazard must be placed in the perspective of agents that are understood at least as well as radiation.

56. Laborious though it may be to make observations on the effects of low doses on large human populations, such observations will be invaluable in complementing and confirming extensive animal experiments. Any large-scale investigation, however, especially in man, requires accurate planning to ensure that there is a reasonable likelihood of obtaining meaningful results.

Both clinical, and vital and health statistical studies of sufficiently large populations living in areas of different radiation background, of the survivors of Hiroshima and Nagasaki, of persons receiving radiation for medical purposes and of occupationally exposed persons require continued support and prompt reporting.

HEREDITARY EFFECTS

1. Genes are the determinants of the inheritable characteristics of organisms, and are characterized by an inherent stability which ensures that at each duplication two identical copies are produced. This stability is not absolute, however, and a sudden and fortuitous change of a gene, and therefore of the character which it determines, can occasionally occur. Such changes are called *gene mutations* and their frequency is increased by a number of chemical and physical agents. Of these, radiation is one of the best known.

2. It will be recalled from chapter II, paragraph 37, that cells of the germ line are diploid until they undergo reduction during meiosis and thus become haploid gametes. Depending on whether their diploid cells carry identical or different genes at a given site (locus) on a given chromosome pair, individuals are called *homozygotes* or *heterozygotes* for that locus, respectively—in other words, if A and A' are two different genes (i.e., alleles) which can occupy the same locus, then AA and A'A' individuals are said to be homozygous, whereas AA' individuals are said to be heterozygous. Heterozygous individuals may show the traits determined by either gene, or an intermediate trait. The gene which manifests itself more strongly in the heterozygote is called dominant, the other recessive.

3. The distinction between dominant and recessive genes is essential for an understanding of the hereditary effects of radiation. Mutations which give rise to dominant genes (dominant mutations) are expressed in the first generation offspring of the subject in whose germ cells the mutation has occurred. Recessive mutations, on the other hand, can become apparent in the offspring only if the offspring receives the same mutation from both parents, and this may take many generations to occur, unless the parents have one or more common ancestors, in which case it is likely to happen sooner.

4. Human diploid cells have forty-six chromosomes. Of these, twenty-two pairs (autosomes) are alike in both sexes. Another pair consists of the sex chromosomes which are alike in females but different in males. This is because all the eggs possess the same set of chromosomes, one of which is known as the X-chromosome. Sperms on the contrary are divided into two classes according to whether they possess an X-chromosome or, alternatively, a Y-chromosome, shorter than the X. Male gametes are called X- or Y-sperms depending on the sex chromosome which they carry, the two categories being produced in approximately equal numbers. Fertilization of an egg by an X-sperm will result in a zygote with two X-chromosomes which will develop into a female organism. Zygotes resulting from the union of an egg with a Y-sperm will develop into males.

5. In man and mouse, and possibly in all mammals, the Y-chromosome seems to have the principal role in determining sex, since it has recently been discovered that exceptional individuals carrying only one X-chromosome are predominantly female in their characteristics whereas other exceptional individuals who carry two

X-chromosomes and one Y-chromosome are phenotypic males, contrary to what is observed in the fruit fly *Drosophila melanogaster*. Sex chromosomes also carry genes determining other traits, although at least in man no such gene is known beyond question to be carried by the Y-chromosome. On the other hand, some thirty loci have been identified in the X-chromosome, where specific mutations determine grossly harmful traits.

6. Characters controlled by genes located on a sex-chromosome are said to be sex-linked. The fact that females carry two X-chromosomes whereas males have only one accounts for the special mode of inheritance of sex-linked characters. Well-known examples are haemophilia and colour blindness.

Natural mutation frequencies

7. Mutations are said to occur naturally or spontaneously when their production results from conditions usually not under the direct control of man.⁰⁴² The fact that mutations are rare events makes any estimation of their frequency of occurrence difficult and uncertain. Under ideal conditions dominant mutations would lend themselves to reasonably accurate estimations, since it would be sufficient to count the affected individuals born of unaffected parents.⁰⁶⁸ In practice, however, diagnostic difficulties and those of ruling out morbid conditions simulating a given hereditary trait may cast doubt on the reliability of the estimates. The situation is even more difficult with recessive gene mutations when most of the genes are hidden (carried by but not manifest) in heterozygotes. Indirect methods when used rest on assumptions which are often not easy to verify.⁰⁶³ The average frequency of occurrence of gene mutations per locus per generation—the mutation rate—may differ from one strain to another and within each species the mutation rate at individual loci also varies.⁰⁹³

8. Various methods are available and have been used to estimate the frequency of occurrence of mutations affecting specific traits.⁰⁶³⁻⁶⁴ The similarity of their results makes it reasonable to assume that the average mutation rate in man is about 1/100,000 per locus per generation. This frequency, however, may not be representative of all the mutations arising in man, but only of those which have been detected.

9. The causes of natural mutations are largely unknown. Various environmental factors, both chemical and physical, including natural radiation, might be responsible for their occurrence, but very little is known about their relative importance. It has been shown, however, that natural radiation cannot account for more than a small fraction of natural mutations in man.

Radiation-induced gene mutations

10. When the germ cells of an organism are exposed to radiation, mutations may arise which can be trans-

mitted to the offspring and their descendants. It is not possible, however, to say whether a given mutation occurring in an irradiated individual has been induced by radiation or has occurred spontaneously. The overall frequency of mutations is always increased by irradiation, and their relative frequency at different loci may not be the same for those of spontaneous and induced origin.⁰¹²⁰

11. Changes in frequency depend on such considerations as the stage of germ cells irradiated, the dose of radiation absorbed by the germ cells and the rate of delivery of the dose of radiation. However, for any single locus increases in frequencies are small, even with the highest doses possible in experimental animals. The study of radiation-induced mutations therefore necessitates the use of large numbers of animals observed over many generations. In man not only is experiment seldom possible but the intervals between generations are long.

12. Knowledge of the nature of the relationship between dose and mutation frequency is of crucial importance to understand the effect of radiation on hereditary material. From experiments on mature germ cells of animals, especially spermatozoa of *Drosophila melanogaster*, it appears that when they are exposed to radiation the mutation frequency is directly proportional to, and depends alone on, the total dose absorbed by the gonads.⁰⁸⁵ These results formed the basis of the assumptions on which the conclusions of the first comprehensive report rested. The proportionality factor was expressed in terms of doubling dose—namely the dose of radiation that is required to double the natural mutation frequency in a species.

13. Recent studies, while confirming that the assumptions were correct with regard to spermatozoa, have shown that the dose-effect relationship is more complex for other cellular stages in the germ-line. The new evidence comes mainly from observations on irradiated mice,⁰⁸⁵ but has also been confirmed in other animal material.⁰⁸⁶

14. It appears from these observations that when immature germ cells (spermatogonia in males and oöcytes in females) are irradiated, the results are not inconsistent with the hypothesis of proportionality between dose and mutation frequency observed with irradiated spermatozoa in *Drosophila*. The proportionality factor, however—and therefore the doubling dose—varies both with the stage of the irradiated germ cells and with the rate of delivery of radiation. The same total dose induces fewer mutations when it is given at low dose-rate than at high dose-rate.

15. The effects of irradiation on spermatogonia and oöcytes are particularly important under conditions of continuous exposure at low dose-rates such as those delivered by sources to which human populations are exposed (e.g., natural sources and fall-out from nuclear explosions). The spermatogonia continue to multiply during the whole reproductive life, some of them giving rise, through meiosis, to mature sperms. Oöcytes, derived from oögonia in the course of embryonic life, remain in a particular stage of the meiotic process until just before ovulation. Sperms and ova survive only for a few weeks if they do not take part in fertilization. It is therefore apparent that, under continuous exposure, the total dose accumulated in sperms and ova is much lower than the total dose accumulated until the end of the reproductive life by both spermatogonia and oöcytes.

16. The mechanisms responsible for the dependence of the mutation rate on the dose-rate have not been elucidated. It has been suggested, however, that at low dose-rates part of the damage caused by radiation to the genetic material can undergo a process of repair.⁰⁹⁷ At higher dose-rates, the mechanisms leading to repair could be impaired or inhibited, thus making the exposure more effective in inducing mutations.

17. The evidence for the existence of repair processes has been considerably strengthened by recent investigations.⁰⁸⁸⁻⁹² These have shown that in lower organisms and in *Drosophila* a finite period of time elapses before radiation damage to the genetic material becomes irreversible. Treatment with various agents interfering with the metabolism of the irradiated cells during that period can prevent the fixation of at least part of the pre-mutational damage.

18. It should be stressed, however, that none of the experiments carried out so far leaves any doubt as to the effectiveness of radiation in producing hereditary damage even at the lowest doses and dose-rates which have been investigated. At the time of the 1958 report, few experiments had been performed in the low ranges of doses and dose-rates. Since then, geneticists have consistently found both in mammals and other animals that the frequency of mutations is affected by radiation throughout the range of doses and dose-rates investigated.

Chromosomal aberrations

19. Like gene mutations, chromosomal aberrations may occur in cells either spontaneously or as a consequence of the action of the same agents which induce mutations. Whereas gene mutations may be considered as changes of the genes themselves, chromosomal aberrations may consist of duplications or deletions of part of, or of whole, chromosomes, transfer or exchange (translocations) of segments of chromosomes or even inversions of the sequence of genes along one or more chromosomes. Addition or loss of a whole chromosome usually arises through unequal distribution of the chromosomes during division.

20. Although chromosome aberrations have been known for a long time to occur spontaneously both in plant and in animal cells, very little attention was paid to them in the first report since no hereditary defects in man had yet been traced to chromosome aberrations. Progress in cytology and in the culture of human tissue cells⁰⁶⁷⁻⁷⁰ has since made it possible to establish the normal human karyotype (chromosome number and form) and to detect abnormalities.

21. In 1959, some of the most important discoveries were made in human cytogenetics, which showed that Down's syndrome (mongolism), Turner's syndrome and Klinefelter's syndrome (both of which involve alterations of the sex characters) are due to chromosome aberrations. In Down's syndrome, one supernumerary autosomal chromosome is observed.⁰²¹ In Turner's syndrome, the individual is an abnormal female who carries only a single sex chromosome, the X-chromosome;⁰²² and in Klinefelter's syndrome the subject, an abnormal male, carries two X-chromosomes and one Y-chromosome.⁰²²

22. The mode of inheritance of chromosomal aberrations in man is not essentially different from that of

dominant gene mutations.⁰⁶⁷⁻⁷⁰ Many of the chromosomal aberrations so far observed in man have been accompanied by complete sterility, which precludes transmission of the anomaly. However, individuals with Down's syndrome can be fertile and some with Turner's syndrome have had offspring. Furthermore, such aberrations as translocations are transmitted and can lead to the occurrence of abnormalities in the progeny of apparently normal and fertile individuals.⁰²⁴

Frequency of chromosomal aberrations

23. Since 1956 technical advances have been made which permit a much more accurate study of human chromosomes. As yet, however, relatively few estimates of the over-all frequency of anomalies are available. Since, however, Down's and Klinefelter's syndromes are each known to have a frequency of about 1/500 at birth, it is considered as not unreasonable to estimate that 1/100 of all live-born children carry some chromosomal aberration.⁰²⁸⁻²⁹

Radiation-induced chromosomal aberrations

24. Aberrations involving deletions or duplications of whole chromosomes occur spontaneously and have also been observed as a consequence of irradiation in *Drosophila* and mice. In the mouse, it has been shown that the frequency of chromosome loss, and the mechanism through which it occurs—namely, chromosome breakage or unequal distribution of chromosomes during division—are markedly dependent on the irradiated cell stage.⁰¹⁰⁸⁻¹¹¹

25. When the anomalies concern sections of chromosomes only, the prerequisite for their occurrence is one or more breaks in one or more chromosomes. It has been shown that the frequency of detectable single breaks is proportional to the dose. As with gene mutations, their frequency is always rather low and here the possibility of restitution through rejoining of the free extremities of the broken chromosomes is well established. Furthermore, in order that complex chromosomal aberrations may be obtained—translocations, for instance—two chromosome breaks are required simultaneously and the probability that this occurs is much lower. In any case it leads us to expect a lack of simple proportionality between frequency and dose.⁰¹⁰⁶

26. Some chromosome anomalies, unlike mutations, are often microscopically visible, and can be studied in the laboratory even on human material. By irradiating human and other cells grown in cell and tissue cultures, the effects of radiation on chromosomes as well as the dose-effect relationship can be studied.⁰¹¹²⁻¹¹⁷ Dose-effect relationships for the occurrence of chromosomal anomalies as derived from study of somatic cells *in vitro* cannot at present be applied to germinal tissues *in vivo*.

27. Studies on *in vitro* production of chromosome anomalies are of great value in showing differences in sensitivity of different animal species to radiation-induced chromosomal damage. Preliminary results on mammalian cells, including human cells, have been obtained, but these do not yet make it possible to decide how human cells compare in this respect with cells from other species.

Effect of mutation in animal populations

28. When a new mutation is transmitted for a few generations, according to the laws governing heredity and in the absence of other factors which will be discussed later, there will be present in the population a fraction A of individuals homozygous for the mutant gene, a fraction B which is heterozygous for it and a fraction C which does not carry the gene. Depending on the dominance of the mutant gene, fractions A and B, or only fraction A, will show the character for which the gene is responsible.

29. When the mutant gene is incompatible with the survival of the individual there are several possible outcomes. If the gene is completely lethal, even in the heterozygotes B, then the condition will not be transmitted, because all who receive it will die. If it is not completely lethal in heterozygotes, then occasionally it will be transmitted through one or more generations. A good example is retinoblastoma, a dominant gene-determined tumour of the eye, which is usually fatal in childhood. Sometimes the tumour retrogresses, however, or may be removed by surgical treatment, thus allowing the individual to grow up and transmit the gene. Dominant mutations less severe in their effects may be transmitted through more generations, e.g. those determining dystrophia myotonica or acholuric jaundice.

30. When the mutant lethal gene is completely recessive, heterozygotes can live and reproduce, whereas homozygotes only are eliminated. The gene will therefore not be eliminated at once but will be maintained for a period of time in the population and its eventual elimination will be completed after a very large number of generations, unless the same mutation is continually produced, so that the frequency of the gene in the population will reach an equilibrium value determined by the mutation frequency. Many severe traits in man are caused by genes which fit the above description. Good examples are phenylketonuria and galactosaemia; both are disorders of metabolism which determine mental deficiencies and are usually lethal in the above-mentioned sense.

31. Recessive lethal mutations seem to be less frequent than mutations which only reduce the average number of the progeny of homozygous individuals by reducing their fertility or the probability of mating, or by making them more vulnerable to a given environment. In such cases the elimination of the mutants proceeds at an even slower pace. Various other situations may also arise when mutant genes are not completely recessive and heterozygotes show a certain degree of disadvantage as compared to individuals who do not carry the gene.

32. Some mutant genes cannot be appraised in absolute terms unless referred to a given environment. In man, a mutant gene is known which in the homozygote gives rise to a serious blood disease, sickle-cell anaemia.⁰⁴⁸ Most of the homozygotes die in the first decade of their life and very few reach the third decade, whereas heterozygotes, although clinically recognizable, live a normal life and show no impairment of fertility. With such a severe elimination of homozygotes it would, at first thought, seem necessary to assume that the trait is maintained in human populations by an unprecedentedly high frequency of mutation. It has, however, been observed that the mutant gene is present mainly in areas where the incidence of malaria is very high and there

is evidence that heterozygous individuals are more resistant to malaria than individuals which do not carry the gene. The loss of homozygotes may thus be more than compensated for by the increased survival, and therefore the more numerous progeny, of heterozygotes as compared to the normal population living in malarial areas.

Magnitude of the hereditary damage

33. Any estimate of the magnitude of the hereditary damage, as measured by the total number of harmful genes present in the germ cells of a population over one generation, must necessarily rest on the observation of the actual occurrence of hereditary defects and diseases. The possibility of estimating this amount in quantitative terms is hampered by our lack of precise knowledge about many harmful traits. It is admitted that genetic factors play an important role in the causation of these traits, but the extent to which they do so is unknown. The discovery of chromosomal aberrations in man enables us to give a more accurate picture of the total hereditary damage than was possible in the last report, since a whole new category of diseases can now be ascribed to known hereditary mechanisms.

34. It is convenient, if crude and oversimplified, to distinguish between visible damage and recessive (hidden) damage. The former is estimated to affect about 6 per cent of all live-born infants.⁰¹⁸⁻³⁷ One per cent are afflicted by known chromosomal aberrations, 1 per cent by defects due to known dominant or sex-linked genes, 1.5 per cent are destined to suffer later from serious mental or constitutional hereditary diseases and the rest have malformations which, although due to environmental factors, may also have some genetic component in their causation. A certain but unknown fraction of miscarriages and still births,⁰³⁸ as well as of total or partial sterility in both sexes is also probably due to dominant mutants or to chromosomal aberrations.

35. The recessive damage cannot be estimated directly, although an indirect method is available which has a very broad scope as it can be applied to very diverse situations and estimate even the recessive damage accounting for foetal deaths and sterility.⁰³⁹⁻⁴¹ Its potentialities have not yet been fully exploited owing mainly to lack of adequate data. The method is based on the principle that spouses who are related are more likely to be heterozygous for the same mutant gene than unrelated spouses. A greater fraction of recessive homozygous offspring, and thus of defects due to homozygosity, is therefore expected among consanguineous marriages than among the others and the size of that fraction is expected to be larger, the more closely related the spouses are.

36. The relationship between the degree of consanguinity and the frequency of traits due to recessive genes is, in fact, a very simple one. By comparing for instance the differential mortality at a certain age between unrelated and variously related individuals of the same population, it is possible to estimate the average number of variously harmful recessive genes per individual which, if present in homozygous conditions, would each, on the average, cause one death at the age which has been investigated. These indirectly observed genes (lethal equivalents) need not be 100 per cent lethal. Indeed, if two such genes each caused 50 per cent lethality

when homozygous, they would achieve the same cumulative lethality as one single completely lethal gene.

37. The use of such an indirect method requires that accurate records of consanguinity and detailed data regarding fertility, morbidity and mortality of both consanguineous and non-consanguineous marriages should be available. The difficulty of securing that kind of information explains why the indirect method has not yet been extensively used. From the results obtained so far, however, it appears that each individual carries on the average from 2 to 4 lethal equivalents,⁰⁴¹ the estimates being based on mortality before thirty years, including miscarriages and still births. The number of equivalents responsible for major malformations and hereditary diseases is not known with any certainty and those responsible for sterility have not so far been studied.

38. It should be pointed out that the visible damage, as estimated from its observable expression, and the recessive damage, as evaluated through the indirect approach, do not lend themselves to straightforward comparisons.⁰⁴⁰ On the one hand their magnitude is assessed through radically different methods, each affected by different sources of error; on the other hand they are expressed on different scales, the visible damage in terms of actual hardship, the recessive one in terms of potentially harmful factors.

39. Furthermore, as most of the manifestations of the visible damage are accompanied by either a total or severe reduction of fertility, the largest part of this damage is confined to the generation being investigated and only for minor detrimental characters can it be carried for a certain number of generations. The recessive damage, on the contrary, is spread over an unpredictable and always very large number of generations and the frequency of its manifestations largely depends on the frequency of consanguineous marriages.

Mutation and hereditary damage

40. Gene and chromosomal mutations obviously contribute to the hereditary damage, and it is important to know what fraction of these mutations occurred in immediately preceding generations. Dominant lethal traits are certainly due to new mutations having arisen in the germ cells of the parents of the affected individuals, since these mutations cannot be transmitted for more than one generation. The same is true for diseases such as Down's and Klinefelter's syndromes where the affected individuals are almost invariably infertile.⁰⁷⁰

41. The role of mutation in maintaining the recessive damage in human populations is difficult to evaluate because completely recessive genes are detectable in homozygous individuals only. Moreover, when recessiveness is not complete, the heterozygous condition may result in reduced fertility and this adds further complexities to the problem of estimating mutation rates.⁰⁴⁴⁻⁴⁶ The same is true of those cases in which the heterozygous condition for a lethal or quasi-lethal recessive gene results, at least in some environments, in an increased fertility.⁰⁴⁷⁻⁵¹ Data on the extent to which recessive heterozygotes are selected for or against are generally lacking.

42. If most recessive heterozygotes were favoured in their present environment to such an extent as to overcome the continual loss of genes due to the elimination

of homozygotes from the population, then the role of mutation in the maintenance of the hereditary damage would be much less important.

43. The present consensus of opinion among geneticists is that most of the recessive damage is supported by mutation, but it should be stressed that such a view is still largely speculative.⁶²

Effect of irradiation on quantitative characters

44. Many hereditary characters can only be expressed in terms of measurements and are distributed more or less symmetrically around a mean.^{61,131-135} Examples are height, weight, birth weight and intelligence as measured by scores in intelligence tests. The effects of an increase of mutation rates on this type of character were considered rather fully in the 1958 report and there is no new information which would alter the conclusions.

45. One of the quantitative characters—viability—is known to be adversely affected by most mutations, so that an increase of mutation rates can be expected to give rise to a substantial reduction of viability even if the mutations produced are not responsible for visible harmful traits. It has in fact been shown in mice that the offspring of irradiated parents have a higher mortality than control animals during the early part of life. This effect on the viability of the offspring could be attributed to the over-all effect of many mutations and perhaps also to chromosomal changes, each with a small effect. It is difficult, however, to express this hereditary damage in terms that can be compared with other types of radiation-induced hereditary damage. It is hoped that much more work will be done to investigate its nature and extent, as it might prove the most important damage affecting the first generations of descendants of irradiated individuals.

Assessment of hereditary effects of radiation on man

DIRECT EVIDENCE OF DAMAGE FROM RADIATION

46. Since 1958 very little new information has been added to our knowledge regarding hereditary effects induced by radiation in exposed human population.

47. The largest group now available is still represented by the descendants of those exposed to radiation in Hiroshima and Nagasaki. The survey made in 1956 revealed no detectable effect on the frequency of prenatal or neonatal deaths nor on the frequency of malformations.^{61,121-122} It should be stressed again, however, that this does not mean that no visible hereditary effects were produced by the irradiation. The number of exposed parents and the dosage received by them was such that we should not have expected a detectable increase in the offspring of the exposed population.

48. A significant change in the ratio between males and females (sex ratio) among children born of irradiated parents in Hiroshima and Nagasaki has been reported.^{61,125} Other more limited and not strictly comparable surveys on the offspring of parents exposed to radiation for medical reasons also show changes of the sex ratio. Shifts in the sex ratio are expected on the basis of simple genetic theory which predicts a lowering in the frequency of males born of irradiated mothers and

a lowering in the frequency of females born of irradiated fathers. Such an expectation, however, has not been borne out by investigations on the offspring of irradiated mice,^{61,130} and a detailed analysis of the human observations has revealed inconsistencies in the sex-ratio changes that cannot at present be explained.

49. The addition to the recessive damage occasioned by radiation has not been studied because recessive genes tend to appear among the offspring of consanguineous marriages. Since marriages between individuals more closely related than first cousins are not practised in most societies, at least three generations must elapse before any child is born to parents who have a common irradiated ancestor.

OTHER CONSIDERATIONS

50. The scantiness of data on the hereditary effects of radiation in man does not preclude the possibility of assessing a part of the expected hereditary damage. For that purpose, the results of experimental studies on other species need to be applied to man. This requires careful biological judgement and is justified only for observations obtained in species for which it is known that the mechanisms of induction, transmission and manifestation of the effects considered are similar to those in man.

51. The possibility of inducing mutations in all the organisms that have been investigated, from bacteria to mice, makes it beyond doubt that radiation can cause the same types of damage in man. It is also reasonably certain that in man, as in other species, the overwhelming majority of newly arising mutations have detrimental consequences and that, if beneficial mutations arise at all, the frequency of their occurrence is so low as to be unlikely to offset the burden occasioned by the harmful ones.

52. In all organisms investigated, the frequency of induced hereditary changes has proved to be dose-dependent even at the lowest doses investigated and there is no reason to believe that this is not so in man.⁶³ Animal species differ from each other, however, in their sensitivity to the mutagenic action of radiation.^{61,101} As far as the induction of chromosome anomalies is concerned, some observations of wide variations in sensitivity even between closely related species of rodents and between these and one species of monkey limit the possibility of straightforward quantitative extrapolation to man.

53. The effect of the dose-rate has so far been found in the mouse, in *Drosophila* and in silkworm,⁶⁴⁻⁶⁷ these species being sufficiently different to allow us to assume that other mammals, and in particular man, may show an analogous pattern of response. The quantitative picture may, however, differ in different species to an unknown extent if, as has been assumed, the dose-rate effect is accounted for by the intervention of metabolically conditioned recovery processes.^{68,7}

54. An increased exposure to radiation therefore adds to the hereditary damage affecting mankind. Of such additional damage, a fraction will become manifest during, and will be confined to, the first few generations following the exposure; another fraction, and perhaps the main one, will become apparent at a later stage in a less conspicuous way but will be sustained by mankind for an unpredictably large number of generations.^{61,146} It should be noted that some of the harm to human popu-

tions both from spontaneous and induced mutations may be spread over more generations because socio-medical care may relax selection against individuals with certain traits.

Conclusions

55. Any increase in the amount of ionizing radiation to which human populations are exposed is expected to bring about a proportional increase in the frequency of mutation. This expectation is based on the fact that ionizing radiation is known to induce mutations in experimental animals at all doses and dose-rates so far investigated. Experimental observations, however, are available only at single doses not lower than 5 rad⁰⁸⁸ and direct information on the dose-mutation relationship in man is presently lacking.

56. Much progress has been made in the field of radiation genetics during the last four years. Recent investigations have added to the information used in assessing the genetic hazards of ionizing radiations to human populations; they have also focused attention on the specific areas most in need of further research. It is now known that the frequency of radiation-induced mutation is not dependent solely on the accumulated dose but is also dependent on rate of delivery. Furthermore, factors such as sex and germ-cell stage are important influencing factors. Nevertheless, under some defined conditions it is possible to calculate a doubling dose for gene mutations in human populations. Calculations in the 1958 report, based on many considerations, including a lower limit estimated from the data from Hiroshima and Nagasaki, suggested that the representative doubling dose for man might well lie between 10 and 100 rad, with 30 rad as the most probable value. Recent information from mouse experiments now suggests that for acute irradiation, the probable combined value for both sexes is somewhat lower than 30 rad but not less than 15 rad.⁰¹⁵⁴ For chronic irradiation the most probable value is 100 rad or possibly higher. No better figures are available for estimates of doubling dose for gene mutation in man. A permanent doubling of the mutation rate would ultimately double the prevalence of those serious defects determined by unconditionally

harmful genes which are estimated to affect about 1 per cent of those born alive.⁰¹⁴⁻¹⁷ Present knowledge of dosage effects on the induction of chromosome anomalies is too scanty to predict a doubling dose.⁰¹⁵⁵ There are indications that monkey chromosomes and hence perhaps those of other primates are more radio-sensitive than those of mice. The Committee is of the opinion that ionizing radiation would increase the prevalence of developmental congenital malformations⁰³⁰⁻³² and of serious constitutional disorders,⁰³³⁻³⁵ but no quantitative estimates can now be made.

57. Accurate and reliable estimates can only be obtained through further progress in both experimental and human genetics. Some fields of investigation will require particular encouragement and support, as those that are most likely to provide answers to the questions arising from exposure to radiation. Studies of the role of repair mechanisms in radiation-induced mutational processes, and of factors which may influence mutation frequencies, may help us understand better how radiation delivered at different rates induces mutations with varying effectiveness. Rigorous *in vitro* and *in vivo* methods of comparing susceptibilities to radiation of various species will provide a sounder basis for applying to man experimental results obtained in other species.

58. Careful, protracted study should be continued on those groups of individuals that are or have been exposed to higher doses of radiation, such as irradiated persons in Hiroshima and Nagasaki, populations living in areas where natural irradiation is high and individuals irradiated for medical reasons. Appropriate methods should be devised to extract from these studies all the relevant information on radiation-induced damage to the hereditary material that they are likely to yield.

59. An understanding of the hereditary effects of ionizing radiation cannot be obtained without a thorough knowledge of the factors which affect the maintenance of hereditary traits in the population—principal among them the pressures of mutation and selection and the genetic structure of the population. To ascertain the respective role of these factors, accurately planned and continued large-scale investigation on human populations living in different environmental, social and cultural conditions should be undertaken or pursued.

CHAPTER V

SOURCES OF IRRADIATION

1. Human populations are exposed to radiation originating from a variety of different sources. It is convenient to distinguish between exposure from natural sources, from man-made sources excluding environmental contamination and from environmental contamination. Each may be further subdivided according to the following scheme:

A. Irradiation from natural sources:

- (1) Cosmic rays;
- (2) Radiation from naturally occurring radio-active materials;

B. Irradiation from man-made sources excluding environmental contamination:

- (1) Medical irradiation due to:
 - (a) Diagnostic X-ray procedures;
 - (b) Radio-therapy (external or from sealed sources);
 - (c) Internally administered radio-isotopes;
- (2) Occupational irradiation;
- (3) Irradiation from miscellaneous sources;

C. Irradiation from radio-active contamination of the environment due to:

- (1) Explosions of nuclear weapons;
- (2) Disposal of radio-active wastes;
- (3) Accidental releases of radio-activity.

A. Irradiation from natural sources

2. Irradiation from natural sources is essentially constant over a period of time in a given place. Geographical variation, however, occurs and populations living in different areas may be exposed to different dose-rates.

(1) COSMIC RAYS

3. Primary cosmic rays are of extraterrestrial origin and are absorbed in the upper layers of the atmosphere where, by interacting with nuclei, they produce secondary radiation, both electromagnetic and particulate, to which living beings are exposed.^{E1-3}

4. Exposure to secondary radiation differs according to geomagnetic latitude and longitude^{E9-12} and also according to altitude.^{E13-14} Exposure is lower at the geomagnetic equator than at the poles, the difference at sea level amounting to about 10 per cent. Along the geomagnetic equator variations are observed amounting to about 5 per cent. The altitude effect is much more marked, since the exposure nearly doubles for each 1,000 metres increase in altitude. Variations of the exposure with time^{E15-18} are also observed, but these are of a cyclical nature so that if measurements are carried out for a sufficient period of time the exposure proves to be fairly constant. Such variations may be considerable at high altitudes.

5. The dose-rate to all tissues due to cosmic radiation

at the sea level in temperate latitudes is normally taken as standard and amounts to about 50 mrem/year.^{E21} The rate may, however, be much higher in areas of high altitude.

6. This is higher than the figure given in the first report of the Committee (30 mrem/year), the difference being due to the fact that the contribution of neutrons, which are among the components of secondary radiation, was not taken into account. The tissue dose due to the neutron component is in fact very difficult to determine since the broad energy spectrum of those neutrons has to be taken into account—both to estimate the energy absorbed and to determine the appropriate RBE values required to express the absorbed dose in rem.

(2) RADIATION FROM NATURALLY OCCURRING RADIO-ACTIVE MATERIALS

External irradiation

7. The most commonly occurring radio-active nuclides in the earth's crust, and those which contribute most significantly to the external irradiation are uranium-238, thorium-232 and their daughters, such as radium-226, as well as potassium-40.^{E19-31} These nuclides are practically ubiquitous but their abundance varies widely from area to area.

8. Soils and rocks containing these radio-active elements emit gamma rays which, owing to their power of penetration, contribute substantially to the irradiation of tissues. Dose-rates inside and outside buildings usually differ, however, since walls may contain the nuclides referred to above, and hence show a gamma activity of their own, and also since walls provide a certain shielding effect against the activity of the ground.

9. Despite wide geographical variations, it is estimated that the average external dose-rate from naturally occurring nuclides to which the world population is exposed is about 50 mrem/year, allowing for the fraction of time spent indoors and outdoors.^{E31}

10. In certain areas, where soil is particularly rich in radio-active ore, dose-rates are much higher.^{E32-33} Such areas are found in Brazil, Niue Island, India and the United Arab Republic. In the areas located in the States of Kerala and Madras (India) where nearly 100,000 inhabitants live, average values of 1,300 mrem/year were observed. This appears to be the only densely populated area where the irradiation from naturally occurring radio-active nuclides is known to be so high.

Internal exposure

11. Air, drinking water and food contain variable amounts of radio-active material of natural origin which may be deposited in the body after ingestion or inhalation. The main natural radio-activity of the body arises from elements of the uranium and thorium series, from potassium-40 and from carbon-14.

12. Elements of the uranium and thorium series are mainly deposited in bone tissue.^{1267, 68} The amount contained in the skeleton depends on the presence of those elements in drinking water and food and therefore varies widely between geographical areas. Our estimates of the average dose-rates to tissues due to the presence of long-lived radium-226 and other bone-seeking radioactive isotopes are now more accurate than in 1958. The cells lining bone surfaces receive about 10 mrem/year, the bone-marrow cells contained in the bone cavities receive about 2 mrem/year, and the gonads 1.6 mrem/year from these sources.

13. A further contribution to internal irradiation is given by the inhalation of the gaseous decay products of uranium and thorium which are present in the atmosphere above the ground wherever those nuclides are contained in the soil.¹²⁶⁷⁻⁴² These gaseous radio-active elements (radon and thoron respectively), once inhaled, diffuse through the lungs into the bloodstream—thus giving rise to dose-rates to body tissues of about 3 mrem/year. The daughter products of radon and thoron become attached to dust particles which may be deposited in the lungs where they locally irradiate the surrounding pulmonary tissues until they are removed by physiological processes.

14. Potassium-40 has a very long half-life (1.4×10^9 years). It is present in a constant proportion (0.012 per cent) of total potassium in all natural materials.¹²⁷⁰⁻⁸³ The concentration of potassium in the human body varies considerably with age. The dose-rate to the gonads from potassium-40 is estimated to be around 20 mrem/year, whereas the mean dose-rate to the blood-forming cells and to cells lining bone surfaces is about 15 mrem/year.

15. Carbon-14 is also a long-lived element (half-life 5,760 years) which originates in nature from the interaction between cosmic ray particles and nuclei of atmospheric nitrogen.¹²⁸²⁻⁸³ Carbon-14 in the form of dioxide is readily mixed in the atmosphere and later diffuses into ocean waters, while plants also assimilate it in proportion to its concentration in the atmosphere. Carbon-14 thus enters into all living organisms, of which carbon is one of the major components. Carbon-14 is fairly uniformly distributed in tissues and shows little geographical variation. The dose-rates to which body tissues are exposed from this nuclide are 1 mrem/year for the gonads and 2 mrem/year for the blood-forming cells and for cells lining bone surfaces.

TABLE I. DOSE-RATES FROM NATURAL RADIATION SOURCES (MREM/YEAR)

Sources	Gonads	Cells lining bone surfaces	Blood-forming cells
External			
Cosmic rays ^a	50 (20) ^b	50 (20) ^b	50 (20) ^b
Terrestrial radiation.....	50	50	50
Internal			
Elements of Ra and Th series (ingestion and inhalation) ..	5	13	5
Potassium-40.....	20	15	15
Carbon-14.....	1	2	2
TOTAL	126	130	122

^a The RBE values used in computing doses are given in annex A.

^b Approximate contribution of the neutron fraction.

16. Dose-rates from natural radiation are summarized in table I. It must be pointed out that these dose-rates are to be considered as approximate only; since variations are wide, the dose to the population will vary with locality. The variation of natural radiation is known in sufficient detail to enable us to compute roughly accurate population-weighted world averages.

B. Irradiation from man-made sources excluding environmental contamination

(1) MEDICAL IRRADIATION

17. This category consists of those irradiations which are administered to patients by radiologists, general practitioners, dentists, etc., for diagnostic or therapeutic purposes. The value of radiological procedures in medicine is so well established that they have become indispensable. At the same time, however, these procedures involve a certain amount of both somatic and hereditary risk which adds to the risk from other sources.

18. Unlike natural background and environmental contamination to which whole populations are uniformly

exposed, medical irradiation is applied only when specifically indicated, so that a fraction only of the population is exposed to it in any one year and within that fraction the amount of radiation received by the individuals varies according to the type of examination or therapy carried out, as well as to the techniques employed.

Genetically significant doses

19. The frequencies of the types of examinations or treatments, and therefore the corresponding per capita mean doses to the gonads, vary with the age of the patients. Since there is a high inverse correlation between age and the probability of having further children (child expectancy) it is apparent that, for equal doses, the amount of genetic damage transmitted to the following generations will depend to a large extent on the child expectancy of the patients undergoing irradiation. It is clear, in fact, that even if mutations are produced in the germ cells of old subjects, they will not be further transmitted.

20. Average gonad doses from medical irradiation, as can be computed when populations are uniformly ex-

posed irrespective of age, do not therefore represent the doses which are relevant in bringing about hereditary effects. Allowance must be made in their computation for the child expectancy of the irradiated subjects. This is done by computing for each type of irradiation a weighted dose to the population which is called the *genetically significant dose*.^{G⁹}

(a) Diagnostic X-ray procedures

21. X-ray examinations are at present the only diagnostic procedures which contribute to the external irradiation. Normally the whole body is not exposed to radiation, various devices and techniques being employed to limit as far as possible the field of irradiation to the relevant part. The contribution to the genetically significant dose from different examinations therefore varies so that a rather detailed analysis of the exposed groups, as has been made in annex G, is necessary in order to obtain a comprehensive estimate of the dose to the population arising from diagnostic procedures. Furthermore, dose estimates have to be made on the basis of a limited sample of the population; these estimates may be liable to bias since rigorous sampling methods have so far been applied in only a few cases.

22. Table II shows the total annual genetically significant doses received from X-ray examinations by the populations of those countries and areas from which data have been made available to the Committee. The values of the genetically significant dose that have been reported to the Committee appear to range from 6 mrem to 60 mrem per year.^{G table XXIII} Such a variability may be due to a number of reasons. Differences in radiological techniques are certainly responsible for part of it, but so are both the over-all and the relative frequency of the various examinations, which may reflect either different epidemiological situations or different medical methods prevalent in each country.

23. More than 80 per cent of the genetically significant dose from diagnostic procedures is contributed by

TABLE II. GENETICALLY SIGNIFICANT DOSES (MREM/YEAR) FROM MEDICAL PROCEDURES

	A	B	C
<i>Country-wide surveys</i>			
Austria.....	16-25		
Denmark.....	29		
France.....	58	3	3
Japan.....	39		
Norway.....	10		
Sweden.....	38		
Switzerland.....	22		
United Kingdom (except Northern Ireland).....	14	4	1
<i>Limited surveys^a</i>			
Argentina (Buenos Aires).....	37		
Federal Republic of Germany (Hamburg)....	18	2	
Italy (Rome).....	43		
Netherlands (Leiden).....	6		
UAR:			
Cairo.....	7		
Alexandria.....	7		
USA:			
Richland.....	45		
Oak Ridge.....	50		

A = Diagnostic X-ray procedures. G table XXIII

B = Radio-therapy in non-malignant conditions. G table XXIX

C = Radio-therapy in malignant conditions. G table XXIX

^a These may be representative only of the particular area surveyed and not necessarily of the practice in the whole country.

less than ten types of examinations representing only a small fraction of the total number of examinations.^{G³¹} The high contribution of those few examinations can be accounted for by the fact that they give rise to high individual gonad doses, by their high frequency or because they are carried out at ages when the child expectancy is high (paras. 19 and 20).

24. While these data refer only to countries with a total population of about 200 million inhabitants, it is to be expected that the populations of countries with comparable hygienic and medical standards may receive genetically significant doses of the same order of magnitude as those recorded in the table. These data may thus be representative of a much larger fraction of the world populations, including those in the USSR and the United States.

25. A comparison between genetically significant doses in countries for which both present and 1958 data are available shows that there has been little change during the last few years. In the United Kingdom, however, the genetically significant dose has apparently decreased from 23 mrem in 1958 to about 14 mrem in 1961. The decrease, however, is probably only apparent and may reflect the fact that the 1961 data, unlike the older ones, are based on a properly devised sample of all the hospitals of the country.^{G²⁸} It may be pointed out that the British data show considerable variability within the country and indicate that, if the best techniques and equipment were used throughout the country, substantial reduction of the genetically significant dose would be achieved.

(b) Radio-therapy (external or from sealed sources)

26. In therapy not only X-rays but also beta and gamma rays are used; the latter provided either by application of sealed isotopes (for instance, radium) or by exposure to cobalt and caesium teletherapy units.

27. The available estimates of genetically significant doses due to external radio-therapy for non-malignant conditions in three areas are also given in table II. These are much lower than the corresponding doses due to diagnostic X-irradiations, although individual doses to the gonads are generally higher. The frequency of therapeutic irradiations is, however, very much lower than the frequency of diagnostic ones and the child expectancy of the patients is also often lower. Little contribution to the genetically significant dose is made by external radio-therapy in malignant conditions where the child expectancy is usually very small.

(c) Internally administered radio-isotopes

28. Internally administered radio-isotopes are used both for diagnostic and therapeutic purposes and are applied on an increasing scale owing to their greater availability in recent times.^{G⁶²⁻⁷⁸} Iodine-131 is used to investigate the function of the thyroid gland where it is selectively concentrated, or to treat thyroid gland diseases, including thyroid cancer. Phosphorus-32 is chiefly used in the treatment of polycythemia, a blood disease, gold-198 in the treatment of certain malignancies. Data on the genetically significant doses due to both iodine-131 and phosphorus-32 are available from four countries. Genetically significant doses from diagnostic applications range from 0.01 to 0.03 mrem per year, those due to therapeutic applications from 0.15 to 0.40 mrem. The largest part of the genetically significant dose is contributed by iodine-131.

* * *

29. From this survey of the various components of the genetically significant dose due to medical irradiation, it appears that the diagnostic use of X-rays is by far the major contributor. Radiological practices are at present the largest artificial source of radiation to which human populations are exposed, at least in countries with good medical standards. Any measure which would reduce the genetically significant dose without decreasing the value of radiological facilities deserves serious attention. Such measures might include the avoidance of all unnecessary examination, especially in younger subjects, and the use of the best techniques and equipment to reduce the individual doses to the gonads.

Marrow doses

30. The importance of marrow doses is due to the fact that the active, or red, bone marrow contains blood-forming cells which, under the effect of irradiation, may give rise to leukaemias. The active bone marrow has an uneven distribution in the body, so that the extent to which blood-forming cells are irradiated depends on the type of examination performed. A knowledge of the marrow distribution is therefore needed to compute marrow doses.^{G79} The active bone marrow is mainly associated with spongy bone so that as much as 80 per cent of it is found in the bones of the head, of the spine and of the lower limb girdle. Accurate quantitative data are limited, however, especially as regards the changes of distribution of marrow with age and with various diseases, and studies in that field should be encouraged.

31. It has been assumed, as a basis for computing bone-marrow doses, that the irradiation of, say, one-tenth of the bone marrow with a given dose has the same effect as the irradiation of the whole bone marrow with a dose ten times lower. This leads to the use of per capita mean doses to the bone marrow as estimates of the population doses from individual irradiations. Two factors, therefore, enter into the computation of the per capita mean dose from a given radiological procedure, the frequency with which that procedure is applied and the mean dose to the bone marrow.

32. A limited number of estimates of the mean bone-marrow doses from diagnostic examinations have been made.^{G81} These indicate that the examinations involving fluoroscopy, such as those of the upper and lower gastrointestinal tract, and examinations of the pelvic region are those which give rise to the highest mean bone-marrow doses. The mean marrow doses received during external radio-therapy treatments may be considerably higher than those received during diagnostic examinations.^{G80}

33. The data submitted to the Committee are not sufficient to make possible an accurate estimate of the per capita mean marrow doses to the population. The data are, however, consistent with the estimates made by the Committee in its first report in which a value of 50-100 mrem was accepted as representative of the contribution to the bone-marrow dose from diagnostic procedures, including fluoroscopy. No reliable estimate of the contribution from therapeutic irradiation can be made at the present time. The Committee is aware that a number of investigations are currently being carried out and expects that these will make possible, in the near future, a more detailed and accurate appraisal of the irradiation of the bone marrow due to medical procedures.

Irradiation of other organs and tissues

34. Although gonads and bone marrow are the organs

of the greatest importance in view of the possible effects of radiation on them, other organs and tissues may also be irradiated in the course of radiological examinations and treatments.^{G91-97} Some of them deserve particular attention during certain procedures, in particular the eye lens during examinations of the head, the thyroid gland during administration of iodine-131, and foetal tissue when radiological examinations are carried out during pregnancy. Here also the reduction of the dose to these organs can be achieved by technical improvements and, in the case of foetal irradiation, by confining radiological examinations during pregnancy to those justified by clear indications.

(2) OCCUPATIONAL IRRADIATION

35. Individuals may be exposed to radiation as a consequence of their occupation, either because they are directly engaged in radiation work (medical practices, industry, research etc.) or because their occupational activities take place where exposure to radio-activity is significant. The exposures can be external or internal, the latter arising through inhalation of radio-active gases and dusts, and through ingestion of radio-active material.

36. Some data are now available from five industrialized countries on the number of subjects occupationally exposed.^{G106-107} These range from 0.3 to 0.8 individuals per thousand of total population, and figures from countries with comparable medical and industrial standards are probably not higher.

37. Data have also become available on the occupational genetically significant doses in three of the countries referred to above.^{G118} These do not exceed 0.5 mrem per year as averaged over the whole population. In one of these countries about 40 per cent is due to irradiation incurred in atomic plants.

38. Such low values were achieved through strict adherence to protection practices based on recommendations of the ICRP.

39. A potentially significant source of occupational irradiation is related to high-altitude flights (above 26,000 metres) during which persons on board aircraft may receive high doses of cosmic radiation.^{G111-114} Such irradiation is of little concern at present, since commercial aircraft seldom fly at altitudes higher than 12,000 metres and flights at higher altitudes are usually of very short duration. A different situation may, however, arise if high altitude flights are operated in the future.

(3) IRRADIATION FROM MISCELLANEOUS SOURCES

40. Many objects in common use contain radio-active material or emit radiation. Luminous watch dials are the most common, but a host of luminous devices are to be found on the market in increasing numbers.^{G117-126} A number of other objects also incorporate radio-activity: these include static charge eliminators, smoke detectors, electronic tubes, and ceramic glazes containing uranium. X-rays are emitted from television sets and from certain electronic devices. The contributions to the genetically significant dose from each of these sources are small, but their total annual dose may be a few mrem.

41. The contribution that X-ray shoe-fitting devices make to the genetically significant dose is difficult to assess. However, when inappropriately used, they may give rise to a substantial gonad dose, both to the customer and to the sales staff, as well as a large dose to the customer's feet.^{G119} The use of such devices has been prohibited in some countries.

C. Irradiation from radio-active contamination of the environment

(1) EXPLOSIONS OF NUCLEAR WEAPONS

42. Nuclear explosions, as mentioned in chapter II, paragraphs 20 and 21, are sudden releases of energy produced by fission or fusion reactions.* The release of energy is accompanied by the production of varying amounts of fission products depending on the extent to which the explosion involves fission processes. In addition, as was explained earlier, both fission and fusion reactions also induce radio-activity in the environment because of the neutrons they produce.

43. Nuclear explosions can be carried out under a variety of conditions, in the atmosphere at various altitudes, underwater or underground. In each case the extent and type of the environmental contamination are different. This report deals mainly with explosions in the atmosphere since these have been, by far, the most significant source of man-made radio-activity in the world environment and because very few data have been received regarding underground or underwater explosions.

44. Underground explosions^{FI 26} should not give rise to significant environmental contamination, but some leakage of radio-active vapours may occur. Since the radio-activity of some fission products persists for a long time at the site of an underground explosion, some contamination of the environment due to water infiltration, or to other factors, may occur.

45. Nuclear explosions result in the production of radio-active nuclides of various half-lives, from a few seconds to several thousand years.^{FI 11-15} The composition of the radio-active debris will therefore be different depending on the time which has elapsed since the explosion, as short-lived nuclides progressively disappear.

46. When an atomic device is exploded in the atmosphere, the extremely large amount of heat produced makes the resulting fireball rise, while the coarser particles caught up in the explosion when this occurs close to the surface, fall out onto the ground in the vicinity of the explosion site. These particles are heavily contaminated with fission products and constitute the so-called local fall-out.^{FI 32-35} Vapours of the substances involved in the explosion which condense into smaller particles continue their upward movement, the height eventually reached by the cloud so formed depending on the altitude and power of the explosion. The debris from explosions up to several tens of kilotons that are carried out at ground level will mainly remain in the troposphere, i.e., in the lower layer of the atmosphere (below approximately 10 km altitude), while that from more powerful explosions will cross the boundary of the troposphere—the so-called tropopause—and reach the stratosphere, and only a small portion will remain in the troposphere.

47. In the troposphere the cloud is carried by winds and by the process of turbulent mixing.^{FI 53-60} It also undergoes both horizontal and vertical movements owing to various meteorological factors such as changes in temperature and pressure. In the course of its movements in

* In a nuclear explosion the total energy release is compared with the energy release by TNT (trinitrotoluene) when it explodes. Thus a 1-kiloton nuclear explosion is one which produces the same energy as the explosion of 1 kiloton (10³ tons) of TNT, namely of about 10¹² calories. Similarly a 1-megaton explosion would correspond to the explosion of 1 megaton (10⁶ tons) of TNT.

the troposphere, the cloud will be progressively depleted of its particles owing to washout by rain, gravitational settling, and direct impaction on surfaces. About one-half of the debris released in the troposphere is deposited in some twenty to forty days.

48. In the stratosphere latitudinal movements also occur, but turbulent movements are much less marked than in the troposphere, owing to the temperature stability of the stratosphere.^{FI 38-47} From the stratosphere, cloud particles are progressively transferred to the troposphere where they are eventually deposited on the ground (stratospheric fall-out). The passage from the stratosphere to the troposphere is, however, normally a slow process, so that the debris injected into the stratosphere remains there for a time before being removed.^{FI 48-52} A stratospheric reservoir of radio-active debris is thereby created.

49. The period during which radio-active debris remains in the stratosphere is of importance, owing to radio-active decay. Depending on the time spent in the stratosphere, a greater or smaller fraction of these radio-active nuclides will have decayed to stable ones by the time they reach the ground, so that the shorter-lived ones may have virtually disappeared. The time spent by the debris in the stratosphere may be expressed as half-residence time, the time required for half of it to be removed.†

50. In the first report the half-residence time was taken, for purposes of evaluation of future fall-out, to be the conservative value of seven years, although the best value was thought to be 3½ years. This estimate was based on simplified assumptions as to the mechanism of removal and on the amount of debris present in the stratosphere, as well as on the observed rates of deposition. More accurate estimates are now available,^{FI 45, 46} as a consequence of direct measurements of the amount of debris in the stratosphere and of improved methods of dating fission products originating from individual explosions. Moreover, the discontinuance of significant stratospheric injections from the end of 1958 to the autumn of 1961 made it possible to study the movement of radio-active debris in the stratosphere without the complicating factor of renewed injections.

51. It has become apparent that the half-residence time of the debris varies with the energy of the explosion since this affects the height to which the products are carried. There is some evidence that half-residence times are shorter for explosions in higher latitudes and also for explosions at lower altitudes. Estimates have ranged from as short as a few months for low altitude explosions in temperate and polar latitudes, to some five years for explosions at altitudes above 45,000 metres in the tropical belt.

Rate of deposition of radio-active debris on the earth's surface

52. The rate and distribution of deposition of debris from nuclear explosions depends on several factors,^{FI 72-76} in particular on the amount of debris in the atmosphere, and on meteorological situations. The latter show wide variations and account for the large differences in fall-out rates observed between different areas and in different periods of the year.

† The mean residence time of the debris in the stratosphere is also frequently used and can be obtained by multiplying the half-residence time by the factor 1.44.

53. The deposition is highest in the temperate latitudes and a peak in the rate of deposition is usually observed in spring.^{FII 80-89} This may be attributable to the rate of exchange of air between stratosphere and troposphere, to the positions where these exchanges take place and to other meteorological conditions.^{FII 48-52}

54. Since the majority of tests were carried out in the northern hemisphere and since exchange between the stratospheric air of the northern and southern hemisphere is slow, the stratospheric reservoir is larger north of the equator than south^{FII 97-99} in the early period after explosions and, accordingly, rates of deposition are higher in the northern hemisphere.

55. The accumulation of the debris depends on the properties of the ground on which it falls since the debris can be washed off by rain from impermeable surfaces. In soil, rain and agricultural practices affect the penetration. Part of the debris falling on plants may also be washed off but some is retained on the surface or absorbed.

56. Many radio-active nuclides of various half-lives are present in fall-out and those radiologically most important are zirconium-95 (9 weeks), niobium-95 (5 weeks), caesium-137 (30 years), strontium-90 (28 years), carbon-14 (5,760 years), iodine-131 (8 days). Some of them contribute to both internal and external exposure, others either to the external or to the internal exposure only.

External irradiation

57. The main contributions to the external irradiation due to fall-out come from the first three above-mentioned nuclides which all emit gamma rays. In estimating the tissue dose delivered from outside the body from deposited fall-out, allowance must be made for the shielding effect of buildings and therefore for the fraction of time spent out of doors which in turn is subject to geographical, age and social variations.

58. On account of the great difference between their half-lives, the respective contribution of zirconium-95 + niobium-95 and caesium-137 to the total tissue dose from stratospheric fall-out depends on the stratospheric residence time. Because of the relatively short half-life of zirconium and niobium, much of their decay, when the residence time is long, may occur before deposition, whereas caesium-137, with a half-life of 30 years, decays mainly after deposition on the ground and consequently still contributes a substantial tissue dose.

Internal exposure

59. Strontium-90, caesium-137, iodine-131 and carbon-14 are the main contributors to internal exposure. The chemical properties of strontium and, therefore, of its isotope strontium-90 (half-life 28 years) are similar to calcium, an essential element for all organisms.^{FII 9-12}

60. Diet, including both plant and animal foods, is the principal source of strontium-90 in man; inhalation and drinking water usually make only a very small contribution. Since the last report, considerable progress has been made in our understanding of the transfer of strontium from fall-out to the human body through the food chain and of the importance of the various factors involved. It has become apparent that, when the amounts currently being deposited are relatively high, the quantity of strontium-90 which enters human diet may depend more on direct contamination of the vegetation

through deposition on leaves, on inflorescences and on the bases of perennial plants than on absorption from the soil by the roots.^{FII 21,108-107} This was generally the case up to the end of 1959. When fall-out rates decline, however, absorption from the roots, and therefore the cumulative amount present in the soil, becomes the predominant factor. This occurred in 1960 and 1961.

61. The amount of strontium-90 taken up from the soil depends on many factors, the most significant of which are the available calcium^{FII 16-17} and the depth to which the strontium-90 has penetrated.^{FII 19} Strontium-90 and calcium enter plants from the soil approximately in the same ratio in which they are available to plant roots; this may, however, be very different from the ratio of the total quantities present in the soil.^{FII 17}

62. The ratio of strontium-90 to calcium is lower in foods of animal origin such as milk, owing to discrimination against strontium-90 relative to calcium in passage through the animal body. Thus the average ratio in milk, both from animals and man, is about one-tenth of that in the diet from which it was derived.^{FII 29}

63. To evaluate the strontium-90 intake of human populations, it is important to know the ratio of strontium-90 to calcium in the total diet.^{FII 41-50} All data available to the Committee are summarized in annex F, part II, table IV. While the information is still incomplete for large areas of the world, enough data have become available since the last report to make indirect estimates possible for some areas where few measurements have been made.^{FII 94-99} The ratio in the diet depends on its composition and on the areas in which its components are produced. Geographic, economic and cultural factors therefore are important. It appears that differences in diet have usually not caused dietary levels to vary more than about twofold in areas of similar fall-out.

64. It has been found that the ratio of strontium-90 to calcium in milk had hitherto borne a relatively constant relationship to that in the total daily intake^{FII 94-99} in diets where milk is the main source of calcium. The ratio in these diets has usually been about 1.4 times that in milk. In countries where milk is important in the diet the magnitude of the ratio of strontium-90 to calcium in the total can thus be inferred for measurements of milk. When, however, milk is of lesser importance, other dietary constituents must be examined to estimate the ratio in the total diet.

65. Once strontium-90 has been absorbed from the gastro-intestinal tract, its distribution in the body follows closely that of calcium. It is therefore deposited in the skeleton and retained for a period of years.^{FII 81,82} The concentration in new bone depends primarily on the ratio of strontium-90 to calcium in the diet, but discrimination against strontium occurs during its absorption through the gut^{FII 83-86} and in other physiological processes, so that the average observed ratio of strontium-90 to calcium in bone is about one-quarter of that observed in the diet.^{FII 83,84} Values for the ratio of strontium-90 to calcium measured in bone from many areas are given in annex F, part II, table XX, and a comparison of dietary and bone values for broad geographical regions in table XXIV. The highest ratios of strontium-90 to calcium in both diet and bone have been found in northern temperate regions, where the deposition has been highest.

66. Considerable age-dependent variations have been observed in the strontium-90 content of bone,^{FII 82-84} the

highest value being for children between one and two years of age. The average level is lower in children born before the beginning of diet contamination and is lower still in adults. The difference between age groups reflects differences in the extent to which bone has been laid down since fall-out commenced.

67. Strontium-90 and its daughter yttrium-90 give rise to beta radiation, which despite its limited range irradiates not only the bone itself but also the bone-forming and blood-forming cells which line or are contained in the bone cavities.

68. With some exceptions^{FTI 124} the absorption of caesium-137 from soils by plant roots is relatively poor;^{FTI 128-127} thus its entry into man's diet depends primarily on the rate of deposition. The cumulative deposit of caesium-137 is also important, however, because it contributes to external irradiation and will enter the diet when the amount in the soil is high compared with the rate of fall-out. Caesium-137 is distributed rather uniformly throughout the body and is retained for a much shorter time than strontium-90, 50 per cent of it being removed in about four months.^{FTI 130-132} Fewer data are available on its concentration in food than for strontium-90, but because it emits gamma radiation the body content of living subjects can be measured directly with whole body counters. The number of these is still limited, but sufficient measurements are available to enable reasonable estimates to be made of the content of caesium-137 in the body, at least in the regions of highest deposition. Because of the relatively rapid turnover in the body, large age-dependent variations do not occur.

69. The explosion of nuclear weapons has considerably added to the amount of carbon-14 in the atmosphere, which rose by approximately 30 per cent between 1953 and 1959, although this increase had a value of only 20 per cent in 1960.^{FTI 01-04, 115} This artificially produced carbon-14 follows the same mechanism of distribution as that produced by cosmic radiation, from which it cannot be distinguished. The dose-rate from the artificially produced carbon-14 is small compared with other nuclides produced by nuclear explosions. Because of its very long residence time in the biosphere, however, the carbon-14 produced by tests up to the present time will continue to irradiate future generations for thousands of years, although at a progressively decreasing rate.

70. Iodine-131 is readily absorbed through the alimentary tract and is selectively concentrated in the thyroid gland. It is also secreted in milk. Owing to its short half-life, iodine-131 is important for only a few weeks after an explosion. It reaches the body through the ingestion of fresh foods, milk being the principal source in many areas.^{FTI 152-153}

Future levels of deposition

71. The global rate of fall-out depends, as was mentioned in paragraph 52, on the amount of debris present in the stratosphere. It also depends on its half-residence time as established on the basis of a simplified model of deposition.^{FTI 105-108} In the absence of tests, depletion of the stratosphere progressively takes place and the rate of fall-out decreases accordingly. Any injection of debris in the stratosphere is followed, after a period of time, by a rise in fall-out rates of a magnitude roughly proportional to the amount injected.

72. The continuation of fall-out will add to the radio-active nuclides already present on the surface of the

earth. The accumulated deposit will increase until it reaches a maximum when the rate of fall-out equals the rate of decay and of removal of the accumulated radio-active material. The maximum will occur at different times for different nuclides, depending on their individual half-lives. When rates of fall-out are lower than the rate of decay and of removal, the amount of radio-active material present on the surface of the earth will decrease until a new equilibrium is set up. In the absence of deposition, the accumulated deposit of radio-active nuclides will eventually be reduced to zero.

73. When the amount of debris present in the stratosphere and its half-residence time are known, it is possible to predict the rates of deposition and the accumulated deposit in the near future for individual nuclides.^{FTI 109} However, as accurate data regarding both the amount of debris injected in the stratosphere and its half-residence time are only available up to the end of 1960, the estimates of future deposition are based on assumptions. According to these, one megacurie strontium-90 and 10^{28} atoms of carbon-14 were injected during 1961 and the half-residence time of this debris is 2.5 years.^{FTI 110-114}

74. No realistic prediction regarding the fall-out from possible future testing can obviously be made, since tests might be carried out in a variety of conditions and at very different rates. Theoretical calculations can, however, be useful insofar as they indicate the magnitude of the contamination of the environment and of the radiation doses under hypothetical and arbitrary conditions of testing. These are assumed for illustrative purposes only, since different conditions of testing and different rates of testing would result in correspondingly different doses.^{FTI 110-114, 119, 120}

75. Knowledge of the mechanism of transfer of nuclides from soil to man through the food chain enables us to predict their expected concentration in the diet from estimates of future deposition on the basis of measured data up to 1960 and of the above-mentioned assumptions regarding 1961.

76. Estimates of the future world average concentrations of strontium-90 in the diet can also be made on the assumption that test explosions will be continued at a steady rate of one megacurie strontium-90 and 10^{28} atoms of carbon-14 injected annually into the atmosphere starting in 1961. Under conditions of testing at a steady rate, an equilibrium between rates of deposition and rates of decay and removal would eventually become established so that the amount of radio-active nuclides accumulated on the surface of the earth, and therefore transferred into food, would become constant. The equilibrium values for long-lived nuclides depend primarily on the rate of testing. They depend to a lesser extent on the residence time of the debris, and therefore on the latitude and altitude of the explosions. For short-lived nuclides, however, the residence time greatly influences the equilibrium values.

Doses of radiation from fall-out

77. The doses of radiation due to fall-out depend on the type and amount of radio-active nuclides present in the environment. Since both the amounts and the relative proportion of different nuclides vary with time, and since deposition shows geographical variations, the problem of estimating doses received by the world population as a whole are particularly complex.^{FTI 1-5, 26-35} The dose-rate in a given year has little interest *per se* because all

the separate and varying yearly rates must be added in order to obtain an estimate of the total dose, and therefore to predict the effects from a given series of explosions. It is therefore more appropriate to compute the total dose contribution that is being, and will be, delivered by the material injected during past explosions.^{H15-21} This contribution is called the *dose commitment* of the population due to these explosions.

78. Table III gives the dose commitment from the

assumed testing practice, from 1954 to 1961, for exposure of the gonads, the bone cells and the bone marrow. It also shows the fraction of the dose commitment that will be reached by the year 2000. The dose commitment is the world average obtained by weighting doses with geographical and population factors allowing for the non-uniform distribution on the globe of both fallout deposits and human population.^{FIII table XI}

TABLE III. DOSE COMMITMENT FROM ASSUMED PRACTICE OF TESTING, 1954-1961
(8 years)

Tissue or organ	Source of radiation	Dose commitment (mrem)	Fraction of dose commitment reached by 2000
Gonads	External.....	30	0.97
	Internal		
	Cs ¹³⁷	11	1.0
	C ¹⁴	70	0.10
	TOTAL	111	0.42
Cells lining bone surfaces	External.....	30	0.97
	Internal		
	Sr ⁹⁰	79	0.91
	Cs ¹³⁷	19	1.0
	C ¹⁴	116	0.10
	TOTAL	244	0.54
Bone marrow	External.....	30	0.97
	Internal		
	Sr ⁹⁰	40	0.91
	Cs ¹³⁷	14	1.0
	C ¹⁴	70	0.10
	TOTAL	154	0.56

79. It appears from the table that the dose commitment refers to an exposure which is almost entirely completed within fifty years, except for the further contribution of the very long-lived carbon-14. It can be shown that only after about 20,000 years will 90 per cent of the total dose due to carbon-14 be delivered, whereas the same fraction of the total dose due to strontium-90 and to caesium-137 is delivered in less than 100 years.

80. Table IV gives the dose commitment per year of future testing at the yearly rate of 1 megacurie of strontium-90 and 10²⁸ atoms of carbon-14 injected into the atmosphere.

(2) DISPOSAL OF RADIO-ACTIVE WASTES

81. The controlled fission reaction which takes place in a reactor produces, as was pointed out in chapter II, paragraph 20, both energy and radio-active fission products. Some of these products have economic value or scientific interest but most have not, and therefore present a problem of long-term storage or disposal. Wastes also inevitably result from chemical processing of radio-active materials and in the industrial and medical uses of radio-isotopes.

82. In an ideal situation no wastes would be disposed of but would be stored in adequate containers so that no leakage would take place. As is well known from experience in the normal chemical industry this is practically impossible to achieve; airborne and aqueous effluents will always contain some amounts, however small, of waste material. It is practicable, however, to store all highly radio-active wastes,^{FIV 8-10} if necessary after concentration so as to reduce their volume, and possibly after reduction to the solid state; in this way the probability of their dispersion becomes very remote.

83. Wastes consisting of very dilute aqueous solutions or suspensions of radio-active materials are customarily released into rivers, lakes and seas, where further dilution is achieved.^{FIV 14-23} Such practices undoubtedly add to the contamination of the environment which may

TABLE IV. DOSE COMMITMENT PER YEAR OF TEST IN THE CASE OF FUTURE TESTING

Tissue or organ	Source of radiation	Dose commitment per year of testing (mrem)
Gonads	External.....	3.8
	Internal	
	Cs ¹³⁷	3.1
	C ¹⁴	22
	TOTAL	29
Cells lining bone surfaces	External.....	3.8
	Internal	
	Sr ⁹⁰	10.5
	Cs ¹³⁷	5.3
	C ¹⁴	37
	TOTAL	57
Bone marrow	External.....	3.8
	Internal	
	Sr ⁹⁰	5.3
	Cs ¹³⁷	3.9
	C ¹⁴	22
	TOTAL	35

necessitate carefully planned monitoring in order to ensure that no danger arises.

84. Once released into the environment, some radio-active materials may be taken up by plants and thus be transferred into animals and man through the diet in a similar manner to fission products from nuclear tests.

85. The still limited use of atomic energy for peaceful uses and the present waste disposal practices are believed to make a negligible contribution to the doses of radiation received by the population of individual countries. It is to be expected, however, that the expanding applications of atomic energy will, in the foreseeable future, make this aspect of the control of environmental contamination increasingly important.

(3) ACCIDENTAL RELEASES OF RADIO-ACTIVITY^{WIV 34-39}

86. Either during the operation of a reactor or during the processing of radio-active material, accidents may occur which may release activity into the environment

and result in the exposure to radiation of persons who are near the place where this happens. The amount and range of contamination obviously depend on so many factors inherent in the accident itself, and in the site where it occurs, as to preclude any simple discussion of this subject.

87. Past accidents have sometimes entailed considerable irradiation of a few people only who were working in the plant where the accident happened. In one case, however, substantial amounts of radio-active fission products, particularly iodine-131, were spread over an appreciable area. As a consequence of the measures taken, such as restrictions in the consumption of milk, the doses received by individuals in the population involved were, however, quite low.

88. The possibility of serious accidents can only be assessed on the basis of past experience. This is still limited but suggests that large accidental releases, of such a nature as to cause concern for the health of individuals in the population, are likely to be extremely rare.

CHAPTER VI

COMPARISON OF DOSES AND ESTIMATES OF RISKS

1. The effects of radiation on human beings have been discussed in chapters III and IV. In the present chapter the contributions of the main individual sources to the total irradiation of the population will be compared on the basis of the effects that they might produce.

2. Among the effects of radiation which may be significant in those dose ranges to which large human populations are exposed, only the induction of mutations, of leukaemia and of bone tumours will be dealt with in the present chapter. Other effects, such as the induction of other malignant tumours or life-shortening might be equally relevant, but our knowledge is still too limited to enable us to assess the importance of radiation in their causation.

Dose-rates and risks

3. The deficiencies in our knowledge of dose effect relationships should be emphasized. In the induction of gene mutations, the frequency of induced mutations is believed to be strictly proportional to the dose, for a given dose-rate.⁸⁸ However, the proportionality factor for man cannot be estimated adequately at the present time.

4. For the induction of malignant changes, the uncertainties are still greater, since it is not certain that the incidence of such effects is proportional to the dose, and the only available information has been obtained at doses and dose-rates much higher than those to which the world population is exposed. No alternative hypothesis regarding the relationship between dose and the frequency of induction of malignant changes is, however, indicated in the present state of our knowledge, and proportionality at low doses will therefore be assumed for the purpose of calculation.^{H8-13}

5. For gene mutations and malignant changes, the effects will be considered to be proportional to the per capita mean doses to the relevant tissues. This follows from the assumption of proportionality between dose and effect, and it implies that the frequency of effects in the whole population would be the same whether, for instance, all individuals received the same dose of radiation, or half of them received twice as much. The basis for this estimate of comparative risks applies particularly to the small doses and dose-rates with which we are concerned and is discussed in detail in annex H.

6. The time in which radiation causes effects need not influence this estimate of comparative risks and the choice of the interval over which to define the expected incidence is immaterial provided that: (a) the latent periods elapsing between the irradiation and the onset of the effect in various individuals are close to the average and (b) the duration of the average latent period is constant at all doses. If condition (a) is not met, allowance must be made for the expectation of life in the population, and therefore for its age distribution. The

latent period for the induction of gene mutations is extremely short. The latent period for leukaemia also may well be short relative to the life-span since there is some evidence that the incidence of leukaemia is declining among the irradiated population of Hiroshima and Nagasaki (chapter III, para. 23). It will be assumed in the present chapter that conditions (a) and (b) are fulfilled.

7. If proportionality is assumed between dose and incidence of effect, only the ratio of the doses due to different sources needs to be calculated in order to obtain the comparative risks from these sources.

8. In the first comprehensive report of the Committee risks were computed using tentative estimates of the relevant proportionality factors between dose and the frequency of effect. The theoretical character of these estimates as well as the hypotheses on which they rested were emphasized. The Committee is of the opinion that less reliance can now be placed on such estimates, as has been explained in chapters III and IV. Comparative risks only will therefore be computed in the present report, by using the ratio of the doses delivered by the different sources. It should be clearly borne in mind that various assumptions are involved even in this approach.

Comparative risks due to irradiation from various sources

9. With regard to irradiation received in the course of occupational exposure, the definition of "maximum permissible doses" rests on the concept of a balance between the practical requirement for the work concerned and the limitation of the hazards involved. While appreciating the necessity in operational control of defining maximum permissible doses for groups of individuals in relation to particular circumstances, the Committee believes that the comparison of doses from various sources with maximum permissible doses valid for different circumstances is likely to be misleading here and would introduce considerations extraneous to the concept of risk, which is based on the appraisal of harmful effects only.

10. Comparative risks can be computed for any two sources of radiation. Since man has always been exposed to natural radiation at an approximately constant rate, natural sources will here be taken as the reference standard on which to base comparisons with other sources. The annual doses arising from natural sources have been given in chapter V, table I. As was mentioned earlier, these doses are subject to geographical variations which are well enough known to make possible the computation of a rough population-weighted world average. Progress in the study of natural sources is, however, desirable because they form a useful basis from which comparisons with other sources can be made.

11. However, for each source of radiation, the com-

parison with natural sources presents some difficulties of its own. Medical irradiation does not involve the whole population of a given country, so that appropriately weighted doses to the population, for example the genetically significant doses (chapter V, paras. 19-20), must be computed. Moreover, medical irradiation involves short exposure times, and the dose-rates may be so much higher than those arising from natural irradiation that the factors of proportionality between dose and effect may be different and therefore comparison with natural irradiation may underestimate the risk arising from medical sources. It must be also recognized that data regarding medical exposure are available only from certain countries and districts with high medical standards. Such areas are not likely to be representative of the entire world situation.

12. Problems of a different nature arise when computing relative risks due to fall-out from any finite period of testing. The whole population is continuously exposed to radiation from such a source, but at a varying dose-rate. Since the rate in a given year is not representative of rates in preceding or following years, the concept of dose commitment due to a certain period of testing was introduced in chapter V (para. 77) to define the total dose to be received by the population from the radio-active material initially injected into the atmosphere.

13. The dose commitment due to fall-out from a finite period of testing is not an annual dose but a total dose delivered over a very long period of time at a decreasing

rate. One way of computing a comparative risk is therefore to compare it with the total dose delivered by natural sources over a finite period of time. The choice of the period of time may be arbitrary, and in this report the eight-year period of testing from 1954 to 1961 is used (on the basis described in annex F). For conditions of continued testing, the relative risk is estimated by a comparison of the dose commitment per year of testing with the annual dose due to natural sources.

14. Table I of this chapter shows the comparative risks from the main sources of radiation in relation to natural irradiation. Comparative risks were estimated on the basis of the figures given in chapter V. The second column of table I is based on the ratio between doses to the gonads (or the genetically significant dose in the case of medical irradiation) from the various sources. The values therefore compare the relative risks that gene mutations will be induced by radiation from the various sources, taking a value of 1 for the risk from natural radiation. The third column gives the ratio between mean bone-marrow doses from various sources and therefore estimates the comparative risks of the induction of leukaemia. Comparative risks of the induction of bone tumours, as estimated from the doses to the cells lining bone surfaces, are given in the fourth column of the table. It must be emphasized that the comparison of risks can only be made separately for hereditary and somatic effects. No comparison can be made between somatic and hereditary risks, nor between risks of leukaemias and of bone tumours.

TABLE I. COMPARATIVE RISKS FROM MAIN SOURCES OF IRRADIATION
(RELATIVE TO THOSE FROM NATURAL RADIATION, TAKEN AS 1)

Source	Hereditary ^a effects	Somatic effects ^a	
		Leukaemia	Bone tumour
Natural sources.....	1.00	1.00	1.00
Medical irradiation ^b	0.30	0.4-0.8	?
Fall-out from tests up to December 1961.....	0.11	0.15	0.23
Fall-out from continued testing.....	0.23	0.28	0.43

^a No comparison can be made between hereditary and somatic effects (see para. 14).

^b Calculated on the basis of all information received, largely from countries with advanced medical facilities.

15. For illustrative purposes the table gives estimates of risks due to fall-out if tests were to be continued at an assumed yearly rate (of 1 megacurie strontium-90 and 10^{23} atoms of carbon-14) injected into the atmosphere.

16. The risk from testing is mainly due to carbon-14. The doses from this nuclide are delivered at extremely low rates over a very long period of time (chapter V, para. 79 and table III).

17. The relative risks due to fall-out from tests during the years 1954-1961 could alternatively be expressed in terms of the number of years of natural irradiation that would be required to deliver a total dose equal to this dose commitment. Thus, the dose commitment to the gonads from these past tests is equivalent to $0.11 \times 8 = 0.9$ years, and that to the bone marrow is equivalent to $0.15 \times 8 = 1.2$ years of exposure to natural sources.

CHAPTER VII

EVALUATIONS AND CONCLUSIONS

1. In presenting its first comprehensive report to the General Assembly in 1958 the Committee emphasized that the conclusions of that report, as with any scientific assessment, must be subject to revision in the light of advancing knowledge. Since then, considerable progress has been made in the field of study of the Committee, so that much more information is now available and our understanding of the effects of radiation is much increased. Although this makes it possible in many instances to give a clearer account of radiation exposure and effects, the complexities of the subject that have been revealed by recent investigations have necessitated a qualification of some previous statements.

2. Earlier chapters of the present report outline the present status of our knowledge of radiation exposures and effects and provide the basis for an assessment of the significance of these exposures. The annexes contain detailed information on which this outline is based. The present chapter gives the conclusions arrived at in the report. The Committee wishes, however, to emphasize that the report should be regarded as a whole and that individual sentences or assessments may be misleading if taken out of their appropriate context.

3. The review and the evaluations made by the Committee are in no way final and will undoubtedly require continuing revision as scientific knowledge advances and new data become available, the present lack of which still limits our understanding of some problems.

4. The Committee hopes that this report, by pointing out subjects which require more investigation and sometimes a fresh approach, will stimulate research and discussion that will result in an improved understanding of the effects of ionizing radiation on man and his environment.

5. The main questions which the Committee has again attempted to answer are:

(a) What are the levels of radiation to which man is exposed from various external and internal sources (including those arising from radio-active contamination of the environment as a result of nuclear tests) and how is this exposure distributed in time, in different geographical areas and within different parts of his body? It has been important to specify in particular what doses and dose-rates of radiation from various sources are received by the gonads (testes and ovaries), in view of their genetic importance, and by those cells in which malignant change may be induced by radiation, such as the blood-forming cells of the bone marrow and those lining bone surfaces.

(b) What are the effects produced by radiation, both on the irradiated individuals and on their offspring, particularly at those levels to which populations are currently exposed?

Levels of radiation

6. The frequency with which harmful effects are caused by each form of exposure depends essentially

upon the radiation dose received by human tissues from each source. A simple comparison of doses does not, however, indicate the likely frequencies of harmful effects if these doses have been delivered at widely different dose-rates. The following paragraphs discuss the sources of radiation to which man is exposed and the doses incurred.

RADIATION FROM NATURAL SOURCES

7. The estimation of the radiation exposure from natural sources has considerable importance, particularly because part of the normal occurrence of hereditary, and perhaps some malignant, diseases may be due to natural radiations. Moreover, as man has always been exposed to such radiation, the dose received from natural sources forms a useful basis of reference with which the doses received from other sources may be compared.

8. Natural sources of radiation include cosmic rays and those radio-nuclides which occur naturally in the environment. The radiation that man receives from these sources is described either as "external" when it reaches the body from the exterior, as from cosmic rays or by gamma radiation from radio-nuclides in the earth's crust or atmosphere, or "internal" when it is derived from naturally occurring radio-nuclides which have become incorporated into the human body.

9. Investigations carried out during recent years have enabled us to achieve greater precision in estimating the radiation dose to which the world population is exposed from natural sources. In particular, the contribution to this dose from the neutron component of cosmic rays, which had been disregarded in the first comprehensive report, can now be taken into account despite uncertainties inherent in its evaluation. The inclusion of this contribution explains why the present estimates of doses from natural sources are higher than those given in the previous report. Accurate estimates of the doses from potassium-40 and carbon-14 have also become available. Combining the estimated average contribution from cosmic rays, that from external radiation from radio-nuclides in the environment, and that from internal radiation from radio-nuclides within the human body, the average yearly dose from all natural sources is now estimated for various tissue and is about 125 mrem to the gonads, 120 mrem to the blood-forming cells and 130 mrem to the cells lining bone surfaces.

10. Wide geographical variation has been observed in the dose from most natural sources of radiation, both internal and external. The exposure from cosmic rays varies mainly with altitude, showing an approximately twofold increase for each thousand metres rise in altitude. The external radiation from radio-active nuclides occurring in the environment also shows geographical variation, depending largely on the composition of underlying soil and rocks. While the average dose-rate from these sources is about 50 mrem per year in most inhabited regions of the world, areas are known, as in parts of the Kerala, and the adjoining coast in India,

where the external dose-rates may be over twenty times as high. The exposure from internal sources also varies geographically owing to the variable intake of radium and of some other naturally occurring radio-nuclides. The contribution to internal radiation from carbon-14, tritium and potassium-40 on the other hand is fairly constant in different places.

MEDICAL EXPOSURES

11. It is now possible to place greater reliance upon the estimates of the dose received from medical procedures. Data from a number of countries with extensive medical facilities and a total population of 200 million are now available. They indicate that for diagnostic radiology the annual genetically significant dose ranged from 6 to 60 mrem in the particular years studied. These countries may be considered as representative of other areas with comparable medical practice on which adequate data are not available in sufficient detail. However, only a small fraction of the world's population is covered and the estimates may not apply to larger areas of the world. The upper limit of the range does not exceed half of the dose received from natural sources, although no simple comparison is appropriate, owing to the much higher dose-rates at which the doses from medical procedures are delivered. A few types of examination, which comprise a small fraction of the total examinations carried out in each country, contribute about three-quarters of the genetically significant dose. One of the most important results of these investigations is the evidence that this dose can be very substantially reduced by the full use of appropriate techniques and equipment. The genetically significant dose due to therapeutic irradiation ranges from 2 to 13 mrem and that from the medical use of radio-isotopes is less than 1 mrem per year.

12. Limited data have been obtained for bone-marrow doses and these are insufficient to furnish accurate estimates of mean doses. They seem to confirm, however, the tentative estimates made by the Committee in its first comprehensive report, in which a range from 50 to 100 mrem was accepted for the yearly contribution to the bone-marrow dose, as averaged throughout the population, from diagnostic procedures, including fluoroscopy. No reliable estimates of the contribution from therapeutic irradiation is possible at the present time.

OCCUPATIONAL EXPOSURES

13. The available data obtained from five industrialized countries show that at the present time the number of workers who are directly engaged in radiation work does not exceed eight per ten thousand in the population. It has been observed that when proper radiation protection methods are used, the great majority of these workers receive very low doses of radiation. From information collected in four countries, the genetically significant dose to the general population resulting from occupational exposures is estimated to be less than 0.5 mrem per year.

OTHER TYPES OF RADIATION EXPOSURES

14. In some countries, individual members of the population may be exposed to various other sources of radiation such as X-ray shoe-fitting machines, luminous dials of clocks and watches, various devices incorporating radio-active materials, and television sets.

Apart from those from shoe-fitting machines, the doses delivered are unlikely to present any significant hazard to individuals. The average exposure from any one of them is likely to be very small, although taken together they may make a small but significant contribution to the total genetically significant radiation dosage of populations in some countries. World average values of the total dose contribution to populations from these sources are not available at the present time.

15. It is important that the exposure of populations to radiation from such sources should be kept under continuing review, as regards both the exposure from each source and the aggregate exposure from them all. The introduction of any new source involving substantial exposure of individuals or of populations should be recognized and evaluated at an early stage. An example in the future might be the exposure of individuals to cosmic radiation in passenger aircraft flying at high altitudes.

ENVIRONMENTAL CONTAMINATION FROM NUCLEAR EXPLOSIONS

16. The contamination of the environment and the radiation exposure of human beings from any nuclear explosion depends very much on the type and yield of the explosion, on its altitude and geographical location, on the construction of the device as well as on whether radio-active products are injected into the upper or lower atmosphere, deposited locally on the earth's surface or into water, or retained underground. The processes by which radio-active material from nuclear explosions causes radiation to human tissues are described in detail in chapter V and in annex F.

17. Since the 1958 report of the Committee, our understanding of the processes involved in fall-out from the stratosphere and the lower atmosphere has been increased considerably by information and continued investigation on these subjects and in consequence of the three-year period during which no significant stratospheric injections of nuclear debris took place. The resultant information has tended to confirm our views as to the way in which fission products are removed from the stratosphere and the mechanisms involved are discussed in detail in annex F.

18. However, it has become clear that owing to meteorological factors, the rate of fall-out tends to increase in the spring, and that the stratospheric half-residence time (or period in which half of any injection is removed from the stratosphere) is often considerably shorter than was estimated in 1958. Geographical as well as meteorological factors have resulted in higher deposition of fall-out in the northern temperate latitudes than in the rest of the world.

19. In our previous report the amount of radio-active debris present in the stratosphere (the so-called stratospheric reservoir) was estimated by calculation from the observed fall-out rate and from a half-residence time which was assumed to be as high as seven years. A high value was assumed as a precaution against underestimating the dose to which human tissues would be subjected from long-lived radio-nuclides. It is now known that the amount of strontium-90 present in the stratosphere was over-estimated in consequence. Direct measurements of the stratospheric reservoir have now been made by means of high-flying aircraft and balloons and the content of the reservoir in very recent years has been estimated by this means.

20. The half-residence time of strontium-90 in the stratosphere has proved to be critically dependent on a number of factors, including the time of year at which the explosion takes place, the latitude, and both the height of the explosion above the earth's surface and the altitude to which the fission products are carried into the atmosphere. Debris injected in polar latitudes appear to have a stratospheric half-residence time of between 6 and 12 months, whereas this time may be as long as 2 years for injections in the equatorial belt. A shorter half-residence time for injections is important because the resultant fall-out will contain short-lived radio-nuclides which will somewhat increase the radiation received by man from fall-out by adding to the exposure due to the longer-lived radio-nuclides.^{FIII 28, 50-58}

21. Much valuable information has become available on the transfer of radio-active materials from fall-out through the food chain, and our understanding of this process is greatly improved. Estimates of the amount of fall-out components, especially strontium-90, are now available from many more areas and we also have more information on the composition of the diet of many populations.

22. There is now much more detailed evidence concerning the importance of direct contamination of the leaves, inflorescences and stem bases of plants in introducing fall-out material into the food chain, in addition to that taken up by the plant from the soil. In some plants such as cereals this effect is of particular importance during the season when the flowers and ears are being formed. The new information has greatly helped our understanding of the transfer of strontium-90 from diets of various types to human beings, in whom it is deposited in bone.

23. Some data have become available on the rate at which strontium-90 may be removed in harvested crops, and also leached or washed down through the soil and so away from the rooting zone of plants. These data indicate that the contribution to human irradiation of an accumulated deposit of strontium-90 in soil is likely to be halved in a shorter period than the 28 years that was assumed for purposes of estimation in the previous report.

24. It has been possible to obtain information on the amount of strontium-90 taken daily in the diet in a number of different regions of the world, and on the ratio of strontium-90 to calcium in the diets of these regions. The ratio of strontium-90 to calcium in the whole diet usually is higher than that in the milk, the difference being less for diets containing a large component of milk and milk products. When the ratio for the diet as a whole is compared with the ratio in milk from the same region, it is found that the over-all value for this type of diet is usually about one and a half. But the value is higher if plant products are important components of the diet.

25. Even for the many regions for which complete dietary surveys are not available, therefore, it is possible to make some estimate of the likely dietary intake of strontium-90, provided that its concentration in milk samples from these regions is known. However, if milk is a minor component of diet, information on the strontium-90 content of other foods also is required. The levels of contamination of several components of diet show wide geographical variations connected with the different cumulative deposition of strontium-90 in the soil and the rate of fall-out. These differences and the characteristics of the diet in different areas combined with the geographical variations of fall-out lead to sig-

nificant variation in the levels of contamination and in the quantity of strontium-90 received by man in food. The estimates made suggest that, over large areas in which the rates of deposition are similar, differences in the composition of the diet seldom result in more than twofold, or in certain types of diet at most fourfold, differences in strontium-90 intakes.

26. Our prediction of possible future concentrations of strontium-90 in dietary constituents continues to be based on the use of two factors, one depending on the rate of fall-out and the other on the accumulated deposition. Better values for such factors are now established for various food materials from survey data and from experimental methods, so that the dependence of dietary and hence of bone contamination on fall-out conditions can be adequately estimated.

27. The highest contamination of human bone with strontium-90 continues to be observed in the northern temperate latitudes. The average human bone concentrations in various parts of the world appear to be simply related to the observed or estimated amounts of strontium-90 present in the total diet, in the manner to be expected from experimental studies. The concentration of strontium-90 relative to calcium in new bone is about one-quarter of that in the diet consumed while the bone was being formed.

28. Caesium-137, unlike strontium-90, contributes to both external and internal irradiation. Caesium-137 differs from strontium-90 also in so far as it is not fixed in the human body but is retained there for a period of time, which is very short compared with that in which its activity is significantly reduced by radio-active decay. The rate of uptake of caesium-137, and therefore its contribution to internal contamination, depends principally on the rate of its deposition on vegetation since caesium contained in most soils is usually very poorly absorbed by plants, though there are some exceptions.^{FIII 124} The contribution of caesium-137 to external irradiation, however, depends on its accumulation on the ground. There is some evidence that the contribution of caesium-137 to external irradiation over undisturbed soil is reduced by about 50 per cent in ten years.^{FIII 16}

29. Several years' data on mean concentration of caesium-137 directly determined in the human body are now available and apply to a large part of the world. Geographical variation seems to be rather small. The concentration of this nuclide, which showed a general upward trend from 1956 to 1959, decreased in 1960 and 1961.

30. The present report deals much more fully than was possible at the time of the previous report with the formation of carbon-14 in nuclear tests and its contribution to human irradiation. As a result of these tests, the concentration of carbon-14 in the atmosphere and in biological material had risen at the end of 1960 by 25 per cent above the concentration of the carbon-14 formed by natural processes, but the concentration of this carbon-14 will decrease considerably in forthcoming decades owing to the dilution of the nuclide in the oceans if tests are discontinued. Although the irradiation of future generations from this source will continue at a decreasing rate for thousands of years because of the long half-life of this nuclide, the dose-rate to human reproductive and other tissues will be small in any one generation.

DISPOSAL OF RADIO-ACTIVE WASTES

31. The operation of atomic plants for the production

of energy and isotopes and the use of the latter for medical and research purposes may involve the release of radio-active material into the air, ground or waters. At the present time the contribution from this source to human radiation exposure is certainly small in comparison with natural radiation and is restricted to local areas. However, with the increased utilization of atomic energy and radio-active substances for peaceful uses, releases into the environment are likely to become greater than they are now, and consequently suitable methods for safe disposal of radio-active wastes should be maintained so as to minimize the dose of radiation from these sources.

Effects of radiation

FUNDAMENTAL RADIO-BIOLOGY

32. The study of the effects of radiation on cellular and subcellular structures is a necessary prerequisite to the understanding of radiation effects on whole organisms, in so far as the basic radiation injury occurs at the lowest level of organization. Fundamental radio-biology has received new impetus from the dramatic advances made in the past few years by biochemistry and biophysics. Our knowledge of the structure and mode of replication of macromolecules and in particular of nucleic acids has greatly increased, so that new insight has been gained into the fundamental problem of how genes act in controlling cellular structures and functions and in ensuring that they are maintained in the products of cell division.

33. The nature of the initial disturbances caused by radiation at the molecular level has become better known, as are the factors which may alter them. The changes produced may be partly reversible, at least when studied at the cellular or at higher levels. This may be the case with gene mutation, which is believed to be due to a specific change in chemically identifiable constituents of nucleic acids.

34. The study of the relationship between dose and effect at cellular and subcellular levels does not give any indication of the existence of threshold doses and leads to the conclusion that certain biological effects can follow irradiation, however small the dose may be. When dose effect relationships are studied at higher levels of organization, however, it is now being increasingly realized that the situation may be much more complex, since many factors play a part between the occurrence of the primary event and the final manifestation of radiation damage.

SOMATIC EFFECTS

35. During the interval since the last report, our knowledge of the somatic effects of radiation on man (those effects which are produced on the individuals exposed) has increased substantially with the demonstration of the induction of certain transient somatic effects by low doses of a few rad of radiation, and with the confirmation that embryonic tissues are more sensitive than many adult ones to injury by radiation. Even low doses may induce developmental disorders or malignant changes in embryos. Recent work has emphasized the complexity of radiation effects, and the importance of the qualifications that we made in our earlier report with regard to the numerical estimates of the frequency of the effects that would be caused by various doses of radiation. The complexity of the dose effect relationships is due largely to the fact that in different dose ranges, different types of biological effect may be produced, and a simple mathematical relationship is unlikely to apply.

The data that have been accumulated since 1958 have neither proved nor disproved the assumption made in the first report that at low doses proportionality can be used to estimate risks.

36. The early effects of large doses of radiation in man have become better known as a result of the close study of people who have been accidentally or therapeutically irradiated. It seems likely that, for short-term whole-body irradiation of man, the dose causing death in 50 per cent of the exposed individuals may be about 400 rad, but possibly as high as 500 rad and as low as 300 rad. Persistent damage from radiation is apparent after large doses approaching the lethal range. The predominant immediate changes after low doses are transitory ones, although persistent effects may be produced after a long period of time.

37. Various chemical, physical and biological treatments have some value in decreasing the effects of radiation exposure in animals, but no specific treatment has been established as having practical importance in man, except for the relief of symptoms that are induced by therapeutic irradiation of parts of the body. Several methods are, however, under investigation for the treatment of acute radiation injury, or to reduce the amounts of radio-nuclides which may have been taken into the body.

38. Radiation exposure of animals, continued for short or for long periods, causes a shortening of the life-span by an amount depending upon the dose received and the dose-rate. It is probable that a similar life-shortening occurs in man but the evidence on this point is inconclusive and no estimate can be given of the amount of any such effect.

39. Irradiation for short or long periods, either of animals or of man, may cause neoplastic changes, of which leukaemia appears to be the earliest to develop in man. There is good evidence that in the range of doses which it has been possible to explore (from 100 rad upwards), the frequency with which leukaemia is induced increases with the dose of radiation received, but no further evidence has been obtained as to the exact relationship between the dose and the frequency of this response. It does appear, however, that the annual incidence of leukaemia in the Japanese survivors of radiation at Hiroshima and Nagasaki, which had been rising after the nuclear explosions in 1945, though still elevated, has been decreasing since 1958. There is evidence to suggest that the incidence of some other forms of malignant disease may now have increased, but it is at present difficult to form a reliable estimate of the extent of any such increase.

HEREDITARY EFFECTS

40. Progress in human genetics has been very significant since 1958. An entirely new field of study has been opened owing to recent cytogenetic findings in man. The normal diploid number of chromosomes for the human species has been accepted as forty-six and certain serious diseases occurring in one per cent of all children born have come to be recognized as due to chromosomal changes. A new class of possible radiation-induced diseases, the importance of which was unrecognized at the time of the first report, has thus been demonstrated. The occurrence of chromosomal anomalies has been demonstrated in somatic cells of irradiated individuals.

41. The concept of mutation induction as an instantaneous process has been revised and evidence accumulates showing that for some mutations a finite period of time elapses between the absorption of radiation energy

and the completion of the mutation process, during which, depending on the physiological state of the cell, at least partial repair of the damage may be possible. The effectiveness of the repair mechanisms may be altered by a variety of agents and conditions, and will also be dependent on the way in which the radiation is distributed in time.

42. The frequency of gene mutations produced by irradiation has been shown to be proportional to the total dose received by the germ-cells. The proportionality, however, has been shown, in mice, fruit flies and silkworms, to vary with certain factors including the dose-rate. The dose required to induce as many mutations as naturally occur, the so-called doubling dose, therefore also changes with the dose-rate. Doubling doses are higher for low than for high dose-rates, the observed difference in mice being fourfold for the male and possibly larger for the female.

43. More data, however, are needed before the possible magnitude of this effect in man can be evaluated so as to enable us to make better comparisons between different conditions of irradiation. In any event the recent findings, while confirming the validity of the concept of doubling dose in particular circumstances for a given dose-rate, have shown that it is not possible to estimate with confidence a representative doubling dose for man.

44. In spite of the preceding reservations there should be no misunderstanding about the reality of genetic damage from radiation. Although individual mutations vary greatly in their effect, there is no doubt that any increase in mutation is harmful. Further, we know that mutations accumulate in germ-cells and we have no evidence from any experimental work for a threshold dose, or rate of delivery below which mutations are not induced. In fact, it has recently been shown that a single dose as low as 5 r increases significantly the number of mutations in the fruit fly. As regards man, the total dose received by the average individual in the population is still the most important indicator that we have of the amount of damage induced.

45. It is likely that the great majority of gene mutations induced by radiation are identical with those which occur "spontaneously". There is some evidence, however, from lower organisms that radiation determines a different proportion of certain harmful mutations than that occurring naturally.

46. The most extensive study is still the investigation of the offspring of parents exposed to the atomic explosions of Hiroshima and Nagasaki. The investigators detected no significant increase in the frequency of malformations or early deaths in the children of irradiated parents. Both this survey and a number of other more limited investigations have, however, consistently shown that in the progeny of irradiated mothers there is a significant excess of females over males. This has been attributed to the radiation-induced (sex-linked) mutations which would reduce the number of males born of those mothers. In the progeny of irradiated fathers a more complex situation obtains which has not yet been fully understood.

Conclusions

47. The review that we have made of the effects of ionizing radiation and of the present exposure of mankind to radiation affords a basis for general comments concerning this source of hazard.

48. It is clearly established that exposure to radiation, even in doses substantially lower than those producing

acute effects, may occasionally give rise to a wide variety of harmful effects including cancer, leukaemia and inherited abnormalities which in some cases may not be easily distinguishable from naturally occurring conditions or identifiable as due to radiation. Because of the available evidence that genetic damage occurs at the lowest levels as yet experimentally tested, it is prudent to assume that some genetic damage may follow any dose of radiation, however small.

49. It must be recognized that the human species has in fact always been exposed to small amounts of radiation from a variety of natural sources and that the present additional average exposure of mankind from all artificial sources is still smaller than that from natural sources.

50. At present even the wide use of radiation in medical diagnosis and treatment in countries with extensive medical facilities does not usually involve more than about a 50 per cent increase in the genetically significant exposure to radiation of their populations, and there is evidence that simple and inexpensive modifications of techniques could reduce the figure considerably without loss of medically important information. Advances in nuclear science and industry are being achieved with only slight resultant increases in the average radiation levels to which populations are exposed, and with only very occasional accidental over-exposure of individuals.

51. At the same time, the exposure of mankind to radiation from increasing numbers of artificial sources, including the world-wide contamination of the environment with short- and long-lived radio-nuclides from weapons tests, calls for the closest attention, particularly because the effects of any increase in radiation exposure may not be fully manifested for several decades in the case of somatic disease, and for many generations in the case of genetic damage.

52. The Committee therefore emphasizes the need that all forms of unnecessary radiation exposure should be minimized or avoided entirely, particularly when the exposure of large populations is entailed; and that every procedure involving the peaceful uses of ionizing radiation should be subject to appropriate immediate and continuing scrutiny in order to ensure that the resulting exposure is kept to the minimum practicable level and that this level is consistent with the necessity or the value of the procedure. As there are no effective measures to prevent the occurrence of harmful effects of global radio-active contamination from nuclear explosions, the achievement of a final cessation of nuclear tests would benefit present and future generations of mankind.

53. The urgent need for research into many aspects of radiation and its biological effects has been emphasized repeatedly in this report. Although we have extensive and increasing information about the levels of radiation to which man is exposed from various sources and about the types of harmful effect which may result, we still know very little about the frequency with which such effects are likely to occur, particularly following small doses of radiation received at low dose-rates. It is of the utmost importance that investigation of this central problem should be actively pursued by all relevant means, including not only studies of the ways in which radiation may induce malignant and other delayed changes in tissues but also well planned surveys of the frequency with which such late effects occur in human populations following any accidental, medical or other relevant type of exposure to radiation or in areas of high natural radiation.

ANNEXES

ANNEX A

DEFINITIONS OF QUANTITIES, UNITS AND SYMBOLS

1. The Committee has used in the present report the radiological quantities and units defined in the 1959 report of the International Commission on Radiological Units and Measurements (ICRU),¹ the relevant part of which is reproduced below.* It should however be noted that ICRU has appointed an *ad hoc* committee to examine the quantities and definitions of units and some modifications of existing definitions may shortly be recommended.

"1.1. *Absorbed dose* of any ionizing radiation is the energy imparted to matter by ionizing particles per unit mass of irradiated material at the place of interest.

"1.2 The unit of absorbed dose is the *rad*. One rad is 100 ergs/g.

"1.3. *Integral absorbed dose* in a certain region is the energy imparted to matter by ionizing particles in that region.

"1.4. The unit of integral absorbed dose is the *gram rad*. One gram rad is 100 ergs.

"1.5. *Absorbed dose rate* is the absorbed dose per unit time.

"1.6. The unit of absorbed dose rate is the *rad per unit time*.

"1.7. *Exposure dose of X- or gamma radiation* at a certain place is a measure of the radiation that is based upon its ability to produce ionization.

"1.8. The unit of exposure dose of X- or gamma radiation is the *roentgen* (r). One roentgen is an exposure dose of X- or gamma radiation such that the associated corpuscular emission per 0.001293 g of air produces, in air, ions carrying 1 electrostatic unit of quantity of electricity of either sign.

"1.9. *Exposure dose rate* is the exposure dose per unit time.

"1.10. The unit of exposure dose rate is the *roentgen per unit time*.

"1.11. *Intensity of radiation* (radiant energy flux density) at a given place is the energy per unit time entering a small sphere centered at that place per unit cross-sectional area of the sphere.

"1.12. The unit of intensity of radiation may be *erg per square centimeter second*, or *watt per square centimeter*.

"1.13. The unit of quantity of radio-active material, evaluated according to its radio-activity, is the *curie* (c). One curie is a quantity of radio-active nuclide in which the number of disintegrations per second is 3.700×10^{10} .

"1.14. *Specific gamma-ray emission* (specific gamma-ray output) of a radio-active nuclide is the exposure dose rate produced by the unfiltered gamma rays from a point source of a defined quantity of that nuclide at a defined distance.

"1.15 The unit of specific gamma-ray emission is the *roentgen per millicurie hour* (r/mch) at 1 cm.

"1.16. *Linear energy transfer* (LET) is the linear-rate of loss of energy (locally absorbed) by an ionizing particle traversing a material medium.

"1.17. Linear energy transfer may be conveniently expressed in *kilo electron volts per micron* (kev/ μ).

"1.18. *Mass stopping power* is the loss of energy per unit mass per unit area by an ionizing particle traversing a material medium.

"1.19. Mass stopping power may be conveniently expressed in *kilo electron volts per milligram per square centimeter* (kev cm²/mg)."

2. According to ICRU:¹

"The absorbed dose, D (in rads), of any radiation must be multiplied by an agreed factor, RBE (relative biological effectiveness), whose values for different radiations are laid down by the International Commission on Radiological Protection (ICRP). This product, called the RBE dose, is expressed in rems where

$$\text{RBE dose (in rems)} = (\text{RBE}) (D)$$

"In the case of mixed radiations the total RBE dose is assumed to be equal to the sum of the products of the absorbed dose of each radiation and its RBE.

"RBE dose (in rems) = Σ [(absorbed dose in rads) (RBE)]."

For the sake of simplicity in the present report 1 roentgen of X-, beta or gamma radiation is assumed to correspond to a tissue dose of 1 rad and, since the RBE of these radiations is conventionally unity, the tissue dose may also be expressed as 1 rem.

3. The RBE values that have been used in the present report are those established by ICRP in establishing protection standards. The table below gives the values of RBE for different types of radiation.² The ICRP Committee on RBE is currently examining the concept and use of RBE in radiation protection calculations and new recommendations may shortly be made.

* The following is quoted from the above-mentioned ICRU report:

"*Symbols and nomenclature.* There are numerous national and international bodies that have reached varying degrees of acceptance of the use of symbols and units for physical quantities. However, there is no universal acceptance of any one set of recommendations. It is suggested that each country modify the symbols used herein, in accordance with its own practices. Thus one may write: kev, keV, or Kev; ¹⁴C or C¹⁴; rad per unit time, rad per time, or rad divided by time; rad/sec, rad/s, or rad.s⁻¹; etc. The most generally accepted system of symbols and units may be that contained in document UIP 6 (1956) prepared by the International Union of Pure and Applied Physics. These are in fairly close agreement with the recommendations of the International Standardization Organization project ISO/TC 12, the Conférence Générale de Poids et Mesures, Union Internationale de Chimie Pure et Appliquée, and the International Electrotechnical Committee."

TABLE I. RBE VALUES

1. *X-rays, electrons and positrons of any specific ionization*

RBE = 1

2. *Heavy ionizing particles*

<i>Average specific ionization (ion pairs per micron of water)</i>	<i>RBE</i>	<i>Average linear energy transfer to water (kev per micron)</i>
100 or less.....	1	3.5 or less
100 to 200.....	1 to 2	3.5 to 7.0
200 to 650.....	2 to 5	7.0 to 23
650 to 1,500.....	5 to 10	23 to 53
1,500 to 5,000.....	10 to 20	53 to 175

For practical purposes, an RBE of 10 is applicable to fast neutrons and protons up to 10 MeV and an RBE of 20 to heavy recoil nuclei for whole-body irradiation and the most sensitive critical organs.

REFERENCES

1. Report of the International Commission on Radiological Units and Measurements (ICRU) (1959). National Bureau of Standards, Handbook 78.
2. Recommendations of the International Commission on Radiological Protection. Brit. J. Radiol. Suppl. No. 6 (1955).

ANNEX B

FUNDAMENTAL RADIO-BIOLOGY

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I. Introduction

1. The effects of radiation on living matter must be envisaged at different levels of organization, those of individual molecules and macromolecules, subcellular structures, whole cells, tissues and organs, whole organisms, and populations of organisms. To understand the action of radiation, each system must be studied independently and in its natural context. The actions become more complicated as the organization level rises. At each level and for each effect studied, it is sometimes helpful to think in terms of the sensitive molecule or structure, the sensitive cell, tissue, or organ.

2. The present annex deals chiefly with macromolecules, subcellular structures, or isolated cells and cell populations. Our knowledge of the molecular organization of various cell organelles is increasing rapidly and

the impact of molecular biophysics on fundamental radio-biology is greater than in the past. The molecular approach will eventually enable us to understand the effects of radiation on the impairment of fundamental processes in the cell. The effects of radiation on macromolecules or subcellular structures are thus of great importance in fundamental radio-biology.

3. This annex deals essentially with ionizing radiation; investigations with non-ionizing radiations are referred to only in so far as they bear on our understanding of the effects of ionizing radiations.

II. Interaction between ionizing radiation and living matter

4. The absorption of ionizing radiation by matter is followed by a complex of events the nature of which

depends on absorbed dose and the chemical and physico-chemical composition of the irradiated material. Various stages can be recognized in the development of radiation effects. These are not sharply demarcated but blend into each other. Distinctions have some value, however, because they permit a partial analysis of the temporal sequence of events.

5. (a) *Elementary reactions.* These occur in a very short period of time, $\sim 10^{-17}$ - 10^{-16} seconds. They are primarily physical and result from the interaction between photons or ionizing particles and atoms and molecules. These interactions give rise to excitations and ionizations. Excited and ionized atoms and molecules are highly unstable and chemically active; rearrangements in the electron configuration of the excited structures lead to the primary products of radiation action which may be stable or unstable molecules, or free radicals.

(b) *Primary reactions.* Radicals and excited molecules formed as the result of elementary processes react chemically with neighbouring molecules and between themselves. This stage, the chemical stage, may last from a fraction of a second to hours.

(c) *Secondary reactions.* Elementary and primary reactions give rise to secondary reactions in which macromolecules of essential biological significance and major metabolic pathways are affected. Secondary reactions result, therefore, in alterations and impairment of cellular structures and functions, and may lead to biologically observable radiation injury. This, the biological stage, may last from a few hours up to years in long-lived multicellular organisms.

ENERGY DISSIPATION BY X- AND GAMMA-RAYS AND BY CORPUSCULAR RADIATIONS

6. The elementary characteristics of ionizing radiation and the way energy is absorbed by ionization have been described in chapter II. Only part of the energy absorbed by an irradiated tissue gives rise to ionizations; the remainder, in a process called excitation, raises electrons of atoms or molecules to a higher energy level without expelling them. In its chemical or biological action, the energy absorbed in the excitation process is not considered to be as important as that absorbed in the ionization process. However information is incomplete on this point.

IONIZATION DENSITY—LET

7. In any interaction of ionizing radiation with matter, the ultimate transfer of energy is carried out by a charged particle. The rate of loss of energy by a particle along its path is proportional to the square of charge and inversely proportional to velocity. Hence, for any particle, the rate of loss of energy is greatest near the end of its track. Linear energy transfer (LET) is defined as the linear rate of loss of energy (locally absorbed) and is usually measured in keV/ μ .

8. At a given dose the biological effect may vary considerably with LET; it may increase or decrease depending on the object irradiated and the effect measured. There is as yet no complete theory on the influence of LET (paras. 31-35).

TRANSPORT OF ENERGY

9. Free radicals, whose intrinsic lifetime is indefinite, usually disappear quickly because of their reactivity. Excited molecules have, in general, only a transitory

existence in condensed systems since they are inherently unstable. Although excitation can lead to dissociation of the molecule, it is less likely to do so in the case of more complex molecules where excess energy can be distributed over many bonds. Energy degradation within the same molecule is known as internal conversion. Through internal conversion, the excited molecule is degraded in energy from a higher to a lower excited state, or returns to the ground state; the excess energy is converted into vibrational and rotational energy and may be transferred to other molecules. Energy can also be transferred from one molecule to another through processes known as exciton interaction and resonance transfer.¹ The increasing emphasis on the mechanisms by which energy migrates and on their role in radiation effects is reflected in recent symposia and reviews.²⁻⁴

III. Quantitative aspects of radiation effects

10. Known dose-effect relationships may be described under a limited number of headings. Their graphic presentation is often simple, linear in a few instances, and in general exponential or sigmoid. Thus, oxidation of ferrous ions and reduction of ceric ions in aqueous solution is, in certain circumstances, directly proportional to dose. These effects may be interpreted as due to radicals induced in the aqueous medium. However, in somewhat more complicated situations, e.g. the inactivation of enzymes in solution or in the solid state, there may be an exponential relationship between remaining activity and radiation dose. This relationship expresses, in part, the fact that inactivated molecules are still able to capture radicals and thus to decrease the number of radicals for inactivation of still intact molecules.

11. Even for complex systems like living cells, the experimental relationship between dose and effect is often a simple one. In the study of these relationships it is essential to define the effect clearly. For isolated cells, reproductive ability has been used most frequently as the criterion of damage. Cells which have lost reproductive integrity may still divide a few times. However, cells affected in this way can sometimes maintain the ability to accomplish for a certain time some metabolic or physiological functions at near normal rates, e.g., respiration,^{5,6} protein synthesis,⁷ motility.⁸ The doses required for impairment of such metabolic functions are usually much greater than those necessary to impair reproduction.

HIT PRINCIPLE (TARGET THEORY) AND DOSE-EFFECT RELATIONSHIPS

12. According to the hit theory,⁹⁻¹¹ the biological effects of ionizing radiation on cells are due to hits in a sensitive component of the cell; hits produced outside this "target" are ineffective. Although, as originally formulated, the hit was considered to be an ionization or excitation produced directly in the target, the theory has been enlarged to include hits produced by diffusible products involved in indirect action.¹²

13. If a cell is inactivated by a single hit in a target or in any of a number of targets, it can easily be shown that the survival curve is exponential. The number of cells escaping biological modification (N) is then related to dose according to the formula $N = N_0 e^{-\alpha D}$, where N_0 is the number of cells originally present, D is dose, and

α is a constant expressing the sensitivity of the cells. From this formula it follows that the number of survivors will be $N/N_0 = e^{-1} \sim 0.37$ for the dose $1/\alpha$ which is the dose that brings about one hit per target on the average. This 37 per cent dose is important in calculations of the volume of the target.

14. When two or more hits are necessary to destroy one target or when two or more targets in one cell have to be hit before the damage shows, the survival curves are no longer exponential but are sigmoid and have an initial shoulder when the logarithm of the survival is plotted against dose. In the latter case (two or more targets), the number of targets can be estimated from the survival curve by extrapolating the linear part of the semi-log-plot to zero dose. The value (greater than one) thus obtained on the survival axis is equal to the number of targets.

15. As a rule, with high LET radiations and neutrons, and in certain cases with X- or gamma-rays, exponential survival curves are observed for the inactivation of viruses and micro-organisms.⁹ When the fraction of cells or subcellular structures affected is small, the number of responses is approximately proportional to dose. This has been found for the induction of mutations in bacteria, *Drosophila*, and other organisms; the mechanism seems to be one hit.

16. X-irradiated polyploid yeast cells^{13,14} and isolated mammalian cells¹⁵ have sigmoid dose-effect curves. The type of curve often depends on the LET of the radiation. Higher LET values may result in exponential survival for cells having sigmoid type curves for low LET radiations.¹⁶

17. Sigmoid survival curves are also expected when a population of individuals is irradiated, the susceptibility of which obeys certain distribution patterns.

18. Both exponential and sigmoid survival curves may have breaks (resistant tails). The interpretation usually offered is that the population studied contains a subgroup which is more resistant to radiation. In general there are two ways in which this could occur:

(a) The heterogeneity may be genetic; the more resistant individuals are mutants of the more sensitive. This situation can be recognized by isolating a clone from cells surviving higher doses and by establishing a new survival curve with the population from this resistant clone. The slope found corresponds to the slope of the resistant tail in the original curve. However, in some cases, attempts to do this have failed. With the widely used strain *E. coli* B, the rate of mutation to resistance is only about 10^{-5} per bacterium per generation and therefore probably too low to account for the appearance of the tail.¹⁷

(b) The heterogeneity may be physiological; in this case, if cells surviving at the higher doses are isolated, the survival curve of the new population shows the same resistant tail as the original one. This holds in haploid yeasts where budding cells appear to be more resistant.¹⁸ There is similar phenomenon with *Pneumococcus* transforming principle.¹⁹ A resistant tail may also be seen with a bacterial population containing cells in both the logarithmic and stationary phase of growth; the logarithmic phase is more radio-sensitive.^{20,21}

THE THRESHOLD PROBLEM

19. The observation of an exponential survival curve may be interpreted as a one-hit process. The same applies

to the linear relationship for mutation induction when the number of mutations is small compared to the number of loci at risk; any dose, however small, has a probability of producing the effect.

20. Sigmoidal survival curves may be interpreted as an indication that inactivation results from multiple hits in a single target or inactivation of multiple targets by one or more hits in each. There is also a finite probability that any dose may produce an effect. Thus the existence of biological responses with sigmoidal dose-effect curves do not necessarily prove the existence of a threshold dose.

21. Even if recovery processes occur at the cellular level, these conclusions remain valid; such recovery merely changes the slope of the dose-effect curve.

22. Without extensive empirical data and detailed knowledge of the various steps between initial absorption of radiation and expression of biological effects, discussion of the threshold question is largely limited to theoretical considerations. In the only instance in which it has been possible to obtain unequivocal experimental data, the induction of phage growth in lysogenic bacteria, no threshold was found; one ion pair per cell was effective.²² It is therefore prudent to assume, as in the last report of the Committee, that "biological effects will follow irradiation, however small its amount".²³

DIRECT AND INDIRECT EFFECTS OF RADIATION

23. Of the models proposed to explain observed dose-effect relationships, the simplest is the target theory based on the assumption that inactivation is caused only by ionizations *inside* the target—"direct action".

24. Although the concept of a "target" has been maintained in most theories, it has become increasingly apparent that at least part of the biological effect is due to chemical events outside the target. In this event damage to the target is secondary—"indirect action".^{16,24}

25. As yet there is no general agreement on the relative importance of direct and indirect action in living cells. The modification of damage by oxygen or chemical protective agents has sometimes been interpreted as evidence that indirect action is predominant. It has however been shown that the effect of oxygen and some protectants is also consistent with direct action, if it is assumed that the effect of radiation on the target is a two-stage one.^{25,26} The primary event might then be partly or totally reversible.

26. The problem of direct versus indirect effects of radiation has been comprehensively reviewed by Timofeev-Ressovski and Rompe² with an analysis of mechanisms of energy migration and transfer in the heterogeneous system. Their theory allows for chance fluctuations in the occurrence of both direct and indirect effects, and for the mechanisms of propagation of radiation injury in time and space. Depending on the structure or function damaged, either direct or indirect effects may be considered predominant.

INFLUENCE OF DOSE-RATE AND DOSE FRACTIONATION

27. Variation of the irradiation rate (fractionation of dose or variation of dose-rate) may influence the biological effect in some instances. When radiation damage is irreparable, no modification of the response is expected; if a modification is seen, it is generally assumed to repre-

sent a repair mechanism. Mice, *Drosophila*, plants, and several other species (C, table VII) have been extensively studied. Other examples are *Arbacia* eggs²⁷ and mammalian tissue culture cells. In *Arbacia* sperm, however, no repair has been observed.^{28, 29}

28. If the phenomenon under study is single hit, e.g. induction of point mutations, repair processes would reduce the magnitude of the slope of the dose-effect curve. Russell³⁰ discovered that low dose-rates were less efficient than high dose-rates in inducing mutations in mouse gonial cells. This dose-rate effect was maximal at 0.82 r/min; further reduction of the dose-rate had no further effect on mutation rates.³¹ Russell's finding, which stimulated similar studies by others, has been confirmed in several species. Low dose-rates also greatly diminish the sterilizing effects of radiation in female mice and increase survival of spermatogonia.³²

29. The effectiveness of fractionated doses to the mouse testes has been demonstrated with doses in the range of 1600 rad.⁴⁰ In experiments with *Drosophila* at low doses and different stages of spermatogenesis, no effect of dose fractionation has been observed.³²

30. The effect of dose-rate on multi-hit processes is not difficult to explain. If the rate of delivery is reduced so as to increase the time between two successive events (hits) significantly, and if the individual lesions due to hits can be repaired within a certain time, lowering the dose rate or fractionation of the dose will result in a diminished frequency of effects for a given total dose. The role of chromosome aberrations may be of particular importance in monkey or human embryonic tissue cultures. Some reports indicate that these tissues are two or three times more sensitive than those of mice.^{33, 34} Investigations of the repair of pre-mutational damage have been carried out with many species, including mammals^{35, 36} insects^{37, 38} and plants.^{26a, 51a} This subject is discussed more fully in annex C.

RELATIVE BIOLOGICAL EFFECTIVENESS

31. With radiations of different quality, the absorbed doses required for a given effect are usually not the same for different types of radiation. The extent to which radiations of different quality differ from each other in this respect is a measure of their relative biological effectiveness (RBE). The RBE of two radiations is defined as the inverse ratio of the respective doses that are necessary to bring about a given effect. The radiation standard chosen by the ICRU is an X- or gamma-radiation having a LET in water of 3 keV/ μ delivered at a rate of about 10 rad/min.

32. In the simplest cases, the mechanism underlying the difference in efficiencies of radiations can easily be explained. For an event which is inhibited by the absorption of a minimal amount of energy, such as the inactivation of an enzyme or virus, the low ion density radiation will be more effective than high ion density, because some of the latter ionizations will be wasted. On the other hand, radiation with a high density of ionization will be more effective when larger amounts of energy are needed (simultaneously or within a relatively short time or within a certain volume) to produce the effect in the sensitive structure.

33. Thus, RBE depends not only on the LET of a given radiation but also on the effect studied, and this dependence may assume various forms. Thus, Zirkle⁴¹ has pointed out that there are experimental situations in

which RBE and LET are directly related, inversely related, in which RBE shows a maximum for a certain value of LET, and in which RBE is constant. Other factors make the picture even more complex; RBE values may depend on dose, dose-rate, presence of oxygen, and physiological conditions.

34. The LET concept itself is complex. The kinetic energy loss of a particle is discontinuous and subject to statistical fluctuations.⁴² Furthermore, it varies along the track. For these reasons an average value must be calculated. In principle, however, RBE not only depends on this average value of LET, but also on LET distribution. The following figure⁴³ attempts to summarize experimental data on bacterial, plant and animal cells.

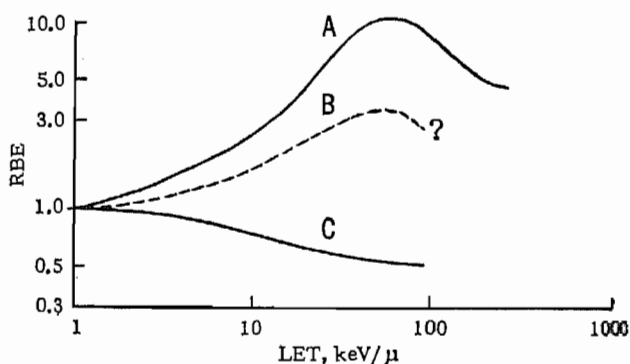


Figure 1. Variation in RBE with LET, for biological materials irradiated in aerobic conditions⁴³

A: plant cells⁵⁷⁷⁻⁵⁸²
B: animal cells^{203, 577, 583-585}
C: two strains of bacteria^{183, 586-587}

35. To assess the RBE of a certain radiation, dose-response curves of the particular biological effect are determined for both test and standard radiations. If both curves coincide when all dose values of the test radiation are multiplied by a constant factor, the RBE is equal to this factor. Sometimes the curves do not have identical shapes; the RBE value then depends on dose. This comparison pertains to absorbed dose. If this dose is not uniform throughout, the average value is used. This may not be strictly correct if the biological effect depends on dose. There are many other complications that make experimental RBE values difficult to interpret. The values are, however, useful in the practice of health physics, where upper limiting values of RBE are used to transform dosages measured in rad to rem.

IV. Radiation chemistry

36. Since water constitutes 70 per cent or more of cell mass, water molecules take up most of the energy imparted to cells by ionizing radiation and may be important in the damage to vital cell components. Knowledge collected during the last decade about the chemical changes induced by irradiation of water and aqueous solutions of simple compounds is therefore of great importance to radio-biology. Work has been done on the radiation chemistry of solutions of nucleic acids and other macromolecules to gain some insight into the mechanism by which reactive intermediates generated in water attack these molecules. The main results from those fields of research will therefore be summarized in this chapter.

37. In interpreting these results, it is generally assumed that free radicals are important in the chemical

reactions resulting from ionization and perhaps from excitation of water molecules. At present, there is abundant evidence to support such a view. Recently, development of the electron spin resonance technique has provided a method for direct study of free radical formation in certain irradiated materials.

WATER AND AQUEOUS SOLUTIONS OF SIMPLE COMPOUNDS

38. Most reactions in irradiated water can be explained satisfactorily by assuming the formation of H° and OH° radicals. Recent reviews⁴⁴⁻⁴⁶ of the chemical effects of ionizing radiation have shown the usefulness of the radical hypothesis in interpreting the rapidly growing body of experimental data, although some uncertainty still exists with regard to the H° radicals and their distribution around the track of an ionizing particle. It might be that what has been called an " H° radical" is in reality a hydrated electron, H_2O^\cdot .

39. For each 100 eV of dissipated energy some 4 H_2O molecules are split into OH° and H° . OH° radicals can combine to H_2O_2 and H° radicals to H_2 . A considerable fraction of the radicals react in this way to give "molecular products" before there is any significant diffusion or reaction with solute molecules. In chemically pure water, however, only very small amounts of molecular products can be detected, because they are reverted to water molecules through back reactions with free H° and OH° radicals.

40. When solutes capable of reacting with H° or OH° radicals, thereby preventing the back reaction, are present, the products H_2O_2 and H_2 are produced in measurable amounts. Their yields depend on LET, a greater LET giving rise to a larger amount of molecular products through combination of free radicals. The molecular yield also depends on the efficiency with which free radicals are scavenged by solute molecules. Some very efficient scavenging solutes can depress the formation of H_2 and H_2O_2 considerably.

41. A very common solute is O_2 . It reacts with H° radicals to give the radical O_2H° . This explains why the yield of various radiation-induced chemical reactions is dependent on the presence of O_2 . The O_2H° radical is more stable than H° and OH° . When no solutes other than O_2 are present, most O_2H° radicals will combine according to the reaction $2 \text{O}_2\text{H}^\circ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$.

42. The primary products in irradiated water may have oxidizing or reducing properties depending on the redox potential of the solute concerned, on the qualities of other solutes (e.g. O_2 , which converts reducing H° radicals to O_2H° radicals which may have oxidizing action), or on pH.

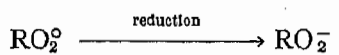
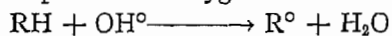
43. The influence of pH is explained by the following ionic equilibria: $\text{H}^\circ + \text{H}^+ \rightleftharpoons \text{H}_2^\cdot$; $\text{OH}^\circ \rightleftharpoons \text{H}^+ + \text{O}^\cdot$ and $\text{O}_2\text{H}^\circ \rightleftharpoons \text{H}^+ + \text{O}_2^\cdot$. It should be noted that, in neutral solutions, O_2H° radicals have far less oxidizing power than at low pH's. The oxygen effect in living systems can therefore probably not be interpreted as an enhancement of oxidation through the reaction $\text{H}^\circ + \text{O}_2 \rightarrow \text{O}_2\text{H}^\circ$.

44. Application of these data to radio-biological systems is by no means straightforward. In the first place, the diffusion range of free radicals in living cells is very limited,⁴⁷ because many molecules can react with free radicals, thereby protecting more vital components. Cell structures can be attacked, therefore, only by radi-

cals formed in close proximity, and the damage to certain molecules will be much less in cells than in dilute solutions. Secondly, the presence of great numbers of simple and complex molecules in cells may give rise to secondary and tertiary reactions which differ from those in simple solutions.

45. Knowledge of the primary reactions in irradiated water has been derived largely from the study of aqueous inorganic solutions. Much experimental work has also been done on aqueous solutions of organic compounds. However, for many changes in solutions of simple molecules, the reaction mechanism has not been unambiguously established.

46. There is evidence for the formation of hydroperoxides in the presence of oxygen:



47. In some instances hydroperoxides are believed to be labile intermediates, but stable peroxides have also been found, e.g. after irradiation of solutions of various amino acids and of pyrimidine bases⁴⁸ and their nucleosides and nucleotides.^{49,50} The formation of hydroperoxides may enhance oxidation, e.g. increase oxidation of ferrous ions in acid solution where there are organic impurities. This can be prevented by addition of Cl^- ions; these react with OH° radicals ($\text{OH}^\circ + \text{Cl}^- \rightarrow \text{OH}^- + \text{Cl}^\circ$) and thus modify the sensitizing action of organic molecules.⁵¹

48. Reactions between radicals and oxygen, and between radicals and hydrogen-atom-donating compounds, have been shown to be important biologically. In the bacterial spore, radicals formed that are biologically effective if they react with oxygen may be removed by hydrogen donors such as H_2S prior to O_2 reaction.^{52,53} Such mechanisms have been proposed for other systems.^{49,54,55}

49. Further chemical reactions which may bear on radio-biology are the oxidative deamination of amino acids,⁵⁶ the decarboxylation of organic acids,⁴⁵ the oxidation of SH-compounds to the -S-S- dimer,⁵⁷ and the decomposition of glucose by ionizing radiation.⁵⁸

NUCLEIC ACIDS

50. Irradiation of nucleic acids in aqueous solutions leads to several different chemical changes which affect both the purine and pyrimidine moieties and the sugar-phosphate backbone. As yet, it is impossible to give a consistent and quantitative description of these chemical effects of irradiation. Because of the diversity and complexity of the chemical changes, only the main pathways are considered to be established.

51. The chemical changes produced by irradiation of dilute solutions of nucleic acids are, for the most part, initiated by radicals formed in the aqueous media. In agreement with results of experiments with simple nucleic acid components, there are two main reaction pathways by which radicals attack nucleic acids in aqueous solutions: (a) destruction of the bases, the predominant site of chemical attack, and (b) oxidation of the sugar moiety.⁵⁹⁻⁶¹ The products of irradiation of the bases in the presence of oxygen differ from

those formed in its absence. In oxygen-free solutions, pyrimidines are converted into products of undetermined structure, without any specific ultra-violet absorption.⁶¹ Some guanine residues are converted to 2:4-diamino-5-formamido-6-hydroxy-pyrimidine which is attached to the sugar by a labelled glycosidic linkage; from this they are gradually released as free bases. It is believed that the attack on adenine forms the corresponding formamido-pyrimidines, although this has not been directly demonstrated in irradiated DNA.⁵⁹ The yield of chemically altered bases is highest for pyrimidine residues and lowest for purine residues,^{59, 61-63} a circumstance which reflects their comparative radio-sensitivity.

52. In aerated solutions of nucleic acids, the hydroperoxides of pyrimidine bases are formed with the saturation of 5, 6 double bonds, and under oxygen this reaction becomes the dominant one.⁶¹ In DNA, only hydroxyperoxides of thymine are stable and only these remain attached to the sugar-phosphate backbone.⁶¹ In the presence of oxygen the sensitivity of all bases in DNA solution is increased two to three times; under these conditions a presumed 80 per cent of radicals attacking DNA combine with the base components.

53. The attack of radicals on the sugar moiety leads to formation of labile phosphate esters. Evidence for this is seen in the large quantities of inorganic phosphate that can be liberated by the acidic hydrolysis of irradiated solutions.⁷² It is believed that this results from oxidative formation of carbonyl groups in sugar moieties.⁶¹ In addition to the formation of labile phosphate esters, the attack on the sugar component breaks phosphodiester bonds and liberates small amounts of inorganic phosphate.^{60, 64} From experiments with simple phosphate esters,⁶⁵ it appears that inorganic phosphate must come from end groups present in the intact molecule, having been formed during earlier stages of irradiation by main chain scissions.

54. The direct measurement, with prostate phosphomonoesterase, of the number of breaks induced in the sugar-phosphate backbone has revealed that the yield from this process is 20-25 per cent of the yield in terms of base destruction.⁶⁶ The same percentage is found if the release of free bases from irradiated DNA is used to measure the attack on the sugar-phosphate moiety.^{59, 62, 67}

55. Studies of physicochemical changes in nucleic acids after irradiation are, so far, chiefly confined to deoxyribonucleic acids. In the double-stranded helical DNA molecule, both types of chemical lesions introduced by ionizing radiation, destruction of bases and breakage of phosphodiester bonds, must lead to an altered configuration in solution and consequently to changes in physicochemical properties. The destruction of the base results in local dissociation of the double-stranded structure, and the break in one of the chains results in increased flexibility; two independent breaks at approximately opposite positions in each of two intertwined chains lead to a scission of the whole molecule. There is much evidence supporting this general picture. Thus, the critical temperature for the thermal denaturation of irradiated DNA is reduced.⁶⁸ Likewise, the intrinsic viscosity of irradiated DNA solutions shows marked decreases that reflect coiling of the partially denatured molecule and a fall in molecular weight.⁶⁹⁻⁷¹ Further evidence for degradation is provided by light-scattering,^{71, 72} flow birefringence,^{72, 73} sedimentation and diffusion studies,^{74, 76} and chromatography on ceteola cellulose column.⁷⁷ The breakdown of some of the secondary

hydrogen-bonded structure has been shown by the increase in ultra-violet absorption near 260 mμ after small doses of irradiation,^{61, 70, 72} and also by titrimetric studies.^{70, 78}

56. Degradation of DNA proceeds for some time after irradiation, as judged by viscosimetric measurements.⁷⁸ This "after-effect" is more pronounced if DNA is irradiated in air-saturated solution.⁷⁰⁻⁸¹ There are several hypotheses to explain this kind of instability; the decay of some unstable pyrimidine hydroxyperoxides,^{60, 61, 82} and hydrolysis of labile acyl-phosphates^{61, 84} are the most plausible of them.

57. In dilute solutions, the indirect action of radiation prevails. With increasing concentration of DNA the relative importance of this effect decreases in favour of the direct action. This has been shown in experiments in which damage to DNA, as a function of concentration, was studied in the presence of iodine ions which almost entirely prevent the indirect effects of radiation.⁸³⁻⁸⁵ Thus, Mekshenkov ascertained that 0.1 per cent solutions of DNA are almost entirely protected against X-radiation by iodine ions (predominance of indirect effect). With increasing concentration of DNA, however, the protective ability of iodine ions decreases so that in a 20 per cent solution, 80 per cent of DNA molecules present are damaged^{86, 87} (predominance of direct effect).

58. DNA molecules irradiated in the dry state or in a slightly moist condition are damaged mainly by the direct action of ionizing radiation. With radiation doses of $\sim 10^6$ rad, in addition to the main chain scission, an intermolecular cross-linking takes place which leads to the appearance of branched molecules as judged by viscosity, sedimentation and light-scattering studies. With increasing doses up to 10^7 rad (the threshold dose depends on water content), this process renders DNA insoluble in water and gives rise to gel formation. Both processes proceed simultaneously, but their relative role in the damage depends on moisture content, presence of oxygen, and nature of ionizing particles.^{88, 71, 88-90}

59. The rates of main chain scission and branching induced by electrons are about the same at moisture contents up to 25 per cent, and are largely unaffected by oxygen. With swollen DNA gels having a water content of 25 to 70 per cent, intermolecular cross-linking predominates over the scission of the main chain in the absence of oxygen. However, in the presence of oxygen, the ratio between the effectiveness of the two processes is reversed. Above 75 per cent water content, and even in the absence of oxygen, no gel is formed.^{88, 89} Alpha-particles are much less effective in the branching process than electrons. With alpha-particles only a limited amount of cross-linkage is found in the absence of oxygen, and this is independent of the moisture content. In the presence of oxygen one main chain break is produced by nearly every alpha-particle traversing a DNA molecule.⁹⁰

60. It is believed that clusters of ionization are responsible for the main chain breaks; cross-links result from the combination of active points formed by ionization^{89, 90} for which carbon radicals are likely candidates. Some direct support for the formation of metastable species is provided by the observation of strong gamma-induced phosphorescence in frozen solutions of DNA and RNA.⁹¹ With direct irradiation of dry DNA preparations by gamma-rays, the ESR method reveals the presence of one radical per 10^5 DNA molecules for a dose of 2×10^3 rad.⁹²

61. It is worthwhile to mention that ultra-violet radiation also causes aggregation of DNA⁹⁴ and, to a lesser degree, of RNA in the dry state.^{95,96} In water solution, irradiation of DNA with ultra-violet light induces covalent crosslinks.^{96,97} The native secondary structure is almost preserved as shown by ultra-centrifugation in caesium chloride. These cross-link processes are probably connected with dimerization of thymine or uracil residues.^{98,99}

PROTEINS

62. Changes in the structure of proteins irradiated in dilute aqueous solution are mainly attributable to attack by free radicals and other active species from water. In cells, free radicals account for $\sim \frac{1}{2}$ - $\frac{3}{4}$ of the effect; in very dilute pure solutions they account for almost the entire effect.¹⁰⁰

63. Thiol groups, when present, appear to be the most sensitive parts of proteins. These -SH groups become oxydized, as shown by titration,¹⁰¹ thus creating new disulphide bonds with a G^* value of about 3. The same process has been observed with enzymes,¹⁰² although the high G value for the oxydation of those enzymes which depend on -SH groups for activity does not always correspond to the G value for inactivation.¹⁰³ Conversely, by other mechanisms, disulphide bonds can be reduced by irradiation, a process which leads to the formation of new thiol groups.^{104,105}

64. Proteins, amino acids, and peptides, in solution, can liberate ammonia on irradiation with large doses, and can at the same time form carbonyl and amide compounds.^{106,107} These products are formed in part from amino-groups and in part from peptide bonds. This reaction involves the formation of imino-groups as intermediates. The imino-groups are hydrolyzed, leading to the rupture of polypeptide chains.¹⁰²

65. The effect on aromatic rings of amino acids in proteins resembles closely the effect on aromatic amino acids themselves. Changes in optical density in the UV absorbing region of some proteins, when irradiated, are similar to those produced in a tyrosine solution.¹⁰⁸ Similarly, a decrease in optical density at 280 $m\mu$ has been found for tryptophan itself¹⁰⁹ as well as for proteins rich in this amino acid.¹¹⁰

66. Protein peroxides have been detected after irradiation of proteins in oxygen-containing solutions.¹¹¹

67. Model experiments with protein solutions have revealed that the latent damage, caused by radiation in myosin molecules responsible for the radiation after-effects, can be eliminated by formation of complex compounds with actin molecules if these are introduced into the solution immediately after irradiation.¹¹²

68. Long-lived activated states persist for a few days in protein molecules irradiated in aqueous solution. Activation is associated with disruption of the protein electron structure; this has been confirmed by the ESR method.^{113,114} The ESR method has revealed prolonged retention, by protein molecules (myosin, pepsin), of unpaired electrons appearing after irradiation of protein solutions. A close relationship has been established between these electrons and radiation after-effects in the same system. When irradiated solutions are slightly warmed there is an accompanying "thermal effect", and

unpaired electrons in the protein molecules disappear. This confirms the previous assumption that prolonged retention of unpaired electron-excited energy is a cause of radiation after-effects.¹¹⁴

69. Model experiments with irradiated myosin have revealed "oxygen effect" at the molecular level. Inactivation of myosin's ATP function by irradiation has two stages: first (without the involvement of oxygen) is the long-lived "excited" state of the protein molecule capable of interaction with molecular oxygen; its enzymatic activity is still preserved at this time. Inactivation occurs in the second stage as a result of interaction with oxygen. In an aqueous solution of myosin, "oxygen after-effects" constitute most of the total "oxygen effect".^{115,116-117} These results from a molecular system correspond well with those from studies on a biological system and thus demonstrate the biological importance of these events. In dry spores of *B. megaterium*, oxygen interaction with radiation-induced states can be almost "immediate" as well as post-irradiation.¹¹⁸ The radiation-induced species have proved to be free radicals in experiments involving post-irradiation heat, nitric oxide, and H_2S treatments,¹¹⁹⁻¹²³ coupled with physical experiments (paramagnetic spin resonance studies) of a similar kind.^{62,124} In these experiments, as in those described above with myosin, most of the oxygen effect can occur for an appreciably long time after irradiation. Furthermore, an intermediate state (the metionic state), the consequence of the reaction of oxygen with radiation-induced active species, has been postulated from studies of another biological system.¹²⁵

70. The damaging effects of heat and oxygen in the after-effect response of irradiated myosin solution have proved to be independent of one another. There are thus two distinct forms of latent damage in the same irradiated protein molecule; this agrees with the data of Gordy and his colleagues, who established, by ESR studies, the presence in irradiated protein molecules of two types of spectra—some modified by the action of oxygen and others insensitive to it.^{126,127}

71. As a consequence of the chemical changes of proteins under irradiation, one can expect changes in physical-chemical properties. Changes in chromatographic,¹²⁸ absorptive,¹²⁹ and electrophoretic¹³⁰ properties have been seen.

72. In contrast to irradiation in the dry state, the molecular weight of proteins increases after irradiation in solution.¹³¹⁻¹³³ From chemical evidence there may be several reasons for this. Attack of the tyrosine moieties may induce polymerization as with tyrosine solutions¹³⁴ (melanin formation). In addition, disulphide linkages may be formed among protein molecules. Finally, a re-aggregation of broken molecules may take place, the molecules being held together by freshly formed hydrogen bonds.¹³⁵

73. Irradiation of certain protein solutions (with doses up to 6×10^5 rad) does not lead to perceptible effects on physical, chemical and biological properties immediately after irradiation. However, exposure to heat,¹³⁶ urea,¹³⁷ or UV,¹⁷⁰ alters X-irradiated protein solutions (coagulation, denaturation) more than non-irradiated solutions.

74. In the case of catalase and trypsin inactivation, an after-effect has also been shown.^{138,139} The extent of this depends very much upon the post-irradiation temperature to which the irradiated enzyme was exposed.¹³⁹

* " G " represents the number of molecules changed or produced for each 100 eV of energy absorbed.

The presence of oxygen after irradiation appears to be, in general, unimportant; the after-effect may be attributable to the formation of protein peroxides, of thermolabile molecules, or to other causes.^{140, 141}

75. According to present knowledge, enzyme inactivation is attributable to the action of hydroxyl radicals.^{142, 143} This hypothesis is supported by the observation that iodine ions serve as protectors for catalase inactivation; it is to be expected that these ions react more readily with hydroxyl than with hydrogen radicals.¹⁴⁴

76. Very little is known of the chemical changes in proteins brought about by irradiation in the dry state. The involvement of disulphide linkages has been demonstrated by the close resemblance between electron spin resonance spectra of a number of proteins and that of irradiated cystine,¹²⁷ and by the fact that irradiated ribonuclease, like ribonuclease with its S-S bonds reduced, can be digested by trypsin whereas the native protein is resistant.¹⁴⁵ A general increase in ultra-violet absorption,^{135, 146, 147} accompanied sometimes by a shift in the position of the absorption maximum, indicates an attack on aromatic amino acids. Changes in content of other amino acids have also been demonstrated^{147, 148} and differences in sensitivity between particular amino acids have been noted.¹⁴⁷ The formation of ammonia and amines with the development of carbonyl and carboxylic end groups in the hydrolysates of irradiated proteins is attributable to an attack on amino acids side chains and on peptide bonds.⁹⁰ Susceptibility of peptide bonds to main chain scission is apparently rather low because no such breaks have been detected in serum albumin irradiated with doses up to 2.5×10^8 rad.¹⁴⁷ The oxygen effect observed upon irradiation of dry proteins seems to be connected not only with the excitation of protein molecules but also with the excitation of oxygen molecules which in turn act on hydrogen bonds within protein molecules.¹⁴⁷ The most typical changes in physical, chemical property are those changes which occur *in vivo*: isoelectric point, decrease in sedimentation coefficient, or aggregation as a result of hydrogen bond formation between molecules with disorganized secondary and tertiary structure.^{133, 135, 147}

77. The important aim of studies of the action of ionizing radiation on proteins is to understand the mechanism of radiation-induced enzyme inactivation. The catalytic capability of an enzyme is determined, most probably, by an active site composed of only a very small number of amino acid residues maintained at the surface of the enzyme molecule by secondary and tertiary bonds. Thus, enzyme inactivation can be accomplished either by chemical alterations in the amino acid residues within an active site or by disruption of essential configuration.

78. The efficiency of inactivation through ionization is very high, with $G \sim 1$. This implies that one ionization or cluster of ionizations anywhere within or near a molecule inactivates that molecule. This makes the hypothesis of inactivation via an attack on the site of specific activity improbable. Consequently, inactivation of enzymes by radiation is discussed here in terms of disruption of the secondary and tertiary structure following the production of an electric charge inside the macro-molecule¹⁴⁹ and migration of the ionizing energy along the covalently bonded structure. Energy then becomes localized on weaker bonds,^{150, 151} particularly on S-S disulphide bridges responsible for maintaining the various chains of the enzyme in the native structure.

79. The most noticeable effect of radiation on polysaccharides is chain degradation. This holds for all conditions of radiation¹⁵² as shown by decrease in viscosity, changes in light-scattering, electrophoretic and ultra-centrifuge patterns. The most probable mechanism of degradation is one involving free radicals formed from water, because Fenton's reagent, used as a source of free radicals, induces the same damage.¹⁵³

80. New acid and aldehyde-reducing groups are formed in polysaccharides after irradiation.^{107, 154} Small fragments have been found, e.g. gluconic and glucuronic acids in the case of dextran. Mass spectrometry data demonstrate the formation of H_2 , CO and CO_2 when dry cellulose is irradiated.

81. While the effects of irradiation on polysaccharides in solution and in dry state are much the same, cellulose and pectin, when irradiated in a dry state show an after-effect, but only if stored dry in the presence of oxygen.¹⁵⁵ This is probably due to long-lived radicals formed with oxygen. In addition to degradation, branching has been observed in the dry state.¹⁵⁶ The branches are random in length and spacing. All branch points are probably tetra-functional. Branching of polysaccharides in aqueous solutions has not been reported.

82. High molecular weight polysaccharides such as hyaluronic acid in solution (synovial fluid) are depolymerized¹⁶¹ when irradiated with relatively low doses of X-rays (9,000 r), and the process continues about twenty-four hours after irradiation. Viscosity and light-scattering measurements have proved that, during the after-effect, depolymerization continues. The most probable sites of depolymerization are the -O-C-phosphoester bonds. The addition of cysteamine¹⁵⁸ protects the synovial fluid, although in the absence of oxygen (presence of nitrogen) synovial fluid is more radiation-sensitive. A detailed study of ESR of irradiated polysaccharide has not thrown any light on the observed chemical changes. Internal crosslinking has been suggested¹⁵⁹ although direct proof, using hyaluronic acid, does not exist.

MACROMOLECULAR COMPLEXES

83. There is growing interest in relating the results obtained by irradiating isolated compounds of macromolecules in aqueous solution, and even in the pure solid state, to those from integrated macromolecular complexes (section VI below). Nucleoproteins are probably the closest models of nucleic acids as they exist in the cell, although the status of nucleoproteins *in vitro* may be very different from that *in vivo*.

84. Protein has a protective effect because it traps radicals that would otherwise reach the deoxyribonucleic acid (DNA), but the extent of this trapping is unknown.¹⁶⁰ However, some protective action of nucleic acids on the denaturation of ovalbumin as measured by the number of titrable sulfhydryl groups has been reported.¹⁶¹

85. Nucleoproteins from the same source but with different protein contents show different radio-sensitivities. Dilute solutions of DNA nucleoprotein with N/P ratio smaller than 2 are more radio-sensitive than DNA with N/P greater than 2. Radiation damage is established from a decrease in viscosity. These differences can be attributed to the influence of protein content on

the configurations of DNA in the complexes rather than to some protective action of protein.^{162, 163}

86. If there is a radio-lesion, several possible sites of disintegration and disruption of a nucleoprotein can be envisaged. These include bonds between nucleic acids and protein. Their response may explain why irradiated nucleoproteins do not swell in water as readily as unirradiated material, and why trypsin yields free DNA more quickly from irradiated nucleoproteins.¹⁶⁴

87. On irradiation with electrons (2×10^4 – 2×10^6 rad), part of the DNA of sperm heads is cross-linked to form a loose gel-like network;¹⁶⁵ this does not appear to be due to secondary valence forces. Such cross-linkage has been postulated to be the cause of inactivation of bacteriophages by ionizing radiation.¹⁶⁶ This seems less plausible than the hypothesis that inactivation is due to production of carbon radicals in phage DNA. Such radicals may combine with oxygen, react with a hydrogen-atom donor, or become inactive by an unknown process if neither oxygen nor hydrogen is present.^{166, 167}

88. It is not yet clear which chemical changes are most important in the loss of biological activity of nucleic acids. No data clearly relate radio-sensitivity of biologically active nucleic acids to chemical changes produced by ionizing radiation. From studies on the inactivation of transforming DNA by ultra-violet radiation, by heat denaturation,^{168, 169} and by radio-mimetic substances,¹⁷⁰ damage to the bases seems important. On the other hand, a break in one of the chains of double-stranded DNA, or even scission of the whole molecule, does not necessarily lead to loss of activity. The molecular weight of the transforming DNA can be lowered approximately one order of magnitude by ultrasonic disruption without completely inactivating DNA.¹⁷¹ The inactivation yields, from decay of P^{32} incorporated into single- and double-stranded DNA phages indicate that, whereas all breaks in single-stranded DNA inactivate the phage, both strands must be broken in double-stranded DNA phages, a fact which accounts for the lower efficiency (ca. 10 per cent).¹⁷²

DETECTION OF FREE RADICALS IN WHOLE CELLS BY ELECTRON SPIN RESONANCE (ESR)

89. Although the radiation chemistry of water and of macromolecules *in vitro* can provide useful information on models of primary reactions *in vivo*, complete information depends on studies on the chemistry of the biological constituents after irradiation of living organisms. Progress in this field has been obtained recently with development of the electron spin resonance technique (ESR); this allows study of free radical formation in biological systems.¹⁷³

90. Through this method, unpaired electrons have been detected in a variety of materials. When applied to detection of free radicals, the material irradiated must be stabilized to prevent diffusion of the radicals, e.g. measurement has to be carried out in solids, in frozen solutions and suspensions, or in dry biological material. In principle, quantitative estimates of the number of unpaired electrons in a sample are possible. In practice, it is difficult to attain reasonable accuracy.

91. Data derived from irradiated biological materials are not easily interpreted. They do not necessarily relate to those free radicals responsible for the biological effects of irradiation because many unpaired electrons arise in biologically less important molecules. From studies of

simpler systems it is known that the presence of even slight amounts of impurities can modify the spectrum appreciably. It is not yet possible to identify those free radicals that give rise to the particular pattern of electron spin resonance absorption in irradiated biological material. Therefore, attempts have been undertaken to show a parallelism between radiation-induced ESR phenomena and biological effects on the same material.

92. In seeds of the grass *Agrostis stolonifera*, the effect of irradiation on growth inhibition decreases when water content increases. This has been related to the observation that the fraction of free radicals persisting for longer times after irradiation also decreases with increasing water content.¹⁷⁴ In seeds of *Vicia faba*, both the sensitivity and free radical concentration after irradiation decrease with increasing water content.¹⁷⁵ In barley seeds, studies have been made of the influence of water and LET on radicals detected by ESR techniques.¹⁷⁶ Attempts to relate biological and ESR results on dry pollen grains have been reported.¹⁷⁷ A parallel between biological end points and ESR data has been established in bacterial spores in studies of the effects of oxygen, heat, and NO treatments on the biological and physical responses.^{62, 63, 118, 124} The ESR method, applied to the investigation of lyophilized tissues of whole-body irradiated rats, also demonstrates the presence of stable radicals which vary with the different tissues. After irradiation with 1,000 rad the amplitude of the spectra does not change in any of the tissues with the exception of spleen where there is a sharp decrease immediately after irradiation.¹⁷⁸ The ESR method has also been used to study the effects of different gases¹⁷⁹ (air, N_2 , NO) and of protective substances like cysteamine and AET on the production of free radicals.^{180, 181}

93. The results obtained so far through the ESR technique are summarized in the following propositions:¹¹

"(a) Ionizing radiation produces free radicals in living material;

"(b) The concentration of free radicals produced by radiation increases with increasing doses;

"(c) The measurable concentration of free radicals depends on the surrounding gas and on the water content of the specimen;

"(d) The concentration of free radicals decreases relatively slowly after irradiation and is still well measurable for minutes or up to many hours according to the material and environmental conditions (water content and gas);

"(e) The opinion, widely held up to the present, that absorption of radiation in biological material generally leads within micro-seconds to states stable in the physical sense, must be abandoned;

"(f) It has been proved in some cases that a molecular interchange exists between protective substances and the protected material, and that it plays a fundamental part in protective action."

V. Chemical factors modifying radiation response in cells

OXYGEN EFFECT

94. The influence of oxygen tension on the response of biological systems to radiation is one of the fundamental phenomena of radio-biology. This influence, ex-

erted during irradiation, is generally called "oxygen effect". Gray's recent review integrates the data in this area.¹⁸² The effect has been observed in a great variety of biological systems and can be described in the following way:

(a) In the absence of oxygen, or at reduced oxygen tension, the effects of radiation are diminished but not eliminated; oxygen acts as a dose multiplying agent. Considerable clarification of the quantitative relations between radio-sensitivity and oxygen tension has resulted from work with the bacterium *Shigella flexneri*.¹⁸³ Since, for this organism, survival is exponentially related to dose at all oxygen tensions, the slope of the curve may be used as a measure of radio-sensitivity. It has been found that, when a sufficiently dilute suspension of bacteria is vigorously bubbled throughout the period of irradiation with gases containing different percentages of oxygen, the relation between radio-sensitivity, S , and the concentration of oxygen (O_2) in the medium in which the organisms are suspended is fairly accurately represented by the simple relation:

$$\frac{S - S_N}{S_N} = (m - 1) \frac{[O_2]}{[O_2] + K}$$

where S_N is the sensitivity under anaerobic conditions, obtained by bubbling oxygen-free nitrogen through the solution, and m and K are constants. In general, m is the ratio between the effectiveness of a given dose when oxygen is freely available and the effectiveness when oxygen is absent. Thus, $(m - 1)$ may be considered as the ratio of the oxygen-dependent to the oxygen-independent components of radio-sensitivity. The constant K is the concentration of oxygen at which the sensitivity is exactly midway between anaerobic and fully aerobic values. The ratio m varies around 3 for a wide range of cell types and effects: inactivation of bacteria,¹⁸³⁻¹⁸⁶ and yeast,¹⁸³ growth,¹⁸⁷ chromosome aberrations,^{189, 200} and mitotic delay²⁰¹ in plant tissues, as well as inactivation of isolated mammalian cells.^{202, 203} The similarity between values of K (in the range of 4.5-5.0 $\mu M/l$) for irradiation of bacteria, yeast,²⁰⁴ ascites tumour cells,²⁰² and plant root cells,¹⁸⁹ may be fortuitous, since a somewhat higher value of K ($10 \pm 2.8 \mu M/l$) has been reported²⁰⁵ for *Tradescantia* pollen tube chromosomes.

(b) In wet metabolizing systems, the presence of oxygen during irradiation appears to be essential since no effect has been seen in bacteria irradiated under anoxic conditions when oxygen is introduced only 20 milliseconds later.²⁰⁶ Even stronger evidence is supplied by studies of the inactivation of *Serratia marcescens* by very short pulses of high intensity electron beams.²⁰⁷ Cell suspensions were irradiated with 1.5 MeV electrons delivered either in a single pulse of two microseconds duration (10-20 krad total dose) or for five minutes at a dose-rate of 1000 rad/min; both treatments were applied either in hydrogen or in a 1 per cent oxygen and 99 per cent nitrogen mixture. When irradiation was very short, the radio-sensitivity of the bacteria was the same as under anoxic conditions, whereas with the longer irradiation, oxygen enhanced the sensitivity by a factor of 2.5. However, in dry bacterial spores two actions of oxygen, one realized only if oxygen is present during irradiation, the other at appreciable times after irradiation, have been shown.^{52, 53, 118}

(c) Oxygen effect is usually less marked when cells are exposed to high LET radiation. An important aspect of the oxygen effect is that the enhancement ratio, m , varies with type of radiation, being highest with radiation of lowest LET.

95. The nature of radio-chemical reactions in the oxygen effect including the possible role of HO_2 radicals and of other reactive products whose yields are influenced by oxygen tension, have been widely discussed in recent years.²⁰⁸ Proof has been cited^{52, 53, 118} that oxygen-free radical interaction takes place in bacterial spores to bring about biological damage by X-rays. However, the spores are semi-dry, and the role of water in these interactions has been studied as yet only in a preliminary fashion.^{209, 210} Consequently, a generalization involving the metabolizing cell cannot be made now. The belief that the oxygen effect depends on cellular aerobic metabolism is challenged by experiments in microorganisms with normal and defective cytochrome systems in which oxygen effect is the same.²¹¹ However, oxygen effect varies with the cell's physiological state. For instance, freshly harvested yeast cells, before starvation, have a considerably higher oxygen enhancement ratio ($m = 3.6$) than cells which have been starved. The ratio m decreases as the starvation period is prolonged, reaching a minimum value of $m = 2$ after two days' starvation.²¹² The observation that oxygen alone causes chromosome aberrations when in high concentrations²¹³ complicates interpretation at this time.

96. This oxygen effect must not be confused with the effect of oxygen given in the post-irradiation period. Since the development of radiation injury depends on metabolism, it is likely that there are systems in which the magnitude of radiation lesions can be altered by changes in oxygen tension after irradiation.²¹⁴⁻²¹⁷ Several papers have also dealt with the effect of anoxia; these have shown that anoxic conditions in metabolizing cells after irradiation reduce damage in some cases,²¹⁸ in others enhance it.²¹⁹

EFFECT OF GASES OTHER THAN OXYGEN

97. If oxygen exerts its radio-biological effects by reacting with radicals induced by radiation, other oxygen-like substances may react similarly.¹²⁵ In *Shigella flexneri* Y6R bacteria,²²⁰ nitric oxide enhances radiation damage in the absence of oxygen. Nitric oxide has been found to enhance the effects of ionizing radiation on plant roots²²¹ and on ascites tumour cells.²²² In *Drosophila*, nitric oxide present during irradiation enhances the production of dominant lethals and sex-linked recessive lethals.²²³ The system seems to differ from that in bacteria and ascites cells in that the same concentration of oxygen does not show an equivalent effect. Although these studies have shown that nitric oxide may frequently simulate oxygen, differences in the effects of the two gases have been shown in dry biological materials. Dry grass seeds irradiated and stored in nitric oxide are less affected by radiation than those irradiated in anoxia. However, when the water content of the seeds exceeds 12 per cent, nitric oxide is as effective as oxygen.¹⁷⁰ In spores of *Bacillus megaterium*, two actions of nitric oxide are known: a small sensitizing action during irradiation and a large protective action after irradiation.¹²¹ The latter action is a consequence of removal of free radicals.^{52, 124} The degree of hydration may influence the size of the two actions.¹⁸²

EFFECTS OF GASES UNDER PRESSURE

98. The oxygen effect on *Vicia faba* roots and ascites tumour cells is prevented when cells are irradiated in liquids in equilibrium with different gases under pressure.^{224, 225} The following gases have this effect:

helium, hydrogen, nitrogen, argon, krypton, xenon, and cyclopropane; the same applies to nitrous oxide in tumour cells. The mode of action has not yet been established; the structures normally injured by radio-chemical reactions involving oxygen may be protected by an absorptive layer of the other gas. Proof that these substances interfere with injuries directly or indirectly dependent on oxygen is provided by the fact that they never reduce the effects of the oxygen outside the limits of anaerobic conditions. This research may provide a most valuable clue to the mechanism of oxygen effect.

HYDRATION

99. The precise significance of water radiolysis in the reactions induced in cells by radiation has still to be determined. New facts on this subject have been given by experiments of Hutchinson *et al.*²²⁶ They measured inactivation of two enzymes (invertase, alcohol dehydrogenase) and of coenzyme A in wet and in dry yeast cells. They found that the sensitivity of these enzyme molecules were two times and twenty times greater respectively in the wet state, than in the dry state. Wet versus dry sensitivity for coenzyme A was estimated as 100 to 1. It has been assumed that the difference between the wet and the dry sensitivities is caused by the migration of chemically active intermediates formed by irradiation of water in the wet cells. Hutchinson⁴⁷ estimates that the migration distances of the water radicals are about the same (30 Angstroms) in all three cases.

100. Although increased water concentration enhances radio-sensitivity in *Aspergillus*,²²⁷ several investigations²²⁸⁻²³¹ comparing radio-sensitivity of dried and wet plant seeds show that it is higher in the dried. Experimental results on *Artemia* eggs^{232, 233} parallel results on plant seeds. It is difficult to draw a general conclusion from the few investigations made on the comparative radio-sensitivities of wet and dry cells. The possibility must be considered that, in some experimental conditions, radio-sensitivity is modified by an inadvertent change in oxygen tension within cells which is very likely to be different for different moisture contents. Also, it may well be that effects of moisture observed in plant seeds and *Artemia* eggs are due mainly to alterations in physiological state rather than to participation of water radicals in primary radio-chemical reactions.^{231, 233}

PEROXIDE AFTER-EFFECTS

101. If phage particles are irradiated in buffer and allowed to remain in the suspending medium after irradiation, the number of damaged particles increases with time.²³⁴⁻²³⁶ Similar phenomena have been reported²³⁷⁻²³⁹ in bacteria, in lysogenic systems, and in phage bacterium complexes. This after-effect may be attributed to the presence of H₂O₂ or of organic peroxides formed in the broth. However, doses exerting profound effects on whole cells are often not high enough to produce damaging concentrations of peroxides in the suspending media. This holds particularly if cells contain catalase, but hydrogen peroxide and organic peroxides in dilute suspensions which contain little protective organic matter may also exert a marked effect. In synthetic media, the concentration of peroxides responsible for the after-effect decreases with time during twenty days after irradiation. During this period the rate of decrease depends on dose, at least in the 1-5 kilorad range.²³⁶ Artificially added inorganic peroxides, e.g. persulfate and urea peroxide,²⁴⁰ can also increase sensitivity of phages and bacteria.

102. A possible clue to the action of peroxides has been found through studies of radiolysis of purines and pyrimidines. The addition of hydrogen peroxide and persulfate to irradiated solutions increases the G value of pyrimidines but leaves the G value of purines unaltered.^{241, 242}

CHEMICAL PROTECTION

103. Certain substances of different composition and distinct physical and chemical properties, when added to cell suspensions, can reduce the effects of subsequent irradiation. Study of the chemical protection of the cell is potentially helpful for understanding the primary events of radio-biological processes. Among "protective agents", the sulphur-containing compounds (cysteamine, cystamine, aminoethyl-isothiuronium, glutathione, etc.) are the more important. A few inhibitors of enzyme activity (sodium cyanide, sodium azide, etc.), some metabolites (gluconate, pyruvate, ATP)²⁴³⁻²⁴⁶ and alcohols,²⁴⁷⁻²⁴⁹ have the same action. Chemical protection requires the presence of the protector before or during irradiation, and is more effective against X-rays than against other ionizing radiations. However, some metabolites can also have positive effects after irradiation, possibly by influencing repair processes.^{245, 246}

104. Protection has for long been associated with the indirect action of radiation. It has even been used as a criterion for distinguishing indirect from direct action. This view can no longer be justified. Experimental evidence has been presented wherein no indirect action can be envisaged.^{141, 250-252}

105. One action of protective agents may be explained by a decrease of oxygen tension.^{253, 255, 256} The anoxic hypothesis implies utilization of oxygen by the protector, e.g. in transformation of cysteamine into cystamine. Support for an anoxic effect of protective agents stems from experiments in which the dose reduction factor with cysteamine is similar to that of simple oxygen removal.²⁵⁴ However, several investigators consider that sulphhydryl compounds are protective by other means than production of anoxia. The most recent observations supporting this have been obtained in *Escherichia coli*,²⁵⁶⁻²⁵⁸ in isolated rat thymocytes,²⁵⁹ and in HeLa cells in tissue culture.²⁶⁰

106. Alternatively, protection may be achieved by combination of the chemical protector with free radicals produced by irradiation. By comparison with chemical data¹³² a competitive type of reaction may be envisaged. This reaction involves free radicals, oxygen, and protector. The protecting molecule may act either by combining with free radicals, thus avoiding formation of an unstable active peroxy-radical, or by attacking the peroxy-radical and making it stable, i.e., non-active.²⁶¹ No clear-cut evidence has been presented in favour of either hypothesis.

107. Another explanation is that protecting molecules attach themselves primarily to cell structures, thus masking sensitive sites. The complex so formed would guard these sites from the attack of free radicals (indirect action). This complex may also dissipate absorbed energy less harmfully (direct action). With SH-containing compounds, Eldjarn and Pihl²⁴³ have proposed a chemical model embodying this concept. The masking-effect hypothesis is supported by experimental results showing that decrease of protective ability of cysteine injected into animals parallels recovery of the metabolic activity which that substance had initially lowered.^{262, 263}

108. Other substances with known pharmacological activities (hormones, amines, neurodrugs), protectors after injection in animals, seem to have no action in cell suspensions. Thus, little information about the primary events of radio-biological action can be obtained from *in vivo* experiments in which they are used except for that concerning their possible interference with metabolic processes.

109. The chemical protective agents are also effective against chromosome aberrations²⁶⁴ and induction of mutations by X- and gamma rays.^{265, 266} However, this subject deserves much more attention, the data being scanty.

110. Accumulated evidence on chemical protection^{243, 244} does not now permit an unequivocal recognition of mechanism. New data are needed to clarify this. The ESR technique may become useful in this area.

VI. Effect of radiation on cellular structures and their function

111. Some of the more spectacular and most extensively studied effects, such as inhibition of cell division, mitotic delay and mutation, are most readily associated with nuclear damage and are apparent after exposure to relatively small doses of radiation. However, inhibition of cytoplasmic functions should be carefully considered in assessment of total damage. Since nuclear and cytoplasmic functions are so clearly intertwined, it is imperative to consider their possible interactions in weighing the relative importance of nuclear and cytoplasmic damage.

112. These interrelationships vary with different systems and different functions. The early works of Winternberger,²⁶⁷ Zirkle,²⁶⁸ Henshaw,²⁶⁹ Hercik²⁷⁰ and Petrova²⁷¹ showed that mitotic delay and cell death are principally manifestations of radiation damage sustained by the nucleus. Recent experiments dealing with partial cell irradiation have shown clearly that irradiation of genetic material is far more effective than cytoplasmic irradiation in producing cell lethality. For example, 50 per cent inhibition of hatching of *Habrobracon* eggs requires 10^7 alpha particles to the cytoplasm; only 1 alpha particle to the nucleus suffices to inactivate the egg.²⁷² Comparable results have been obtained in similar experiments with newt heart cultures.²⁷³ Conversely, situations may be expected where cytoplasmic damage is relatively more effective in impairment of specific cell functions. For example, changes in isoelectric point of mitochondrial nucleoproteins of the adult nerve cell occur during or immediately after irradiation with small doses.²⁷⁵⁻²⁷⁷ This indicates alteration of metabolic functions and, in particular, of oxydative phosphorylation.^{275, 278}

113. Non-nucleated cells (*Acetabularia*, amoebae,²⁷⁹ *Paramecia*,^{280, 281} tissue culture cells)²⁸² ultimately die, but they may survive for a considerable time and even continue to differentiate (*Acetabularia*).^{280, 283, 284} Lethally irradiated *E. coli* cells retain the ability to synthesize active bacteriophage.^{286, 285-288} Owing to this high degree of cytoplasmic autonomy, nuclear radiation damage affecting cytoplasmic functions may escape detection during the observation period.

114. Conversely, cytoplasmic damage affecting the physiology of the cell may not become permanent if the

"genetic" or "non-genetic" factors necessary for recovery of the damaged structure are functional. The contribution of the cytoplasm in radiation injury has been partially clarified by recent investigations. In particular, the presence of toxic products²⁸⁹⁻²⁹⁰ and the existence of changes in IEP (isoelectric point) perhaps associated with changes in RNP (ribonucleoproteins) localized in cytoplasmic microstructures may imply disturbances in nuclear cytoplasmic interaction.²⁹¹⁻²⁹³

115. Particular emphasis has been placed on the metabolism of deoxyribonucleic acid (DNA) and on its interaction with ribonucleic acid (RNA) and protein metabolism. These metabolic functions are so intimately intertwined in the way they influence cell division and replication that it seems logical to treat them integrally to assess how radiation may affect this complex.

DNA SYNTHESIS

116. Recently Kornberg and associates²⁹⁷⁻²⁹⁹ have synthesized DNA *in vitro* from deoxyribonucleoside triphosphates using purified extracts from *E. coli*. The system requires "primer" DNA which, during the reaction, replicates. The product has a base composition identical with that of the native primer. Single stranded (denatured) DNA preparations also provide excellent primers.³⁰⁰

117. This mechanism is compatible with present concepts on DNA replication *in vivo*. These postulate that double-stranded DNA may split wholly or partially into single strands that serve as templates and receptors for complementary strands. Moreover, Kornberg *et al.*,³⁰¹ identifying all the dinucleotides in synthetic DNA, have shown that the *in vitro* system produces double-stranded DNA molecules with each single spiral running in the opposite direction as compared with its mate; this result provides excellent support for the Watson Crick model.

118. The presence of polymerase, first found in *E. coli* extracts, has also been demonstrated in extracts of mammalian cells from ascites tumours, thymus, regenerating liver, etc.³⁰²⁻³⁰⁵

119. In the nuclei of tissue cells, DNA synthesis is limited to a definite period during interphase. In the first hours after mitosis there is usually no DNA synthesis (G_1 -period). In the next period (S -period), lasting several hours, the DNA content of the cell doubles. The interphase is concluded by the G_2 -period. This sequence of events in the interphase may be subject to modifications; thus, in ascites tumour cells the G_1 -phase is absent. Precursors of DNA are probably produced in the G_1 -phase and activated (to nucleosidetriphosphates) at the expense of energy-generating processes (e.g. nuclear oxydative phosphorylation). Nuclear synthesis of RNA also occurs in this phase, associated with the production of new enzymic proteins. In the synthetic period, the assembly of activated precursors most probably occurs with the help of the newly synthesized enzymes and with the original DNA serving as template and primer. In the G_2 -period DNA is further prepared for its subsequent role in the imminent cell division. In cells of lower organisms this stratification into well separated division stages does not occur. Probably, however, the sequence of metabolic events is similar.

120. Since the discovery by Hahn and Hevesy³⁰⁶ that phosphorus incorporation into DNA is inhibited by ionizing radiation, a fact confirmed by similar evidence on incorporation of various labelled precursors such as

adenine, orotic acid, formate, phosphate and thymidine, it has been generally accepted that DNA synthesis is a particularly radio-sensitive metabolic process. Recent investigations have cast serious doubt on the correctness of this opinion. They lead, rather, to the conclusion that relatively low radiation doses do not affect the rate of DNA synthesis in various types of cells. It is now realized that a diminished incorporation of precursors into DNA after irradiation may not necessarily represent primary inhibition of DNA synthesis. It may be the consequence of other differences between the irradiated and the control cell populations,⁸⁰⁷⁻⁸¹¹ namely:

(a) Accumulation of cells in the G₂-phase as a result of mitotic inhibition;

(b) Changes in the distribution of the various cell types of a mixed cell population;

(c) Increase of the fraction of dead cells in the irradiated population. The same argument obviously applies to the synthesis of RNA and protein.

121. Recent developments in the use of microspectrophotometry and autoradiography for the study of single cells often make it possible to account for these complications and thus to arrive at a more correct evaluation of the biochemical effects of irradiation. Another method, although at present often more difficult, uses more or less synchronously dividing cells. The following survey considers investigations using these techniques.

122. Irradiation of HeLa-cells with 550 r leads to a considerable increase in the fraction of cells synthesizing DNA as compared with control cultures.⁸¹² This increase amounts to 100 per cent six hours after irradiation (this represents a larger fraction than can be accounted for by inhibition of mitosis). Apparently, cells irradiated during active DNA synthesis continue to synthesize for longer periods than normal; this may be related to giant cell formation. Moreover, Painter⁸¹³ found that when post-irradiation mitosis resumes, added tritiated thymidine results in a lower fraction of labelled cells in mitosis of these cells than in mitosis of unirradiated controls. This could be due to sluggishness of irradiated cells in the G₂-phase and/or in mitosis of the next division stage.

123. In contrast, Harrington⁸¹⁴ did not see any direct effect of exposure to 500 r on the fraction of U-12 fibroblasts in DNA synthesis. The percentage of cells synthesizing DNA began to drop after an interval corresponding to the duration of the G₁-phase; this decline must be wholly attributed to inhibition of mitosis.

124. A similar conclusion has been drawn from studies of L cells (mouse fibroblasts)^{815, 816} in which DNA synthesis continued in the absence of mitosis until the double premitotic content per cell was reached. Very high doses (4000-5000 r) retarded DNA synthesis instantaneously. After exposure to 2000 r the cells still completed an average of three divisions, whereas after 5000 r, only 20 per cent of the cells were still capable of a final division. Such DNA synthesis as was observed thereafter was in giant cells and occurred at a considerably lower rate than in normal unirradiated cells.

125. X-irradiation (800-1250 r) of Ehrlich ascites tumours has not been found to inhibit DNA synthesis.^{817, 818} Mitotic activity is arrested instantaneously but volume, dry weight and total nucleic acid per cell continue to rise considerably. The DNA content per cell rises to the pre-mitotic level. Harbers and Heidelberg⁸¹⁹ cultured and irradiated Ehrlich ascites tumour

cells *in vitro* using doses of 750-3000 r. They found inhibition of the incorporation of (2-C¹⁴) uracil in DNA thymine, but the possibility that this effect was due to inhibition of mitosis has not been excluded. Further results have been reported by Budilova⁸²⁰ on the incorporation of several precursors into DNA molecules of isolated thymus cells nuclei; incorporation was greatly reduced in nuclei irradiated *in vivo*, whereas there were no changes when nuclei were irradiated *in vitro*.

126. In bone marrow cells *in vitro*, high doses of radiation (> 500 rad) directly inhibit DNA synthesis. Lower doses (< 300 rad) cannot inhibit DNA synthesis in cells already in the synthetic period. However, cells in the G₁-phase at the time of irradiation enter the S-phase only after an appreciable delay. More recent observations by Uyeki⁸²¹ are in accord; the number of cells entering DNA synthesis after 800 r is strongly depressed.

127. Low doses of X-radiation (50-140 r) prevent division of root tip meristem cells of *Vicia faba* but do not interfere directly with DNA synthesis.^{822, 823} However, cells not yet in synthesis at the time of irradiation pass on to the synthetic phase only after a delay of 10 hours or more. In contrast, Das and Alfert⁸²⁴ have reported an immediate effect of irradiation on DNA synthesis; even a dose as low as 200 r enhances DNA synthesis, whereas 800 r increases the uptake of tritiated thymidine to approximately five times the control value.

128. From studies in regenerating liver^{825, 826} it has been concluded that DNA synthesis itself is not primarily affected after partial hepatectomy by relatively feeble radiation doses.^{826, 826} In resting liver there is no appreciable DNA synthesis, but when regeneration is induced by partial hepatectomy, synthesis begins 15-18 hours after the operation and reaches a maximum at 24-29 hours. In this first stage of regeneration there is reasonable synchronization of DNA synthesis. High radiation doses (up to 2,000-3,000 r) are needed to inhibit synthesis once it has begun; a dose of 500 r is ineffective. However, the latter dose is quite effective in postponing synthesis when given before the beginning of the synthetic period.

129. Few experimental data are available on the sensitivity of DNA synthesis in micro-organisms to X-irradiation. Billen⁸²⁷ studied mutants of *E. coli* and, in particular, the influence of "unbalanced growth" and radio-sensitivity. He concluded that X-irradiation inhibits the synthesis of protein required for DNA replication.

130. In dividing *H. influenzae*, *E. coli* B and B/r, irradiation with doses between 19 and 100 k rad is followed by breakdown of cellular DNA; after a certain time this process stops and is followed by an increase in DNA.^{828, 829}

131. In *H. influenzae*, the biological activity of DNA, as characterized by its transforming activity, has been determined after irradiation. All remaining DNA and DNA formed after irradiation is functionally normal. No relation has been found between killing and severity of DNA breakdown. From this it has been concluded that observed DNA breakdown is not the immediate radiation-induced process leading directly to cell death.⁸²⁹

132. DNA is in a highly polymerized state in bacteriophages^{830, 831} and certain tissues.^{832, 833} After irradiation, depolymerization is seen,⁸³³⁻⁸³⁵ and shifts in the purine/pyrimidine ratio in DNA synthesized after X-irradiation of spleen cells *in vivo* have been observed.^{836, 837} Changes

in the thymine/adenine ratio in DNA synthesized after irradiation of plants have been reported by Kusin and Tokarskaya.^{888, 889} These changes seem to be closely related to disturbances in nucleotide metabolism.⁸⁴⁰⁻⁸⁴²

RNA AND PROTEIN SYNTHESIS

133. In contrast to DNA, most RNA is in the cytoplasm; only a small fraction resides in the nucleus.

134. Little is known about the secondary structure of RNA. It is probably single-stranded. Physico-chemical data suggest that it may fold locally into incomplete double spirals stabilized by H-bonds; these orderly structures would be held apart by unarrayed segments of the RNA chain.⁸⁴³

135. Nuclear RNA is not homogenous; an important fraction is probably in ribosomes, as observed in thymus nuclei. Cytologically, RNA may be divided into chromosomal and nucleolar RNA. Biochemically, two fractions of nuclear RNA may be distinguished, one extractable by low concentrations of saline (n-RNA₁), another remaining undissolved (n-RNA₂). Generally, n-RNA₁ incorporates labelled precursors less readily than does n-RNA₂.⁸⁴⁴⁻⁸⁴⁶ According to Zbarskii and Georgiev^{847, 848} n-RNA₁ represents the chromosomal RNA and n-RNA₂ forms part of nucleolar RNA.

136. In the cytoplasm, RNA occurs in the cell sap (S-RNA) and in the microsome (liver, pancreas) and ribosome fractions. The molecular weight of S-RNA is relatively small (20,000-40,000); that of microsome RNA is considerably larger (approximately 1.7×10^6). The possibility cannot be excluded that the latter molecular weight represents aggregates of molecules of lower molecular weight as it has been shown that ribosomes may disintegrate into smaller particles depending on the Mg⁺⁺ concentration of the solvent. The RNA in the smallest ribosomes, the so-called 30 S particles, has a molecular weight of only 5.6×10^5 . Small amounts of rapidly turning over "messenger" RNA of an intermediate size, between the latter RNA and S-RNA, are present in uninfected and phage-infected bacteria.^{849, 850} This RNA attaches itself to existing ribosomes and confers on them the code for protein synthesis.

137. Recent studies provide evidence that RNA is synthesized exclusively in the cell nucleus, and is transported from nucleus to cytoplasm after synthesis. Thus, Goldstein and Plaut⁸⁵¹ transplanted P³² RNA labelled nuclei from intact amoebae into enucleated amoebae; after a while the cytoplasm of the host contained labelled RNA. As these amoebae were viable, it seems unlikely that leakage from damaged nuclei was responsible for the effect.

138. So far, the type of the nuclear RNA transported into the cytoplasm has not been established. Woods and Taylor⁸⁵² have suggested that RNA is primarily synthesized in chromosomes and subsequently stored in the nucleolus; from there it would be transferred to cytoplasm. This hypothesis is supported by other investigators^{853, 854} who have found that, with a labelled RNA precursor, radio-activity is first detected in chromatin and only later in the nucleolus; continued incubation in the absence of labelled precursor leads to an earlier and faster fading away of the radio-activity of the chromosomal than of the nucleolar RNA.

139. Whether this hypothesis has general validity for all types of cells is not known. From experiments on

selective irradiation of the nucleolus by UV microbeams, Perry *et al.*⁸⁵⁵ have concluded that RNA transport into the cytoplasm originates from both nuclear locations of RNA. From recent autoradiographic studies of the incorporation of tritiated precursors into RNA of HeLa-cells, in which several correction factors were applied for the conversion of grain counts into actual incorporation, the same authors state that their data do not show a transport of RNA from chromatin to nucleolus.⁸⁵⁶ Moreover, a few instances are known where labelling of the nucleolus precedes that of the chromatin.⁸⁵⁷

140. Little is known about the mechanism of RNA synthesis. An enzyme, polynucleotide phosphorylase, that catalyzes the synthesis of RNA from ribonucleoside diphosphates has been found in micro-organisms by Ochoa and associates.⁸⁵⁸ The purified enzyme requires a primer, but any tri- or tetranucleotide may serve in this capacity, and it is not the primer but the available nucleotide diphosphates that determine the base composition of the product.⁸⁵⁹⁻⁸⁶¹

141. On the other hand, extracts, not only from micro-organisms but also from animal cells, polymerize ribonucleoside triphosphates to RNA.^{862, 863} When DNA is present, treatment with DNA-ase destroys its activity. Enzymatic activity depends also on the simultaneous presence of the triphosphates of all four nucleosides. Furth *et al.*⁸⁶⁴ and Weiss and Nakamoto⁸⁶⁵ have shown that newly synthesized RNA is a copy of the base composition of the added "primer" DNA. The enzyme produces polyadenylic acid or poly-uridylic-acid when primed with polythymidylic- or poly-adenylic-thymidylic acid respectively. With *M. lysodeikticus* or T₂-DNA as a primer, the newly synthesized RNA has the same nearest-neighbour base frequency as the primer.⁸⁶⁶ The resemblance of this enzyme to the polymerase of DNA synthesis is striking.

142. From experiments with labelled RNA precursors, it has been shown that synthesis of RNA occurs during the entire interphase, although in some cells the process is slower during S-phase. During mitosis, no RNA seems to be synthesized.

143. Within the nucleus, DNA transfers its genetic information to RNA.^{867, 868} The presence of an RNA polymerase requiring DNA for action, and copying its base composition, supports this concept. RNA formed in the nucleus then passes into the cytoplasm, carrying its information to protein synthesizing sites. Rich⁸⁶⁹ has demonstrated that, in principle, a single-stranded RNA molecule can unite with a complementary single-stranded DNA molecule. Moreover, Hall and Spiegelman⁸⁷⁰ have shown specific hybrid formation between single-stranded T₂-DNA and the RNA synthesized subsequent to infection of *E. coli*. Geiduschek *et al.* do not favour single-stranded DNA as a necessary intermediate in RNA synthesis *in vitro*.⁸⁷¹

144. Apparently, the base sequence of the DNA is transcribed into newly formed messenger RNA, triplets (or multiples of 3) of nucleotides carrying the information for various amino acids (para. 151). The most direct proof of the ability of RNA to carry genetic information is provided by the information that purified tobacco mosaic virus RNA is apparently infectious. How information transfer between DNA and RNA is effected is not known. Leslie⁸⁷² recently postulated, from studies on human liver cells and from the literature, that coding for micro-organisms and for somatic cells of higher organisms may differ.

145. About twenty years ago, a relationship between RNA and protein synthesis was independently advanced by Caspersson³⁶⁷ and Brachet³⁶⁸ as a hypothesis; this hypothesis has now become a firmly established biological concept.

146. Protein synthesis has been most studied in micro-organisms and in the microsomal fraction of the cytoplasm of higher cells. The first step is activation of amino acids in a reaction with ATP resulting in an amino acid adenylate. The latter compound does not appear freely in solution but remains attached to the enzyme; amino acid activation is therefore usually studied from the exchange between labelled pyrophosphate (one of the reaction products) and the phosphate groups of ATP or by the chemical transformation of the amino acid adenylate by hydroxylamine into hydroxyamic acid.

147. The activated amino acid then becomes attached to the transfer or soluble RNA (S-RNA). It is bound in the manner common to all amino acids, via the terminal nucleotide sequence cytidylic-cytidylic-adenosine; the amino acid residue is bound in ester linkage to the C_{5'}-atom of adenosine. Although the method of binding is identical, each amino acid has a high specificity for the S-RNA to which it becomes attached. There are different S-RNA molecules for each type of amino acid. The specificity of S-RNA resides in its base sequence.

148. The function of S-RNA is that of acting as a carrier which brings the amino acid to the template. Investigations of Bosch *et al.*³⁷⁸ have shown that S-RNA can be firmly bound to the ribosomes. On the other hand, it is possible that this "transfer"-RNA resides permanently in the ribosomes. Thermodynamically, this latter hypothesis is more attractive; it may be significant that in one of the very scanty examples of net synthesis of enzymatically active protein *in vitro* this could be accomplished by a cell-free system in which S-RNA formed part of the ribosome particles.³⁷⁴

149. The last phase in protein synthesis is the assembly of activated amino acids into polypeptide chains by peptide linkages, and release of these chains from ribosomal particles. For this step GTP is required. The process is greatly stimulated by SH-compounds.^{374, 375}

150. Protein synthesis has been studied in microsomes of cells of higher organisms. It is, however, by no means confined to this system. Net synthesis of cytochrome-c has been demonstrated by Bates *et al.*³⁷⁶ in mitochondria. Moreover, it has been shown by Allfrey and Mirsky³⁷⁷ that protein synthesis in the nucleus is very similar to that in the cytoplasm. These investigators suggest that the energy for protein synthesis in the nucleus is provided by phosphorylation in mitochondria.

151. The part played by RNA in carrying genetic information for the production of proteins is clearly shown by the discovery of Astrachan and Volkin³⁷⁸ that infection of *E. coli* by various bacteriophages immediately induces the production of a new RNA which resembles, in base composition, the DNA of the phage. Nomura *et al.*³⁷⁹ found that, after T₂ infection, there is no synthesis of typical ribosomal RNA and that phage specific RNA sediments at a slower rate (8 S) than ribosomal (16 S and 23 S). Apparently, the genetic information for the synthesis of phage protein does not reside in the usual ribosomal RNA but is induced in pre-existing ribosomes by a phage specific RNA which may be considered a messenger RNA. Brenner *et al.*,³⁸⁰ using isotope labelling techniques followed by careful separation of the various RNA-containing fractions,

actually demonstrated that the new RNA (which, according to Volkin and Astrachan,³⁷⁸ has a base composition corresponding to that of the phage DNA) is associated with pre-existing ribosomes and provides them with the necessary information for specific protein synthesis. Gros *et al.*,³⁴⁹ in "pulse experiments" with tracers, have shown that exactly the same situation prevails in uninfected bacteria where an RNA component with rapid turnover and which is physically distinct from ribosomal RNA or S-RNA can be demonstrated. The fraction behaves in the ultracentrifuge and towards pre-existing ribosomes in high Mg⁺⁺ concentrations exactly as the phage specific RNA induced by T₂ infection; it becomes associated with the active 70 S ribosomes, the site of protein synthesis. According to this concept, the typical ribosomal RNA carries no genetic information. The concept of messenger-RNA has been greatly elucidated and amplified by experiments of Matthaei and Nirenberg³⁸⁰ who demonstrated that, in cell-free extracts of *E. coli* containing ribosomes, poly-uridylic acid can induce the synthesis of poly-phenylalanine. At present, triplet code letters have been assigned by Speyer *et al.* to 14 amino acids.³⁸¹

152. The influence of ionizing radiation on RNA and protein synthesis has not been studied to the same extent as that on DNA synthesis, and available data do not permit a satisfactory analysis of the effects.

153. Painter,³¹³ using 1,500 r, did not find a significant disturbance of the uptake of tritiated cytidine into the RNA of HeLa cells. Neither did Harrington³¹⁴ see any effect on the incorporation of tritiated cytidine into nuclear RNA of U 12 fibroblasts after 500 r. Shabadash, on the other hand, showed that cellular ribonucleoproteins are extremely responsive to penetrating radiations.^{277, 291} This was recently confirmed biochemically.²⁹⁵ Ribonucleoproteins localized in structures of different organelles do not have identical physico-chemical properties, as indicated by differences in their iso-electric points,³⁸² which are more acid in mitochondria than in microsomes. The former is more sensitive to penetrating radiation.^{293, 296}

154. Klein and Forssberg³²¹ irradiated Ehrlich ascites tumour cells *in vivo* with 1,250 r and found no changes in RNA synthesis. However, *in vitro* irradiation of these cells inhibits incorporation of labelled uracil into RNA of the nucleus but not into that of the cytoplasm.³¹⁹ This result is difficult to understand in view of the probable nuclear origin of most RNA.

155. From the studies of Logan and collaborators,^{383, 384} it has been concluded that irradiation of isolated liver and calf thymus nuclei *in vitro* distinctly reduces the rate of incorporation of labelled precursors into nuclear RNA. A similar effect on the incorporation of P³² into nuclear RNA can be obtained with regenerating liver, if irradiation is given at the earliest stage of regeneration.³⁸⁵ This observation agrees with data on the synthesis of certain enzymes necessary for the synthesis of DNA in regenerating liver. Thus, Bollum *et al.*³⁸⁶ have found the synthesis of the enzymes DNA polymerase and thymidine kinase to be inhibited by radiation doses of 375-1,500 r if irradiation is given 6 hours after partial hepatectomy. The same doses, given sixteen hours after the operation, are ineffective. Other authors have also found that polymerase synthesis is inhibited by irradiation in the first phase of the regeneration process.^{387, 388}

156. Relatively low doses of radiation can postpone the onset of DNA synthesis in various types of cells.

It seems reasonable to assume that inhibition of enzyme synthesis is at least one cause of this delay.

157. Ionizing radiation also reduces the synthesis of enzymes in micro-organisms. Pauly³⁸⁰ has reported a 37 per cent dose of 7×10^4 r for the inhibition of the induction of lysine decarboxylase in *Bacterium cadaveris*. Radio-sensitivity was the same for the rate of synthesis and the maximum level of enzyme formed. This finding leads to the conclusion that every cell possesses one or more "centres of synthesis", each producing a definite number of enzyme molecules. These synthetic centres would be destroyed according to single-hit kinetics. The induction of catalase by O_2 in a diploid mutant of *S. cerevisiae*, however, is stimulated by a radiation dose of 10^5 r. This stimulation may be due to the production of peroxides in the cell, as suggested by Chantrenne and Devreux.³⁸⁰ Using serological techniques and also various tagged amino-acids in newly synthesized proteins of individual organelles of cells, Ilna and Petrov^{381, 382} showed that qualitatively altered proteins are formed after irradiation.

EFFECTS OF RADIATION ON ANTIBODY SYNTHESIS

158. Inhibition of antibody formation is a special case in the formation of specific proteins, and appears to be highly radio-sensitive. It involves the formation of a specific protein complementary in structure to the inductor antigen. The normal processes of antibody formation are only just beginning to be understood, and a generalized theory has still to emerge from several contradictory hypotheses. Antibodies are formed in the plasma cells of lymphoid tissues which themselves originate from undifferentiated cells of the reticular system. The mechanism of radiation inhibition of antibody formation, recently reviewed,^{393, 394} thus must account for:

(a) The effect of radiation on the multiplication and differentiation of these reticular cells and their descendants;

(b) The process of antibody synthesis, which probably occurs in the microsomes of plasma cells.

159. One of the characteristics of radiation is its greater efficiency in inhibiting antibody production when administered prior to the antigen. The final titer of antibody is lowered only if irradiation occurs some hours before antigen injection. In this case, and also when irradiation takes place immediately before or after antigen injection, the latent period before the titer begins to rise is increased and the rate of synthesis decreased. Taliaferro³⁹⁵ has distinguished a highly radio-sensitive (effects become detectable on the final titer for doses of 100 r) pre-induction period but this is not well defined in cytological or biochemical terms. The cause of this inhibition could be twofold:

(a) Decreased production of plasma cells from their "reticular ancestors", or from other types of cells also involved in the process;

(b) Delay and inhibition of the synthesis of new protein when antigen is injected.

160. Stevens³⁹⁶ has shown a correlation between depression of the number of plasma cells formed after irradiation and inhibition of antibody synthesis. Furthermore, experiments by Taliaferro suggest that antibody formation depends on cell multiplication in irradiated animals; this does not exclude the possibility that *specific* effects on the induction of synthesis of new proteins are also involved. The antibody-producing period ap-

pears to be more resistant to radiation. Apparently, antibodies formed when the system is irradiated during this period do not differ fundamentally from normal antibodies. Studies of the degree of radiation sensitivity of the secondary response to antigen injection have yielded conflicting results; there have been several explanations, each of which might be acceptable for the particular antigen studied.^{393, 394}

GENERAL CONSIDERATIONS OF RADIATION EFFECTS IN CELLULAR METABOLISM

161. The importance of radiation effects that are closely linked with cell division and replication, and which include mitotic inhibition, loss of reproductive power and mutations, has been stressed. It would be attractive to describe these changes within the frame of a unitarian mechanism, although such a treatment would be arbitrary. At least two key effects indicate a disturbance in the genetic properties of the cell.³⁹⁷ One of these is the production of mutations. The other is that delayed effect on cell division in which cells multiply immediately after irradiation but nevertheless fail to form macroscopic colonies.

162. The failure of cells to divide even once when given higher radiation doses is also probably due to damage of genetic material. The inhibition of mitosis might be explained similarly, although here the implication that genetic material may be directly involved is less obvious. Much may be said for the concept that the main radiation effects are at some stage mediated through DNA; this explains why emphasis is laid upon the metabolism of DNA. DNA synthesis has been used in a restricted sense throughout this report to indicate the stage where precursors are assembled into polynucleotides. Subsequent stages may include many more biochemical reactions before the full-fledged DNA-protein molecule is formed and incorporated into daughter chromosomes. These late stages of DNA metabolism presumably take place in late interphase and in prophase.

163. There is some evidence, at least with radiation-induced mitotic delay, that the G_2 stage and early prophase may be the most radio-sensitive stages in the mitotic cycle of many cells.³⁹⁸ Painter's work,³¹³ mentioned earlier, may also be interpreted in this way. The dependence of radio-sensitivity on division stage may not always prevail in somatic cells of higher organisms;³⁹⁹ survival curves of somatic mammalian cells usually show no evidence of resistant fractions.⁴⁰⁰ Because of considerable radio-sensitivity during the G_2 period, metabolic processes during this period are important. Unfortunately, biochemical knowledge of G_2 and subsequent mitotic stages is still extremely scanty. Therefore it is not yet possible to describe the effect of radiation at a molecular level on these phases.

164. In cells of higher organisms two patterns of synthesis of DNA probably occur. In tissue cultures and ascites tumour cells, DNA synthesis continues more or less unhampered if irradiation occurs during *any* period of the division cycle, at least when doses are not excessive; in cells of bone marrow, plant root tips and regenerating liver, DNA synthesis may be delayed when lower doses of radiation are delivered before synthesis has begun. This latter effect is probably due to inhibition of the formation of necessary enzymes as a result of interference with RNA synthesis. No inhibition, and sometimes even acceleration occurs in either pattern when all ingredients are available for synthesis. Mitotic inhibition interferes eventually because a feed-back

homeostatic mechanism precludes, or at least inhibits, DNA synthesis beyond the premitotic level.

165. This concept has been confirmed by Lajtha *et al.*⁸¹⁰ and by Berry *et al.*⁴⁰¹ they found that dose-effect curves for inhibition of DNA synthesis in bone marrow cells differ from those in ascites tumour cells. For bone marrow cells the curve has two exponentials, a "sensitive" one and an "unsensitive" one, characterized by 37 per cent doses of 500 and 1,300 r respectively. The curve for ascites cells lacks the sensitive component. Ord and Stocken⁴⁰² have, from similar curves for thymus tissue, suggested that the sensitive component may represent the inhibition of nuclear phosphorylation described by Creasey and Stocken.⁴⁰³ This inhibition would lead to a shortage of DNA precursors. However, there is no evidence for such a shortage; Ord and Stocken⁴⁰⁴ reported an accumulation of deoxyriboside mono- and triphosphates after irradiation of the thymus. The significance and reproducibility of the inhibition of nuclear phosphorylation seems doubtful.

166. Both cell types also differ in ploidy; tissue-culture and ascites tumour cells are usually aneuploid. The problem of the relationship between ploidy and radio-sensitivity is complex (para. 182) but it is not impossible that the high resistance of these cells may be a consequence of the aneuploidy. This suggests that DNA itself is the primary target. The work of Opara-Kubinska *et al.*⁴⁰⁵ and many studies on bacteriophages indicate that this is probably so, at least for transforming activity and survival in micro-organisms.

167. The "primer" function of DNA in RNA synthesis by the RNA polymerase enzyme means that the explanation given for the delay of DNA synthesis, namely interference with RNA metabolism, is at least not incompatible with a primary radiation lesion in DNA itself (in this case, the primer) (para. 155). This does not exclude the possibility that effects on DNA-RNA protein metabolism, even when mediated through DNA, may not result secondarily from quite another primary radiation lesion, e.g. lesions on larger subcellular structures, proteins, membranes, lipoids.

EFFECTS OF RADIATION ON INTEGRATED FUNCTIONS

168. When irradiated in comparable conditions, different cellular populations react in similar patterns. With increasing doses, effects often become experimentally measurable in the following order: modifications of growth rate, mitotic delay, inhibition of mitosis, delayed or reproductive death and interphase death.

Growth rate

169. Under chronic irradiation, the total mass of cell cultures first increases and then decreases.⁴⁰⁶⁻⁴⁰⁸ The initial increase of the total cell mass of the culture accompanies the emergence of giant cells, the volume and usually the ploidy of which increase without division. This phenomenon has been observed among bacteria, yeasts and mammalian cells, and seems therefore to be fairly general. As dose accumulates, the total weight of the culture diminishes and becomes lower than that of controls. In general, radiation reduces growth rate and increases generation time; however, under certain metabolic conditions, the generation time can be shorter than in control cultures once irradiation is discontinued.^{409, 410} Interference with growth rate has also been detected in isolated cells. In *Phycomyces blakesleeana*, Forssberg⁴¹¹ has shown a lowering of the growth rate of sporangiothecae with extremely low doses of ~ 0.001 r.

Mitotic delay

170. When a cell has been irradiated before prophase, division is delayed. This delay can be modified by dose rate⁴¹² and by oxygen concentration; this may mean that metabolic processes are involved.⁴¹³ The most informative experiments have been those of Carlson and Gaulden⁴¹⁴ with neuroblasts of grasshoppers' embryos. During mitosis there is a critical stage coinciding with the condensation of chromosomes into visible filaments and with the disappearance of the nuclear membrane and nucleolus. If a dose as low as 1 r is given to a cell before that critical stage, development of mitosis is delayed. However, this delay does not occur when the same or an even slightly higher dose is given later. In this latter case subsequent mitoses are delayed. More recent experiments have shown that the critical stage may be somewhat earlier in the mitotic cycle, i.e., in mid-prophase. Gaulden irradiated one of the two nucleoli of neuroblasts with a UV-microbeam and concluded that all cells treated at stages from late telophase to the middle of mid-prophase immediately show a permanent cessation of mitotic progress. This picture of mitotic delay looks slightly different when other types of cells are studied. In particular, the critical sensitive period and the duration of the various phases of mitosis may differ in different types of cells. In consequence, precise comparisons are difficult.

171. The main characteristic of mitotic delay is its temporary nature. Although the mechanism of mitotic delay is still far from being understood, some attempts have been made to explain it. Since DNA metabolism is known to be affected by radiation, it is tempting to attribute mitotic delay to inhibition of DNA synthesis.⁴¹⁵ This explanation is speculative, and it may well be that reduction in DNA synthesis, when observed, is the consequence rather than the cause of mitotic delay. In particular, the radio-sensitive period for producing mitotic delay usually occurs when DNA synthesis is already complete. In some instances, DNA metabolism is apparently normal despite inhibition of cellular division, e.g. in irradiated mammalian cells in tissue culture. This suggests that delay in division may be a consequence of injury to an unknown mechanism controlling the onset of division,⁴¹⁶ and that there is no direct involvement of DNA synthesis. Yamada and Puck showed that a reversible mitotic lag is produced by a block in the G_2 period after X-ray doses of 34-135 r in hyperploid S 3 HeLa cells.²⁷⁴ They proposed that this reversible mitotic lag, like irreversible reproductive death, is due to chromosomal damage, and that the reversible lag may reflect interference with chromosomal condensation just before, and perhaps in, the early stages of mitosis. Other hypotheses have also been advanced: interference of radiation with oxydo-reduction of sulphhydryl compounds produced during cellular division,^{417, 418} and inhibition of the division mechanism of the cytoplasm⁴¹⁹ or of the formation of the spindle.⁴²⁰ Production of anti-metabolites may be responsible, as suggested by Kuzin,^{206, 421-424} who used plant material from which he was able to demonstrate antimitotic quinones.

INHIBITION OF MITOSIS AND CELLULAR DEATH: REPRODUCTIVE AND INTERPHASE DEATH*

172. With increased doses, cellular death usually occurs. Cells can be killed either immediately (interphase

* Under doses higher than 100,000 rad, instantaneous death is observed, due mainly to protein coagulation.

death) or after a few divisions (delayed or reproductive death). In general, the doses required to achieve interphase death are higher, although there are cells which undergo interphase death even if irradiated by relatively small doses, e.g. small lymphocytes, primary oocytes in insects and mammals, mammalian neuroblasts, insect ganglia cells. Reproductive death occurs in bone-marrow, intestinal crypt cells, lymphomas and spermatogonia.⁴²⁵ It should be noted that the latter group consists of cells with a high mitotic index; with these, interphase death would probably require a higher dose.

173. The processes leading to reproductive or to interphase death are still unknown; it is likely that more than one mechanism is involved. In delayed death, chromosome breaks and mutations have been invoked as possible mechanisms. The mechanisms resulting in cellular death may be better understood when the role of repair processes in irradiated cells have been studied, since the ultimate expression of a radiation effect depends not only on initial injury but also on the ability of the cell to repair the injury.⁴²⁵ Most chromosome breaks rejoin; metabolic and synthetic processes take part in healing,⁴²⁶ energy from ATP being required.^{427, 428} Recent experiments by Elkind and Sutton⁴²⁹ have made it clear that repair operates in mammalian cells and influences the ultimate expression of late effects.

174. A clear distinction should be made between biochemical processes leading to delayed death and those leading to interphase death. In the former, synthesis of nucleic acids and proteins continues.³¹⁵ Radiation-induced interphase death is sudden and marked by an arrest of metabolic processes in cells with very wide differences in metabolic behaviour, e.g. cells which are not dividing (lymphocytes), cells dividing infrequently (oocytes), and cells continually dividing (B spermatogonia).

175. The biochemical causes of interphase death are not understood, but it is possible that Creasey and Stocken's work⁴⁰⁸ on nuclear phosphorylation provides a first clue. Their data indicate that nuclear phosphorylation is an extremely radio-sensitive process and is rapidly inhibited. As yet, this process has been detected in nuclei of so-called radio-sensitive tissues only; it has, therefore, been suggested that cells dependent upon this source of energy are those which undergo interphase death at small doses. Creasey and Stocken remark, however, that failure to show nuclear phosphorylation in radio-resistant cells may be due to an increased activity of degradative enzymes rather than to absence of this metabolic process.

176. Nuclear phosphorylation could also be involved in reproductive death if the energy necessary to heal chromosomes was provided by this phosphorylation. A role of mitochondrial oxydative phosphorylations in interphase and reproductive death cannot be excluded. X-irradiation *in vivo*, in fact, damages mitochondria in liver cells⁴³⁰⁻⁴³² even at doses as low as 25 r. Mitochondrial oxydative phosphorylation in plants is immediately and greatly reduced after a single dose of 3,000 r, the effect being more pronounced when cells are irradiated *in vivo* than *in vitro*.⁴³³ Similar effects are also seen in microbial cells.⁴³⁴

177. It is difficult to draw a coherent picture of the biochemical basis of cellular death at this time. The possible role of nucleic acids and protein synthesis has been discussed, but much more extensive information is needed on the cytological alterations of sub-cellular

structures produced immediately after irradiation. Nor can other biochemical processes affecting permeability,⁴³⁵ the maintenance of ionic balance^{437, 438} or the disruption of nuclear and cytoplasmic membranes,⁴³⁹ be ignored as factors in the mechanism of cellular death.

VII. Biological variables influencing radiation response

CONCEPT OF RADIO-SENSITIVITY

178. Various criteria, e.g. death of cells, inhibition of mitosis, impairment of biochemical and physiological functions, are currently used to determine radio-sensitivity. However, when radio-sensitivities of different types of living organisms are compared, survival after irradiation is usually chosen as the parameter. The selective action of radiation on different parts of the cell and the relations between differentiation, mitotic activity, and radio-sensitivity were described within a decade of the discovery of X-rays. In 1906, Bergonié and Tribondeau⁴⁴⁰ formulated the principle that cells in active proliferation are more sensitive to irradiation than non-proliferating cells, and that radio-sensitivity varies inversely with degree of differentiation. Radio-sensitivity depends on various factors, physical (e.g. temperature), chemical (e.g. oxygen tension, hydration), biological (e.g. ploidy, phase in the division cycle in which the cell is irradiated). Radio-sensitivity further depends on the metabolic state of the cell.

VARIATIONS IN RADIO-SENSITIVITY WITH STAGE OF DIVISION

179. The different phases of mitotic and meiotic divisions have different sensitivities to radiation. Attempts have been made to link these variations in sensitivity to various phases in the formation of new chromosomes and to the synthesis of nucleic acids during division.

180. Cell survival, gene mutation frequency, and frequency of chromosomal aberrations all respond differently according to when the cell is irradiated. It is difficult to define the most critical moment as it may vary for different cell types and for different lesions.^{413, 414} Most experimental efforts to clarify this issue have been carried out on germ cells, in particular on both fertilized and unfertilized eggs of several organisms. The end-effects most frequently used as criteria of damage are either survival, or frequency of chromosomal alterations in these cells. It is widely held that variation in sensitivity during division is a general phenomenon and is present in all cells, whatever lesion is taken as the end-point of irradiation.

181. Nevertheless, some recent results suggest that sensitivity of mammalian tissue culture cells to the lethal effect of radiation is independent of the division stage in which the cells are exposed. Survival curves^{397, 400, 441-443} obtained with mammalian somatic cells both *in vivo* and *in vitro* have failed to show the existence of a resistant fraction in cell populations despite the existence of heterogeneity in stage of division. However, experiments with synchronized cultures of HeLa cells have revealed some fluctuations in sensitivity during mitotic division.⁸⁶ Cellular morphology does not affect radio-sensitivity of these cells appreciably since the LD₃₇ of different cellular strains (epithelial, fibroblastic, etc.) ranges between 75-166 r only.

182. Ploidy is one of the biological factors affecting cellular radio-sensitivity at the level of the primary radiation injury. The shape of yeast survival curves depends on the ploidy of the strain. Latarjet and Ephrussi¹³ showed that survival of haploid strains exposed to X-rays follows a one-hit curve whereas that of diploid cells follows a two-hit curve. These authors, and subsequently Tobias,⁴⁴ propounded the hypothesis that inactivation of a haploid cell is caused by a single recessive mutation whereas to inactivate diploid cells two homologous sites must be injured.

183. Extending such studies to higher polyploids, Mortimer found that radio-resistance reaches a maximum for diploid strains and then diminishes with increasing ploidy.¹⁴ Mortimer's results have been confirmed by Magni,⁴⁵ but these authors interpret their findings differently. According to Mortimer, haploid strains are mainly inactivated through lethal recessive mutations, whereas with strains of higher ploidy dominant lethal mutations are chiefly responsible for the inactivation. Both types of mutations would be produced in haploid and polyploid strains, the problem being to evaluate quantitative relationships of the two types. Magni suggests that, in addition to recessive and dominant mutations, non-genetic injury accounts for a sizeable fraction of radiation lethality.

184. In some other systems a positive correlation between increasing ploidy and radio-resistance has been seen. Sparrow *et al.*^{46,47} found that, on the average, doubling of chromosome number in plants increased radio-resistance by a factor of 1.67. Analogous results were obtained with polyploid cereal seeds⁴⁸ and with hyperploid tissue culture cells.⁴⁹⁻⁵¹ In contrast, Till⁵² found identical dose-effect curves for cell lines with different chromosome numbers and Rhynas and Newcombe⁵³ have described radiation-resistant cell lines of the *L* strain with a lower number of chromosomes than the radio-sensitive line. Of interest in a consideration of the influence of polyploidy is the inverse relation between nuclear volume and radio-sensitivity in 23 diploid species of plants.⁴⁷ The role of ploidy in cellular radio-sensitivity becomes more complex when stage of development is considered. Clark⁵⁴ showed that, in *Habrobacon*, diploid female embryos are more sensitive to irradiation than haploid males during the cleavage stage, whereas during larval and pupae stages haploid males are more radio-sensitive. Tul'tseva⁵⁵ and Astaurov have found that, during certain stages of development, radio-resistance increases with increasing ploidy in *Bombyx mori* but that tetraploids are more sensitive than diploids at the end of the larval stage.

GENETIC CONTROL OF RADIO-SENSITIVITY IN BACTERIA

185. A number of mutations causing differences in radio-sensitivity in *E. coli* are known. The increased resistance of strain B/r results from a single mutational step in its parental strain B.¹⁷ Later, Hill discovered and investigated a more radio-sensitive strain, B/s. This strain also differs from strain B by only a single mutational step.^{456,457} A stable strain containing about three times as much protein, RNA, and DNA per cell, isolated by Ogg and Zelle⁴⁵⁸ after camphor treatments of strain B/r, was about 2.5 times more radio-resistant to ionizing radiations and in addition had a sigmoidal survival curve rather than the exponential survival curve typical of strain B/r. This radiation resistance segregated in a fashion similar to any unselected marker in genetic

recombination tests.⁴⁵⁹ Adler and Copeland⁴⁶⁰ have produced evidence which indicates that radio-sensitivity in *E. coli* K 12 is influenced by at least 4 genes. The approximate locations of the four genes have been determined in genetic recombination tests. In *E. coli* B, Rousch *et al.*⁴⁶¹ have recently found mutations at two different loci which have a cumulative effect in increasing radio-sensitivity. They too have determined the approximate location of these genes in the genetic map by recombination tests. Furthermore, comparative biochemical studies of these two independent mutations show that one leads to loss of the tendency to form filaments, the other to a strong inhibition of growth and of nucleic acid and protein synthesis after radiation or other treatment. Such comparative studies of mutant strains which differ genetically in response, seem especially promising in elucidating the physiological basis of radiation sensitivity and resistance.

VIII. Primary genetic effects of radiation

186. The tremendous headway in the last decade in the analysis of genetic function and genetic material has led to a clearer view of the need for a more full understanding of the mechanisms of radiation mutagenesis. Some problems are related to the already-mentioned macromolecular chromosome structure, others are related more particularly to the function and structure of the genes. Since Muller's discovery in 1927 that radiations are mutagenic, much work has been accomplished, but no complete answer to the mechanisms of radiogenetics has been given. It has been clear from the beginning that genetic effects include visible chromosomal aberrations. On the other hand, many mutations do not involve any abnormalities at the level of the light microscope, and it has become practical to divide radiation genetics into the studies of *point mutation* and of *chromosome damage*.

THE GENETIC MATERIAL

187. While one of the most important advances in genetics came from the studies of Morgan, who discovered the linear arrangement of genes along the chromosomes from investigations on *Drosophila*, the most important hypothesis advanced in recent years, derived from work on micro-organisms and viruses, is that of the linear arrangement of genes along the DNA double helix.* Recombination studies in bacteriophages, bacteria, and moulds, in combination with the demonstration that the genetic information is effectively carried in the DNA (or in some cases in the RNA), give convincing evidence.⁴⁶⁸ Furthermore, the existence of viruses containing single-stranded DNA⁴⁶⁴ or of viruses, whose information is coded in single-stranded RNA molecules, indicates that only one of the two strands of a DNA or RNA molecule may carry genetic information. On the other hand, it has also become clearer in recent years that DNA replication probably concerns double-stranded DNA. Even in the one-stranded ϕ X-174 virus, there seems to be a double-stranded stage during replication,⁴⁶⁵ although priming of DNA synthesis *in vitro* is much more efficient if the double-stranded molecule has previously been "melted" to single-stranded units.⁸⁰⁰

188. Hypotheses concerning the structural integration of DNA chains into chromosomes must take into account the existing basic proteins and ribonucleic acids which

* For a review of the subject, see references 462 and 463.

are beginning to be thought of as factors stabilizing, regulating or repressing the genetic units.^{372, 468} These more refined concepts, fairly well established for micro-organisms, will have to be extended to more complex metazoan cells.

189. A big bar to understanding genetic processes in higher organisms is ignorance of chromosome organization at the molecular level. Although the chromosomes from thymus are 90 per cent nucleohistone, plus non-histone protein, RNA and phospholipids,⁴⁶⁷ it is not known how these are made up into the chromosome structure seen under the microscope. Electron microscope studies have repeatedly shown strands of 200 Å diameter,⁴⁶⁸ but nucleohistone strands are ten times narrower. Urea and versene can dissociate chromosome fibrils or nucleohistones; this indicates the importance of hydrogen bonds and of metal ions (Ca^{++} and Mg^{++}) in holding structures together.⁴⁶⁹ The fact that the UV action spectrum for chromosome aberration⁴⁷⁰ is similar to that of nucleic acid indicates that nucleic acid may well play a major role in forming the backbone of the chromosome. That this might well be DNA is supported by the fact that lampbrush chromosomes can be broken *in vitro* by deoxyribonuclease but not by ribonucleases or proteases.⁴⁷¹ On the other hand, Ca^{++} and Mg^{++} deficiency is known to induce chromosome breaks and rearrangements in plants⁴⁷² and other organisms, which indicates that these metal ions may play a role in chromosome integrity.

POINT MUTATION

190. The definition of the mutagenic event deserves special attention because of the analysis of the genetics of bacteriophage by Benzer.⁴⁸² The size of the genetic material (DNA) depends on the test used to study the mutations. According to the genetic test used, Benzer distinguishes three units:

(a) The cistron or unit of gene function is what is being studied when phenotypic changes are observed.

(b) The muton or unit of mutation is the sequence in nucleotides which has to be altered for a mutation to occur. Benzer has calculated that a muton could consist of no more than a sequence of 4-5 nucleotide pairs in the r II region of phage T4. As the same phenotypic change (loss of an active enzyme, for instance) may be the result of the alteration of many loci, the size of the cistron is difficult to determine precisely but it is much larger, probably of the order of several hundred nucleotide pairs.

(c) The recon—or unit of recombination—is what is assayed when recombination tests are made. One altered muton can be made to recover through recombination, as the result of the replacement of *one* or *two* nucleotide pairs which constitute the recon.

191. At present there is no reason to believe that mutation processes in complex organisms are very different from those in micro-organisms; it is becoming increasingly evident that similar concepts will eventually be applied. It has been demonstrated that the mutation leading to sickle cell anaemia in humans results from the substitution of only *one* amino acid by another in one pair of the four peptide chains of the normal haemoglobin molecule; the 2A chains each have one of their glutamic acid residues substituted by a valine residue.⁴⁷³ This minute error in the protein is likely to be the result of a corresponding error in the DNA code.

192. Studies are being conducted on the amino acid

sequence of specific bacterial or bacteriophage proteins like β -galactosidase and alkaline phosphatase; it is hoped that correlations between alterations of DNA obtained by mutagenic agents and protein sequences will throw some light on the problems of genetic coding. The error in DNA, then, would be replicated in a minutely altered "messenger"—RNA carrying specific genetic information to ribosomes assembling activated amino acids in a specific sequence.^{350, 474} This very much oversimplified picture of the mechanism of phenotypic expression enables one, however, to understand present concepts of mutagenesis and abnormal phenotypic expression.

RADIATION-INDUCED MUTAGENIC EFFECTS

193. Damage to DNA of cells by radiation cannot be so controlled that mutations can be obtained independently of lethal events. Although all lethal effects of radiation should not be attributed exclusively to effects on DNA, any alteration of DNA is liable to cause death or mutation of the particular cell. So far, the damage caused *in vivo* by ionizing radiation is not precisely known; the absence of damage to purines and pyrimidine in nucleohistones irradiated *in vitro*⁴⁷⁵ proves clearly that effects found in nucleotides or pure DNA cannot be extended to the same material *in vivo*. There are indications that DNA from irradiated bacteria has a slightly lower "melting point", suggesting that H-bonds have been weakened. Different elution patterns of DNA from irradiated thymus cells have been obtained;⁴⁷⁶ these indicate some change in DNA structure or molecular size. Finally the sequence of a certain number of short nucleotide chains may be changed.⁴⁷⁷ UV irradiation of bacteria appears to lead to the dimerization of some of the pyrimidines, but other reactions, such as hydration of pyrimidines, are also probable. More work is needed to follow the new leads given by recent advances in radiation and photochemistry.^{90, 478, 479}

194. DNA could also be altered as result of uptake, through normal metabolic processes, of an X-ray-altered precursor; this is to be expected from work demonstrating the mutagenic activity of certain purine or pyrimidine analogues. On the other hand, Doudney and Haas have postulated that UV alteration of purine and pyrimidine precursors RNA might lead to mutations after having been incorporated into an abnormal RNA.⁴⁸⁵

OXYGEN EFFECT

195. Mutation to streptomycin independence, investigated by Anderson⁴⁸¹ is not influenced by changes in oxygen tension, whereas other mutations in the same bacterial strain depend on oxygen tension during irradiation by ionizing radiation.⁴⁸¹⁻⁴⁸³

196. Another important point needs clarification. Does radiation induce mutation by affecting DNA directly or is the DNA altered as a result of secondary action? When DNA in the form of transforming principle,⁴⁸⁴ or bacteriophage,⁴⁸⁵ is irradiated *in vitro* under conditions where indirect effects are presumably reduced to a minimum, there is no oxygen effect. In bacteriophage, DNA appears to be more sensitive to reducing than to oxidizing radicals. This indicates that X-rays do not act primarily on DNA, but that in certain circumstances this molecule is altered as the result of secondary reaction. However, Hutchinson showed that inactivation of DNA in solution becomes oxygen dependent in the presence of cysteine.⁴⁸⁶

197. Important progress has come from the study of the effect of several chemical mutagens on DNA or RNA and their correlation with lethal and mutagenic activities in viruses and micro-organisms. Both purine or pyrimidine are known to be chemically changed by a variety of mutagens. Nitrous acid is able to remove the amino group of adenine, guanine, and cytosine;⁴⁸⁷ formaldehyde can hydroxymethylate amino groups, but its mutagenic activity in *Drosophila* depends on the presence of adenylic acid in the medium which, after alteration, could become incorporated into DNA.⁴⁸⁸ Alkylating agents appear⁴⁸⁹ to react in many cases with the N-7 of guanine; this could become unstable and be removed from the DNA chain. Glyoxal derivatives appear to affect guanine. Hydroxylamine⁴⁹⁰ appears to react chiefly with cytosine; hydrazine, to remove pyrimidine; a low pH treatment,⁴⁹¹ to remove purine. Acridines, like proflavines, are mutagenic; their action is believed to result from fixation of this reagent between two adjacent base pairs, thus increasing their separation. A comparison of the mutagenic effects of these chemicals with that of radiation could be of great value. The linear dose response curves found in several cases of chemical mutagenesis indicate that, as for most radiation-induced mutations, the process involves a single event. In this case the alteration involves a single nitrogen base in one DNA molecule.

UPTAKE OF ABNORMAL PRECURSORS

198. A number of base analogues have also been found to be either lethal or mutagenic. Bromouracil (or bromodeoxyuridine) once incorporated into bacteriophage,⁴⁹²⁻⁴⁹⁴ bacteria, and mammalian cells^{495, 496} can produce mutations and lead to increased sensitivity to X or UV radiation.^{405, 493, 497}

199. 2-amino purine, another mutagen, is believed to be incorporated or to permit the uptake of another base (perhaps adenine) instead of guanine.⁴⁹⁸⁻⁵⁰⁰

COMPARISON BETWEEN VARIOUS MUTAGENIC AGENTS

200. When the frequencies of spontaneous and chemically-induced mutations in bacteriophage T₄ are studied, it appears that some regions of the genome mutate much more frequently than others; the same region does not necessarily mutate with comparable frequency after treatment with various mutagens.⁴⁸²⁻⁵⁰¹ Proflavine seems to induce a pattern of mutations which differs from that produced by base analogues; the patterns produced by base analogues show some differences when compared with the pattern of spontaneous mutations. One must, therefore, suspect the existence of several classes of mutagens; of these, the base analogue class induces a mutation pattern similar to those produced by five bromodeoxyuridine and the proflavine class. Close study of specific chemical mutagens, and their comparison with spontaneous and radiation-induced mutations, will no doubt bring much light on the molecular basis of mutagenesis.

BIOCHEMICAL ASPECTS OF MUTATION PROCESSES

201. From work on mutagenesis of various analogues and UV radiation, it appears very probable that mutation becomes fixed during DNA replication. Examples of bromouracil-induced mutations are pertinent to this hypothesis.⁵⁰⁰ If, as postulated by Freese,⁵⁰² mutation

can result from replacement of one base pair (A-T) by another (G-C) (or *vice-versa*), then a mistake would appear in the DNA chain.

202. In the mutagenic action of bromodeoxyuridine on T₄ phage, the analogue might take the place of 5-hydroxymethylcytosine and pair with guanine (error in pairing); this would lead to the replacement of a guanine-5 hydroxymethylcytosine (G-H) pair by an adenine-thymine pair after three DNA replications. Alternatively, the bromouracil moiety of the analogue might replace thymine during the first replication (error in replication) and pair with guanine at the next. This would lead to the replacement of A-T by G-H after the third replication.⁵⁰² Effectively, mutants appear in a culture after the third DNA replication. 2-amino purine could also lead to the replacement of G-C by A-T, and would, like bromodeoxyuridine, on the basis of this hypothesis, be a good agent for back mutating a mutation due to bromouracil incorporation; examples of chemically-induced mutation and back mutation, interpretable in these terms, are now becoming known.

203. However, it is not at all certain that the reversion of a mutation to wild type is necessarily the exact reversal of the forward mutation, and different base pairs might conceivably be involved in the forward and reverse process as postulated by Brenner, Barnett, Crick and Orgel.⁵⁰³ It is very possible that the hypothesis of Freese is an oversimplification of the facts. A mutation and back mutation with proflavine might result from addition or deletion of a base-pair; this might lead to a much more substantial alteration of the protein, such as a break or an alteration of sequence in the polypeptide chain. With radiation, it is difficult at present to make any hypothesis, but the concepts of chemical mutagenesis will certainly have to be considered in radio-biology when radiation-induced chemical changes in DNA are better known.

204. It had been known for a few years⁵⁰⁴ that the frequency of mutants in bacteria increases with cell division. More recently, Witkin has shown that if protein synthesis is inhibited by amino acid starvation or by chloramphenicol, a lower frequency of bacterial mutants is obtained.^{505, 506} This suggests that irradiation produces pre-mutational damage which can eventually be lost, or which can become fixed as a result of protein synthesis. In a study of lethal mutations in *Paramecium*, Kimball⁵⁰⁷ has shown that loss of pre-mutational damage is probably due to metabolic repair of localized chromosomal lesions. Lieb has recently shown⁵⁰⁸ that when DNA synthesis is retarded by treating the cells with chloramphenicol, the increase in mutants, observed when growth is continued after the chloramphenicol "challenge", parallels the increase in DNA; this strongly suggests that the terminal event in this mutational process is DNA synthesis. Much has still to be learned about induced mutagenesis. The role of RNA suggested by Doudney and Haas⁴⁸⁰ is not yet clear. However, one important fact emerges: it is possible to inhibit to some extent mutation fixation in micro-organisms by delaying protein or DNA synthesis.

MUTATION EXPRESSION

205. The biochemical processes underlying the synthesis of cell constituents are becoming better known each year. One of the major problems of present-day biochemistry is the way specific enzymes necessary for these synthetic processes become synthesized themselves. Nisman⁵⁰⁹ has succeeded in synthesizing *in vitro* an

enzyme of *E. coli*, β -galactosidase, in the presence of ribosomes of these bacteria, a mixture of the four ribonucleoside triphosphates, and the DNA of a strain of *E. coli* possessing the enzyme. The synthesis does not occur with DNA extracted from an inducible but non-induced strain of the same bacteria. Furthermore, Novelli has shown⁵¹⁰ that this synthesis can be inhibited by X- or UV-irradiation, and that restoration can be obtained by adding the genetically competent DNA to the system. These experiments are pertinent to an understanding of radiation-induced mutagenesis and, together with those on chemical mutagenesis, are the first leads to an analysis of mutation processes at the molecular level. Treatment of the genetic material (RNA) of Tobacco mosaic virus with nitrous acid leads, after infection of the plant, to the synthesis of viral protein with only three abnormal amino acids.^{511, 512}

206. The problem of mutation expression is therefore one of information transfer from the DNA to the cellular sites of specific synthesis, many of which are cytoplasmic. One major problem concerns the formation of ribosomes; the way in which they receive their information for specific protein synthesis is at present being extensively studied (para. 140).

CHROMOSOME BREAKS

207. Point mutations in higher organisms probably result from processes similar to those described for micro-organisms, but the complexity of the chromosomes may complicate the process. On the other hand, chromosome aberrations have been thoroughly analysed in various organisms and described at length in many valuable reference papers. Ionizing radiations can induce breakage of chromosomes or chromatids followed by restitution or illegitimate reunions. This may lead to a variety of aberrations⁵¹³ which are visible at the first division after irradiation, or in some instances, only after very many cell generations. However, these aberrations often lead to unequal distribution of chromosomes between daughter cells; these usually lead to cell death. Restitution may be at the morphological level only, and a point mutation, probably due to DNA damage may eventually appear.

208. Similar chromosome damage may also occur after UV irradiation,⁵¹⁴ but is less frequent than after ionizing radiation. It may also occur as an effect of alkylating agents⁵¹⁵ or after incorporation of C¹⁴- or H³-thymidine^{514, 515} or of bromodeoxyuridine⁴⁹⁷ in cellular DNA.

209. Studies of agents influencing chromosome damage have led Wolff⁵¹⁶ to postulate the existence of two types of chromosome breaks: some which rejoin rapidly and which presumably involve linkages through metal ions, and some which are influenced by post-irradiation protein-synthesis and which are believed to involve covalent links.

210. The relative role of direct and indirect mechanisms in chromosome breakage has been partially clarified by comparing the modifying effects of various chemicals with damage due to chemically induced radicals and radiation.^{88, 89} The effect of radiation in producing breaks is mainly direct; it certainly is so for dry DNA. Evidence in favour of direct effect on DNA *in vivo* is provided by experiments carried out with bone marrow cells *in vitro*.⁵¹⁷

FACTORS INFLUENCING THE PRODUCTION OF CHROMOSOME BREAKS

211. The effect of oxygen on the occurrence of chromosome breaks produced by radiation is complex. On the one hand, anoxia during irradiation reduces the production of breaks;⁵¹⁸ on the other hand, since the rejoining of chromosome fragments is a phenomenon which requires energy, the absence of oxygen diminishes the frequency of rejoining.⁵¹⁸ Probably connected with the oxygen effect is the effect of temperature.⁵⁰³ The number of breaks increases with a decrease of temperature; this is consistent with the fact that the tension, and therefore the availability of oxygen, is reduced at lower temperatures.

212. Strictly mechanical agents such as centrifugation and ultrasonics, when applied at the moment of irradiation, increase the amount of chromosome breakage. When cells are irradiated with ultra-violet⁵¹⁹ or infra-red rays either prior to or after exposure to ionizing radiation, the frequency of chromosome breaks is reduced in the former case but is raised in the latter. Infra-red irradiation seems to act through changes in metabolic processes.^{520, 521}

213. Biological factors also influence sensitivity to chromosomal damage.⁵²² Cells from different tissues show different sensitivities.^{523, 524} On the other hand, the frequency of breaks per unit of radiation depends on the stage of division during which cells are irradiated.⁵²⁵ The highest frequencies are observed when cells are irradiated during metaphase and anaphase.⁵²⁶⁻⁵²⁸ In the meiotic process, the diplotene stage is most sensitive in animals.⁵²⁹

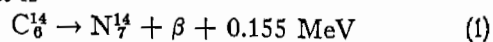
GENETIC EFFECTS OF INCORPORATED RADIO-ACTIVE SUBSTANCES

214. Radio-isotopes introduced into organisms may be incorporated into critical molecules. Although most effects are due to ionization by the charged particle emitted from the isotope, some may result from disturbance of the molecule by transmutation of the incorporated atom. The new atom not only has different and, in most instances, incompatible bonding characteristics, but also, in transmutation, gives off recoil and excitational energy.

215. Ionization and excitation from the ionizing particle are so large compared with the energy from transmutation that they usually outweigh the importance of transmutation in radiation injury. However, certain isotopes incorporated preferentially in vitally significant molecules could, by transmutation, cause unique effects not accomplished by ionization or excitation from a charged particle. Accumulating evidence, along with theoretical considerations, indicates that transmutation should be considered as a factor in the toxicity of internal emitters. The atomic number of the radio-isotope, its type of decay, the particle emitted, and the energy released, are obviously important in gauging the significance of transmutation.

POSSIBILITY OF TRANSMUTATION EFFECT WITH C¹⁴

216. The disintegration by which C¹⁴ exerts its biological effect is



The mean energy of the β -particles is 50 ± 5 keV; thus the reaction gives rise to fast charged particles for which

the RBE of the energy they release is probably 1. Most of the energy of the reaction (1) passes via the kinetic energy of the emitted β -particle into ionization and excitation of the surrounding material; a lesser part appears at the site of the transmutation reaction itself.⁵⁸⁰ Because carbon is a part of every organic molecule in living systems, transmutation may significantly affect key molecules, especially those of the genetic apparatus. Indeed, Totter *et al.*⁵⁸¹ have suggested that the mutational consequences of C^{14} transmutations might be comparable in magnitude to those from the associated β -particles. However, according to Pauling,⁵⁸² they are unlikely to amount to more than about 10 per cent of the total.

217. Although it is certainly established that P^{32} , when incorporated into the genetic material of a variety of organisms, produces biological effects by transmutation (*E. coli*,^{581, 583, 584, 588} bacteriophage,^{586, 587} *Paramecium*,⁵⁸⁸ *Drosophila*⁵⁸⁹⁻⁵⁴¹), the data concerning C^{14} transmutation effects are less plentiful and less consistent. Apelgot and Latarjet, in tests with H^3 , P^{32} and C^{14} labelled DNA in *E. coli* B/r found that, whereas the lethal effect with H^3 was due largely to the emitted beta-particle, transmutation was mainly responsible for the effect with P^{32} and C^{14} .⁵⁴² Kuzin *et al.*⁵⁴³ have reported that the efficiency of incorporated C^{14} in producing chromosome breakage in *Vicia faba* is 10-20 times greater than that of external Co^{60} gamma radiation. By

contrast, Williams and Scully⁵⁴⁴ failed to observe an increased rate of somatic mutations in *Antirrhinum majus* grown in a $C^{14}O_2$ atmosphere as compared to external gamma radiation. The work of McQuade and Friedkin⁵⁴⁵ is especially interesting, for despite the fact that no comparisons were attempted with external radiation controls, the frequency of chromosome breakage in *Allium cepa* root tips was about twice as great when the chromosomes were labelled with C^{14} thymidine bearing the C^{14} in the methyl group as was the frequency observed when the C^{14} was in the 2' position.

LOCAL CONSEQUENCES OF TRANSMUTATION

218. Three processes may cause disturbances at or very near the site of a nuclear transformation in which a β -particle is emitted:

- (a) Chemical changes; $C \rightarrow N$;
- (b) Mechanical recoil of the nucleus which emits the β -particle;
- (c) The production of residual electronic excitation energy due to the non-correspondence of orbital electrons and nucleus following the transmutation.⁵⁴⁶

219. These and other features of transmutation reactions of especial biological interests are summarized below.

PROPERTIES OF CERTAIN ISOTOPES RELEVANT TO TRANSMUTATION PROBLEMS

	C^{14}	P^{32}	P^{32}	S^{35}	H^3
Half-life.....	5,760 yrs.	14.3 d	25.4 d	87.1 d	12.5 yrs.
Max. β -energy (MeV).....	0.155	1.701	0.27	0.167	0.0176
Mean β -energy (MeV).....	0.050	0.71	0.093	0.055	0.006
Max. recoil energy (eV)....	6.9	77.3	6.0	3.0	3.2
Mean residual excitation energy (eV).....	44.5	60.3	60.3	61.7	24.5
Chemical change.....	$C \rightarrow N$	$P \rightarrow S$	$P \rightarrow S$	$S \rightarrow Cl$	$H \rightarrow He$

220. Except for P^{32} , by far the largest part of the energy locally released is the residual electronic excitation of the transmuted atom. This energy and its magnitude closely resemble the corresponding release in a primary or secondary ionizing event by a fast charged particle. The effects of this electronic disequilibrium are therefore qualitatively indistinguishable, except for site, from those of the emitted ionizing particles.

221. In P^{32} decay, the large recoil energy is clearly sufficient to remove the disintegrating atom from the molecule in which it was previously bound, and to carry it into a neighbouring molecule, together with its associated electronic energy.⁵⁴⁶ The recoil energies of all of other transmutation reactions summarized above are much lower and are comparable to the relevant covalent binding energies. Moreover, experimentally determined chemical-binding energies are presumably lower than the activation energies for reactions, even if reactions take place by optimal paths in phase space; the isotropically distributed but directional nature of recoil momentum is likely to make a substantial part of it useless in respect of the optimal reaction path. Hence, even though its chemical binding is simultaneously weakened by the change in its chemical nature, it is doubtful whether, in substances of biological interest, atoms undergoing transmutation other than P^{32} , effectively leave the molecule in which they were bound. An interesting possibility, with a transmuted atom that does not detach from a macromolecule, is that conversion of the recoil momen-

tum to vibrational and other kinetic energy of surrounding atoms may suffice to break significant numbers of important hydrogen bonds in these molecules.

222. The most interesting possibilities of C^{14} transmutation lie in the chemical change, $C \rightarrow N$; this may leave a molecule altered rather than destroyed in function, giving rise to a special class of subtle and viable changes in the genetic system different from those induced by the more destructive ionization or excitation. The significance of the possibility of such changes under conditions of uniform contamination is discussed below.

IONIZATION DOSE PER TRANSMUTATION UNDER UNIFORM CONTAMINATION

223. As will be shown below with uniform incorporation, the practical limitation upon the effect of transmutation itself is likely to be dosimetric. Under such conditions, for every transmutation of a C^{14} atom within an important molecule, $\sim 5 \times 10^4$ eV of ionization and excitation energy will also be liberated; this proportionality will only break down when the molecule under consideration is part of a unit of dimension significantly less than the mean range of the C^{14} β -particle ($\sim 30 \mu$) and isolated from other carbon-containing units by distances significantly greater than the range. If the efficiency of transmutation in causing a certain effect is $\eta\tau$, and that of the ionization-excitation energy of conventional ionization (34 eV) is η_i , then the fraction

added to the ionization-excitation effect by transmutation is only $6.8 \times 10^{-4} \eta\tau/\eta\mu$. This relation suggests at once that, even for high τ , C^{14} transmutation can be significant only when $\eta\mu$ is very small; unfortunately, it is not of much quantitative worth, since appropriate values are not available. The only estimates available for $\eta\tau$ are from P^{32} incorporated into DNA, where $\eta\tau$ is probably 0.01 or lower,^{501, 548} although the efficiency with which the DNA molecule is broken may be in the region of 0.1 for a double helix⁵⁴⁷ and reach a value close to unity for single-stranded DNA.^{464, 548} For the destruction of infectivity of bacteriophage by P^{32} incorporation in DNA, $\eta\tau$ and $\eta\mu$ values are available, and the ratio $\eta\tau/\eta\mu$ is about 10.^{536, 549}

224. Mutation does not necessarily consist only of damage of this kind in the DNA molecule. Changes in at least three types of material might cause mutation:

(a) The gene code itself, i.e., in the double-helical DNA (in most organisms);

(b) Associated stabilizing material such as histone;

(c) The machinery (other than the original gene) by which a gene-replica is made, whether or not this machinery at any stage embodies the gene-code itself in a non-DNA physical form.

The P^{32} data presented relates almost solely to the first of these, and even there is limited to events in the backbone of the DNA molecule rather than the nitrogen bases whose sequence presumably determines the information. Four of the carbon atoms of each average nucleotide of DNA are likewise in the backbone, but chemical transmutation of carbon into nitrogen at most of the others—4 or 5 in the nitrogen-base, 1 in deoxyribose linking nitrogen-base to backbone—could conceivably give rise to subtle viable changes unlikely to be duplicated by gross ionization damage or by P^{32} disintegration in the backbone. In bacteriophage, some protein synthesis necessarily precedes DNA synthesis and gene replication after infection.^{550, 551} Experiments on inactivation by P^{32} decay suggest the possibility of a stage at which the genetic information itself is carried in a non- P^{32} containing form.⁵⁴⁷

225. In conclusion:

(a) From theoretical considerations based on the large ionization-excitation dose per transmutation, the contribution of transmutation to the biological effect would not be expected to be significant under conditions of uniform incorporation of C^{14} unless the efficiency of transmutation in producing the effect is very much greater than that of ionization. Although experimental data are as yet meagre and inconsistent, certain data indicate that C^{14} transmutation may contribute significantly to chromosome breakage;

(b) Because the C^{14} recoil energy is low and the energy of electronic rearrangement strongly resembles the usual ionization-excitation energy, such a contribution is most likely to be mediated through the $C \rightarrow N$ chemical change;

(c) The area in which to seek such a contribution would seem to lie in phenomena brought about with very low efficiency by ionization: probably not in simple damage to the genic material but perhaps in abnormalities in the components of replicative apparatus where ionization-excitation would, in contrast, be more likely to cause total inactivation.

IX. Recovery at the cellular level

226. The concept of "recovery" at the cellular level covers various phenomena with different mechanisms. At least three should be distinguished:

(a) Spontaneous recovery of damaged molecules and structures of the cell; this constitutes genuine recovery;

(b) Recovery through action of physical or chemical agents immediately or soon after irradiation; this constitutes a kind of "treatment" of the damaged cells;

(c) Replacement of damaged molecules or structures by corresponding molecules or structures from undamaged cells. Here there is no recovery but there is a restoration of cell function.

227. The interval between irradiation and the biological expression of the primary damage indicates a complex process and suggests the possibility of interfering with it to promote the repair of injury. Much work deals with phenomena in bacteria and their related bacteriophages using ultra-violet light. Some results have been extended by the use of ionizing radiation. The inclusion of ultra-violet data in this chapter is justified by the similarities and differences found between the action of ultra-violet light and ionizing radiation. These can enlighten several aspects of molecular biology, in particular those associated with the structure, replication, and biological activity of nucleic acids.

228. Restoration is sometimes obtained by destruction of some intermediate compound before the damage is irreversibly established, e.g. photorestitution of ultra-violet damage,^{552, 553} restoration by catalase of lysogenic systems treated with ultra-violet,^{238, 239, 554} and restoration by ultra-violet light of X-irradiated yeast and bacteria.^{555, 556}

229. Photorestitution (restoration by radiations of the range 3,100-5,500 angstroms) is very general and has been verified in a great variety of biological systems. The study of photorestitution of a transforming factor *in vitro* has led to the discovery of an enzyme in yeast and bacteria which is necessary for restoration.⁵⁵⁷ Work with this system will soon give valuable information on the mechanisms of ultra-violet inactivation and photorestitution. Recently, Marmur and Grossman⁹⁷ have shown that the PR (photorestitution) enzyme is able to reverse induced linking of DNA strands by UV light.

230. Several radio-biologists have attempted to achieve photorestitution after exposure to X-rays. Dulbecco⁵⁵⁸ has shown that coliphage T_2 , inactivated by X-rays in synthetic medium (predominant indirect effect), cannot be restored by visible light, but that the same phage inactivated in organic medium (predominant direct effect) shows a slight photorestitution. Similar results have been obtained by Watson,^{559, 560} with coliphages T_2 , T_4 , and T_6 . In general, however, there is no photorestitution after irradiation with ionizing particles.

231. Some of the lethal damage provoked by UV light in the coliphage T_4 can be repaired by some cellular reactivation mechanism linked to the presence in this phage of the gene μ . This gene determines the difference in ultra-violet sensitivity between coliphages T_2 and T_4 . The primary UV lesions are identical in both phage types, but the presence of the μ allele in T_4 (as opposed to the μ allele in T_2) results in reactivation of about 50 per cent of the otherwise lethal damage. Lethal UV damage reactivable by the μ allele action is almost identical to photoreactivable damage.⁵⁶¹

232. The restoration effect of ultra-violet light subsequent to X-irradiation has been observed by Elkind *et al.* in yeast cells.⁵⁵⁵ Ultra-violet light increases the fraction of cells surviving the exposure to X-rays by a factor of 3 or 4. Analogous effects with spores of *Streptomyces aureofaciens* have been reported by Goldat *et al.*⁵⁵⁶ In the latter instance, the restoring action of the ultra-violet was observed for both lethal effects and mutation induction.

233. Restoration by catalase of ultra-violet-induced damage^{288, 299, 554} is more restricted, as it applies only to lysogenic systems and is linked to the destruction of organic peroxydes formed in these systems during irradiation.

234. The supply of metabolites to micro-organisms which have lost the capacity to synthesize them can be considered as one possible mechanism of recovery; in this case, however, restoration is apparent only, since the intrinsic damage has not been repaired. Restitution would be achieved if there was a possibility of replacing the damaged molecules or sub-cellular units by non-irradiated ones.

235. The phenomenon of cross-reactivation or "marker rescue" was discovered by Luria with the T-even phages (T₂, T₄, T₆). When a bacterium is infected with active and inactivated phages differing from each other in a few of their genetic loci, some genetic markers of the inactivated parents may appear among the progeny resulting from such a mixed infection. These studies were subsequently carried out in great detail by Doermann *et al.*^{562, 563} and were extended to the coliphage λ ,⁵⁶⁴ and to the *Salmonella* phage P₂₂. This phenomenon may be explained by assuming that the UV lesion, while preventing or delaying the reproduction of the whole phage, destroys only a small piece of its genome. The cross-reactivated loci would be those of the undamaged parts of the irradiated phage which would reproduce only after their "rescue" from the injured genome through genetic recombination with the unirradiated parent.^{562, 564} After X-irradiation and after decay of incorporated P³², marker rescue has also been observed in the T-even phages^{569, 568, 567} and in the *Salmonella* phage P₂₂.⁵⁶⁵

236. A bacterium infected with a single inactivated phage does not yield active virus; but if two or more inactivated virus particles infect a bacterium, active phage may be released.⁵⁶⁸ The phenomenon of multiplicity reactivation has been interpreted by Luria as being due to genetic exchange of uninjured parts of the genome of the parental phages. Further studies⁵⁶⁹ have not supported some aspects of Luria's original theory of multiplicity reactivation, but recently Harm⁵⁷⁰ and Baricelli⁵⁷¹ have amended Luria's theory to reconcile it with the experimental data. Multiplicity reactivation seems to be restricted to certain strains of phages and to certain types of radiation damage. It occurs with the T-even phages and T₆ with high efficiency; it is less effective with T₁, λ and P₂₂, and not at all effective with T₃, T₇ and the *Pyocyanea* phage P₈.⁵⁴⁷ Multiplicity reactivation occurs with high efficiency only when the phage-bacterium complex is exposed to irradiation. To explain the different response to X-rays of intracellular and extracellular phage, Weigle and Bertani⁵⁷² assumed the occurrence of an "early step" damage connected with DNA injection which prevents the uninjured parts of the irradiated genome from participating in the sequence of events conducive to reactivation. Although it has been reported that no multiplicity reactivation occurs in T₄

phage incorporated by P³² decay,⁵³⁷ a more recent study has detected this phenomenon.⁵⁷³

237. The fact that some of the phenomena of recovery of genetic structures are only seen after UV irradiation is, in general, interpreted as being due to the different primary effects which follow UV and X-ray absorption in nucleic acid molecules. It appears that UV radiation primarily damages bases whereas X-rays primarily produce breaks in the DNA backbone.

238. The damage produced by UV light in temperate bacteriophages can be repaired to a certain extent by the host cell.^{565, 574-576} It seems that the normal host cells possess a genetic component which is capable of repairing the UV damaged virus. This is explained by Garen and Zinder in terms of genetic homology between the genome of the phage and the genome of the bacteria in lysogenic systems. The homologous part of the bacteria could replace the injured part of the virus genome through a process of genetic recombination. Similar phenomena have been reported with Rous sarcoma virus¹⁹⁰ and with the measles virus¹⁹¹ in host animal cells.

239. Another phenomenon of host reactivation has been described by Weigle;¹⁹² it applies to temperate and virulent phages. Among the progeny of irradiated phages grown in irradiated bacteria, a certain fraction of plaque-mutants is observed. These mutants are not seen among progeny of the same phage grown in non-irradiated bacteria. This suggests that the phenomena of reactivation and production of mutants are connected.

240. A restoration phenomenon linked to diploidy has been observed by Latarjet and Ephrussi¹⁸ in *Saccharomyces cerevisiae*; after X-irradiation, haploid and diploid cells can undergo a few abortive divisions before dying (delayed death). In diploid cells, however, a restored cell with normal morphology may sometimes arise after a few abortive divisions. Repair of radiation damage may occur in diploid yeast cells if they are starved after irradiation.¹⁹³

241. The replacement of damaged macromolecules by intact ones inside cellular structures also offers a possibility of repair. For instance, survival of *E. coli* B/r to irradiation is higher on a synthetic medium enriched with yeast extract than on synthetic medium only.¹⁹⁴ Similar experiments are those of Daniels *et al.*¹⁹⁵⁻¹⁹⁷ with the large multinucleate amoeba *Pelomyxa illinoisensis* in which individuals lethally irradiated with ionizing radiation may be restored to reproductive viability by means of fusion with fragments of unirradiated individuals. When the contents of this amoeba are stratified by centrifugation, the heavy third containing nuclei are most active in restoring irradiated cells. Some desoxyribonucleotides were reported to have favourable effect on restoration of hematopoietic cells from radiation injury *in vitro* as well as *in vivo*.¹⁹⁸

242. Restoration of cells can also be obtained by treatments that modify the post-irradiation metabolism of the cells such as temperature, presence of certain nutrients, metabolic inhibitors. This subject, which is related to the variations in the conditions of the cell populations after irradiation, has been extensively reviewed recently by Alper.¹⁹⁹ Characteristically, the results reported indicate that most treatments which reduce the response to irradiation provide an environment which is sub-optimal for growth.

243. Some physiological functions of cells impaired by radiation may also be repaired. At present, knowledge of recovery mechanisms after ionizing radiation is in its

infancy. This subject is of such importance to radio-biology that research on all aspects of the problem should be emphasized.

X. General conclusions

244. The main conclusions of radio-biology in the 1958 report remain valid and will not, in general, be repeated here. However, because of the importance of the threshold problem, it seems prudent to restate the earlier conclusion that "biological effects will follow irradiation, however small its amount". This conclusion, based largely on theoretical considerations and on the exponential character of many dose-effect curves, is supported by new data on the effects in macromolecular solutions, intracellular structures, viruses, bacteria, and other cellular systems.

245. The main development since the last report has been spectacular progress in the study of biological effects at the molecular level. This applies in particular to the genetic material, DNA, and the way in which this substance replicates itself (DNA synthesis) and controls the synthesis of specific proteins transcribing its information to RNA by a triplet code. In the wake of molecular biology, a molecular radio-biology is now developing and, although still in its initial stages, has already provided some important results. Thus, evidence is now coming forward that the most significant radiation effects (inhibition of mitosis, reproductive and interphase death, mutation), at least in a number of instances, are due to primary damage of the genetic material, namely the chromosomes and, in particular, DNA. How these lesions interfere with DNA, RNA, and protein synthesis has already been much clarified; it is expected that studies on cell-free systems *in vitro*

now in progress will provide many answers to still open questions.

246. Understanding of radiation damage in nuclear material has been increased by studies of the effects on the physical and chemical properties of macromolecules, especially nucleic acids and nucleoproteins *in vitro* and *in vivo*. The ESR method seems promising for detection and determination of the fate of free radicals produced by radiation in biological materials.

247. New knowledge of the effects on cytoplasmic functions has contributed to an understanding of the problem of radiation damage to cells. Only by taking into account the mutual interaction of damaged structures in the nucleus and cytoplasm can this complex problem be understood.

248. The important role of recovery at the cellular level in determining final radiation effects has been more appreciated, especially the partial reversibility of initial mutational damage in cells of various origins. However, knowledge in this field is fragmentary; further research is needed.

249. Biological effects after incorporation of P^{32} , C^{14} , and H^3 have been studied. It seems that under most conditions, biological effects are due to radiation rather than to transmutation. However, it has been shown that under certain conditions, particularly after P^{32} and C^{14} are incorporated into essential molecules like DNA, transmutation may lead to chromosome breakage.

250. Radio-sensitivity studies have received new stimulus from recent analysis of genetic factors determining radio-sensitivity in bacteria and from investigations of how these genetic factors are metabolically expressed.

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ANNEX C

THE HEREDITARY EFFECTS OF RADIATION

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I. Introduction

1. In its consideration of the hereditary effects of ionizing radiation upon man this report, as did that of 1958,¹ centres its attention on the possible consequences of the increases in the level of radiation to which human populations are currently exposed.

2. The Committee's 1958 report presented a comprehensive outline of the genetic hazard of ionizing radiation; the available evidence in man and other organisms was reviewed thoroughly and a variety of approaches was used to elucidate the problem. At the same time it was emphasized that current knowledge was insufficient to complete this task with more than partial success.

3. Since that time several significant developments have been made in radiation genetics and in related disciplines. In particular, progress has been very rapid in the area of human cyto-genetics; considerable attention is now being focused on the induction of gross chromosome aberrations as a serious genetic hazard. In addition, remarkable advances have been made through investigations with mice. These have indicated the existence of previously undetected intricacies in the dose-mutation relationship.

4. Developments such as these have been of great help in understanding the basic problems of radiation genetics. At the same time they have re-emphasized its complexities. The present annex gives particular attention to the effect which these recent advances have had on our ability to estimate the extent of hereditary damage which may be induced in populations by ionizing radiation. In stressing current problems, the report does not enumerate but is nevertheless based on a vast amount of information which has been accumulated over many years in the field of radiation genetics. For an account of earlier data and well-established genetic concepts, reference should be made to the previous report. However, to make this annex self-contained, this older information is summarized at relevant places.

5. All organisms are subject to hereditary diseases and defects. In man, estimates of the size of this burden of undesirable traits are based on the frequencies of:

- Abortions, still births and neonatal deaths;
- Infertility;
- Hereditary diseases and defects;
- Detrimental deviations from normal in continuously varying traits such as intelligence, life-span and resistance to disease.

6. Deleterious genetic traits are a direct consequence of the presence of specific basic faults in the genetic constitution of affected individuals. These faults may be either undesirable alleles or chromosome aberrations. However, the prevalence of deleterious hereditary traits in a population does not, in itself, provide a complete picture of the amount of genetic damage present. In some instances the fault is partially or completely masked in the heterozygote. In other instances, its phenotypic expression is so different in the homozygous and heterozygous states that it is impossible to express the total detriment to populations in simple terms. Furthermore, environment, in the form either of the remainder of the genotype or of external conditions, frequently has a great influence on the manner in which the fault is expressed.

7. There is no doubt that any increase in the frequency of radiation-induced mutation contributes to the burden of undesirable traits. It is equally evident that the evaluation of this contribution must rely upon an understanding of the genetic structure of a population and the environmental forces to which it is exposed. Moreover, the effect of an increase in the amount of genetic damage, from whatever source, must be considered in terms of a time interval; once inflicted on a population the damage may persist through future generations and may be expressed only intermittently and with varying degrees of severity.

8. There are a number of complementary approaches to the problem of estimating the detrimental hereditary effects of an increase in rate of mutation in human populations. Estimates of genetic hazard can be obtained empirically by the observation of irradiated populations. However, information obtained in this way is meagre, and estimates are more often calculated from what is known about the induction of genetic damage by radiation and from a knowledge of the way in which this damage will be expressed. These more indirect approaches require information on:

(a) The magnitude of natural genetic damage within a population as ascertained from a knowledge of the role of heredity in morbidity, mortality, and infertility;

(b) The role of recurrent natural mutation in maintaining the prevalence of this genetic damage;

(c) The qualitative and quantitative relation between a given dose of irradiation and the corresponding increase in mutation rate.

9. Every approach has its own difficulties and limitations. The direct approach is impeded not only by a meagreness of data but also by the absence of proper controls. Furthermore, in man it is quite impractical, through direct observation, to ascertain the spread of damage over what may be many generations. On the other hand, more indirect approaches require a knowledge of the genetic structures of populations and of genetic mechanisms which we do not fully possess at this time.

10. All approaches often make use of investigations with other organisms because the mechanism by which hereditary information is transmitted is basically the same in all forms of life. Experimental observations in a wide variety of organisms can thus provide a working model of the effects of ionizing radiation on man. However, there may be radical differences in genetic structure between populations because this structure is undoubtedly affected by the environmental conditions under which a population exists. Furthermore, many hereditary de-

fects that are slight but nevertheless of importance to humans are not easily recognized in other species. As a consequence, generalizations based on the results of investigations with experimental organisms entail many uncertainties.

II. The prevalence of naturally-occurring hereditary defects and diseases

11. It is generally accepted that there is a genetic component in much, if not all, illness. This component is frequently too small to be detected; in other instances the evidence for its presence is unequivocal. Nevertheless, the role of genetic factors in the health of human populations has not in the past been considered seriously in vital and health statistics. As a consequence, data on the prevalence of hereditary diseases and defects are now largely restricted to that collected by geneticists for special purposes in limited populations from a small number of countries.

12. An assessment of the hereditary defects and diseases with which a population is afflicted does not necessarily provide a measure of the imposed burden of suffering and hardship on the individual, the family, or society. Such evaluations require, among other things, consideration of the development of medical services and of the cultural values in communities.²

SURVEY OF HEREDITARY DISABILITIES

13. In the 1958 report, a detailed examination of data accumulated in Northern Ireland over many years led to a figure of about 4 per cent as the incidence of more readily detected hereditary diseases and defects. That survey has been the most comprehensive undertaken to date, and although limited to a single geographical region, it has provided a useful base on which to formulate overall estimates. New information now permits a revision and reclassification of these. For instance, it is now possible to estimate the frequency of chromosome aberrations and to transfer some conditions, such as Down's syndrome (mongolism), to a different category. The estimate of the incidence of congenital malformations has also been increased. The revised values are summarized below. Disabilities are placed in any of four categories. They are classified according to the role which mutation is believed to play in maintaining their frequency. This subject will be discussed in more detail in section III.

Category Ia

14. This includes harmful traits whose mechanism of inheritance is understood and whose prevalence is determined mainly by the frequency of individual gene, or point, mutations.

15. Several hundred traits determined by single gene substitutions have been identified. A majority of the traits, perhaps 70 per cent, are determined by autosomal dominant genes. Approximately 5 per cent are sex-linked recessive traits, and the remaining 25 per cent are determined by the homozygous expression of autosomal recessive genes.

16. The majority of dominant traits are sufficiently mild in their effects to be transmitted through several generations. In contrast, the detrimental recessive traits now recognized in man are very severe in their effects and, with few exceptions, are lethal in the genetic sense. As a result, although about 70 per cent of well-established specific traits are determined by dominant

genes, in perhaps 90 per cent of persons who show monomeric traits, these defects are determined by dominant genes. In terms of gene frequency, however, genes for recessive harmful traits must far outnumber those for dominant harmful traits in a given population. Furthermore, many hundreds of traits are encountered in man for each of which a recessive mode of inheritance is suggested, but each is so uncommon that adequate evidence for this is lacking. It seems likely that many of these traits are in fact the homozygous expressions of recessive genes and that they contribute in total more than any other class to the frequency of detrimental traits in populations.

17. Traits listed in this category are at present estimated to affect about 1 per cent of all live-born.

Category Ib

18. Harmful traits which are determined by cytologically demonstrable chromosome aberrations are included in this category. Their frequency is maintained mainly by recurrent mutation.

19. There is direct evidence that congenital and other physical defects are sometimes due to chromosome aberrations. This important information has been acquired as a consequence of improved techniques in human cytogenetics. Because most research in this area is new, the subject will be considered here in some detail.

20. As with those traits caused by the action of specific alleles, there is often considerable variation in the clinical severity of defects caused by chromosome aberrations. For this reason, all the clinical aspects of some specific defects remain to be described. Different degrees of mosaicism may be partly responsible for this variation in expression. Many associations of physical impairment with chromosome aberrations are now being reported and it must be suspected that some of these associations are due to chance. Reasonably well-established associations are presented in table I, others, necessitating further confirmation, in table II. All the disabilities noted in tables I and II are congenital, but some diseases of somatic origin are known to be associated with chromosome aberration. Two of these are granulocytic chronic leukaemia³ and Waldenström's macroglobulinaemia.⁴ Such diseases are discussed in annex D.

21. The fact that some well known defects occur as a consequence of anomalies in the number of autosomes was discovered in 1959, when it was demonstrated that Down's syndrome is associated with trisomy of one of the small acrocentric chromosomes (number 21 under the Denver Convention).^{5,6} There are two other well-established instances of trisomy syndromes. One involves a member of the 17-18 group,⁷ the other a member of the 13-15 group.⁸ All three kinds of trisomy are associated with mental retardation.

22. Some detrimental traits are attributable to anomalies in the number of sex chromosomes. This was established when it was shown that a condition known as Klinefelter's syndrome can be caused by an XXY constitution.⁹ Related clinical symptoms have now been attributed to XXXY,¹⁰ XXXXY¹¹ and XYY¹² karyotypes. Turner's syndrome has been associated with an XO constitution.¹³ Females with XXX and XXXX karyotypes have also been described.^{14,15}

23. Defects attributable to the presence of chromosome rearrangements have also been detected. Some

individuals with Down's syndrome are known to have a forty-six chromosome complement in which part of an extra chromosome 21 is translocated to another autosome.¹⁶⁻¹⁸ Other disabilities that have been associated with translocations or other types of aberration are listed in table II.

24. Defective traits caused by chromosome aberrations are sometimes, as might be expected, inherited through successive generations. A chromosome rearrangement which permits Down's syndrome to be transmitted by phenotypically normal females with a translocation in the balanced state has been demonstrated repeatedly.¹⁷⁻²⁰ Cases have also been reported of translocation-carrying phenotypically normal males whose children exhibit Down's syndrome.^{20,21} Other balanced and unbalanced karyotypes have been noted in parental and child generations (table II). There are indications of differential transmission of aberrant chromosomal types in the two sexes.²²

25. Mental retardation is one of the common consequences of gross chromosomal aberration. Relevant data have been obtained through the procedure of nuclear sexing of buccal mucosa to detect sex-chromosome anomalies. This procedure reveals deeply staining chromatin bodies within nuclei. The number of these Barr bodies per cell is, in general, one fewer than the number of X chromosomes present; the cells of a normal male are chromatin negative, whereas those of a normal female contain one Barr body. In five surveys, the combined frequency of chromatin-positive individuals among males attending special schools for the mentally backward was 8.77/1,000 (29/3,306).²³⁻²⁷ Five surveys of male inmates of institutions for mental defectives indicated a frequency of 9.51/1,000 (70/7,358) chromatin-positive cases.²⁸⁻³² Two surveys of female inmates of institutions for mental defectives showed a combined frequency of 4.46/1,000 (12/2,689) females with double sex-chromatin bodies and one chromatin-negative female.³¹ These figures may be compared with those found in the general population (para. 28 below).

26. Sterility is a frequent consequence of chromosome aberration. Males with sex-chromosome abnormalities are almost always sterile.³³ A study of men attending an infertility clinic showed that about 3 per cent of the patients were chromatin-positive.³⁴ Among sixty-eight women with a presumptive diagnosis of primary amenorrhoea, 28 per cent were found to have sex-chromosome anomalies.³⁵

27. Some cases of still birth and abortion are attributable to chromosome aberration. In a survey for sex-chromosome anomalies in still-born children by nuclear sexing, none of fifty-two females was found to be abnormal, but two of forty-nine males were chromatin-positive.³⁶ In two instances of miscarriage the embryos have been shown to be triploid.^{37,38} Here it was possible to culture material from foetal remnants.

28. A general picture of the prevalence of defective traits caused by gross chromosome anomalies is beginning to emerge despite the newness of this field of research. Some specific traits are extremely rare. However, the frequency of Down's syndrome is about 1.5 per 1,000 total births in Europe, North America, and Japan.³⁹⁻⁴¹ Comparative figures from other parts of the world are rather scanty. Current data on the frequency of sex-chromosome abnormalities have recently been summarized.³³ Cases of Klinefelter's syndrome (XXY), or at least karyotypes containing a Y and more than one

X, are relatively common, whereas cases of Turner's syndrome (XO) are rare. Three surveys by nuclear sexing of buccal mucosa, have been made among consecutive live-born. A frequency of 2.65/1,000 (18/6,801) chromatin-positive males was found in the combined data. Chromosome studies of seven of the anomalous cases showed that four were XY/XXY mosaics and three had an XXY complement. The frequency of abnormal nuclear sex among females was 0.90/1,000 (6/6,642).^{30, 42, 48}

29. It is now estimated that about 1 per cent of all live-born have some harmful trait determined by chromosome aberrations sufficiently gross to be detected by present techniques. Many of these individuals are mosaics. Rather more than half of the aberrations are anomalies in chromosome number. The rest are intra-chromosome changes, translocations or combinations of these with numerical changes. Only a small fraction of these aberrations are transmitted to subsequent generations. It is likely, however, that estimates of the frequency of transmissible chromosome aberrations would be greater with more refined techniques since these aberrations, being less gross, are more difficult to detect.

Category II

30. This category includes developmental malformations whose mechanism of inheritance is ill understood. Environment is influential in the aetiology of these traits. Drugs, certain infections, and radiation are known to be teratogenic at critical stages of organogenesis, and maternal (intra-uterine) environmental factors are also known to have a great influence on prevalence. The role of mutation in maintaining the frequency of these traits has not yet been ascertained. They often show some familial concentration, but this fact does not necessarily prove the existence of a genetic component.

31. Some of these malformations may be caused by chromosome aberrations. However, no cytological evidence of this has been found in many of the more commonly-occurring malformations.⁴⁴⁻⁴⁶ It is of course possible that chromosome changes too small to be identified by current techniques are responsible. Alternatively, complex genotypes and unusual environments may be causal factors; it has been suggested that a fraction of congenital malformations are caused by an insufficient degree of such heterozygosity as is necessary to ensure normal development.^{40, 47} However, it is difficult to distinguish between conditions due to individual recessive genes of low penetrance and any that may arise because of a deficiency of heterozygosity at a multiplicity of loci.

32. Many of these traits are detectable at birth. The frequency of live-born so affected is now estimated to be about 1.5 per cent, but is higher if still births are included. At the age of five years, an additional 1 per cent of affected children can be detected.^{40, 48}

Category III

33. In this category have been placed serious "constitutional" disorders in which the mechanism and contribution of inheritance are ill understood.

34. Included here are mental illnesses such as schizophrenia and manic depressive reactions as well as disorders such as diabetes mellitus, pernicious anaemia and some affecting the thyroid gland.

35. There is general agreement about the existence of a major genetic component in these traits and, on occa-

sion, a simple mode of inheritance has been postulated for some of them. However, their frequency in the face of strong selection and their distribution in families are difficult to reconcile with a monomeric hypothesis. As a consequence, simple modes of inheritance are not usually assumed.⁴⁹ Each of these traits is common and prevalent over most of the world. They were collectively estimated in the 1958 report to affect at least 1.5 of all adults, but this estimate is very uncertain.

Category IV

36. This category includes harmful traits which are determined at single loci, but it is highly unlikely that the frequency of the alleles is substantially influenced by mutation.

37. The frequency of these traits tends to be high in localized areas of the world. This high frequency is a consequence of the fact that each of the traits exists as a part of a system of balanced polymorphism; selection pressures maintain the related genotypes in a state of balance. Included in this category are sickle-cell anaemia and thalassaemia. Many other traits, such as fibrocystic disease of the pancreas, probably belong here. On the other hand, a change in environment at some time in the future might remove some traits from the category. Except in certain localized areas in the world, the prevalence of these traits as currently recognized is extremely low. The subject of balanced polymorphism will be discussed in greater detail in a later section (paras. 47-52).

ROLE OF HEREDITY IN PREMATURE DEATH

38. Abortions, still births and neonatal deaths present special problems in a survey of hereditary defects; not only is the frequency of these defects greatly affected by environmental factors, but the role of heredity in their cause is difficult to ascertain because they are not transmitted to the next generation. In consequence, with the exception of those cases known to be caused by gross chromosome aberration, these defects are not considered in categories I-IV. Nevertheless, breeding experiments in animals have shown that simple genetic mechanisms contribute to their incidence. In other instances the additive effects of several genes with slight individual effects may be responsible.

LETHAL AND DETRIMENTAL EQUIVALENTS

39. All the genetic damage within a population is not expressed phenotypically in any one generation. To a large extent, this is because many detrimental traits are partially, if not completely, recessive; complete expression occurs only in the homozygote. The amount of this recessive damage is an important measure of the genetic health of a population. It can be estimated indirectly from a knowledge of the increase in mortality and morbidity observed in the progeny of consanguineous marriages; in these circumstances the hidden genetic damage can be described in terms of lethal and detrimental equivalents. A lethal equivalent has been defined as a group of mutant genes of such number that, if dispersed in different individuals, it will cause one death on the average.⁵⁰ This death occurs with homozygosity. In the same manner, genes leading to visible recessive defects can be defined in terms of detrimental equivalents.⁵¹

40. The procedure outlined above is a powerful tool with which to estimate the amount of recessive genetic damage within a population. However, lethal and detri-

mental equivalents do not represent genes determining any special category of recessive detrimental traits; when expressed phenotypically in the homozygote, the traits may fall in any of the lists of defects in paragraphs 13 to 38. Furthermore, an estimate of the frequency of equivalents does not provide any direct measure of that fraction of genetic damage within a population which is expressed in the heterozygous condition. Nor does a knowledge of the size of the pool of recessive lethal and detrimental genes, by itself, indicate the mechanism by which these genes are maintained in a population.

41. Estimates of lethal equivalents obtained from available surveys are presented in table III. The surveys are of very unequal scope and reliability, the one carried out in Japan being by far the most extensive. In spite of inconsistencies in the results, including some between the two cities in Japan, it seems reasonable to conclude that individuals in human populations carry from two to four lethal equivalents which are expressed, in homozygotes, before the age of twenty to thirty. In addition, each individual carries approximately the same number of detrimental equivalents.

III. The role of mutation in supporting the prevalence of hereditary disabilities

42. Mutation may be broadly defined as any change imposed in the genetic constitution of a cell. In the present annex, mutation is considered in terms of the two fundamental units of heredity, the gene and the chromosome. Natural mutations are generally referred to as spontaneous though in fact it is understood that there are causal factors over which we do not usually have any direct control. One of these factors is undoubtedly naturally-occurring ionizing radiation. Other physical and chemical variations that occur in nature, and the gene complement itself, probably influence mutability.

43. Two mechanisms are involved in maintaining the prevalence of detrimental hereditary traits within a population. One of these is recurrent mutation. The other is direct transmission of the basic genetic faults through successive generations. The role of transmission is generally expressed in terms of genetic fitness of the relevant genotypes, i.e., the number of their progeny which reach maturity. The importance of mutations in human populations cannot be considered independently of genetic fitness because reliable estimates of specific natural mutation rates and of the over-all contribution of mutation to ill health are frequently dependent on accurate information about this fitness.

RELATIVE GENETIC FITNESS

44. The relationship between mutation, genetic fitness, and the prevalence of hereditary disabilities is concisely expressed by the principle which holds that each mutation, whether fully lethal or slightly detrimental, will on the average, result in the death of a descendant or in a failure to reproduce.^{52, 53} The more genetically unfit of these mutations, as for instance dominant lethals, will be eliminated quickly, and occasionally without provoking any suffering or undue hardship on the population. Mutations which have less drastic effects on fitness will usually be transmitted through many generations and their phenotypic effects will be expressed in correspondingly more descendants.

45. Genetic damage can affect the phenotype of individuals in either the homozygous or heterozygous states.

It is known that few dominant diseases and defects are completely dominant and it is becoming increasingly clear that many recessive traits may not be, in fact, completely recessive. This partial dominance can reflect on the genetic fitness of heterozygotes. The effect that even a minor change in heterozygotic fitness may have on the estimated mutation rate required to maintain the frequency of a defect at a constant level can be illustrated with a trait such as phenylketonuria. This trait occurs with a frequency of 25×10^{-6} in the population of England and the genetic fitness of the homozygote is nearly zero.⁵⁴ Under the assumption that the heterozygote has the same fitness as the homozygous normal, a mutation rate of 25×10^{-6} per locus per generation is required to maintain the gene at its present level in the population. If, however, the fitness of the heterozygote is 1 per cent, 2 per cent, or 5 per cent lower, as has been suggested, then the corresponding mutation rates would be three, five and eleven times the previously mentioned rates.^{50, 51, 53} In contrast, if a slight heterozygous advantage is assumed, a very different estimate is obtained; with only a 0.1 per cent or 0.2 per cent advantage in fitness, the estimated mutation rate would be only 4/5 or 3/5 that of the original rate.⁵⁰ With an advantage of 0.5 per cent, mutation would not be required to compensate for the loss of genes due to deleterious homozygotes; in fact, the gene frequency would increase to a higher level.

46. Genetic fitness of heterozygotes cannot be treated as an invariable property of the two alleles under consideration. Rather, fitness can be influenced not only by the remainder of the genotype, as in the intricate situation involved in populations carrying genes for both thalassaemia and glucose-6-phosphate dehydrogenase deficiency,⁵⁵ but also by the external environment. For such reasons an individual estimate of fitness may be valid for the immediate future but less valid when applied over several generations.

47. One of the advances in human population genetics has been the discovery of several balanced polymorphic systems (category IV). The term polymorphism, as used here, describes "the occurrence in the same habitat of two or more discontinuous forms of a species maintained by a balance of selective forces, as opposed to maintenance by recurrent mutation".⁵⁶ Such systems arise when a gene confers reduced genetic fitness in some circumstances and increased fitness in others. The increase in fitness may be a consequence of a shift in the macro- or micro-environment or it may be a consequence of heterozygosity as contrasted with homozygosity. The role of mutation in supporting the frequency of polymorphic traits is minor. To predict the over-all consequences of an increased mutation rate it is therefore essential to know the extent to which balanced polymorphic systems contribute to the burden of detrimental hereditary traits. It is also essential to know what fraction of new mutants are equivalent to alleles that are already part of a polymorphic system.

48. The existence of balanced polymorphism is suspected when excessively high mutation rates must be postulated to maintain the frequency of a detrimental trait under the assumption that the heterozygote is neutral. An example of heterozygous advantage in genetic fitness is provided by sickle-cell anaemia, a trait which is fatal in the homozygote. The distribution of the sickle-cell trait has been investigated over large areas of the world and is very uneven; the trait is completely absent in a number of populations, yet the homozygote

has a frequency of 3 to 4 per cent in some populations of Asia and Africa.⁵⁷ It has now been demonstrated that heterozygous individuals have an increased resistance to malignant tertian malaria and a consequent selective advantage in a malarial environment.^{57, 58} It is likely that other serious haemoglobinopathies, including thalassaemia, are maintained by a similar mechanism. Current world-wide measures to eradicate malaria will have the effect of reducing the genetic fitness of heterozygotes. As a consequence, a reduction in gene frequency is to be expected. However, the rate of reduction will be slow and the trait will continue to be carried for many generations. It has been suggested that the inexplicably high frequencies of some detrimental traits are a consequence of relatively greater genetic fitness of heterozygous carriers at some time or place in the past.⁵⁹

49. The frequency with which balanced polymorphic systems occur in human populations has yet to be determined. Relevant to this problem are two contrasting but not mutually exclusive hypotheses that have been proposed for the construction of extreme models of gene behaviour. One has been termed the classical, the other the balance hypothesis.⁶⁰ Under the classical hypothesis, it is assumed that genetic variability is maintained by recurrent mutation. Furthermore, it is assumed that almost all mutations are unconditionally deleterious and subject to selective elimination; heterozygous advantage is restricted to a small number of loci although it may contribute greatly to existing genetic variability. The balance hypothesis, on the other hand, assumes that genetic variability is to a large extent maintained by heterozygous advantage; mutation may not be unconditionally deleterious and a certain level of heterozygosity is essential to high fitness.

50. Using the concepts of lethal and detrimental equivalents, it is possible to deduce the relative importance of these two models. It has been calculated that an inbreeding depression of such a high degree as has been detected experimentally cannot be expected from systems of balanced polymorphism; this has led to the conclusion that most hereditary defects revealed by inbreeding are maintained by recurrent mutation.⁶⁰ A similar conclusion has also been reached from different evidence; an analysis of the frequencies and modes of inheritance of deaf-mutism, limb-girdle muscular dystrophy and low grade mental defects has suggested that the mean genetic fitness of a population would be impossibly low if the prevalence of these and other traits were not maintained by mutation.⁶¹ On the other hand, in a recent study of two Japanese populations, the detected inbreeding depression was so slight as to indicate that the role of balanced polymorphic systems in maintaining the prevalence of hereditary effects is greater in those populations than in others previously studied.⁶²

51. Investigations with irradiated experimental organisms have also produced conflicting evidence,⁶²⁻⁶⁷ a fact which may well reflect the importance of strain differences and environment in the phenotypic expression of notypes. It is also possible that a variation in frequency of gross chromosomal aberrations with different doses of radiation contributes to differences between results.

52. In the absence of complete information about the role of balanced polymorphic systems it is usually assumed that most of the genetic damage within populations is mutation-maintained; this avoids the risk of derestimating radiation damage. Even if this assumption is incorrect, it is possible that most new mutant

alleles at loci involved in polymorphic systems are unconditionally harmful in contrast to those alleles which support the polymorphic systems in nature. In these circumstances it is important to know the average reduction in fitness of the heterozygote, since this value determines the number of generations over which a temporary increase in mutation rate would be felt by a population. It also determines to some extent the magnitude of the total damage. There is no general information about this value in man. In *Drosophila*, extensive studies have indicated that the average reduction in fitness of heterozygous lethals and semi-lethals is about 2 per cent.^{50, 68} It would probably be larger in poor environmental conditions.^{69, 70}

NATURAL MUTATION RATES AT INDIVIDUAL LOCI IN MAN

53. The frequency of mutation at a locus can only be studied when the mutation determines a specific detectable trait. Mutation is always an uncommon event; a freshly-arisen specific mutation seldom occurs with a frequency of more than one in fifty thousand gametes. It follows that very large populations must be studied to obtain a reliable estimate of this rate.

54. In many respects man is a very suitable organism for the observation of mutation rates because large free-living populations can be defined and close relatives are easily identified. Furthermore, the high efficiency of medical diagnostic procedures renders relatively easy the identification of many traits in man that might be missed in experimental animals. For these reasons, more estimates of natural mutation rates are available for man than for most species other than micro-organisms. There are, however, difficulties in relating traits to specific mutant alleles in man. These difficulties do not arise as frequently in animals, because planned breeding and genetic analysis can be employed.

55. Some of these problems are specific to dominant, some to sex-linked, some to recessive gene mutations, and some are common to all three. Those common to all three derive from the following circumstances:

(a) Certain mutant gene traits are mimicked by phenocopies. These are identical or nearly identical traits determined not by the genotype but by abnormal development in the embryo of foetus *in utero*. However, careful clinical study often serves to distinguish such phenocopies, as for example in the case of certain cataracts, and in cases of congenital deafness;

(b) Certain traits which are difficult if not impossible to distinguish clinically, are sometimes determined by mutations on different chromosomes. For example, ichthyosis vulgaris is determined by an autosomal dominant gene and also by a recessive gene on the X-chromosome;

(c) Some clinically identical traits seem to be inherited as if they were autosomal dominant at some times and recessive at other times. Examples are achondroplasia and a number of degenerations of the choroid in the eye. This variation may be a consequence of mutations to different alleles at the same locus, of mutations at different loci on the same chromosome, or of mutations at loci on different autosomes;

(d) Some traits, though apparently inherited in the same manner, show differences between families which suggest that the causal mutations are different in kind. Although different loci may be involved in these cases, it is conventional to express mutation rate in terms of a

single locus. Such difficulties lead to over-estimates of mutation rates.

56. Precision in the estimation of the mutation rates of genes determining harmful traits in man depends upon the completeness of ascertainment of the character in a large defined population. High precision can only be achieved where the medical and social services for the population are well organized. Even so, complete ascertainment is virtually impossible and can never be assumed as certain. Incompleteness of ascertainment tends to result in under-estimation of mutation frequency.

57. In generalizations of the mutation rates per locus in man one further factor must be considered. If the mutation rate of a gene is very low the trait may arise too infrequently to be recognized as of genetic origin, or even if so recognized, it may not attract study because of the great difficulty of collecting a sufficient number of cases. In consequence, only those traits occurring with a sufficiently high frequency to give a reliable estimate of mutation rate are selected for investigation.

Autosomal dominant traits

58. A direct method is applicable for estimating rates of mutation to dominant traits. This method attempts to identify all cases of a certain trait in the offspring of parents not affected by the trait. If it is assumed that the gene is fully manifested, then each case must represent a mutation in the germ cells of one parent. As each birth results from two gametes, the mutation rate per gamete is one-half the frequency per birth. This method can seldom be employed and can be fallacious if unrecognized phenocopies occur.

59. An indirect method can also be used. This method assumes that an equilibrium has been reached in which the frequency of the trait is more or less constant. At this equilibrium, the number of fresh mutations arising in the population in each generation is approximately balanced by the number of mutations eliminated by selection. The equilibrium equation is $\mu = \frac{1}{2} (1-f) x$, where μ is the mutation rate per gamete per generation, x is the trait frequency in the population, and f is the relative fertility of the individuals bearing the trait. In such an equilibrium the value of f is of great importance. It is, however, difficult to estimate with accuracy. If f is zero then the condition is not recognized as genetic in origin. On the other hand, relative fertility of the affected individuals can be estimated only if it is as low as 85 per cent. As a result, estimates of mutation rate tend to be made for traits with a value of f between 0.0 and 0.8. A number of estimates are listed in table IV.

Sex-linked traits

60. Estimates of the recessive mutation rate at loci on the X-chromosome must be made by an indirect method. The equilibrium equation is $\mu = \frac{1}{3} (1-f) x$. In this case, it is assumed that the fertility of heterozygous females is the same as that of homozygous normal females in the population.

61. The most reliable estimates of mutation rates for a sex-linked recessive gene are those for Duchenne-type muscular dystrophy. However, there is some evidence that even this trait is clinically heterogeneous. In consequence, current estimates may represent the sum of mutations at more than one locus.

62. No reliable estimates of the mutation rate for haemophilia A have been made since haemophilia B (Christmas disease) was identified as a separate entity.

The proportion of haemophilia types A and B varies in different countries. Possibly the older estimates of the mutation rate for haemophilia, if reduced by about one-tenth, serve as reasonable estimates for the locus determining haemophilia A. However, the trait can be so mild that ascertainment is almost certainly incomplete. This tends to produce under-estimates of the true mutation rate. Some estimates are presented in table V.

Autosomal recessive traits

63. Only indirect estimates of autosomal recessive mutation rates can be made and these are of very uncertain reliability. The equilibrium equation is $\mu = (1-f) x$. In man, the value of f is zero or extremely low for the great majority of recessive homozygotes. Exceptions are albinism and some forms of recessive deaf-mutism. Even with these conditions, however, the value of f is not over 0.5. If f has a value of zero then the estimate of mutation rate corresponds to the trait frequency. Here, however, there are many difficulties. It is assumed, as for sex-linked genes, that the fertility of the heterozygote is the same as the average in the population. However, a high proportion of all mutant genes in the population are in heterozygotes. For this reason any selection in favour of or against the heterozygote has a much greater effect on the prevalence of a trait at equilibrium than has the loss due to homozygosis. Furthermore, a shift in the environment can upset the population equilibrium by affecting the genetic fitness of the different genotypes. When this happens, many generations may pass before equilibrium is restored. Again, changes in marriage customs can affect the frequency of different genotypes. A decline in the amount of inbreeding has been noted in Europe during the last century or two; such a circumstance is likely to lead to estimates that are too low.⁷¹ Some estimates of autosomal recessive mutation rates are presented in table VI.

64. In spite of all the reservations, there is a large group of grossly harmful mutations, autosomal dominant, recessive, and sex-linked recessive, whose estimated mutation rates cluster around 10×10^{-6} per generation. However, this clustering may be conditioned largely by the selection of traits for study.

NATURAL MUTATION RATES AT INDIVIDUAL LOCI IN EXPERIMENTAL ANIMALS

65. With experimental animals it is possible to estimate natural mutation rates with methods that involve test matings. In the mouse, the rates of natural visible mutation have been estimated at seven loci. These loci are identified by recessive visible alleles namely: *a* (non-agouti), *b* (brown), *c* (chinchilla), *d* (dilution), *p* (pink-eye), *s* (piebald spotting), and *se* (short ear). The loci are distributed on five of the twenty chromosomes. There is linkage between *d* and *se* and between *c* and *p*. These alleles were selected for various radiation studies and should not be considered a random sample. The over-all mean mutation rate is estimated to be about 7.3×10^{-6} per locus per gamete (table X).

66. Estimated values of natural mutation rates at specific loci in *Drosophila* were discussed in the previous report and in a recent review.⁷²

NATURALLY-OCCURRING CHROMOSOME ABERRATIONS IN MAN

67. Man has a relatively stable karyotype; the diploid chromosome number is forty-six.^{73, 74} Nevertheless,

with the development of improved techniques in mammalian cytology, examples of aberrations already well known in plants and insects are being accumulated. The detection of chromosome anomalies in man is aided by the relative ease with which associated abnormal phenotypes can be recognized. On the other hand, cytogenetic techniques are not yet far enough advanced to permit the detection of less obvious aberrations. Those which are not now detectable include reciprocal translocations of nearly equal size, inversions and either small duplications or small deletions having a length less than 10 per cent that of the affected chromosome. Other aberrations may be undetected because they are lethal at a very early stage in embryo development.⁸⁸

68. The most common of detected aberrations are trisomies of the smaller autosomes and either monosomy or polysomy of the sex chromosomes. It seems likely that monosomy and trisomy of autosomes other than that producing Down's syndrome, are rare or usually lethal.⁷⁶ Triploidy has been detected,^{87, 88, 76} and translocations and other aberrations are frequently reported (tables I and II).

69. Whole-chromosome anomalies may be a consequence of either chromosome loss or "non-disjunction". Monosomy can result from either process, but polysomy is attributable only to non-disjunction. It seems likely that the majority of whole-chromosome aberrations occur in meiotic divisions of a parent or in early cleavage divisions of the zygote. Little is yet known about the relative importance of non-disjunction and chromosome loss during meiosis. However, there is considerable evidence that one or both of these processes frequently occurs in mitotic divisions following fertilization. This evidence is supplied by the existence of mosaics⁷⁸⁻⁸² and of exceptional twins.⁸³ The occurrence of whole-chromosome anomalies during mitosis may be more frequent than present data suggest; mosaicism is not likely to be detected when it does not originate in early cleavage divisions. Moreover, selection pressures may eliminate one of the stem lines. The possibility that the processes leading to mosaicism tend to recur in a cell line is suggested by the fact that two or three types of cells are sometimes present in the growth from a single biopsy of bone marrow or even of skin.⁸⁴

70. For one reason or another, most individuals with hereditary traits caused by gross chromosome aberrations fail to produce progeny. Exceptions so far recognized are those phenotypically normal persons with balanced translocations. The general incidence of such translocations is, however, low. As a consequence, the incidence of gross chromosome aberrations in a population tends to correspond with their mutation rate. For estimates of frequency, see paragraphs 28 and 29 above.

NATURALLY-OCCURRING CHROMOSOME ABERRATIONS IN EXPERIMENTAL ORGANISMS

71. In the mouse, non-disjunction of sex chromosomes has been shown to occur in meiotic divisions. However, non-disjunction in the first meiotic division is rare in the male and possibly non-existent in the female. In contrast to man, XO karyotypes occur much more frequently than XXY karyotypes.⁸⁵ There is evidence that XO individuals most often result from the loss of the paternal sex chromosome some time between sperm entry into the oocyte and the first cleavage. This evidence is based on the observation that when $X^M O$ and $X^M X^P Y$ mice are crossed simultaneously (the superscripts M and P design-

nate maternal and paternal derivations of the X chromosome) the relative frequencies are 0.7 per cent and 0.02 per cent, and on the fact that primary XO's are not randomly distributed.^{86, 87} Deficiencies and monosomies that would have been detected in extensive experiments on certain genetically marked autosomes in the mouse have so far not been found.^{85, 88} Spontaneous translocation has been observed in the rat.⁸⁹

72. In *Drosophila*, maternal non-disjunction and meiotic loss of whole chromosomes from dividing cells both operate to produce abnormal eggs. This information has been deduced from the fact that the frequency of eggs with two X chromosomes is less than that of eggs with no X chromosomes. The frequency of abnormal eggs that arise as a result of non-disjunction has been estimated at 0.08 per cent and the frequency of those arising as a result of meiotic loss of the X chromosome at about 0.12 per cent. This produces an XO:XXY ratio of about 4:1.⁹⁰ There is also a considerable rate of non-disjunction of sex chromosomes in males; the ratio of scored $X^M O$ to $X^M X^P Y$ individuals is 2.8:1.⁹¹ Monosomy and trisomy of the small fourth chromosome occurs spontaneously but non-disjunction or loss of the second and third chromosomes has not been detected by genetic or cytological methods of analysis. It is probable that these events occur but that monosomy or trisomy of long autosomes leads to elimination in embryonic stages.⁹⁰ An early study showed that aging of females by itself has no effect on the natural rate of non-disjunction, although the frequency of non-disjunction following irradiation of virgin females increases through the first ten days.⁹² More recent studies have confirmed that maternal age *per se* has no appreciable effect on the frequency of spontaneous non-disjunction.⁹³ In view of the recognized increase in frequency of Down's syndrome with advancing maternal age⁸⁹ and similar observations on the two other autosomal trisomies,⁹⁴ this observation shows the difficulty of comparing natural chromosomal mutation rates of flies and man.

FACTORS AFFECTING THE FREQUENCY OF NATURAL MUTATION

73. It has long been observed that the frequencies with which natural mutations are found may vary in different circumstances. This variation provides an opportunity to identify and study individual causal or influencing factors. In man, some of these factors can be detected because a relatively long childhood and reproductive span permit the factors to work over a prolonged period of time.

74. With some hereditary diseases and defects it has been observed that mutant frequency among offspring increases with parental age. Such conditions are epiloia, neurofibromatosis and retinoblastoma. This effect of time suggests a simple dependency of mutation frequency on the accumulated dose of the causal factor. Here, by implication, some cumulative influence is involved.⁹⁵ In other conditions, such as Down's syndrome, an increase in mutant frequency accompanies rising maternal age but not rising paternal age. Again, a contrasting situation holds with achondroplasia, where the increase in the occurrence of the anomaly is associated only with rising paternal age. Each of these latter examples suggests the presence of influencing factors which are not common to both sexes. Thus, when paternal but not maternal age affects mutant frequency, a dependence of mutation on frequency of cell division in gametogenesis may be involved.

75. A number of factors are known to affect natural mutation frequency in experimental organisms. One of the most studied of these is sex; the spontaneous mutation rate to sex-linked recessive lethals is apparently lower in females than in males of *Drosophila*.^{95, 96} An effect of sex on mutation frequency in the silkworm has been noted. Here locus specificity is a factor; at one locus the frequency of mutation is higher in the male, at another it is lower.⁹⁷ In the mouse, the data on seven loci under detailed study provide some indication that mutation frequency is lower in females than in males (table X). Females have yielded one mutant among 98,828 offspring. In contrast, males have yielded thirty-two mutants among 544,897 young. However, in man, a study of mutation to the sex-linked trait, Duchenne-type muscular dystrophy, has provided no evidence of a sex difference.⁹⁸

76. Genetic constitution can also affect the frequency with which naturally-occurring mutations are found. A number of specific genes in *Drosophila* have long been known to modify the natural mutation rate by a factor of ten or more over at least a segment of the entire genome.⁹⁹ A difference between two geographical races in the frequency with which sex-linked lethals are produced has been demonstrated.¹⁰⁰ In addition, there is no doubt that the mutation rate varies with different loci. The mutability of a gene is also affected by its position in the chromosome.^{827, 828}

77. In man, tendencies towards diverse chromosome aberrations in the same individual and towards familial occurrence of diverse chromosome aberrations have been noted. For example, cases of Down's syndrome (trisomy 21) and Klinefelter's syndrome (XXY) in the same individual have been described.¹⁰¹⁻¹⁰⁵ Associations of XXY with a translocation between chromosomes 14 and 15¹⁰⁶ and of XXX with trisomy 18¹⁰⁷ have been reported. Trisomy for the 13-15 group and an XO constitution has been noted in two sisters.¹⁰⁸ Trisomy 21 has been reported in the progeny of a female carrying an autosomal translocation.¹⁰⁹ Such clustering of gross chromosome aberrations has led to the suggestion that the cells of some individuals may be labile in this respect,²¹ or that the occurrence of a first aberration predisposes the chromosomes of a cell towards a second.⁸⁴

78. There is evidence that natural mutations occur at different rates in cells in different stages of gametogenesis. Relevant investigations in *Drosophila* have recently been reviewed.⁷² Some loci are more mutable in the germ line than in the soma, while for others the reverse applies.¹¹⁰

79. No doubt other as yet unrecognized influencing factors exist. For instance, a significant increase in the frequency of sex-linked recessive lethal mutations has been reported in each of two strains of *Drosophila* as a consequence of space flight.¹¹¹ Similar circumstances are also reported to result in an increased frequency of chromosome anomalies (non-disjunction) in germ cells of *Drosophila*.¹¹² The intensity of cosmic radiation during flight was insufficient to account for these phenomena, and an influence of some other factors must be suspected.

80. It has been hypothesized that the genetic response of a species to the factors influencing mutation rate is itself modified through selection. This concept presupposes the existence of an optimum mutation rate for survival of a species;¹¹⁸⁻¹¹⁹ if the mutation rate is too high the species may be crushed under a heavy mutational load and if it is too low the species may not be able to adapt to

environmental changes. This concept has been formulated as a mathematical model by introducing what is called the principle of minimum genetic load.¹¹⁶ A species must adapt itself to progressive changes in the environment and the ability to do so comes from genetic variation, the ultimate source of which is mutation. The importance of new mutation for the future adaptation of the human species is problematical.

IV. The induction of mutation by radiation

81. For obvious reasons, most of our information on the induction of mutation by radiation comes from experimental organisms. However, there is ample evidence that the mutation process is fundamentally similar in all forms of life and there is no reason to suppose that man is exceptional in this respect.

FACTORS AFFECTING THE FREQUENCY OF RADIATION-INDUCED MUTATION

82. The genetic hazards to populations cannot be determined in the absence of a knowledge of the relationship between frequency of mutation and dose of radiation. It is now well recognized that many factors can influence this relationship. The foundation for our knowledge in this field was laid through investigations with *Drosophila*. More recently, studies with mammals have yielded significant information.

Linearity of the dose-effect relationship and absence of a threshold

83. The assumption of a linear dose-effect relationship down to zero dose, and thus of an absence of threshold for mutagenic effects has been considerably strengthened by the results of investigations with *Drosophila*. Studies of mutations at more than fifty loci which affect minute bristles have indicated that acute doses as low as 5 r have a significant mutagenic effect and that the dose-effect curve is linear from lower to higher doses.¹¹⁷ A linear relationship in the low dose range down to 5 r has also been found for radiation-induced recessive lethals.¹¹⁸ However, in germ cell stages such as spermatogonia and oöcytes, where the repair of some of the pre-mutational damage is possible, the effect at low doses may turn out to be somewhat less than expected on a linear basis from the mutation frequency at high doses.¹¹⁹ A departure from linearity has been found for mutations induced with high doses of acute radiation in mouse spermatogonia. A dose of 1,000 r produced significantly fewer mutations than expected on the basis of linearity with results at lower doses.¹²⁰ The view that this effect might be due to cell selection gains some support from the finding that fractionation of the dose gave a higher mutation rate which was consistent with linearity.¹²¹ In *E. coli*, evidence of a linear relationship down to doses as low as 8.5 r has been presented.¹²²

The dose-rate effect

84. The rate of delivery of ionizing radiation has now been demonstrated to affect the frequency of mutations induced by a given dose. This has been shown for both mice and insects.

85. In mice, the effect of differences in dose-rate on the frequencies of mutations induced at seven specific loci has been studied.^{119, 121, 123-127} It has been observed that (table X):

(a) When spermatogonia are exposed to doses of 300-600 r at a rate of 8.5×10^{-3} r/min (90 r/week), the frequency of induced mutations is less by a factor of about four than is the frequency following the same dose delivered at a rate of 90 r/min;

(b) There is an even more pronounced dose-rate effect in parallel studies of irradiated oocytes;

(c) The dose-rate effect for spermatogonia is not demonstrably greater when the lower rate of delivery is reduced from 8.5×10^{-3} r/min to 1×10^{-3} r/min;

(d) Most of the dose-rate effect in spermatogonia is displayed within the range of 24 r/min and 0.8 r/min, whereas in females the range of effectiveness appears to be greater;

(e) As in *Drosophila*, no dose-rate effect is evident in spermatozoa.

86. In *Drosophila* a significant dose-rate effect on ethal mutations in chromosome II has been reported with irradiation of oögonia¹²⁸ and spermatogonia.¹²⁹ In spermatogonia, a lowering of the intensity from 0.10 r/min to 0.01 r/min at a total dose of 200 r results in a significant reduction in mutation frequency. However, a dose-rate effect for contrasting doses of 2 r/min and 000 r/min at a total dose of 3,000 r gamma radiation has not been observed. In the silkworm there have been found two different types of dose-rate dependence of mutations affecting egg colour and induced during early larval development.⁹⁷ In one type the mutagenic effectiveness of chronic irradiation at 0.15 r/min is lower than that of acute irradiation at 320 r/min, and in the other the mutagenic effectiveness is higher with chronic irradiation than with acute irradiation. The former is observed only in the very young larval stage when primordial cells are prevalent in the gonads, whereas the latter is found when germ cells are irradiated in later stages of development. This latter result, which is opposite to the expected effect of dose rate, may not be a dose-rate effect on the mutation process, for it is suspected that cell selection is influencing the yield of mutants at the high dose rate. In any case, it resembles an effect observed at a high dose rate in the mouse, where a dose of 1,000 r gave fewer mutants than a dose of 600 r.¹²⁰ Cell selection was invoked to account for this odd result also. In the chalcid wasp *Albomimus* no significant dose-rate effect on mutations affecting eye colour has been found when female larvae receive a total dose of 1,000 r at 1,000 r/min and at 0.17 r/min.¹³⁰

87. Although some of the factors that affect the dose-rate phenomenon have been uncovered, investigation has not yet proceeded far enough to elucidate the mechanism involved. Nevertheless, there is strong evidence that it is the mutation process itself which is affected. Thus, cell selection, which may at times play a role, can, in some specific instances, be eliminated as the causal factor. For example, the effect is observed in those mouse oöcyte cycle stages in which cell-killing by the doses of radiation used is negligible.^{119, 121} Furthermore, the amount of spermatogonial killing induced by radiation is approximately constant over a range of dose rates in which the dose-rate effect on mutation is evident.^{125, 131, 132} If the mechanism for the dose-rate effect does indeed involve the mutation process itself, then it seems likely that some form of "repair" of pre-mutational damage must be taking place at the lower dose rates.¹¹⁹ It has been suggested¹³³ that many of the mutations observed at the *h* loci under study may be a consequence of multi-hit chromosomal aberrations which would be expected to occur with reduced frequency at low dose rates.^{134, 135}

However, there are several lines of evidence, including the shape of the dose-effect curve, that suggest that, although multi-hit aberrations are easily induced by radiation in mouse spermatozoa, the specific-locus mutations induced in mouse spermatogonia are almost never associated with such multi-hit effects. Most mutations in *Drosophila* spermatogonia also appear not to be a result of multi-hit aberrations. This evidence supports the view that the specific-locus mutations induced in spermatogonia of the mouse are point mutations or extremely small deficiencies,^{88, 136, 137} and that it is repair of the pre-mutational damage associated with this type of mutation that is involved in the dose-rate effect.¹²⁷ Current investigations in other organisms confirm the existence of processes of natural repair or elimination of pre-mutational (primary) damage at low dose rates. The subject of repair will be discussed in detail in the next section.

"Repair" of pre-mutational damage

88. Studies of a variety of organisms have indicated that the process of induction of mutation is not irreversibly fixed at the time of irradiation, but that there is a limited interval between the absorption of radiation energy and the completion of the mutation process during which, depending on the physiological state of the cells, modification of pre-mutational damage is possible. Repair of broken chromosomes by restitutional unions of the breakage ends has been known for a long time and has been studied in some detail. The subject has recently been reviewed.¹³⁸ Though there are some reasons to think that restitution and recovery from pre-mutational damage are separate though analogous phenomena, this distinction has not been established by experimental means.

89. In *Paramecium*, post-irradiation treatments are known to alter the extent of recessive damage from a given radiation exposure, provided they are applied before a certain critical stage has been reached in the subsequent division cycle. Moreover, in cells not receiving post-irradiation treatment, the effect of irradiation is increased the later it is administered prior to that critical stage.¹³⁹⁻¹⁴¹ It was shown earlier that a large fraction of the mutational effect of exposure of bacterial cells to ionizing radiation can be reduced by post-irradiation treatment with chemical reagents in certain circumstances.¹⁴² A similar pattern of results has been observed when investigators have worked with UV instead of ionizing radiation.¹⁴³⁻¹⁵⁰ It now appears that all these results are consistent with the hypothesis that the terminal event for fixation of some major part of the potential mutation corresponds to the first post-irradiation replication of DNA.^{144, 147, 148, 151}

90. Recent data obtained with *Drosophila* show that modification of pre-mutational damage is possible in spermatids, meiotic stages, and late spermatogonia.¹⁵²⁻¹⁵⁷ In cells with peak sensitivity, spermatids and spermatocytes, post-treatment with cyanide following exposure to X-rays at a high dose rate may lead to either an increase or a decrease in radiation-induced mutation frequency. Inhibition of oxidative respiration by means of post-treatment with nitrogen causes an increase in mutation frequency in spermatids, meiotic stages, and spermatogonia. On the other hand, fractionation of a dose given at an intensity of 55 r/sec results in a decrease of the mutation frequency in exactly those stages where cyanide is effective. Inhibition of protein synthesis by means of pre-treatment with either chloramphenicol or ribonuclease leads to a significant reduction in the frequency of mutation in spermatids, and in the case of chlorampheni-

col, in the earlier stages as well. Since a ring-shaped X chromosome has been used in such experiments, the reported changes refer to lethal gene mutations and possibly to small deletions. These results have been explained by assuming that, in analogy to the findings in *Paramecium*, two contrasting processes are involved, one associated with the rate of disappearance of pre-mutational damage, the other with the time or rate required for its fixation.¹⁴¹ Thus, the enhancement of mutation frequency after post-treatment with nitrogen is thought to result from an inhibition of the metabolic repair process. On the other hand, the reduced mutation frequency observed after pre-treatment with both chloramphenicol and ribonuclease suggests that inhibition of protein synthesis prolongs the time-span available for repair of pre-mutational damage. Although it is not known at present what process is involved in fixation of pre-mutational damage in spermatids, the reported findings suggest a correspondence of repair mechanisms in such widely different organisms as *Drosophila* and *Paramecium*.

91. The interaction of oxygen and X-rays in the production of genetic damage, as detected in the progeny of irradiated males of *Drosophila*, has been studied extensively.¹⁵⁸⁻¹⁶⁶ Dose-fractionation experiments, in which part of the dose is delivered in nitrogen and part in air or oxygen, indicate that X-irradiation destroys a protective oxygen-sensitive system. It has been variously postulated that this system acts to reduce the initial amount of damage and that it acts to increase the amount of repair. The system affects both recessive lethals and chromosome aberrations.

92. Table VII summarizes some of the phenomena and material studied both before and since the drafting of the Committee's 1958 report. The similarity of the effects observed is striking, considering the wide range of organisms observed. From these data it can be concluded that a proportion of radiation-induced mutational or pre-mutational changes are subject to natural repair for a finite but relatively brief period after they occur, and that the natural repair process itself is subject to interference by radiation and by metabolic inhibitors. It is important to determine whether this effect is applicable to man, and if so, the single dose-levels or continuous dose-rates at which the natural repair processes are effective, and the critical period of time and the circumstances under which they act. It is emphasized that probably not all pre-mutational damage is reparable and that a linear dose-mutation relationship independent of dose-rate is to be expected at low doses which do not appreciably affect the repair process.

Locus specificity

93. Both the natural and induced rates of mutation have long been known to vary markedly at different loci in various organisms. This observation has now been firmly established in the mouse.^{88, 158} Among the seven loci under study, the lowest and highest rates for mutations induced in spermatogonia differ by a factor of thirty. This information is based on 174 mutations induced with doses of 300-1,000 r and high-dose rates. Of these, seventy-one mutations were induced at locus *s*, ninety-nine were induced among the four loci, *b*, *c*, *d* and *p*, and only four were induced at the two loci, *a* and *se*. Ninety-two of the mutations were analysed for viability of the homozygotes. Seventy-one (77 per cent) were lethal prior to maturity and twenty-one were viable. There was some variability among the seven loci in this respect also. All the twelve mutations at the locus *d* and

all thirty-eight at the locus *s* were lethal. In contrast, of those at loci *b*, *c* and *p*, twenty out of thirty-eight were viable.

Sex and stage of gametogenesis

94. The frequency of radiation-induced mutations can be influenced both by sex and by stage of gametogenesis. The cell stages of greatest importance in determining radiation hazards to man are the oöcyte and spermatogonial, and the genetic effect of ionizing radiation on these stages of the germ cells of mammals has received considerable attention.¹⁶⁸⁻¹⁶⁸ The most extensive investigations have been concerned with the mouse.

95. Male mice irradiated with doses as high as 1,000 r maintain their fertility briefly, and then undergo a period of sterility. Near-normal fertility is then resumed. The temporary sterility is a consequence of the fact that certain spermatogonial stages are extremely sensitive to irradiation.^{169, 170} Cells in these stages have an LD₅₀ of 20 to 40 r. However, a few of the early type A spermatogonial cells survive high radiation doses; these cells repopulate the germinal epithelium and are responsible for the resumption of fertility of the irradiated animal. The existence of the sterile period aids in distinguishing between genetic effects induced in spermatogonial and post-spermatogonial stages.

96. Irradiation of female mice with doses as low as 50 r can result in permanent sterility after an initial period of post-irradiation fertility. A dose-rate effect on this induced sterility has been detected.¹⁷¹ The permanency of induced sterility is attributable to the fact that the majority of oöcytes are in early stages of follicular development, and are extremely sensitive to radiation. Since there is no new formation of oöcytes in the adult mouse ovary, sterility sets in when the supply of radio-resistant oöcytes in older follicles is exhausted.

97. It has been possible to distinguish two kinds of radiation-induced cell death in different types of germ cells in mouse gonads. Most spermatogonia die immediately after irradiation, while spermatocytes show no response until they reach the meiotic divisions. In both cell types, chromosome damage in the classical sense of aneuploidy can, at most, account for only a small part of the cell loss.¹⁷² A similar situation has been found in the rat-kangaroo.¹⁷³ These studies suggest that chromosomal damage is a minor cause of cell death in spermatogonia irradiated with moderate doses. The subject of the radio-sensitivity of the gonads is treated more fully in annex D.

98. Peak sensitivity to the induction of dominant lethals and recessive visibles in the mouse has been found in spermatids and spermatocytes¹⁷⁴⁻¹⁷⁸ for the male, and metaphase primary oöcytes for the female.¹⁷⁹ With an acute dose of 300 r of X-rays, the mean frequency for mutations at specific loci following irradiation of post-spermatogonial stages is twice that induced in spermatogonia.¹⁷⁸ It has also been shown that exposure of adult females to an acute dose of 200 r of X-rays results in more mutations than a similar exposure of 17½ day old foetuses. In males the induced-mutation frequency has also been observed to be higher in adults than in foetuses, but the difference is not statistically significant.¹⁷⁶

99. The ratios of induced mutation frequencies at the seven loci under study in mice differs with irradiation of spermatogonial and post-spermatogonial stages.^{88, 168} Deficiencies large enough to involve both the *d* and *se* loci (with cross-over value of 0.16 per cent) are common among the mutations induced in post-spermatogonial

cells, but irradiation of spermatogonia yields such deletions only with extremely low frequency, if at all. Such deficiencies are, however, induced in oocytes. It thus seems that mutations contributed to progeny as a result of spermatogonial irradiation differ systematically from those due to post-spermatogonial and oocyte irradiation.

100. In *Drosophila*, the influence of sex and stage of gametogenesis in radiation-induced mutations is well documented.^{72, 180, 181, 829} The lowest and highest frequencies of induced mutation for a given radiation dose vary by a factor of fifteen. Spermatogonia and oögonia are the least sensitive; oocytes are somewhat more sensitive than oögonia. In contrast, spermatocytes and spermatids are several times more sensitive than spermatogonia. Spermatogonia vary in sensitivity depending on their stage of maturity. The difference in radio-sensitivity between *Drosophila* sperm and spermatids is attributable both to differences in O₂-tension^{164, 182-186} and to changes associated with protein synthesis.¹⁵⁸⁻¹⁵⁹

Species specificity

101. Species differ widely in their genetic sensitivity to radiation. The induced rate of mutation at the seven loci studied in mice is about fifteen times that for a comparable group of loci in *Drosophila*.¹⁸⁷ Comparisons of dominant lethals in mammals and *Drosophila*¹⁸⁸ and of chromosome mutation in plants¹⁸⁹ have likewise indicated the existence of species specificity. Radio-sensitivity in different species of rodents has been determined in terms of the number of chromosome rearrangements in the nuclei of spermatogonia exposed to a low acute dose of 4 r.^{190, 191} Such measurements are difficult to make because the frequency of chromosome breakage varies greatly in different cell stages, a fact which can lead to the confounding of species and cell-stage differences. Nevertheless, the percentage of cells with rearrangements has been reported to vary from 2.6 in guinea pigs to 0.6 in rats, 0.2 in mice, and 0.1 in rabbits. A comparison of the cytogenetic radio-sensitivity of germ cells of the monkey and mouse at doses from 50 to 400 r has suggested that sensitivity of monkeys is twice that of mice.^{188, 192}

INDUCED CHROMOSOME ABERRATIONS

102. Because some serious hereditary defects in man have recently been found to be associated with chromosome aberrations, the role of ionizing radiation in producing these anomalies will be considered in detail. The fact that radiation can cause extensive chromosome changes has been known for many years; investigations in plants¹⁹³ and in animals⁹⁰ have been reviewed in detail. Actually, it is not always possible to make a sharp distinction between gene mutation and chromosome aberration. Minute chromosome aberrations often cannot be distinguished from gene mutations. Furthermore, rearrangements of chromosome segments sometimes involve "position effects" in which the phenotypic expression of genes is altered.⁸⁶

Observations on experimental organisms

103. One of the most suitable organisms for studies of induced chromosomal changes is *Drosophila*; in this organism small chromosome changes can be detected cytologically by examination of salivary gland chromosomes. Furthermore, detailed information on the linear sequence of specific loci is available. Although observations made with this organism cannot be used for direct extrapolation to man, they nevertheless serve as a useful

guide to those effects which might be expected. They are briefly summarized here.

104. Most of the *Drosophila* information has been obtained through irradiation of spermatozoa. Aberrations are detected in either the first or subsequent generations following irradiation. Cytological as well as genetic techniques can be used for this purpose.

105. Viable aberrations resulting from chromosome breakage include duplications, deficiencies, and intra- or inter-chromosome rearrangements. The ability of individuals with deficiencies or duplications to survive this aneuploidy depends upon the length and genic content of the segments involved. Both duplications and deficiencies upset genic balance, and tend to lower viability and to be transmitted as recessive lethals. Viable intra- and inter-chromosome rearrangements include inversions and transpositions of segments within chromosomes, as well as translocations between chromosomes. These aberrations do not involve aneuploidy, and affected individuals are phenotypically normal if "position effect" is not involved. However, their progeny may be genetically normal, or again contain the balanced rearrangement, or be aneuploid.

106. At low doses, the frequency of individuals with aberrations caused by single breaks tends to increase linearly with dose. In some instances it has been noted that small intercalary deficiencies also increase linearly with dose. The frequency of individuals with aberrations caused by two breaks, such as inversions and translocations, increases more rapidly than the first power of the dose, approaching the second power of the dose at lower levels of treatment.

107. Whole-chromosome aneuploidy in *Drosophila* is also caused by ionizing radiation. The induction of primary non-disjunction was first reported in 1921.^{194, 195} Using irradiated females of *Drosophila virilis* it has been demonstrated that there is a linear increase in the occurrence of primary XO males in the dose-range 400-1,200 r, and that the induced rate of occurrence of XO males is approximately $1 \times 10^{-5}/r/egg$.^{196, 197} The rate of occurrence of XO males is approximately fifteen times that of XXY females. The ratio of XO:XXY flies is thus greater than the naturally-occurring ratio which is about 4:1. More recently a similar investigation has been carried out with *Drosophila melanogaster*.⁹⁸ With exposure to doses of 600 r, 2,400 r, and 3,600 r, the frequency of non-disjunctional males increased at a rate of approximately $2.5 - 3.0 \times 10^{-5}/r$. Non-disjunctional males were more frequent than non-disjunctional females by about one order of magnitude.

108. In mice, gross chromosomal anomalies are rarely found as a consequence of irradiation of parental pre-meiotic germ cells. This rarity has sometimes been attributed to failure of transmission rather than to lack of occurrence. However, for at least two types of chromosomal aberrations, reciprocal translocations and deletions, this explanation does not seem to be correct. Translocations induced in post-meiotic stages can be transmitted through subsequent meioses to become heritable traits.¹⁹⁸ Thus, a more likely explanation for the rarity of these aberrations following pre-meiotic irradiation is either that the necessary chromosome breaks do not occur or that the broken parts do not exchange. The same situation exists for deletions. An exhaustive study of what appear to be deletions in the *d-se* region of linkage group II in the mouse has shown that these are produced as a consequence of post-spermatogonial and

oocyte irradiation, but not of spermatogonial irradiation.⁸⁸ Transmission of the induced deletions ranges from poor to normal or near normal. Since transmission is possible, it is apparent that either lack of breakage or rejoining is responsible for the non-appearance of the deletions following spermatogonial irradiation.

109. Some types of chromosomal damage are, however, produced with high frequency by irradiation of spermatogonia. Many abnormal anaphases have been found in spermatogonial cells of monkeys two years after exposure.¹⁹⁸ More recently, cytological evidence of chromosome damage in irradiated spermatocytes has been noted at the first post-irradiation cell division in mice.¹⁷² Those particular types of aberration probably cause cell death before maturation of the gametes. However, a recent report suggests that structural changes induced in pre-meiotic germ cells can occasionally be transmitted to progeny.¹⁹⁹

110. Data on the induction of whole-chromosome changes in the mouse are at present largely restricted to sex-chromosome changes. Experimental work in this field has developed rapidly in recent years.⁸⁵ The availability of useful sex-linked marker genes and improvement in cytological techniques have contributed to this progress. The sex-determining mechanism of man has recently been shown to be much more similar to that of the mouse than it is to that of *Drosophila*.

111. In mice, irradiation of sperm increases the frequency with which paternal sex-chromosomes are lost: 1.3 per cent of progeny suffered such a loss after a dose of 600 r as compared with 0.1 per cent in the control.^{200, 201} However, the bulk of spontaneously occurring XO individuals are believed to arise from events following sperm entry into the vitellus.^{85, 202, 203} Irradiation of the zygote in the interval between sperm penetration and the first cleavage is particularly effective in inducing loss of a sex chromosome. Thus, 100 r yielded 5 per cent XO individuals as compared with 1 per cent for controls. Both maternal and paternal losses can be induced by radiation, whereas only paternal losses have occurred in the controls. No autosome loss has been detected in these experiments in which four and in some cases five autosomes carried genetic markers. This suggests that such losses, if they occur with an appreciable frequency, are lethal.

112. Extensive investigations of the *in vitro* cytogenetic effects of radiation on mammalian somatic cells have been undertaken. Although from the point of view of heredity the important chromosomes are those of the germ cells, these studies of the radio-sensitivity of somatic cells provide a direct method for determining the effect of radiation on chromosomes. It is to be expected that they will play an important role in the future. Measurements are usually based on the frequencies of aberrations detected at the first post-irradiation cell division because many types of aberration are lost in subsequent divisions. Commonly-used mammals include the Chinese hamster,²⁰⁴⁻²⁰⁹ the mouse²⁰⁷⁻²⁰⁹ and the monkey.²⁰⁶

113. Most of the previously known types of aberrations have been detected in these investigations. Breaks are of the chromatid or chromosome type depending upon whether the chromosomes are effectively double at the time of irradiation. Data on the frequency of breaks are not always in good agreement and it is apparent that one of the influencing factors is the method by which cells are cultured. Nevertheless reproducibility of results is good under standard conditions.

114. As is to be expected, terminal deletions increase linearly with the dose but total breakage occurs more fre-

quently than the first power of the dose.²⁰⁰ At low doses a measure based on linearity is of practical use but a more accurate measure of damage is the "coefficient of aberration production".²¹⁰ Values for chromatid aberrations in *in vitro* cultures of epithelioid-type cells of monkeys and Chinese hamsters have been found to be in general agreement with those for *Tradescantia* microspores.²¹¹

115. With experimental mammals it is possible to compare the *in vitro* and *in vivo* rate of induction of visible chromosome aberrations. Somatic cells cultured *in vitro* frequently have a much higher spontaneous mutation rate than do *in vivo* cells.²¹² However, investigations with Chinese hamsters and with monkeys indicate that the radiation-induced aberration rate of epithelioid-type cells cultured *in vitro* is not greatly different from that of rapidly dividing cells *in vivo*.^{205, 206}

Observations on human cells

116. No measure of the radiation sensitivity of human germ cells has yet been made. Nor have extensive quantitative measurements been made of chromosomal damage induced in somatic cells of individuals. However, it has been clearly shown that chromosomal aberrations are produced.^{46, 212-216} This subject is dealt with in annex D, paragraphs 155 to 158.

117. The effect of ionizing radiation on chromosomes of human cells cultured *in vitro* has received considerable attention in recent years.^{206, 217-223} As with experimental mammals, data on the frequency with which breaks occur are not in good agreement. For epithelioid-type cells the observed rate at metaphase is about 0.3/cell/100 r^{206, 211} but for "fibroblasts" the rate is about 2/cell/100 r.^{218, 220} The frequency of chromosome breaks has been reported to be 0.9/cell/100 r for fibroblast-type cells²²⁰ and 2/cell/100 r for leucocytes in freshly-drawn human blood.²²¹ The coefficients of aberration production for chromatid breaks in epithelioid-type cells *in vitro* and for chromosome breaks in leucocytes are in remarkably good agreement with those for *Tradescantia* microspores and for chromatid breakage in epithelioid-type cells of the monkey and Chinese hamster.²²²

COMPARABILITY OF RADIATION-INDUCED AND NATURALLY-OCCURRING MUTATIONS

118. Mankind has long been exposed to natural radiation and it is to be expected that an increase in the level of exposure would not result in any mutations which have not occurred in the past. Nevertheless, natural radiation is only one of the causes of "spontaneous" mutation and it is therefore possible that there may be differences between the spectra of radiation-induced and naturally-occurring mutations.

119. Evidence concerning the comparability of the two sorts of mutations was presented in the Committee's last report.²²⁴ Most of this information came from studies with lower organisms and suggested that, in general, mutations induced by ionizing radiation are similar in kind to those of natural origin.

120. There is evidence that in *Drosophila* the radiation-induced and natural rates of sex-linked recessive lethal mutations are similarly affected by sex and stage of gametogenesis.⁷² Close correspondence between induced and spontaneous mutations is not found, however, in mice.¹³⁷ Furthermore, in mice loss of the maternal X chromosome can easily be induced by irradiation but spontaneous maternal loss is very rare.⁸⁵ There is also

very good evidence from *E. coli* that the natural mutabilities of loci are sometimes not correlated with their radiation-induced mutabilities.¹²²

V. Effects observed in descendants of irradiated populations

INDUCED MUTATIONS IN THE IMMEDIATE PROGENY OF IRRADIATED HUMANS

121. Direct observations of the genetic consequences to man of exposure to ionizing radiation are now limited to observations of first-generation offspring. Such surveys can be expected to detect only autosomal dominant or sex-linked gene mutations and chromosome aberrations. Among the difficulties of such inquiries are those of estimating the gonad doses actually received by parents, and the small absolute and relative increases to be expected in the frequency of traits determined by such mutations.

122. In these surveys, the data are usually concerned with such matters as abortion, still birth, neonatal death, congenital malformation, and shifts in the sex-ratio of progeny. Results frequently indicate a detrimental effect of radiation but this is seldom statistically significant. One study detected a significant effect of radiation on the frequency of congenital malformations in the progeny of irradiated individuals but interpretation is hampered by the incomplete response to the questionnaires used.²²⁵ Another similar study failed to show this effect.²²⁶ The most extensive survey was carried out in the Japanese cities of Hiroshima and Nagasaki following the atomic bombings; data were collected on more than 30,000 offspring of irradiated parents and on a comparable control group.²²⁷ Observations were made of still births, neonatal deaths, birth weight and congenital malformations. Analysis of these data failed to detect a significant effect of radiation on either the frequency of early death or congenital malformations. It did, however, detect a significant shift in the sex-ratio of immediate progeny. More recently, an analysis of the same data by an independent investigator has produced statistical significance of radiation effects for some other categories of defects and also for over-all early death of progeny.^{228, 229}

123. The comparatively high frequencies of Down's and Klinefelter's syndromes permit the effect of parental radiation on the incidence of these defects in offspring to be studied with relatively little effort. Three such investigations have already been reported. In one of these the radiation history was obtained of the mothers of eighty-one children with Down's syndrome, ninety-one children with cleft lip and seventy-one children with no defect. A possible association between maternal irradiation and Down's syndrome was indicated.²³⁰ However, results of the other two investigations, one of which involved fifty-one patients with Down's syndrome and fifty-one controls,²³¹ the other 197 patients and 197 controls,²³² were completely negative.

124. A survey of the incidence of congenital malformations in different regions has indicated that higher incidences are associated with geographical areas with high background radiation.²³³ Another survey has reported that the frequency of malformation varies with the magnetic latitude to which is related the cosmic-ray energy flux.²³⁴ However, it is difficult to prove that natural radiation is the direct influencing factor.

125. A shift in the proportion of male offspring of irradiated individuals has been considered one of the best

available methods for detecting induced genetic damage in humans and for estimating its extent. Six such studies have been reported.^{225, 227, 235-238} In interpreting the results, the effect of maternal irradiation is more appropriately considered independently of the effect of paternal irradiation. The effect of maternal irradiation on the proportion of male offspring is summarized in table VIII. A consistent reduction in proportion of male offspring has occurred following maternal irradiation. In terms of the simplest genetic interpretation, this can be attributed to the induction, in irradiated women, of sex-linked recessive mutations having a lethal effect on the foetus. The effect of paternal irradiation is summarized in table IX. These latter data are not amenable to a single interpretation; the proportion of male offspring is apparently increased with higher doses, but, in at least some instances, reduced with low doses. The former effect is interpretable in terms of the induction of dominant sex-linked lethals. However, the validity of such a simple genetic interpretation has been questioned on the grounds that the Y chromosome cannot be considered genetically inert.²³⁹ In addition, the induction of XO and XXY karyotypes may also affect the relative frequency of male and female offspring. Furthermore, explanations based on the assumption that the effect on sex ratio is due to damage to sex chromosomes cannot be accepted without reservation. For instance, the drop in proportion of males which has sometimes been noted could be attributed to autosomal mutations which further increase the existing higher mortality of males. The occasionally erratic control values must also be considered in any interpretation.

INDUCED MUTATIONS IN THE IMMEDIATE PROGENY OF IRRADIATED MAMMALS

126. By means of properly controlled experiments it is possible to detect induced dominant mutations in the immediate progeny of irradiated mammals. Current information has been obtained principally from mice. In mammals it is particularly difficult to distinguish between gene mutations and minor chromosomal changes. Reduction in litter size, following irradiation of spermatozoa or oocytes, is most plausibly explained in terms of the induction of chromosome aberration, although gene mutations may also be involved.

127. Spermatogonial cells and oocytes are of greatest concern in a consideration of radiation hazards. Oocytes are not replenished, and it has been shown that there is no significant change in mutation rate with time after irradiation of spermatogonia.²⁴⁰ Irradiation of spermatogonia has much less effect on litter size than does irradiation of later germ-cell stages. This no doubt reflects a drastic reduction in frequency of gross chromosome aberrations. For instance, individuals with deficiencies involving more than one gene locus are commonly found after irradiation of post-spermatogonial cells but irradiation of spermatogonia yields such deletions only with extremely low frequency, if at all. These aberrations do occur, however, among progeny produced after irradiation of oocytes.^{88, 137}

128. The fact that dominant detrimental mutations are induced and transmitted after irradiation of post-spermatogonial stages has been demonstrated by a shortening of the life span in the offspring of male mice exposed to neutrons.²⁴¹ In another study, a significant increase in certain types of skeletal abnormalities was found in the first-generation descendants of irradiated male mice.²⁴² Evidence that some dominant lethality is transmitted after irradiation of spermatogonia has been provided by

analysis of the cause of litter-size reduction following exposure to 1,200 r.¹⁰⁹ The same data indicate that translocations are occasionally found in progeny following irradiation of spermatogonial cells.

129. The specific-locus method of detecting mutations in mice has yielded further information on the dominance of mutations induced in spermatogonia. About three-quarters of all the induced mutations have been recessive lethals. However, some of these have a visible effect on the heterozygote.¹³⁸ In a freely-breeding population these mutations might well produce greater total damage as heterozygotes than as homozygotes.

130. In mice, several studies of the effect of paternal irradiation have not revealed any consistent effect on the sex ratio of offspring.^{130, 239, 248} Another comprehensive investigation has shown that although the presence of sex-linked recessive lethals in the second generation progeny of irradiated males can be detected, nevertheless sex-ratio changes do not now provide a reliable method of estimating the genetic hazards of radiation because of the complexity of factors governing this ratio.²⁴⁴ This complexity has been emphasized by the fact that strain differences in the ratio can be obtained through differential selection for low and high blood pH.²⁴⁶ In fowl, a significant decrease in the frequency of female progeny resulting after exposure of male birds to 600 r has been noted.²⁴⁸ In *Drosophila*, most investigations have demonstrated some tendency toward an excess of males among the progeny of irradiated males.^{247, 248} A significant shift in this direction has been reported recently.²⁴⁹ Research on sex-ratio shifts needs to be continued in the hope of laying a firm foundation for the application of this method in analyses of radiation-induced mutation in man.

POLYGENIC TRAITS

131. The subject of polygenic traits was treated at some length in the 1958 report with special reference to intelligence, life span and birth weight.²⁵⁰ Attention was drawn to the paucity of information regarding the inheritance of continuously varying, or quantitative, traits. These traits, which are influenced to varying degrees by many genes, present a special problem in the estimation of genetic hazards of ionizing radiation to populations. For example, intelligence is influenced by certain rare genes having major effects and by a multiplicity of genes, each with a small effect. In those instances where a mutation has a drastic effect on the trait, or concomitant effects on some other trait, it is individually identifiable and classed as a qualitative mutation. Mutations resulting in such conditions as phenylketonuria and mongolism belong to this category. Where the effect is less drastic no such identification is possible. Furthermore, the frequency of mutations having minor effects is many times greater than is the frequency of mutations having major effects. Finally, a great deal of genetic variability within these traits is common in a normal population, and phenotype is, in addition, often strongly influenced by the environment. In such circumstances the relative contributions of heredity and environment to the over-all phenotypic variability are difficult to determine. A few traits, such as dermal-ridge count, are relatively unaffected by environment after birth; here a more accurate genetic analysis can be made.²⁵¹ However, the role of mutation in supporting the genetic variability of polygenic traits has defied any simple analysis.

132. Because rates of mutation of the individual genes in a polygenic system cannot be studied, most investi-

gators have adopted the procedure of expressing induced mutation in terms of the resulting increase in the genetic component of the variance, with or without reference to the genetic component observed in natural outbred populations. The extent of this increase has, in general, been measured either directly by variance analysis or indirectly by calculation of the capacity of an irradiated population to respond to selection. Pertinent information from experiments concerned with natural and radiation-induced mutation rates is summarized in table XI.

133. Such experiments are of special value in indicating whether the genes determining polygenic traits differ in their pattern of mutability from those individually recognized through discrete changes. Estimates of doubling dose for abdominal and sternopleural bristles in *Drosophila* agree well with those for major genes.²⁵² On the other hand, the estimated induced rates for polygenes controlling viability are high.²⁵³

134. Loss of genetic variance per generation in an unselected, random-mating *Drosophila* population of limited size is only a small portion of the natural variability of the species. Polygenic traits are evidently well buffered against the effects of mutation. Thus the radiation damage from an increased rate of polygene mutation, although possibly considerable when summed over many generations, is probably small in its impact on the first few generations. Variability in these traits may be maintained in part by a balance of selective forces, a possibility which further complicates the estimation of radiation-induced mutational damage to polygenic systems in an organism such as man, that cannot be directly experimented on.

135. The learning ability, as measured by a maze test of a population of rats which were irradiated in each generation has decreased in preliminary experiments.²⁵⁴ If further experiments exclude other interpretations, these results will support the view that radiation results in the induction of many small but deleterious mutations. Again, a significant accumulation of recessive or sublethal mutations affecting ability to survive irradiation has been reported in mice after ten generations of chronic gamma irradiation.²⁵⁵

VI. Interpretation

136. The preceding sections of this annex were concerned with the genetic concepts and information now available for estimating the hereditary effects of an increase in the level of ionizing radiation. The present section considers the practical problems involved in formulating reliable estimates from this knowledge.

DIRECT APPROACH

137. An estimate of the genetic hazards of radiation to man can, in principle, be obtained by a direct comparison of the descendants of irradiated with those of control populations. To be reliable, such surveys must be extensive, since most severe genetic defects tend to be rare. Furthermore, many aspects of genetic well-being must be considered and it is desirable to continue the observations over many generations. These conditions have not been fulfilled in any study to date. All surveys made so far have, in addition, been hampered by problems of dosimetry and the difficulty of obtaining proper controls. In the most extensive of these, that dealing with the populations of Hiroshima and Nagasaki, the investi-

gators were unable to detect a significant effect of radiation on either the frequency of early death or the occurrence of malformations. At least, this negative finding suggests that the human genetic mechanism is not substantially more sensitive to radiation than are those of other organisms that have been investigated. It has been suggested that the acute dose required to double the frequency of mutations causing the defects under study is probably more than 10 r.²²⁷ The Japanese survey detected, as did others of lesser scope, a shift in the proportion of first generation male offspring suggestive of the induction of sex-linked lethal damage in irradiated parents. The precise nature of this damage is not known at present.

INDIRECT APPROACHES

138. Indirect approaches attempt to predict the genetic consequences of exposure to ionizing radiations through an understanding of basic genetic mechanisms and their reaction to radiation. More specifically, estimates are derived through a knowledge of the prevalence of naturally-occurring hereditary ill health within a population, the role of mutation in supporting this burden, and the relation between the dose of radiation and the mutation rate in man.

The prevalence of hereditary diseases and defects

139. There is probably a genetic component in the aetiology of most diseases. It is now estimated that about 6 per cent of all live-born suffer at some time during their lives from serious disabilities in which this component is either known or suspected to be of major importance. Without doubt the estimate of natural genetic burden will increase with future research. In about one third of these disabilities, those of categories Ia, Ib, and IV, the genetic component is high and the underlying genetic mechanism is understood. Of these defects, about half are associated with what appear to be specific alleles, and about half are associated with gross chromosome anomalies. For the remainder of the defects, the developmental malformations and serious constitutional disorders of categories II and III, neither the size of the genetic component nor its underlying genetic mechanism is known with any assurance. These disabilities are almost certainly heterogeneous in aetiology; some are probably almost completely environmental in origin, but in others genotype may be an important factor. However, even where the importance of genetic constitution is suspected, the basic nature of the fault is not clear; complex constellations of genes, specific alleles of low penetrance, or cytologically undetected chromosome aberrations may be responsible.

140. The amount of recessive damage, that hidden in heterozygotes, has been estimated at 2-4 lethal equivalents and an equal number of detrimental equivalents per individual. When exposed by homozygosis, the lethal equivalents are expressed as an increase in miscarriages, still births and in neonatal, infant, and juvenile deaths. The detrimental equivalents are associated with viable malformations and overlap the previous listing to some extent. A comparable measure of genes producing recessive infertility has not been made. No similar method is yet available for estimating the amount of dominant genetic damage within populations.

The role of spontaneous mutation in maintaining the frequency of hereditary disabilities

141. Various mechanisms by which detrimental traits can be maintained in a population are well recognized. A

gene sometimes conferring reduced fitness, but never conferring increased fitness, must be maintained entirely by recurrent mutation. On the other hand, if a gene confers increased selective advantage in some circumstances, mutation may have only a minor influence on its frequency.

142. The extent to which such balanced selective forces are responsible for maintaining hereditary disabilities in human populations is unknown at present. Of the defects listed in section II, only among the specific disabilities now recognized to have a high genetic component is it possible to discriminate between those that are mutation-maintained (categories Ia and Ib) and those that are maintained by a balance of selective forces (category IV). At present, traits of category IV provide but a small fraction of the total amount of serious ill health of known or suspected genetic origin. Suitably designed studies will undoubtedly produce more examples in the future. In the meantime, estimates of the importance of balanced selective forces are dependent on the use of indirect procedures or are based on concepts of the genetic structure of human populations which have yet to be confirmed.

143. When the prevalence of defective traits is maintained by recurrent mutation, the genetic hazards of radiation can be estimated if the factor by which mutation rate will be increased by a given radiation dose is known. However, when the frequency of induced mutations has been determined at only one dose it is necessary to know the spontaneous rates to estimate the hazard. Reliable estimates of spontaneous rates can be made only when the genetic fitness of both homozygote and heterozygote is known. It is possible to measure fitness where dominant traits are concerned. However, with recessive traits it is difficult to determine genetic fitness of heterozygotes; as a consequence, reliable estimates of natural mutation rates are rare. Point mutation rates so far estimated cluster around the value 10×10^{-6} per locus per generation. The total mutation rate for gross chromosomal aberrations is now estimated at about 1 per cent per generation.

Dose-mutation relationship

144. The genetic effects of ionizing radiations cannot be understood without establishing a firm relationship between frequency of induced mutation and the dose of irradiation delivered. Most of the earlier information about this relationship was accumulated from the results of experiments with *Drosophila* sperm. Past research led to the working assumptions that: (a) the dose-mutation curve is linear in the low-dose range, (b) there is no threshold dose, and (c) mutation frequency is not dependent on dose rate over the range under consideration. Much effort has been put into the task of either confirming or disproving these three assumptions. Recent investigations have strengthened the first two, but have disproved the last. It has now been conclusively demonstrated that rate of delivery of radiation can have an effect on the frequency with which mutations are found. In male mice, low dose-rates of ionizing radiation produce one fourth as many mutations as do high dose-rates. In females, this phenomenon is even more pronounced.

145. Recent research has increasingly emphasized the fact that radiation-induced mutation frequency can be drastically affected by circumstances other than dose and dose rates:

(a) Radiation-induced mutation rates may vary for genes in the same species and this variation need not

correspond to the variation in natural rates. In mice the induced rates per unit dose in spermatogonia at seven specified loci may vary by a factor of thirty.

(b) Rate of radiation-induced mutation per unit dose varies in different species. Furthermore, it has been reported that the frequency of cytologically observed induced chromosome abnormalities in spermatogonia of the guinea pig is nearly thirty times that of the rabbit, a closely related species.

(c) It is clearly established that sex and stage of gametogenesis can have a profound influence on both spontaneous and radiation-induced mutation frequencies. The existence of such interactions between radiation effect and the circumstances of its delivery add to the complications of estimating radiation effects in humans. For example, it increases the possibility that errors may be involved in extrapolating from one species to another, from non-gonadal tissues to germ cells, and from one germ-cell stage to another.

The doubling-dose concept in indirect assessments

146. The indirect methods for assessing the hereditary effects of an increase in level of ionizing radiation to which a population is exposed involve the estimation of "doubling dose" and the assumption of linearity of the dose-effect relationship. The doubling dose for a particular mutation is that dose which will increase the mutation rate to double the spontaneous rate. A prediction of the phenotypic effect of an increase in mutation rate can be calculated from the fact that the number of affected persons arising as a consequence of a doubling dose delivered in one generation, is equal to the number of affected persons normally present in any one generation as a result of recurrent mutations of natural origin. This increase in affected individuals will be spread over one or more generations depending on the genetic fitness which specific mutations confer on their carriers. The genetic fitness of the heterozygote is of more importance than that of the homozygote in most cases, because rare mutant genes occur much more frequently in the heterozygous state in a random-breeding population. When genetic fitness of the heterozygote is very low, most of the impact of the new mutations will be felt in the subsequent generation; if fitness is reduced by one-fifth, most of the effect will appear within the first five generations; if reduction in fitness is slight the effect will spread over very many generations. A permanent doubling of the mutation rate eventually results in a permanent doubling of the incidence of those traits normally maintained by recurrent spontaneous mutation. On the assumption of an average reduction of 2 per cent in genetic fitness of heterozygotes, most of the impact of a permanent doubling of mutation rate would be felt in about fifty generations. Where systems of balanced polymorphism are in force, natural mutation is a relatively minor factor in the maintenance of genetic variability and a doubling of the mutation rate would have little effect on the prevalence of the associated traits.

147. The usefulness of the doubling-dose procedure was considered in detail in the 1958 report of the Committee. To a large extent this usefulness stems from the fact that whole classes of mutation can be handled as a unit in the absence of any information about the number of loci involved or their individual mutation rates. Tentative numerical estimates of the doubling dose for man were presented in the 1958 report. It was pointed out at that time that little direct information was available on the sensitivity of human genetic loci to radiation. Esti-

mates of doubling dose were consequently based on several other considerations. These included a simple genetic interpretation of sex-ratio changes in man based on the assumed induction of sex-linked dominant and recessive mutations having a lethal effect *in utero*. Account was also taken of the investigation of seven specific loci in mice and of extensive observations on sex-linked lethal mutation in *Drosophila*. As expected, advances in our knowledge have indicated that this estimate is in need of revision.

148. The usefulness of sex-ratio changes in estimating a doubling dose must be considered doubtful because of inconsistencies in the sex-ratio change in the progeny of irradiated fathers (table IX). Furthermore, there is no significant effect on the sex-ratio in the progeny of irradiated male mice.

149. Recently acquired information has also stressed the fact that, apart from the radiation dose alone, there are a number of specific factors which should be taken into account in calculating the doubling dose. Dose rate, sex, and stage of gametogenesis are all factors which affect the frequency and quality of mutation in both mice and *Drosophila* and it must be suspected that they are effective in man. An example of the influence of rate of dose on the calculated doubling dose can be obtained from table X where the main results of irradiation of spermatogonia and oöcytes of the mouse have been summarized. The most important single comparison is that for males between the dose rates of 80-90 r/min and 8.5×10^{-3} r/min. The former rate provides a doubling dose of 30-40 rad, the latter 100-200 rad. A significant dose-rate effect is also evident for oöcytes, and the doubling doses for acute and chronic irradiation show an even greater spread than in males.

150. It is becoming increasingly evident that the spectrum of mutations in man is too wide to be included in a single category for the purpose of estimating a meaningful representative doubling dose. For instance, the doubling dose for gross chromosome mutations may well differ drastically from that for point mutations. If so, the frequency-distribution of hereditary defects resulting from a specific increase in the level of exposure to radiation would not be parallel to the natural spectrum.

151. In view of the undoubted complexities of the dose-mutation relationship, it is evident that this method of assessing hereditary effects of ionizing radiation can easily yield imprecise estimates. At the same time it is equally evident that none of these recently discovered complexities invalidates the doubling-dose concept itself; they merely emphasize that the method must be applied under carefully defined conditions if accurate estimates are to be obtained. In particular, it is important to discriminate between the genetic hazards of chronic low-level exposures and more acute medical and accidental exposures.

152. The difficulties of obtaining information on the hazards of ionizing radiation would be reduced if the large amount of data collected in other organisms could be applied directly to humans. Differences in species introduce into this procedure uncertainties the extent of which is difficult to estimate. A second approach is through the observation of human cells grown in tissue culture; reproducible results relating to radio-sensitivity of cells can be obtained in this way. However, here also extrapolation of information is at present associated with uncertainties. Nevertheless it is clear that *in vivo* and *in vitro* research in different organisms will ultimately

provide a valuable source of information. Such investigations must be accompanied by an understanding of the genetic structure of human populations and the respective roles of mutation and selection in moulding that structure.

Conclusions

153. Sufficient information is not now available to calculate with a useful degree of accuracy a representative dose which would double the mutation rate (doubling dose). Nor is it yet possible to predict directly the quantitative or qualitative effects of such a dose on populations. Nevertheless, information regarding some aspects of the genetic hazards of ionizing radiation can be obtained by the doubling-dose method. This involves the calculation of separate doubling doses for different dose rates, and, in addition, for different specific categories of defects. The complexity of the calculations is reduced by the fact that differential sensitivity of germ-cell stages within each sex can be largely ignored; as far as the genetic hazards of radiation to man are concerned, the significant germ-cell stages are the spermatogonia and the oöcyte. This is true whether irradiation is chronic or acute.

154. The group of disabilities to which the doubling dose can, at present, be most usefully applied are those severe defects maintained by recurrent point mutation (category Ia). Calculations of the 1958 report suggested that the over-all representative doubling dose for man might well lie between 10 and 100 rad, with 30 rad as the most probable value. This estimate was based on studies which involved acute irradiation and the production of point mutations. In the absence of better evidence, the doubling dose for acute irradiation of males does not require revision. However, there is evidence that this value is lower in females; experiments with mice have shown that oöcytes are somewhat more sensitive to acute (but not to chronic) irradiation than spermatogonia. The doubling dose for the two sexes combined must therefore be lower than that for males and may well be about half this value. For chronic irradiation of males, new information from mouse experiments suggests that the

doubling dose is about four times the 1958 value of 30 rad. For chronic low intensity irradiation of females, mutation rates seem to be lower than in males. The combined doubling dose for both sexes cannot exceed twice the value for males and is not likely to be much lower than that value. For these estimates, uncertainty due to species extrapolation and the limited number of loci used in experimental studies probably does not exceed three-fold in either direction. A permanent doubling of the mutation rate would ultimately double the prevalence of the serious defects under consideration. These are now estimated to have a prevalence at about 1 per cent.

155. The doubling dose for the defects of category Ib, those due to gross chromosome aberration, cannot now be estimated for lack of data. However, the effect of radiation on the frequency of gross chromosome mutation is amenable to study, and it can be expected that continued research in this field will enable estimates to be made in the near future. A doubling of the mutation rate in one generation would almost certainly double the prevalence of these defects in the next generation. This prevalence is now estimated to be about 1 per cent.

156. It is not possible to estimate the doubling dose for the genetic changes contributing to developmental malformations and serious constitutional disorders of categories II and III. The prevalence of these defects might be doubled by a doubling dose but the increase would probably be much less; environment is suspected to have a strong influence on their aetiology, and unrecognized balancing selective mechanisms may also be effective in maintaining their frequency.

157. Significant progress towards an understanding of the genetic effects of ionizing radiation has been made in the last four years. The Committee emphasizes that: (a) all research has confirmed the fact that ionizing radiation produces genetic damage at all doses and dose rates so far tested, and (b) further progress in understanding the genetic hazards of radiation will come not only from *ad hoc* research in radiation genetics but from an increase in all types of genetic research in man and in experimental organisms.

TABLE I. CHROMOSOME ABERRATIONS ESTABLISHED IN MAN

Associated clinical condition	Chromosome complement	Chromosome number	First reference
I. Anomalies related to chromosome number			
Down's syndrome (mongolism)	Autosomes: Trisomy-21	47	6
Complex congenital malformations	Trisomy-(17-18)	47	7
Complex congenital malformations	Trisomy-(13-15)	47	8
Klinefelter's syndrome	Sex-chromosomes: XXY	47	9
Klinefelter's syndrome	XXXXY	48	10
Klinefelter's syndrome	XXXXY	49	11
Turner's syndrome	XO	45	13
Mild mental defect	XXX	47	14
Mental defect	XXXX	48	15
II. Structural anomalies			
Down's syndrome with trisomy-21	21 ~ (13-15)	46	16

TABLE II. DISABILITIES WHICH HAVE BEEN ASSOCIATED WITH
ABNORMAL KARYOTYPES, EXCLUDING KNOWN MOSAICS

Clinical condition	Chromosome complement	Chromosome number	Reference
I. <i>Anomalies related to chromosome number</i>			
Klinefelter's syndrome.....	XXYY	48	12
Klinefelter's-Down's syndrome.....	XXY, trisomy 21	48	102
Prenatal death.....	Triploidy	69	37
Mental retardation.....	Trisomy 6(?)	47	256
Facial anomalies.....	Trisomy 22(?)	47	257
II. <i>Structural anomalies</i>			
Polydyspondyly.....	22 ~ (13-15)	45	258
Familial mental and speech defect.....	22 ~ (13-15)	45	109
Primary amenorrhoea.....	X + partly deleted X	46	259
Down's syndrome.....	21 ~ 22	46	18
Down's syndrome.....	21 ~ 21, or trisomy 19 and monosomy 21	46	21
Convulsive disorder.....	(1-2) ~ (6-12)	46	260
Klinefelter's syndrome.....	XXY and 14~15	46	106
Congenital abnormality.....	16 ~ 21, or trisomy 21 and monosomy 16	46	261
Pseudo-hermaphroditism.....	21 ~ Y	46	262
Turner's syndrome.....	Enlarged X	46	263
Familial Marfan's syndrome.....	Enlarged satellite	46	264
Transmissible hypospadias.....	Y deletion	46	265
Gonadal dysgenesis.....	X or Y deletion	46	266
Auricular septal defect.....	2 ~ (6-12)	46	267
Familial malformation of central nervous system.....	Enlarged satellite	46	268

TABLE III. LETHAL AND DETRIMENTAL EQUIVALENTS DERIVED FROM STUDIES OF OFFSPRING FROM FIRST-COUSIN MARRIAGES
(Modified after Newcombe²⁶⁹)

Place	Condition	Consanguineous (first cousin only)			Control			Difference (%)	Lethal or detrimental equivalent	Reference
		Affected	Total	Frequency (%)	Affected	Total	Frequency (%)			
U.S.A.										
	Infant death; juvenile death..	637	2,778	22.93	134	837	16.01	6.92 ± 1.50	2.21 ± 0.48	270
	Death under 20 years.....	113	672	16.82	370	3,184	11.62	5.20 ± 1.55	1.66 ± 0.50	271
	Miscarriage.....	36	248	14.52	25	194	12.89	1.63 ± 3.29	0.52 ± 1.05	
	Still birth; neonatal death....	7	212	3.33	5	196	2.98	0.35 ± 1.73	0.11 ± 0.55	272**
	Infant death; juvenile death..	14	205	6.34	1	164	0.61	5.73 ± 1.81	1.83 ± 0.58	
	Abnormality.....	31	192	6.15	16	163	9.82	6.33 ± 2.91	2.03 ± 0.93	
France										
	Still birth.....	43	1,043	4.12	84	4,094	2.05	2.07 ± 0.65	0.66 ± 0.21	
	Infant death.....	87	982	8.86	182	4,010	4.54	4.32 ± 0.96	1.38 ± 0.31	273
	Death from 1 to 30 years....	104	886	11.74	227	3,822	5.94	5.80 ± 1.12	1.86 ± 0.36	274
	Abnormality*.....	169	1,043	16.20	176	4,094	4.30	11.90 ± 1.18	3.81 ± 0.38	
Japan										
	Still birth; neonatal death....	125	2,798	4.47	2,091	63,145	3.31	1.16 ± 0.40	0.37 ± 0.13	
	Infant death.....	54	822	6.57	808	17,331	4.66	1.91 ± 0.88	0.61 ± 0.28	40
	Juvenile death.....	41	352	11.65	31	567	5.47	6.18 ± 1.96	1.98 ± 0.63	275
	Abnormality*.....	69	4,845	1.42	651	63,796	1.02	0.40 ± 0.17	0.14 ± 0.05	

* Indicates some overlap with the preceding classes.

** Controls drawn from offspring of sibs of the consanguineous pair.

See also Böök²⁷⁰ who found no significant difference in the mortality in small samples of offspring of first-cousin and control marriages, but a considerably greater proportion of the cousin

offspring having hereditary diseases (16 versus 4 per cent), and having lower than average intelligence (26 versus 15 per cent). Since the individual offspring were observed for varying periods of time the mortality data are not readily presented in the above form. An average of three recessive deleterious genes per person is estimated from these data.

TABLE IV. ESTIMATED MUTATION RATES AT LOCI DETERMINING AUTOSOMAL DOMINANT DISEASES IN MAN

(Modified from Stevenson²⁷⁷ and Penrose²⁸⁰)

Trait	Region	Estimated rate/locus/gen. ($\times 10^{-4}$)	Reference
Epiloia	England.....	8	278
Achondroplasia	Denmark.....	43*	279
	Sweden.....	68*	280
	Northern Ireland.....	13	281
Aniridia	Denmark.....	5	282
	Michigan.....	4	283
Microphthalmos	Sweden.....	5	284
Retinoblastoma	England.....	15	285
	Michigan.....	23	286
	Northern Ireland.....	29	287
	Germany, Fed. Rep. of.....	4**	288
Neurofibromatosis	Michigan.....	100+	289
Huntington's chorea	Michigan.....	5	290
Arachnodactyly	Northern Ireland.....	6	291
Acrocephalosyndactyly	England.....	3	292

* This estimate probably includes phenocopies.

** This figure is adjusted for presumptive phenocopies.

TABLE V. ESTIMATED MUTATION RATES AT LOCI DETERMINING SEX-LINKED DISEASES IN MAN

(Modified from Stevenson²⁷⁷)

Trait	Region	Basis of estimation $\mu = 1/3 (1 - f) x^*$	Estimated rate/locus/gen. ($\times 10^{-6}$)	Reference
Haemophilia.....	England	$f = 0.25$ Est $x = 0.8 \times 10^{-4}$	20	293
	Denmark	$f = 0.286$ Est $x = 1.33 \times 10^{-4}$	32	294, 295
	Denmark and Switzerland	$f = 0.333$ $x = 489/4,092,025$	27	296
	Utah, USA	$f = 0$ $x = 18/63,000$	95	297
Duchenne type muscular dystrophy.....	Northern Ireland	$f = 0$ $x = 48/271,896$	59	298
	England	$f = 0$ $x = 16/138,403$	39	299
	England	$f = 0$ $x = 15/105,310$	47	300
Limb girdle muscular dystrophy.....	Northern Ireland	**	34	51
Recessive deaf-mutism.....	Northern Ireland	**	13	51

* μ = Mutation rate/locus/generation. f = Relative genetic fitness. x = Frequency of trait in population.** Estimates made by special methods.⁵¹

TABLE VI. ESTIMATED MUTATION RATES AT LOCI DETERMINING
AUTOSOMAL RECESSIVE DISEASES IN MAN
(Modified from Penrose⁸⁹)

Trait	Region	Basis of estimation ($\mu = (1-f)x$)	Estimated rate/locus/gen. ($\times 10^{-5}$)	Reference
Juvenile amaurotic idiocy.....	Sweden	$f = 0$ Est $x = 3.8 \times 10^{-5}$	38	301
Albinism.....	Japan	$f = 0.5$ Est $x = 5.5 \times 10^{-5}$	28	302
Ichthyosis congenita.....	Japan	$f = 0$ Est $x = 1.1 \times 10^{-5}$	11	302
Total colour blindness.....	Japan	$f = 0.5$ Est $x = 5.5 \times 10^{-5}$	28	302
Infantile amaurotic idiocy.....	Japan	$f = 0$ Est $x = 1.1 \times 10^{-5}$	11	302
Amyotonia congenita.....	Sweden	$f = 0$ $x = 1/44109$	23	280
Epidermolysis bullosa.....	Sweden	$f = 0$ $x = 2/44109$	45	280
Microcephaly.....	Japan	$f = 0.02$ Est $x = 5 \times 10^{-5}$	49	303
Phenylketonuria.....	England	$f = 0$ Est $x = 2.5 \times 10^{-5}$	25	54

* μ = Mutation rate/locus/generation.
 f = Relative genetic fitness.
 x = Frequency of trait in population.

TABLE VII. STUDIES OF TIME-DISTRIBUTION OF DOSE—MODIFICATION OF PRE-MUTATIONAL
DAMAGE AND ASSOCIATED PHENOMENA

Material	Radiation	Mutations	Phenomenon	Remarks	Reference
Mouse spermatogonia.....	X, γ	Recessive visibles and lethals at seven selected loci	Fourfold reduction in effect at low dose-rate	Differential viability of cells, radiation quality eliminated	119,124, 127,132
Mouse oöcytes.....	X, γ	Recessive visibles and lethals at seven selected loci	More than fourfold reduction at low dose-rate	Inter-cell selection differential viability, radiation quality eliminated	121,123 304
<i>Drosophila</i> oögonia.....	γ	Sex-linked recessive lethals	Reduced effect at low dose-rate		128
Silkworm, early stages of spermatogonia and oögonia.....	X, γ	Egg-colour mutants at two specific loci	Reduced effect at low dose-rate	After elimination of cell selection and later stages	97
<i>Dahlbominus</i> , wasp oögonia.....	γ	Eye-colour mutants in female larvae	No effect at intensity differences of 1,000 r/min and 0.17 r/min	Probably oögonia	130
<i>Drosophila</i> spermatogonia.....	γ	2nd chromosome recessive lethals	No intensity effect at 2,000 r/min and 2.0 r/min	Total dose 3,000 r	129
<i>Drosophila</i> spermatogonia.....	γ	2nd chromosome recessive lethals	Reduction at intensity differences from 0.01 r/min to 0.10 r/min	Total dose 200 r	129
<i>Drosophila</i> spermatogonia.....	X	Sex-linked recessive lethals	Reduced (?) effect of fractionated dose	Shifts in brood pattern of mutation rates cannot be excluded	305
<i>Drosophila</i> spermatogonia.....	X	Sex-linked recessive lethals in ring-X chromosome	No effect of dose fractionation; enhancement by post-treatment with N ₂ ; reduction by pre-treatment with chloramphenicol	Intensity of radiation for fractionation and N ₂ post-treatment 55 r/sec	153,154, 155,156
<i>Drosophila</i> spermatogonia (?).....	X	Sex-linked lethals	Decrease by feeding of larvae with actinomycin D and penicillin	Stage not defined, probably spermatogonia	306,307

TABLE VII. STUDIES OF TIME-DISTRIBUTION OF DOSE—MODIFICATION OF PRE-MUTATIONAL DAMAGE AND ASSOCIATED PHENOMENA (continued)

Material	Radiation	Mutations	Phenomenon	Remarks	Reference
<i>Drosophila</i> spermatids and spermatocytes...X		Sex-linked recessive lethals in ring-X chromosome	Reduced effect of dose fractionation and of pre-treatment with chloramphenicol and ribonuclease; enhancement by post-treatment with N ₂ ; both increase and decrease by post-treatment with HCN	Gene mutations and possibly small deletions; radiation given at high dose-rates; inhibition of metabolic repair and delay of mutation fixation	152,153, 154,155, 156,157
<i>Drosophila</i> sperm.....X		Sex-linked recessive lethals in ring-X chromosome	Increase by pre-treatment with ribonuclease and chloramphenicol		153,154
<i>Drosophila</i> sperm.....X		Sex-linked recessive lethals; chromosome breaks	Reduced (?) effect of dose-fractionation in absence of O ₂	Critical period ~ 40 min; critical dose for breaks	158,161
<i>Drosophila</i> sperm.....X		Chromosome breaks	O ₂ affects both breakage and rejoining of chromosome fragments; no saturation of O ₂ sensitivity systems	Radiation given in N ₂ , air, or at 1 At of O ₂	163
<i>Drosophila</i> oöcytes.....X		Half-translocations, detachment of attached X-chromosomes	O ₂ affects both breakage and restitution of breaks	N ₂ between X-ray fractions, or as a post-treatment increase half-translocation frequency	308,309
<i>Tabrobracon</i> oöcytes.....X		Hatchability of eggs treated in first meiotic metaphase	Post-treatments with N ₂ and CO increase radiation damage	Realization of potential radiation damage	310
<i>Drosophila</i> spermatids.....X		Translocation	Cyanide post-treatment increases frequency	After both low and high dose-rates; CN delays restitution of breaks, more translocations	152,311
<i>Artemesium</i>X, UV, α		Recessive lethals expressed after autogamy	Effect of time between irradiation and chromosome duplication	Effect of various post-treatments (nutrition, metabolic inhibitors)	139,140
<i>E. coli</i> ; <i>Streptomyces</i> spores; <i>Serratia</i>UV, X		Biochemical reversions, "EMB colour"	Observe mutation frequency decline, mutation stabilization, mutation fixation, and mutation expression	Pre- and post-treatment with various temperatures, nutritional factors, and metabolic inhibitors, relations to protein, RNA and DNA synthesis	143,144, 145,146, 147,148, 149
<i>Neurospora</i>UV		Biochemical mutation	Protein synthesis decreases mutation at low UV doses, but increases mutation at high doses	RNA derivatives increase mutation frequency at low doses only	150
<i>Trifolium</i>		Somatic mutations at leaf marking locus	Reducing effect of dose fractionation	Protection by dose of 12.5 r, dependent on O ₂ -tension and temperature	312
<i>Neutria</i>X, Neutron		Chromosome breaks	Process of rejoining inhibited by radiation	Repair requires cellular metabolism and protein synthesis	313,314

TABLE VIII. EFFECT OF IRRADIATION OF MOTHERS ON THE PROPORTION OF MALE OFFSPRING

Country	Control		Dose range rads	Irradiated		Reference
	No. live births	Per cent male		No. live births	Per cent male	
Japan.....	43,544	52.085	ca. 8 ca. 75 ca. 200	19,610 3,958 2,268	51.979 51.440 51.190	227, 315
U.S.A.....	Control not available		50-200	407	49.1	235
France.....	355	54.6	200-400	161	44.7	236
Netherlands.....	674	50.1	2-10	797	52.2	
	225	53.3	300-600	221	48.0	238

TABLE IX. EFFECT OF IRRADIATION OF FATHERS ON THE PROPORTION OF MALE OFFSPRING

Country	Control		Dose range rads	Irradiated		Reference
	No. live births	Per cent male		No. live births	Per cent male	
Japan.....	43,544	52.085	ca. 8 ca. 60 ca. 200	5,168 1,226 753	51.587 53.263 52.722	227, 315
	609	51.72	Many doses of unknown amount	4,201	53.64	237
	Average for Japan	51.24				
U.S.A.....	3,491	52.42	Many small doses	4,277	51.39	225
France.....	1,185	51.5	200-400	656	56.1	236
	1,926	52.7	2-20	1,394	46.0	
Netherlands.....	828	46.6	300-600	635	52.3	238
	657	52.3	1-10	668	53.4	

TABLE X. NATURAL AND INDUCED MUTATION RATES AT SEVEN SPECIFIC LOCI IN ADULT MOUSE SPERMATOGONIA AND OOCYTES

Details of irradiation				Mutations in spermatogonia		
Source	Total Dose (r)	Dose Rate (r/min)	No. of offspring	No. of mutations	Mean no. of mutations per locus per gamete ($\times 10^{-4}$)	Reference
X-ray.....	300	80-90	40,408	25	8.84	119
X-ray.....	600	80-90	119,326	111	13.29	119
X-ray.....	1000	80-90	31,815	23	10.33 ^a	119
X-ray.....	600 + 400 ^b	80-90	4,904	10	29.13	121
X-ray.....	600	60-70	10,761	11	14.60	126
Co ⁶⁰	600	24	44,352	33	10.63	121, 316
X-ray.....	600	9	28,339	14	7.06	317
Cs ¹³⁷	600	0.8	27,840	10	5.13	125
Cs ¹³⁷	300	0.009	58,457	10	2.44	121, 316
Cs ¹³⁷	516	0.009	26,325	5	2.71	121
Cs ¹³⁷	861	0.009	24,281	12	7.06	121
Co ⁶⁰	603 ^c	0.007-0.009	10,763	2	2.65	126
Co ⁶⁰ and radium.....	37.5 ^d	0.0011-0.0078	63,322	6	1.35	318
Cs ¹³⁷	86	0.001	56,993	6	1.50	121
Control.....	—	—	544,897	32	0.84	119, 121, 316, 318
Mutations in oocytes						
X-ray.....	400	92-96	12,853	16	17.78	121, 123
Cs ¹³⁷	400	0.8	36,083	13	5.15	304
Co ⁶⁰	600 ^c	0.05	10,117	1	1.41	319
Cs ¹³⁷	258	0.009	27,174	2	1.05	121, 123
Control.....	—	—	98,828	1	0.14	121, 123, 316

^a For a possible explanation of the low mutation frequency, see paragraph 83 above.

^b The two fractions were delivered 15 weeks or more apart.

^c Delivered in 90 12-hr. or 16-hr. days.

^d Delivered in 5, 25, or 35 16-hr. nights.

^e Delivered in 12 16-hr. nights.

TABLE XI. POLYGENIC TRAITS: MUTATIONAL DATA

Material and characters	Treatment	Method	Results: increase in genetic variance	Comments	Reference
<i>Drosophila melanogaster</i>					
Abdominal bristle number.....	(a) 1,800 r per generation as adults (b) Nil	Response to selection for high and low lines (10/25)	3.3×10^{-6} rad Not significant but > 0.006 /generation	Natural genetic variance cited as 5 units for abdominals and 1.7 units for sternopleural	320
<i>Drosophila melanogaster</i>					
Abdominal bristle number.....	Nil	Analysis of increased variance associated with second chromosome Ditto	0.0014/generation		321
Sternopleural bristle number.....	Nil	Ditto	0.0004/generation		
<i>Drosophila melanogaster</i>					
Abdominal bristle number.....	Nil	Analysis of variance associated with second chromosome Ditto	0.006/generation 0.002/generation		322
Sternopleural bristle number.....	Nil	Regression of variance on dose for large chromosomes Ditto	8.7×10^{-5} /rad 3.5×10^{-5} /rad	Details of X-ray treatment and dose not given	323
<i>Drosophila melanogaster</i>					
Sternopleural bristle number.....	(a) 3,000 r X-rays every generation (b) 3,000 r X-rays every other generation	Selection for high no. (a) Top 15% every generation (b) Top 15% every other generation	$> 4.7 \times 10^{-4}$ /rad* $> 2.5 \times 10^{-5}$ /rad*		324
Rice					
Heading date.....	6 or 12,000 r X-rays to seeds	Variance analysis 5 generations after irradiation of highly inbred line	$1.5 \times 10^{-4}(\text{day})^2/\text{rad}$ $8.4 \times 10^{-4}(\text{cm})^2/\text{rad}$	If suppose inbreeding system leaves variance equiv. of 3-5 generations of spontaneous mutation, can calculate spont. rates of $8-10 \times 10^{-3}(\text{day})^2/\text{generation}$ for heading date and $6-7.5 \times 10^{-2}(\text{cm})^2/\text{generation}$ for plant height	325
Plant height.....	Ditto	Ditto			
Maize					
9 attributes.....	Nil	Analysis of shifts in plot means over 6 generations of selfing doubled monoloids	Average of 4.5×10^{-4} mutations per attribute per gamete 2×10^{-8} /rad	Variance analysis failed to give significant results because of high environmental component Variance of flowering data in natural populations not known. Controls probably not significantly different from ~ 0.00043 ; good linearity with dose obtained	326
<i>Arabidopsis thaliana</i>					
Logarithm of flowering data.....	0-150 kr X-rays to dry seeds				

* Secretariat calculation.

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ANNEX D

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I. Physical factors influencing somatic effects

INTRODUCTION

1. The present annex summarizes knowledge of the biological effects of ionizing radiations on animals and man; the object is to assess the effect of radiation on the individual.

2. The principal physical factors determining the biological effects of ionizing radiation are the absorbed dose (rad), its distribution in time (instantaneous dose-rate, fractionation, short-term or long-term exposure), its spatial distribution (anatomical region, fraction of total body, organ depth, distribution, etc.) and the quality of radiation (energy: α -, β -, γ -, X-rays, neutrons, etc.)

The inhomogeneity of dose in man, particularly after accidental exposure, raises an important practical difficulty in assessing exposure in man: one can ascribe no single meaningful value for the dose delivered.

DEFINITIONS

3. To facilitate prospective and retrospective classification and study, definitions used by the United States National Academy of Sciences-National Research Council Sub-committee on Hematologic Effects (1961)¹ are recommended. Some terms cannot be defined precisely. Others, because of ambiguity, e.g. "acute" and "chronic", are best avoided in describing exposure and effects and reserved for use in their usual medical sense.

Short-term exposure

4. Short-term exposure includes: (a) total or substantial body exposure to radiation over a short time (e.g. in nuclear warfare from direct exposure to initial radiation from the detonation of nuclear weapons and nuclear reactor or accelerator accidents), and (b) exposure of limited yet substantial body areas in which the radiation is given either as a single dose or fractionated over a few days or weeks (e.g., in therapeutic radiation, diagnostic radiology, or tracer or therapeutic use of radio-active isotopes). A dose ≥ 50 rad is defined, for the purposes of the present report, as a high dose, < 50 rad as a low dose.

Long-term exposure

5. Long-term exposure refers to continued or repeated exposure to radiation over months or years. Such exposure is greatest in certain occupations and in persons containing radio-active isotopes with relatively long effective half-lives. X-ray examinations repeated frequently over a long time also constitute long-term exposure, as do exposures to cosmic radiation, naturally-occurring radio-active isotopes, and fall-out.

Cumulative dose

6. Although the *total dose* of radiation is important in long-term exposure, it is sometimes useful and convenient to indicate degree of exposure as dose per unit time, usually cumulative dose per week:

- (a) Very low weekly dose < 100 mrad.
- (b) Low weekly dose: 100-1,000 mrad.
- (c) High weekly dose $> 1,000$ mrad.

7. The very low weekly dose is less than that implied by the 1960 maximum permissible dose (MPD) recommended for occupational exposure by the International Commission on Radiological Protection (ICRP)² and the United States National Committee on Radiation Protection and Measurements (1958).³ The dividing line between low and high dose corresponds to the first MPD recommendations of these groups in effect between 1936 and 1948.

Consequences of exposure

8. The initial effects produced by radiation may lead to observable alterations expressed promptly or months or years after irradiation. The development of clinical findings depends not only on the nature and extent of the initial radiation injury, but also on the operation of secondary factors, e.g. the influence of hormonal secretions on the development of radiation-induced mammary tumours. A distinction should also be made between those effects that produce only a cytologic abnormality, e.g. binucleate lymphocytes, and those that produce a serious disease, e.g. leukaemia.

9. It is not possible to distinguish sharply between early and late effects since effects observed soon after radiation may persist. Nevertheless, it is convenient to consider as *early*, effects observable within a few weeks after exposure. *Late* effects are those that appear later not obviously related to the early effects. Late effects include cataracts and tumours; they may not appear until many years after exposure.

TYPE OF RADIATION

10. Different kinds of radiation produce essentially similar biological effects at the macroscopic level, though

there are possible differences at the microscopic level; but superimposed on this uniformity they may have a different relative biological effectiveness (RBE), e.g. densely ionizing particles (α rays, neutrons) are more efficient in producing most forms of cellular damage than γ - and X-rays giving lower ion densities. The RBE quoted for a particular kind of radiation depends on the specific biological effect observed, the tissue irradiated, dose, and rate at which it is given. Annex B details the concept of RBE; difficulties in its application to internal emitters are described in section VI of the present annex.

TIME DISTRIBUTION OF DOSE

11. A dose which is lethal if given in a short time may, if spread over a long time, produce effects difficult to relate to the exposure or, especially when recovery intervenes, to detect at all. This poses the key question in assessing somatic effects in man: what are the effects of low doses, single or long-term?

EARLY EFFECTS

12. The early effects in man of large doses are fairly clearly known from the therapeutic use of X-rays and of radio-nuclides such as Ra^{226} (used in teletherapy) and I^{131} , from atomic energy workers in nuclear accidents and from clinical studies on atom-bomb survivors. The acute radiation syndrome is detailed in section IV below.

LATE EFFECTS

13. Late effects in man are inferred from knowledge of specific effects produced in animal experiments, from large-scale observations on population, and from occupational and medical exposures in man. Late effects comprise:

- (a) Many, if not all types of neoplasm, including leukaemia;
- (b) Local effects on tissues, e.g. skin changes, precancerous lesions, cataract and sterility;
- (c) Changes in life-span;
- (d) Effects on growth and development, e.g. irradiation of the foetus can produce abortion, still birth and developmental abnormalities;
- (e) Effects on subsequent generations, covered in annex C.

In general, the late effects are not unique to radiation; for the most part they are indistinguishable from disease states induced by other causes commonly present in the population.

14. Although the main late effects are known—indeed familiar—the possibility of other effects being produced cannot be excluded, notably in the foetus. Not enough is known about the relationship between dose and incidence of late effects. Accurate measurement of dose and incidence may be very difficult.

ANOXIA

15. Reducing the oxygen concentration inside cells during irradiation with X- or γ -rays diminishes cell sensitivity by a factor of 2-5, as measured in several ways. This effect of anoxia in the active bacterial cell is independent of events later than 0.02 seconds after irradiation.⁴ Analysing such phenomena within such time limits is not easy.⁵ The effect of oxygen is reviewed in an-

nex B and anoxia is discussed further in section VIII below (Protection and modification of radiation injury) because of circumstantial evidence suggesting that many protective agents act by interfering with oxygenation of the cell.

TEMPERATURE

16. Lowering temperature soon after irradiation, thus temporarily slowing metabolism, promotes recovery in microorganisms. In amphibia and mammals, lowering body temperature after irradiation may delay the onset of symptoms, but there is so far no evidence of an increased degree of recovery.

NATURE OF RADIATION INJURY

17. A big bar to understanding the nature of radiation injury arises from the difficulties in discerning the immediate processes in the interaction between radiations and living cells: (a) the low concentration of the reaction products between initial interaction and final expression of damage after biologically effective doses of radiation, makes characterization of these reactions difficult by present physico-chemical techniques; (b) the very rapid completion of these interactions allows little time for detection of the intervening events.^{6, 9, 7}

CHROMOSOME DAMAGE

18. Much evidence points to chromosome damage as the central mechanism of radiation-induced cell injury and death. This and the considerable effort to explain effects biochemically are reviewed in annex B.

II. Lethal and lesser damage in cells, tissues, organs, neoplasms, and organisms

INTRODUCTION

19. Knowledge of the comparative radio-sensitivity of different cells and organisms is significant in studying somatic effects. A theory explaining the large differences in radio-sensitivity among different cells and organisms would be decidedly valuable in understanding radiobiology. Differences in the radio-sensitivity of organs are the principal factors defining the organ whose damage by a given radiation dose impairs the body most.

END-POINTS

20. Various end-points are used to determine comparative radio-sensitivities: (a) death of cells; (b) dose to inhibit mitosis; (c) alteration or loss of functions; (d) time taken to regenerate; (e) time taken to atrophy; (f) LD₅₀. In general the morphological end-points hitherto used cannot be regarded as satisfactory and determination of radio-sensitivity is better based on functional criteria, e.g. the concept of radio-resistance of nerve tissue based on morphology has proved incorrect, since functional transient changes in synaptic transmission result from doses of ~ 0.025 r.⁸

21. The apparent radio-sensitivity of a cell or tissue thus depends on the method of observations, e.g. lymphocyte damage may be measured by structural changes in the cell nucleus, by change in DNA content, or by degree of lymphopenia; bone marrow damage may be measured by examination of bone marrow smears, blood counts, haemoglobin and haematocrit estimations in the periph-

eral blood, by Fe⁵⁹ incorporation in bone marrow and by blood cells, by degree of aplasia, or by the likelihood of leukaemia being induced years after radiation.

Death of cells as end-point

(a) Law of Bergonie and Tribondeau

22. In 1906, Bergonie and Tribondeau⁹ proposed a "law" of cellular radio-sensitivity which on the whole is valid in radio-therapy: the most radio-sensitive cells are those which (i) have the highest mitotic rate, (ii) retain the capacity of division the longest, (iii) are the least differentiated.

(b) Radio-sensitivity of cells in the adult mammal

23. Cells in the adult mammal can be arranged approximately in the order of decreasing sensitivity on the basis of clinical and experimental data with death of cells as end-point: lymphocytes, erythroblasts, myeloblasts, megakaryocytes, spermatogonia, egg cells, cells of jejunal and ileal crypts, epithelial cells of cutaneous appendages, cells of eye lens, cartilage cells, osteoblasts, endothelial cells of blood vessels, glandular epithelium, liver cells, epithelial cells of renal tubuli, glia cells, nerve cells, alveolar lining cells of lungs, muscle cells, connective tissue cells, and osteocytes.¹⁰

(c) Radio-sensitivity of tissue in the adult mammal

24. The body's organs reflect differences in the radio-sensitivities of their cells, usually of those in the generative compartment. The radio-sensitivities of different cells, tissues, and organs of mammals are detailed in section III and quantitative relationships between effect and dosage in section VII of the present annex.

AGE AND RADIO-SENSITIVITY

25. Man's sensitivity depends on age at the time of exposure. Embryonic neuroblasts are killed by a much smaller dose of radiation than that which kills adult nerve cells. Children are more susceptible than adults in a number of respects. For example, the child's growing bone is more sensitive than the adult bone. These are but a few examples of the relation between age and susceptibility to radiation. The radio-sensitivity of embryos and foetuses is discussed more extensively in section III, and of children in subsequent sections covering effects on man.

Mammalian cell survival curves

26. Puck *et al.*¹¹⁻¹² plotted the first survival curves for mammalian cells cultivated *in vitro*; they measured the reproductive potential of each individual cell after radiation. They found that human squamous carcinoma (HeLa) cells responded with a two-hit type inactivation curve, and that the logarithmic fraction of surviving cells was linear with increasing dose beyond the initial shoulder of the curve. The D₃₇ was only ~ 100 rad in contrast to $\sim 10^5$ rad for virus inactivation. They suggested that the more sensitive mammalian cells may have more unit targets vulnerable to inactivation.

27. Estimates of D₃₇ by Puck for various normal and neoplastic cells *in vitro* have been very close to one another. This may reflect the high rate of growth of normal cells in tissue culture; indeed there is strong evidence of malignant transformation in many types of cells *in vitro*.

28. Hewitt and Wilson¹³⁻¹⁴ and Till and McCulloch¹⁵⁻¹⁶, in ingenious extensions of the Puck technique

to *in vivo* conditions estimated the sensitivity of mouse leukaemia cells and haematopoietic stem cells irradiated *in vivo* in mice. In both experiments survival curves were very similar to those obtained with human tumour (HeLa) cells irradiated *in vitro*. These observations are important for radio-biological theory, but much work remains to be done to determine how far the results apply to cells in their normal *in vivo* environment. The significance of the shapes of the survival curves for the basic mechanisms involved is still obscure. Elkind's work¹⁷ underscores the considerable significance of repair mechanisms in the response to fractionated or protracted exposure.

RADIO-SENSITIVITY OF MALIGNANT TUMOURS¹⁸

29. Radio-sensitivity of a tumour depends primarily on the radio-sensitivity of the cell of origin. Gross reduction in tumour size depends on the proportion of cells immediately affected by radiation. A lack of immediate visible response does not necessarily indicate radio-resistance. Radio-sensitivity is not synonymous with radio-curability.

30. Therapeutic irradiation of malignant neoplastic tissue may induce almost immediate inhibition of mitosis followed soon after by increased abnormal mitoses and cell death.¹⁹ If new radiation reinduces this effect, complete tumour destruction may be expected; but in many tumours intensive radiation may not induce this response and the tumours keep growing.

31. Cells within a tumour may differ widely in susceptibility to radiation. In tumours of predominantly radio-sensitive cells (lymphosarcoma, myeloma) a small dose of radiation destroys immediately most cells with evident reduction in tumour size, although the growth may recur rapidly. In tumours having cells in different stages of differentiation (epidermoid carcinoma), even a large dose of radiation may not visibly affect the most differentiated cells: no gross effect may be seen for days or weeks, yet destruction of basal cells eventually causes complete disappearance of the tumour. In tumours of radio-resistant cells (malignant melanoma, rhabdomyosarcoma), a most intense radiation may not cause any immediate or late effect.

32. Misunderstanding of response of tumours to radiation has resulted in semantic confusion about radio-sensitivity (see discussion of this situation by Stewart and Warren²⁰⁻²¹). The number of mitoses or the proportion of undifferentiated cells may indicate the immediate response of radio-sensitive malignant tumour, but anaplasia and reproductive activity are not *per se* signs of radio-sensitivity in any or all malignant tumours. Marked differentiation in an epidermoid carcinoma may imply a lesser degree of radio-sensitivity, but no epidermoid carcinoma merits the description radio-resistant; nor does a basal-cell carcinoma simply because it fails to disappear as rapidly as others.

33. Clinical observation has established a scale of radio-sensitivities of malignant tumours, in order of decreasing radio-sensitivity: malignant tumours arising from haematopoietic organs (lymphosarcoma, myeloma); Hodgkin's disease; epidermoid tumours of the upper air passages; seminomas and dysgerminomas; Ewing's sarcoma of the bone; basal-cell carcinomas of the skin; epidermoid carcinomas arising by metaplasia from columnar epithelium; epidermoid carcinomas of the mucous membranes, mucocutaneous junctions, and the skin; adenocarcinomas of the endometrium, breast, gastroin-

testinal system, and endocrine glands; soft tissue sarcomas; chondro sarcomas; neurogenic sarcomas; osteosarcomas; and finally, malignant melanomas. Even among the latter radio-resistant tumours there may be rare instances which show unpredictably a higher degree of radio-sensitivity (fibrosarcoma and melanoma). One variety of liposarcoma is definitely radio-sensitive and is even radio-curable; this is an exception to the experience that radio-sensitivity of malignant tumours depends upon radio-sensitivity of their cell of origin. This list represents only average radio-sensitivity in each group, individual tumours may show more or less radio-sensitivity than their place. Rare tumours of uncertain radio-sensitivity are omitted.¹⁸

34. Clinically it has been known for a long time that interference with blood supply of a radio-sensitive tissue diminishes its radio-sensitivity²² and the important effect of anoxia on radio-sensitivity has already been discussed.

FACTORS INFLUENCING RADIO-SENSITIVITY

35. Factors influencing radio-sensitivity are reviewed in annex B as are the radio-sensitivities of viruses, bacteria, protozoa, and other unicellular organisms.

LD₅₀ values for mammals

36. The data on LD₅₀ values (table I)²³ permit tentative generalizations. Other references to LD₅₀ values are: mouse and rat,²⁴⁻²⁸ hamster,²⁹ monkey,³⁰⁻³² dog,³³⁻³⁸ burro, swine, sheep and cattle.³⁹ Additional LD₅₀ values for guinea pig will be discussed below.

37. There is a clear demarcation of LD₅₀ values (expressed as midline absorbed dose) between small and large animals. Air doses do not reveal this relationship. The LD₅₀ for large species is ~ 250 rad or less for X-rays with uniform dose distribution in tissues, that for small species is approximately double this value or greater.

38. The tissue-dose LD₅₀ values for small animals presently available are all ~ 400-800 rad for X-radiation, and between ~ 550-800 rad if the guinea pig is excluded. The differences might be smaller if different species were irradiated with identical relative dose distributions. The monkey (*Macaca mulatta*) cannot be considered, radio-biologically or haematologically³⁷ any "closer" to man than any other small species. Man is difficult to simulate quantitatively in total body radiation TBR studies with smaller animals (table I).³⁸ The dog is not large enough for direct comparison.

39. The data on guinea pigs given by several previous investigators^{24, 30-41} are often difficult to evaluate owing to dosimetric and statistical difficulties; possible effects of animal strain; possible disease in some animals.^{24, 42, 43}

40. Large animals exposed under similar geometrical conditions have rather uniform LD₅₀'s (again, the higher LD₅₀ values for animals given γ -radiations should be corrected for RBE, and dose rate factors before strict comparison with X-ray data), perhaps partly because large animals, unlike small, provide their own constant, maximum scatter.

LD₅₀ and age

41. The average or median acute lethal dose (LD₅₀ = 30 days) for young adult mammals is within ~ 300-900 rad. While it is customary to give the LD₅₀ for a given strain independently of age, age causes variations.

42. In the mouse susceptibility is maximal at 30 days, decreases rapidly to that in young adults, remains constant until advanced age and then increases rapidly. In the rat the LD_{50} at age 3 months is \sim double that at 3 weeks; beyond 3 months it diminishes approximately linearly with age. More study of this relationship is needed, but it is now evident that susceptibility of a whole population cannot be adequately denoted by a single LD_{50} . Published values are usually obtained from young adults and are therefore maximal or nearly so for the strain. This age-dependence must be taken into account in estimating the LD_{50} for man.

LD_{50} in man

43. Several sources of data are relevant to the LD_{50} in man, but each has serious limitations. There are data on large animals, and also on Japanese at Hiroshima and Nagasaki, on Marshallese, and on patients given therapeutic TBR.

44. If the data for large animals apply also to man, the acute LD_{50} for man should be \sim 250 rad for uniform total body radiation, dose expressed as absorbed dose at the midline. This accords with the low value estimated from the Marshallese exposed to fall-out γ -radiation^{38,44} and indicates that the true value probably lies well below the 450 rad air dose commonly quoted. From the Marshallese data, the near sub-lethal dose for man could be estimated; this fixes the lower part of the survival curve at \sim 200 rad. In dogs and swine an increase of 100 rad over that received by the Marshallese would be well within the lethal range. If one uses the same slope for man as for dogs, the 90 per cent mortality dose is about 500 rad. By splitting the difference, the LD_{50} for man, in the absence of complicating thermal injury, trauma or therapy, is \sim 360 rad.⁴⁵ Recent data on patients treated with TBR also indicate this low value.^{44,46,47} 200 r TBR depresses haematopoiesis severely but one must recall that these subjects are already infirm. Blair⁴⁸ extrapolating from the same Marshallese data, concludes that the LD_{50} (air dose) for man probably is not below

400 r. Both authors, using the Marshallese findings, extrapolate from data in animals, and emphasize the large uncertainty in the quantities deduced. Conflicting facts of trauma, thermal injury, poor nutrition, high and low neutron component in the Hiroshima and Nagasaki bombs, and incomplete knowledge of the position of individuals and surroundings, complicate calculation of the LD_{50} for man from the Hiroshima and Nagasaki data.

45. Recent data on large doses of radiation on man^{49,54} do not suffice for accurate estimation of the LD_{50} .^{53,55} Difficulties in evaluating complicated dosage situation in reactor accidents have been reviewed elsewhere,⁵⁴ and are discussed later in sections IV and VIII on effects in man and on treatment.

LD_{50} and dose-rate

46. Figure 1⁵⁶ summarizes data on the relation between LD_{50} and dose-rate. For all species the LD_{50} increases with decreasing dose-rate.

RADIO-SENSITIVITY

47. This discussion has dealt with only certain aspects of radio-sensitivity. A survey of the different radio-sensitivities of cells, tissues, organs, neoplasms, and organisms indicates that radio-sensitivity is a complicated concept: theory is incomplete (para. 20) and radio-sensitivities of isolated cells may apparently differ from those of the same cells *in vivo*. Investigators should be aware of these differences and not use radio-resistant organisms in their study of radiation effects from fall-out or for those circumstances in outer space where low dosages are to be expected. Different radio-sensitivities of cells, tissues and organs underlie the hierarchy of deaths in the different lethal dose ranges and also the different patterns of recovery after radiation below this range. This is discussed in section III.

III. Somatic radiation injury and its repair, particularly in mammals

MODES OF DEATH WITH TBR

48. Acute total-body and regional exposure may cause various syndromes or modes of death depending on dose level time after exposure, type of radiation, and species.⁵⁷⁻⁵⁹ Very high doses (tens of thousands of rad) cause death in mammals in minutes or hours; this syndrome⁶⁰⁻⁶¹ depends on irradiation of the brain. The marked symptoms of brain dysfunction suggest that death may be from neurological damage. This type of death can also be produced by radiation of the head only.⁶²⁻⁶³

49. The order of events preceding death are dose-dependent. As dose is reduced, survival time increases until the 3-4 day "gastrointestinal" type of death is seen. This familiar dose-survival time-curve⁵⁸ has been examined for X-rays, thermal neutrons, and fission neutrons.⁶⁴

50. In the "bone-marrow" syndrome, in the low-lethal dose ranges, no doubt the sequelae of pancytopenia (infection and haemorrhage) cause death; the precise mechanism of death remains open.⁶⁵⁻⁶⁸ Sporadic deaths occur in the few weeks after the bone-marrow death period, when the marrow has essentially recovered. The cause of these deaths remains obscure.

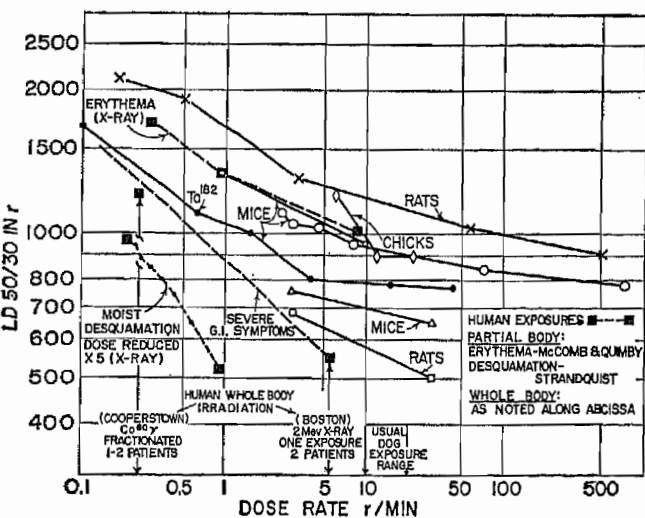


Figure 1. Dependence of $LD_{50}/30$ on dose-rate⁵⁶

$Co^{60}\gamma$ {
 x Rats (SPRAG-DAW) Logie, Harris *et al*⁷⁷⁴
 o Chicks ($LD_{50}/21$) Vogel and Stearns⁷⁷⁵
 o Mice (CF-1) Vogel, Clark and Jordan⁷⁷⁶
 • Mice (CF-1) Thomson and Tourtellotte⁷⁸¹
 250 kVp {
 x Mice (WR-BAGG) Dacquist and Blackburn⁷⁷⁷
 X-ray {
 x Rats (WR-CF) Dacquist and Blackburn⁷⁷⁷
 o Mice (CBA) Neal⁴⁰⁷

51. Quastler *et al.*⁶⁷ have reported deaths two weeks after irradiation of the head, jaw or tongue of the mouse with 1,500 r or more. The mechanism remains obscure. Similar deaths have been reported after 1,500 r to the head of rats.⁶⁸ Dogs given 1,750 r to the head only survived five months or longer.⁶⁹ In the "total head" (brain) studies of Mason *et al.* judging from survival time, the effect described by Quastler⁶⁷ probably caused death.

52. The gut syndrome is identical if caused by TBR or by local irradiation of a large segment of bowel.^{57-59, 71-72} Re-section of irradiated intestine increases survival beyond the time when death from the gut syndrome would otherwise be lethal.⁷³ Depletion of fluids and electrolytes contributes greatly to the immediate cause of death since massive fluid replacement prolongs survival.⁷⁴ Death from this syndrome can be prevented in some animals by shielding only a small portion of the duodenum or ileum, but not by shielding the caecum or stomach;⁷⁵ the authors feel that protection operates through protection of some bowel function rather than by repopulation as in spleen or bone-marrow protection.⁷⁶

53. The bone-marrow syndrome and shielding have also been studied by Lamerton *et al.*⁷⁷⁻⁷⁹ They showed clearly by weight changes two phases of radiation injury, and confirmed that shielding of even a small portion of bone-marrow minimized haematopoietic depression. They also emphasized the importance of anaemia in the acute bone-marrow syndrome in the rat. The remarkable protection given by marrow shielding and the degree to which this may be masked by bowel damage have been shown by Swift *et al.*⁸⁰

54. Maisin *et al.* in Belgium have studied shielding in detail⁸¹⁻⁸³ and concluded that:

- (a) There are at least two syndromes after TBR;
- (b) Shielding of bone-marrow or bowel prolongs survival; and
- (c) Protection of bowel and bone-marrow by shielding acts synergistically.

These conclusions agree with those of many workers.^{57, 58, 75, 84, 85}

EARLY AND LATE ORGAN EFFECTS

Blood and blood-forming organs

55. Haematopoietic tissue is one of the most radio-sensitive tissues with cell death as end-point. In general, the sensitivity of bone-marrow of different species increases from rat, rabbit, mouse, chick, man, goat, guinea pig to dog.⁸⁶ After an LD₅₀ dose the mitotic index falls and erythroblasts decrease within an hour. Within a few hours there are many dead cells and cellular debris. Myeloid elements regress increasingly with cytoplasmic and nuclear disintegration. After 9-10 days, the marrow, filled with a gelatinous, relatively acellular mass containing degenerating cells, has only the relatively radio-resistant fibroblasts, blood vessels, and primitive reticular elements. Animals which will survive, regenerate normoblasts and myeloblasts from spared haematopoietic precursors, and eventually the marrow may be completely regenerated. In rats and rabbits, after doses in the lethal range, erythropoiesis regenerates earlier than myelopoiesis;⁸⁷⁻⁸⁸ in mice both types regenerate at the same time, or myelocytes first.⁸⁷⁻⁸⁹ The effect of radiation on bone marrow has been reviewed extensively.⁸⁸⁻⁹¹

56. Levels of cells in the peripheral blood reflect changes in number and maturation time of precursors and their own life span and changes in their distribution throughout the body. With some species variation, lymphocytes decrease most rapidly, granulocytes a little more slowly; later, platelets decrease and much later, erythrocytes. Usually an overwhelming bacteremia accompanies profound granulocytopenia; germ-free animals die of anaemia.⁹²

57. Leukopenia appears faster and is more severe in irradiated weanling rats and hamsters than in adults, but recovery is more rapid, indicating a more labile homeostasis.⁹³⁻⁹⁴

58. Extracellular fluid and plasma volume increase after irradiation in dogs,⁹⁵ rats,⁹⁶ mice,⁹⁷ and rabbits⁹⁸ at the expense of intracellular fluid. An initial decreased plasma volume of rats accompanies radiation diarrhoea.⁹⁹

59. In rodent spleen, as in marrow, LD₅₀ irradiation inhibits mitosis and damage to lymphocytes is evident within an hour. In survivors regeneration begins on days 9-10 but in lymph nodes, destroyed follicles may not be restored for three weeks. As in bone-marrow, injury increases with dose within certain ranges. In different species, a particular dose-level damages lymphatic tissue similarly, regardless of lethality.⁹⁹

60. Cell destruction shrinks lymphoid tissues. The dose-dependency of the weight response of spleen and thymus is discussed in section VII (dose-effect relationships). Weight loss is in part directly due to radiation damage and in part indirectly mediated through the adrenal has a stress effect.¹⁰⁰

Digestive tract

61. Sensivity of the epithelium of the small intestine is second only to bone-marrow in deciding survival after TBR with X- and gamma rays. After irradiation at high LET, the intestine may be the critical organ determining survival at the LD₅₀ in mice.¹⁰¹ In mice, doses below 1,000 r damage the intestinal mucosa but animals do not generally die from this cause but rather between days 10-14 from bone-marrow damage. From 1,000-10,000 r, mice die 3-4 days after irradiation with complete denudation of intestinal epithelium;⁷¹ death is due to failure of food absorption, dehydration from diarrhoea, and bacterial invasion, and toxemia.^{102, 103}

62. The radio-sensitivity of the various parts of the alimentary system varies greatly: stratified squamous epithelia are of the same sensitivity as the epithelium in the skin;¹⁰⁴ intestinal mucosa is much more sensitive than gastric mucosa; small bowel more than large.^{105, 106} "Oral" radiation death has been described in mice.⁶⁷ Death does not resemble that from intestinal or bone-marrow damage.

63. The stomach and esophagus are more radio-resistant than the intestine.^{107, 108} Two effects may be seen in the stomach: (a) functional and degenerative morphological changes with subsequent repair; (b) development of gastric ulcers in man several weeks after 1,600 r tissue doses given to the gastric fundus over ten days in divided doses via anterior and posterior fields.¹⁰⁹ Destructive changes seen as early as thirty minutes after moderate doses in rabbits exposed to LD₅₀/30 days of X-rays ~ 800 r are most pronounced after eight hours and repaired within four weeks.¹¹⁰ Similar effects are seen in mice after 350 r, in rats after 400 r, and in chickens after 800 r total body radiation. There is hyperplastic regen-

erative activity with continued degeneration of many cells for the first few days. At twenty-one days all mucosae, possibly with the exception of duodenal crypts, are normal. Damage is greatest in duodenum, least in colon and rectum.

64. Doses of 1,000-1,200 rad given locally^{111, 112} diminish gastric acidity and gastric ulcers may develop after several weeks.¹¹³⁻¹¹⁶ Although radiation increases intestine tone and contractions, gastric emptying is delayed.¹¹⁷⁻¹¹⁹ In dogs, gastric emptying time is prolonged only after three or four times the LD₅₀,¹²⁰ but after as little as 25 r in rats.

Reproductive organs

65. Acute doses of radiation causing only marginal changes in the gut or blood-forming tissues may induce permanent sterility and endocrine dysfunction in the female. Males may become temporarily sterile, but the acute doses required to produce permanent sterility in the male are above LD₁₀₀ in all species that have been studied. Understanding the effects of radiation on the reproductive organs is important because those germ cells which survive to form gametes can transmit the genetic changes induced by radiation. Since genetic damage is qualitatively as well as quantitatively dependent on the germ-cell stage in which radiation was received^{89, 121-124} it is obviously important to know the relative radio-sensitivities of various germ-cell stages over a wide range of doses and dose-rates.

Male animals

66. In the male, the various stages in the development of spermatozoa, from the earliest spermatogonia to the mature spermatozoa, have very different sensitivities to radiation. An understanding of normal spermatogenesis is, therefore a prerequisite in understanding radiation effects on the testis.

67. The spermatogonia of monkeys can be divided into type A₁, A₂, B₁, B₂, B₃.¹²⁵ In rodents spermatogonia can be divided into type A (dusty) and type B (crusty) by cell morphology and developmental potentiality; a transitional type between A and B, designated as intermediate spermatogonia, can also be identified in rodents. In mammals, type A spermatogonia are the true stem cells and through stem cell renewal form an unlimited number of spermatocytes while maintaining a constant cell population. This wave of activity leading to new spermatocytes is cyclic. In the monkey, type A spermatogonia undergo mitosis and transform into type A₂ spermatogonia and so on until type B₃ spermatogonia divide to form resting primary spermatocytes. In the mouse and rat type A spermatogonia undergo a series of mitoses, and most of the products of the final division transform into intermediate spermatogonia. The intermediate spermatogonia divide to form type B cells, which in turn divide to form resting primary spermatocytes. Determination of the developmental potentiality of individual spermatogonia takes place before the last division of type A cells, in which certain spermatogonia form the stem cells for the next multiplication cycle.^{127, 128} This basic process is essentially the same in all mammals studied including the monkey and man,^{125, 129} variation associated with differences in the number of identifiable spermatogonial types and duration of spermatogenesis.

68. Because of the similarity in normal gametogenesis, the radiation response of the testis is basically the same

for all mammals, but modifications are required in extrapolating from the response of laboratory animals to that of domestic animals and man. Thus species may differ in: (a) duration of spermatogenesis (i.e., the time for type A spermatogonia to develop into mature spermatozoa), e.g. spermatogenesis takes 35 days in mice, and according to Arsenyeva and Dubinin ~70 days in monkeys.¹²⁹ It is probable that duration of spermatogenesis in man is nearer that of the monkey than that of the mouse; (b) time for spermatozoa to travel from the testis to the ejaculate; (c) regeneration rates, which are a function of (a) above; and (d) possibly, intrinsic sensitivity.

69. Adult male mice given acute doses of 200 to 1,000 r either to the testes only or to the whole body (high doses, of course, are limited to partial-body exposure), are initially fertile, owing to continued development and utilization of gametes irradiated as mature spermatozoa, spermatids, and possibly spermatocytes. An infertile period follows owing to destruction of spermatogonia. A few type A spermatogonia, however, survive and repopulate the seminiferous epithelium, and almost normal fertility eventually is regained. Doses of 100 r cause temporary sterility in the monkey for ~2 to 3 months.¹²⁹

70. Sensitivity of the different stages in spermatogenesis has been most thoroughly investigated in the mouse. Intermediate spermatogonia and early type B spermatogonia have LD₅₀'s in the range of 20-24 r.¹²⁸ Type A spermatogonia show a wide range of sensitivities. At doses below 25 r, survival is comparable to that of intermediate spermatogonia; but, at higher doses, survival is relatively much greater.¹²⁸ A few type A cells survive doses as high as 1,500 r. Thus the paradox of high sensitivity of spermatogonia, which results in the temporary sterile period coupled with high resistance, which leads to return of fertility, is readily explained.¹²⁸ The primary effect leading to depletion of spermatogonia is cell death, mostly in interphase or early prophase, before cell division.¹³⁰ With doses of 100 r or more, some cells die after cell division, probably because of chromosome imbalance; a few cells appear to divide several times before degenerating, but these effects involve only a very few cells. As a result of extensive necrosis, particularly in interphase and early prophase, it is difficult to estimate the amount of spermatogonial depletion arising from mitotic inhibition; this inhibition is probably comparable with that seen in other germinative tissues.¹³¹ Doses of 100 r caused the death of all B₁, B₂, and B₃ spermatogonia in the monkey.¹²⁹

71. In mice, spermatocytes show no immediate damage even after radiation doses of 1,000 r, but degenerate during meiotic division. From the number of spermatids formed, LD₅₀'s ranging from 205 r for preleptotene to 837 r for diakinesis/metaphase I have been obtained.¹³² In the monkey, resting spermatocytes are damaged after 100 r.¹²⁹ Spermatids formed by irradiated spermatocytes show anisocytosis, indicative of aneuploidy and heteroploidy; this later results in many abnormal spermatozoa in the ejaculate.

72. Spermatids and spermatozoa show no morphological changes after irradiation nor is the rate of spermiogenesis altered. Mature sperms may be motile after 50,000 r.¹³³ Such sperms, however, have such severe genetic damage that normal development of a resulting zygote is precluded.

73. The efficiency of fractionated *vs.* single doses is influenced by size of the fractions, intervals between

doses, and total dose. In the mouse, fractions given within a 4-day period act as a single dose.¹⁸⁴ Maximum effectiveness of fractionated doses in different species depends on duration of normal spermiogenesis and reproductive potential. Because information is scarce on the dynamics of spermiogenesis in species other than mouse and rat, contradictory assumptions have been made, in planning experiments and in interpreting data. In dogs, a single total body dose of 300-375 r results in only a partial and temporary reduction in spermiogenesis, with return to normal within a year. This contrasts with complete aspermia after 375 r given over twenty-five weeks at 15 r/wk, there being no sign of recovery within a year after irradiation.⁴⁶ In the dog, long-term radiation gradually reduces the number, motility and viability of sperm. Such damage is one of the most sensitive indicators of chronic damage seen so far in dogs given 3.0 r/wk, i.e. 30 times the average maximum permissible dose-rate (occupational).

74. With prolonged exposure at low dose rates, an equilibrium is established between the cell death, mitotic inhibition, and regenerative activity of the seminiferous epithelium,¹⁸⁵ this equilibrium being dependent on dose rate rather than total dose. If dose rates are low enough, e.g. 10 r/wk in the mouse or 0.1 r per day¹⁸⁶ in the dog and some other species, fertility remains unaffected even after thirty weeks' exposure. Histologically, however, a decrease in cell populations can be demonstrated after 100 r at this dose rate.¹⁸⁷ At 90 r/wk, cell populations are severely depleted, and if doses of 300 r or more are given, temporary sterility is comparable to that following the same dose of acute irradiation.¹⁸⁸

75. Testis weight as a biological indicator of radiation damage is discussed later under "Dose-effect relationships" (section VII).

Man

76. A single dose of 400-600 r to the testes may cause permanent sterility.¹⁸⁹ Temporary sterility of twelve-months' duration usually follows 250 r; even 30 r to the human testis may be injurious.¹⁴⁰ In relating studies on laboratory animals to the response in man, it is of primary importance that corrections be made for differences in time-sequence arising from differences in the rates of normal gametogenesis. Such a correction factor would for example explain the slower recovery in man.

Female animals

77. Since there are no cells comparable to type A spermatogonia (stem cells) in the adult mammalian ovary, females of some species are more easily permanently sterilized than are males. The supply of oocytes if once destroyed is not replaced.

78. The adult female mouse given 300 r acute TBR produces, on the average, 1.4 litters as compared with 14.9 in controls. A dose of 100 r TBR produces complete sterility in twelve weeks, 50 r in twenty-two weeks.¹⁴¹ Even 30 r, given in three divided doses at weekly intervals, produces sterility in some animals.¹⁴² The mouse ovary tends to develop invaginated tubular downgrowths of germinal epithelium and ovarian tumours. These changes, which are readily increased by relatively low doses of radiation, are, however, not the cause of sterility: sterility results from the killing of oocytes in developing follicles. Since oögonia are no longer present in the adult, there can be no repopulation of germ cells.

79. In the adult mouse, all oocytes, except those about to be ovulated, are in dictyate stage. Dictyate oocytes in early follicles are the most radio-sensitive cells in the adult ovary, and are completely destroyed by 50 r.¹⁴³ As the follicles mature, resistance of the contained oocyte increases, and at least one litter usually is obtained from females given 400 r.¹⁴¹ A similar increased resistance with development of the follicle has been observed in the rat,¹⁴⁴ but the dose required to sterilize the female rat is higher. Resistance of mature follicles also is shown in women, since there are a few ovulations after 300 r; early follicle stages must be resistant, however, because, after a period of amenorrhea, ovulation begins again.¹⁴⁵

80. Species comparisons are very difficult in the female, since meiotic prophase stage, relative frequencies of resistant and sensitive oocytes, rate of follicle growth and number of oocytes required for normal fertility undoubtedly vary widely. Valid comparisons of intrinsic sensitivities require more information on the cytology and dynamics of normal oögenesis.

81. In mice lowering the dose rate decreases the sterilizing action of a given dose of radiation. The shortening of the breeding period—the characteristic effect of radiation on female fertility—is dependent on dose rate. Fractionation and even more directly, long-term administration of a given total dose postpones the onset of sterility. The greater the fractionation and the more protracted the long-term dose, the longer is the onset of sterility postponed. These results indicate that some radiation damage to oocytes can be repaired, and that repair is greater at lower dose rates.¹⁴¹ Conflicting conclusions in the literature¹⁴⁶⁻¹⁴⁸ are due to the use of the first post-irradiation litter, not length of breeding period, as the index of effect.

Sexually immature animals

82. Studies in laboratory mammals show that germ cells may change sharply in radiation-sensitivity as the animal develops. In the female mouse, for example, the late foetus¹⁴⁹⁻¹⁶¹ and the newborn¹⁶² are relatively more resistant than the adult; but, only two days after birth, a two-week period of extreme sensitivity sets in, during which sterility is much more readily induced than in the adult.¹⁶²

83. The fertility of animals irradiated *in utero* or in early post-natal life can be understood only in terms of the normal development of germ cells and the sexual dimorphism which exists in this respect. During mitotic divisions of the primordial germ cells or their precursors, males and females are about equally sensitive to radiation-induced depression in fertility. In the mouse, both sexes, when irradiated with 200 r as 7½ or 9½ day embryos, show somewhat depressed fertility throughout their lives.¹⁶³ In the female, the fertility depression becomes greater following irradiation at a later stage, day 11½ postfertilization, and even greater for day 13½.¹⁶³ Similarly, the developmentally corresponding stage in the rat, day 15 is, by histological criteria, the most sensitive of the foetal stages.¹⁶⁴ It should be noted that mitosis of the primordial germ cells in the female is at a maximum at this stage. In the male rat, on the other hand, sensitivity continues to increase and is highest on day 19.¹⁶⁵

84. With the onset of meiotic prophase, sensitivity is found to decrease, well in accord with the relative radiation-resistance of this stage demonstrated in a wide variety of organisms. In the female mouse and rat, meiotic

prophase begins about four days before birth. In male foetuses of the same age, however, the germ cells present are still in a primordial stage and undergoing mitosis. This sexual dimorphism in development explains the apparent reversal from the adult situation of differential sensitivity of the sexes that has been observed for late foetal stages¹⁴⁹⁻¹⁵¹ when males are more sensitive than females.

85. Shortly after birth, when the progress of meiotic prophase ceases in the female, and the oocytes assume the early dictyate phase, a period of extreme sensitivity sets in. This has been demonstrated by fertility studies¹⁵² and histologically¹⁵³ in the mouse, and histologically in the rat.¹⁴⁴ In the mouse, an LD₅₀ of 8.4 r (95 per cent confidence limits: 7.2 and 9.7 r) has been observed for oocytes in the smallest follicles of ten-day old females¹⁵¹ and even long-term irradiation has severe effects on fertility.¹⁵²

86. It may provisionally be assumed that the mouse and rat results here summarized can be extrapolated to equivalent germ-cell stages (rather than equivalent ages in other species. In particular, the existence of periods of extreme sensitivity at certain stages in the development of the human ovary is a possibility of the utmost importance.

87. The effect on foetal cells is discussed further under the section on embryos in this chapter.

Nervous system

88. The brain is more radio-sensitive than generally supposed. Although no morphological change has been seen at LD₅₀ doses, transient functional changes have been reported at low doses. Doses of 100,000-200,000 r kill almost instantly, probably by destruction of medullary centres.¹⁵⁷ With lower doses that kill hours after exposure, there is a question how much brain damage is caused directly by radiation and how much is secondary to vascular destruction. The effects of 2,500-10,000 r have been described in rabbits¹⁵⁸⁻¹⁵⁹ and monkeys.¹⁶⁰⁻¹⁶² Doses in the LD₅₀ range¹⁶³ cause no EEG changes in monkeys but these are induced within 1-2 minutes after radiation at 1,000 r/min.¹⁶⁴ Single exposures of 1,000-5,000 r of X-rays may quickly kill a few oligodendroglia and some neurons.¹⁶⁵ The developing nervous system is much more susceptible to radiation injury. Single doses of a few 100 r kill the most primitive embryonal neural cells, and as little as 20-30 r are damaging to animals.¹⁶⁶ This is discussed later in this section (paras. 170-192).

89. In contrast to the brain, the spinal cord and peripheral nerves are highly resistant. No alteration in structure or function of monkey spinal cord was found after twenty-four hours γ -radiation at 135 r/hour.¹⁶⁷ Damage of the spinal cord blood vessels by doses of 300 r and more can induce occlusive disease leading to haemia of the cord, i.e., radiation myelopathy as a late effect.

90. Radiation can condition the behaviour of rats, mice and cats so that they avoid identifiable stimuli previously associated with radiation exposure.¹⁶⁸⁻¹⁷⁰ Fast neutrons as well as γ - or X-rays can condition such behaviour. A TBR dose of 7.5 rad given animals was sufficient to alter preference for saccharin. Animals learn to avoid a compartment in which they had been irradiated, and this avoidance is more pronounced when the cues are coupled with radiation exposure. Localized

radiation to the abdomen of 54-108 r induced avoidance; similar doses to other areas of the body failed to do so, but such limited exposure was not as effective as TBR. Changes in the conditioned reflexes of dogs have been reported after single TBR and local head irradiation at 5, 10 and 20 r.¹⁷¹ Work in the USSR on effects of radiation in the central nervous system¹⁷² and on its sensitivity to low-level radiation was recently reviewed.¹⁷³ Some effects of low doses, interpreted as effects on the nervous system, are based on the concept that the CNS controls all reactions in the organism. Thus, post-irradiation pancytopenia is considered an effect mediated via the CNS.¹⁷²

Eye

91. The lens of the eye is highly susceptible to irreversible damage by radiation. Sensitivity varies with subjects and with type of radiation. Doses of 15-30 r, X-rays and possibly 1 rad of fast neutrons¹⁷⁴ induce minimal lens opacities in the mouse; the threshold sensitivities of rats, rabbits, dogs and man decrease progressively for X-rays, β -rays and neutrons.

92. The retina is more resistant than the lens. In the monkey, 2,000 r destroys the rods; 30,000 r induces morphological change in all retinal elements.¹⁷⁵⁻¹⁷⁶ Retinal haemorrhages, retinitis, choroiditis, and iridocyclitis developing days to weeks after TBR are due to systemic alterations.¹⁷⁷

93. Some very low doses—0.5 to 1.0 mr—give the sensation of light in man.¹⁷⁸ In frogs, electroretinograms (ERG) and the discharge of nerve impulses by retinal ganglion cells in response to retinal irradiation have been measured.¹⁷⁹ Less than 11 r caused an immediate temporary rise in the light threshold, and 0.7 r caused an immediate temporary rise in the X-ray threshold 5 \times greater than the rise in light threshold caused by a threshold light stimulus. Doses of 5-100 r, after temporary intensification of the electrical response of the retina to light depress it down to complete loss even after the lowest dose.¹⁸⁰ The conclusion that high-energy irradiation of the eye produces effects with doses as low as 0.5 mr needs further study.¹⁷⁹

Liver

94. Judging by morphology, the liver is radio-resistant as compared with other organs although minor cytological changes have been seen.¹⁸¹⁻¹⁸⁵ A low (6 per cent) casein diet tends to result in cirrhosis several months after rats are given 500 r.¹⁸⁶⁻¹⁸⁷ Liver regeneration, as measured by weight recovery, is not impaired by 20,000 r.¹⁸⁸ On the other hand, sublethal TBR greatly increases the frequency of abnormal mitoses in regenerating liver of the rat for at least 250 days.¹⁸⁹ Decreased incorporation of P³² into DNA of irradiated regenerating liver¹⁹⁰ may, in part, be due to decreased uptake by reticulo-endothelial cells.

95. Changes in liver mitochondria were found in mice 6-8 hours after 500-1,200 r; their structural stability decreased; they became vesiculated, globulated, and fragmented; and were also decreased in number.¹⁹¹ These alterations are not specific for radiation.

Kidney

96. Because impairment of renal function does not contribute to mortality after TBR, the kidney is considered radio-resistant; this is supported by clinical

radio-therapeutic experience. Only if several times the lethal dose is given the kidney are marginal changes in renal function seen in dogs¹⁹² and rats.¹⁹³

97. Nephrosclerosis developing several months after exposure has been described in mice given 500 r;¹⁹⁴ mice surviving doses of 800 r after treatment with splenic homogenates died probably of renal failure.¹⁹⁵ Similar lesions (radiation nephritis) have been seen in dogs and man after local irradiation of the kidney region with larger doses. Avian kidneys are much more sensitive than mammalian kidneys.¹⁹⁶

Circulatory system

98. Within a few hours after exposure to single doses of X- or γ -radiation in the LD₅₀ range, arterial blood pressure drops. It usually soon returns to normal and remains so until a few hours before death. Although this initial decrease has been reported in every species examined, death from circulatory collapse may be induced by LD₅₀ doses in the rabbit, chick, duck and burro.

99. Although only massive doses of radiation induce histological change in the heart, ECG changes have been found in dogs,¹⁹⁷ hamsters,¹⁹⁸ and rats¹⁹⁹ after LD₅₀ doses. ECG changes are at least in part due to change in potassium concentration in serum;²⁰⁰ radiation causes release of potassium from the isolated rabbit heart and from the heart irradiated *in situ*.¹⁹⁹ Doses of 1,000-2,000 r produce slight vasodilation in the perfused isolated rabbit ear; doses of 2,500 r and above bring immediate vasoconstriction;²⁰¹⁻²⁰² after 8,000 r flow is completely inhibited for fifteen to twenty minutes; the blood vessels are damaged at all those doses as indicated by the appearance of increased amounts of protein in perfusion fluid.

Endocrines

100. In general, doses in the LD₅₀ range induce few signs of damage in endocrine tissue. The normal adult thyroid gland is fairly radio-resistant: 17,200 r given locally causes negligible changes in rats;²⁰³ 10,000 r may cause histological change in dog thyroid.²⁰⁴ Local irradiation of the thyroid of young or mature rats with 5,000 r X-rays does not cause morphological change, modified basal oxygen consumption, or loss in body weight.²⁰⁵ In tadpoles more than 20,000 r are needed to alter the thyrotropic function of the pituitary.²⁰⁶

101. Doses of 5,000 r alter the alpha cells of the islets of Langerhans in the pancreas; beta cells show little change below 20,000 r.²⁰⁷ Adrenals show degenerative changes after heavy local irradiation (> 5,000 r) but after 1,000 r only minimal morphological change in cortex and medulla.^{208, 209}

Skin

102. Degree of skin damage after irradiation depends on the dose received and also on the species of animal. Individual differences in sensitivity are fairly large. Furthermore, the various structures of the skin have large differences in sensitivity.

103. Epithelial changes in the skin of the mouse ear have been described after a dose as low as 35 r.²¹⁰ Epidermal mitoses are much reduced. After 600-800 r TBR some inflammatory reactions with slight hyperemia and some oedema are seen.^{89, 104, 211, 212} After higher doses the epithelial cells become swollen and vacuolated. Vascular changes presumably play a great role. After severe irradiation the inflammatory changes may be followed by sclerosis with loss of elastic fibres and hyalini-

zation of the collagen. The skin reactions generally are more severe after exposure to less penetrating radiation.

104. From extensive studies on the effects of locally applied radio-isotopes on the skin, it has been found that exposure of the skin to external β -irradiation may induce severe skin lesions.

105. According to Moritz and Henriques²¹³ β -irradiation of pig skin produced epidermal atrophy, appearing one to two weeks after exposure and lasting for two to three weeks, often with ulcerations and transepidermal necrosis. Healing was slow, and often a chronic radiation dermatitis persisted.

106. Presumably the late deleterious changes in irradiated skin are the direct result of radiation damage to epithelial cells and indirectly the result of starvation and anoxia of these cells due to vascular radiation trauma. Radio-sodium clearance measurements have, however, led to the startling observations that the effective blood flow in these densely fibrotic, scarred, and atrophied tissues is functionally unimpaired at any time up to years after irradiation.²¹⁴ This indicates that vascular damage plays little role in the deleterious changes after skin irradiation. Some of the changes in the skin after irradiation may be secondary to infection in radiation-induced ulcerations.

107. The skin is more resistant to tumour induction by irradiation than most internal organs. Cutaneous tumours, however, were the first noted in man, owing to the relatively soft X-radiation used earlier and lack of adequate filtration.

108. In animals, tumours of the skin have been induced mainly by β -radiation, and co-carcinogenic or promoting effects have been observed from application of chemical carcinogens²¹⁵ or croton oil²¹⁶ respectively.

Bone

109. Bone tissue is generally believed to be relatively radio-resistant. Some observations, however, indicate that bone tissue damage may follow even a rather low dose. This is especially so in young individuals. The foetal skeleton is highly radio-sensitive; the system responsible for bone growth may be especially severely damaged by irradiation. The growth of long bones may be inhibited. This is seen in rats after a dose of 600 r.²¹⁷ A single dose of 400 r TBR of rats reduced the number of osteoclasts.

110. The retardation in osteogenesis is permanent and irreversible after 2,000 r local irradiation in rats, and 5,000 r to the femurs of guinea pigs caused a complete osteonecrosis.

111. A characteristic feature after irradiation of bone tissue is the absence of any demarcation between normal and irradiated parts. Irradiated bone is more easily infected than normal bone, especially if necrotic spots are present but healing of fractures is not significantly altered after moderate doses.

112. The effects of internal irradiation on bone are described in section VI below.

LATE EFFECTS

*Life-shortening*²¹⁸

Introduction

113. In mammals radiation in substantial doses to whole- or part-body shortens life-span. In part-body

exposure, the life-shortening effect is variable depending on the kind and amount of tissue irradiated as well as dose. Radiation may shorten life-span by: (a) damaging a specific tissue (e.g., dermatitis followed by skin cancer); (b) inducing a specific disease (e.g. leukaemia); (c) producing more generalized changes (e.g. lowered immunity, damage of vasculo-connective tissue and premature aging).

114. Data for man are yet inadequate to assess the effect of radiation on life-span. From animal data and the increased incidence of leukaemia in man after total-body or marrow irradiation, some life-shortening is to be expected.

115. Comparisons of mortality rates of United States radiologists with other physicians and the general male population indicate that occupational exposure may have slightly increased mortality rates of radiologists in past decades. The cumulative doses are not known for individuals; the dose-life-shortening relationship cannot therefore be measured. British radiologists showed no clear increase in mortality rates. This subject requires further study.

116. In animals, the survival time for given dose rates is generally shorter the more energy absorbed. Life-shortening is less for a given dose absorbed over a long time than over a short one. Some evidence suggests that radiation-induced life-shortening depends on genetic constitution, age, and clinical status at exposure.

117. Animals irradiated with substantial but sublethal TBR, after recovery from the acute early illness, die prematurely. They develop the diseases of their species earlier than usual and deteriorate sooner than non-irradiated controls, with various physiological and histopathological changes suggestive of senescence. At a first approximation, comparison of mortality curves of survivors of acute radiation mortality and controls suggests that radiation causes premature aging in an actuarial sense.

118. Some premature deaths after radiation are due to the increased incidence of such diseases as malignant neoplasms. This is especially true after localized irradiation from external sources or from locally deposited radio-active materials. After TBR the number and variety of diseases induced are greater than after localized irradiation. At their respective median death times, animals whose lives are shortened by single TBR and controls usually have approximately the same diseases, although not necessarily the same proportions. Irradiation may separately induce each of the diseases of advanced age or cause a general deterioration of body tissues that advances the onset of most diseases to roughly the same extent. Some animal species or strains are unusually susceptible to certain diseases, e.g. ovarian tumours and lymphatic leukaemia in mice, and mammary tumours in rats.

119. In general, irradiation increases the incidence and severity of recognizable diseases at given chronological ages. When these diseases appear rarely or not at all in controls, or are thought to have different pathogeneses from similar diseases in controls, they are regarded as having been induced by radiation. Diseases common to the population which appear earlier in irradiated animals than in controls are regarded as having been advanced by radiation. In many experiments both effects may be combined, with induction relatively greater after local radiation and advancement relatively greater after TBR.

120. The life-span of animals often falls short of the potential because infectious diseases kill many well before senescence. In man, the counterparts of these life-limiting diseases have been largely eliminated in countries with adequate medical services; non-infectious diseases associated with senescence are prominent. In animals, diseases of long latency may rarely or never develop spontaneously within the life-span observed. Consequently, it is possible that some, if not all, diseases considered induced by irradiation may be diseases of long latency whose onset has been advanced. When intensive, localized irradiation causes a high incidence of certain diseases, induced or advanced, to the irradiated part, the incidence depends on the latent period of the disease relative to the development of other terminal diseases to which the animals are susceptible. This, in turn, depends on the age of the animals.

121. These considerations on the effects of irradiation on life-span, mortality curves, cause of death, and time of onset of disease, together with available information on clinical, physiological and histopathological effects of irradiation, indicate a resemblance between the pathological events underlying radiological life-shortening and premature aging processes. Whether the two processes are similar is not clear, and whether they are identical cannot be decided until the causes of radiological life-shortening and physiological aging are better understood.

*Life-shortening by single doses in animals*²¹⁸

122. Recent data demonstrating life-shortening of mice and rats by single TBR with X- or γ -rays have been given.²¹⁹⁻²³¹ Data on rodents indicate that the life-shortening effectiveness of single TBR with X- or γ -rays increases as dose increases. The life-shortening can be expressed either as an absolute time interval or as a percentage reduction of life span. The use of the latter definition in the following paragraphs does not imply that a value obtained for one strain or species will necessarily hold for another of different life-span. For doses up to 300 rad, the reduction per 100 rad is constant or slowly increases with dose, but increases rapidly for doses approaching the LD₅₀. Other data are not inconsistent with a linear relationship.²³² At doses from 200-500 rad (γ), the reduction is 2-4 per cent per 100 rad depending on dose. As one approaches the LD₅₀ (600-800 rad) etc., reduction of life-span is accelerated about 25-50 per cent (5-10 per cent per 100 rad).

123. Doses < 200 rad do not usually significantly shorten life in the numbers of rodents tested to date. On the assumption that effect remains proportional to dose down to the smallest doses, extrapolation from present data gives an upper limit of ~ 1-5 per cent per 100 rad to the life-shortening effect of single doses below 200 rad. It is possible that effectiveness falls below this value for 10 rad or less.

124. Female mice show more life-shortening than males at all dose levels, presumably due to endocrine disturbance after radiation damage to the ovary. The extraordinary radiation sensitivity of mouse ovary has no known parallel in other species, nor is there evidence of disproportionate life-shortening in female rats or guinea pigs. There is no basis for expecting a large sex differential in life-shortening in man.

125. The RBE of fast neutrons for shortening life is compared to X- or gamma-radiation ~ 2-3 at the LD₅₀ level. The RBE for life-shortening is thus about the same as that for acute lethality. Although survival data

after a wide range of neutron doses are not yet available, accumulating evidence suggests that life-shortening is nearly proportional to dose, rather than an accelerated function as after X- and gamma-rays. Consequently, the neutron RBE for life-shortening increases as dose decreases. If the X- and gamma-ray effectiveness becomes proportional to dose, at sufficiently small doses the RBE for life-shortening by fast neutrons may approach a limiting value. The highest value so far experimentally seen is ~ 10 .

126. Several studies are in progress^{220, 238, 234} on life-shortening after a wide range of dosages; data from Operation Greenhouse¹⁹⁴ remain the most extensive. The conclusion²³⁵ that life-shortening is a non-linear function of dose, with an accelerating rate of loss of life with increasing dose, has been challenged.²³⁶ The data of Gowen and Stadler²³¹ covering a wide dose range indicate a curvilinear relationship; and the data of Storer and Sanders²²⁶ compatible with a linear relationship, do not permit a choice between the alternatives. No studies to date provide direct evidence for or against a threshold dose below which radiation is ineffective.

*Life-shortening by multiple doses or protracted irradiation in animals*²¹⁸

127. Small animals given comparatively small daily doses of X- or γ -radiation for several months or more have about 11 per cent life-shortening per 1,000 rad. The effect is proportional to dose, or nearly so, for accumulated doses of 500-2,000 rad or more. This factor is consistent with the rough estimate given for life-shortening by small single doses.

128. The dose-effect curve for exposures over days and weeks falls between those for single doses and those for highly fractionated exposure; the slope of the curve diminishes as exposure time lengthens. But, there is no sharply defined point on one side of which response is similar to that with a single dose and on the other response is similar to that for continuous exposure. Effects intermediate between single and continuous exposure have been shown.²³⁵ At present, data are insufficient for formulation of empirical relations to predict responses for all conceivable fractionation schedules. One difficulty is the variable response of different strains of mice. Appropriately timed fractionated exposures are clearly more leukaemogenic than single exposures^{237, 238} for certain strains with a high susceptibility to radiation-induced lymphatic leukaemia. In such mice if leukaemia is a major cause of death, fractionated exposures may be more potent in life-shortening than single exposures²³⁸ even though the incidence of degenerative diseases, such as nephrosclerosis, decreases with increasing fractionation. Such data can be corrected for the high incidence of leukaemia, or other strain or sex specific tumours to evaluate life-shortening from other causes.²²⁴ Corrected data, unfortunately, are not usually reported. Data on life-shortening effect of a long-term protracted radiation with fast neutron compared to X- or gamma-radiation suggest an RBE of around 10.

*Age effects*²¹⁸

129. Kohn and Guttman²²⁹ studied the important problem of the effect of age at time of radiation on life-shortening in mice. Mice given single X-ray exposures at ages 160, 435 or 535 days had less life-shortening than mice irradiated at later ages. Total gross tumour incidence was also decreased. In another study, Kohn²³⁹

found that exposure of mice 730 days old did not reduce life-span. An explanation for this decrease in effect with age is perhaps found in experiments²⁴⁰ in which mice 435 days old exposed to 500 r of TBR had an increased death rate over controls twenty-four weeks later in male mice and sixteen weeks later in females. Thus the damage which induces premature death evolves slowly and since twenty-four weeks are an appreciable fraction of normal life-span, irradiation of animals late in life does not allow sufficient time for damage to express itself.

Partial-body exposures

130. Partial-body exposure of mice and rats is far less effective in shortening life-span than TBR.^{228, 230, 242-248} The extent of life-shortening depends on area irradiated, size of field, and total dose. Maisin *et al.*²⁴² found that in rats survival curves had different shapes depending on body part exposed. They concluded that the TBR survival curve is a composite of partial-body curves and that injury to various body regions summates to produce the total-body effects. Lamson *et al.*²⁴⁰ reported that life-shortening was roughly proportional to the percentage of body radiated. But no clear-cut relationship allows direct extrapolation of TBR information to partial-body exposure.

*Role of genetic constitution and physical status*²¹⁸

131. Information on the influence of genetic constitution on long-term survival after radiation is meagre but permits preliminary discussion. Most work on genetic constitution in radiation-sensitivity of mammals examines differences in response of genetically homogeneous (inbred) mouse strains and their hybrids. Susceptibility to early, acute death differs by somewhat less than a factor of 2 between the most sensitive and the most resistant strains. Resistance to acute death is apparently correlated with general vigour; most radiation-resistant strains are longer-lived and less susceptible to spontaneous infectious disease. A short life-span, if due to high susceptibility to leukaemia does not appear to influence susceptibility to acute death.

132. Lifetime follow-up of several inbred strains and their hybrids after radiation indicates that the number of days lost varies less between strains than does acute sensitivity. Most strain differences in life-shortening is due to strain difference in susceptibility to radiation-induced leukaemia; when leukaemia mortality is excluded, life-shortening due to all other causes varies comparatively little between strains and is independent of normal life expectancy. Thus, in the mouse, a major component of life-shortening is independent of genetic make-up, aside from the variable susceptibility to leukaemia and ovarian tumour. The contribution of these strain-specific diseases to total mortality is greater in the mouse than in other species for which data are available; nevertheless, the range of variation in over-all life-shortening between strains is less than a factor of 2.

133. These results only partially answer the role of genetic constitution on life-shortening even in the mouse. Inbred mouse strains are highly selected genetic material from which many genes that could alter viability may have been eliminated. These genes are maintained in wild populations by various mechanisms, some of which could make an additional contribution to life-shortening by radiations. Furthermore, several of the most widely used mouse strains are genetically related, and are therefore unrepresentative of the genetic potentialities of the species.

134. Human populations are genetically heterogeneous. There is as yet no way to determine the influence of this heterogeneity on radio-sensitivity from individual to individual. Ethnic differences in spontaneous leukaemia incidence suggest that, in man, as in the mouse, genetic constitution plays a role in susceptibility to radiation-induced leukaemia.

• 135. A fraction of the human population may have hereditary traits giving extraordinary susceptibility to radiation-induced malignancies. Existence of such a trait can only be established from data on familial tendency towards such susceptibility or from a demonstrated correlation between such malignancy and some other genetically determined trait. Large numbers of presumptive radiation-induced cases would be required; may they never become available.

136. Vigour or fitness probably correlate with acute radiation-sensitivity in man—as in experimental animals. Study of the influence of nutrition, exercise, disease, and other environmental and physiological variables on radiation effects has only begun; present judgements must therefore be based on incidental clinical and experimental observations.

137. Stresses may activate chronic or latent diseases. Radiation may so act in certain disease; e.g. *inactive tuberculosis* in monkeys and man and diseases caused by *Bartonella* or *Salmonella* in rats. The nature of activation is unknown, but is probably due to impairment of immunological response.

138. In contrast, a therapeutic or prophylactic effect of irradiation on certain infectious diseases can mask the life-shortening effect in experimental animals. The observed life-span of animals is sometimes greater with daily doses of 1 rad or so throughout adult life than that of their controls.

Life-lengthening

139. Data on rodents exposed to small accumulated doses (about 100 to 400 rad per lifetime) at low dose rates were puzzling because such animals frequently survived longer than controls.^{244, 245} Although sampling errors and bias in experimental conditions may have contributed, some recent findings suggest this effect may be real.²⁴⁶ In many experiments showing increased survival, there was considerable intercurrent mortality early in life in control animals, presumably from infectious disease, whereas irradiated animals had less mortality in the same period. There is no evidence the maximal life-span is extended in this situation, or that the incidence of cancer or degenerative disease is decreased. Since the cause of the prolonged survival is unknown, the significance for man is unknown.

Nature of the lesion in life-shortening

140. The primary lesions responsible for non-specific life-shortening in irradiated animals have not been identified. Casarett and co-workers^{247, 248} view arteriolo-pillary fibrosis as the major radiation effect. If they are correct, it should be possible to show deficits in circulation in various organs and decide whether these deficits go with normal aging. Such findings would not prove a cause-and-effect relationship, but would at least show an association. Various hypotheses and models to explain aging and life-shortening by radiation have not proved as guides for histological or physiological studies. Formation theory and somatic mutation²⁴⁹⁻²⁵⁵ do not indicate experimental approaches going beyond the

presently recognized genetic apparatus. Statistical theories based on fluctuations in mean physiologic state^{254, 256} point to whatever the investigator is familiar with as potential areas for study. Theories based on irreparable levels of injury^{257, 258} point out methods for measuring the level without achieving its identification and similarly the hypothesis of progressive loss of ability to repair damage²⁵⁹ does not tell anything about the repair function itself. Life-shortening probably summarizes so many insults that one must be careful not to single out any particular lesion as of primary importance—at least not without overwhelming new evidence. The only clear candidate as an especially vulnerable site of radiation damage is the replication of DNA as noted earlier.

Radiation carcinogenesis

141. Data from irradiated animals and man indicate that enough radiation to almost any part of the body increases the incidence of malignant neoplasia.⁸⁹

142. Radiation-induced tumours often take long to develop, not beginning necessarily immediately after obvious changes in the cells. Obvious tissue disorder need not exist at the site of origin of the cancer: radiation can induce malignant disease through physiological mechanisms as with e.g., ovarian, thymic and pituitary tumours in mice which are clearly indirect (i.e., where irradiation of the cells of origin of the neoplasm is not the critical factor).

143. Most animal experiments, usually with relatively homogeneous populations, have shown that there are dose levels that induce no detectable increase in incidence of certain neoplasms. Some investigators construe such data to mean that there is a threshold dose of radiation below which certain neoplasms cannot be induced or their age-specific incidence increased. It must be recognized that no dose-incidence experiment can prove the existence of a true threshold dose since, however large the number of animals used, the tumour incidence at a given dose may be too small to be demonstrated. On the other hand, a linear dose-effect relationship extrapolating back to zero dose would strongly suggest the absence of a threshold dose. This has been demonstrated in a few experiments for certain types of tumour.

144. A major difficulty in short-lived laboratory animals is that at low doses the latent period for tumour induction may exceed the life-span and hence no effect may be seen.

Relation to rate of mitosis²⁶⁰

145. Although neoplasia arises most commonly in proliferating tissues, in the long-term effects of Operation Greenhouse (mice exposed to atomic bomb radiation—table II) tumours of lung, liver, mammary gland stroma, and anterior hypophysis—sites of relatively slow cell turnover—were more frequent than those of skin, bone marrow, and intestinal mucosa—sites of more rapid cell turnover.

Relation to age

146. In the same study²⁶⁰ the incidence of all tumours increased with time after irradiation, with one exception. This was lymphoma of thymus, which reached a maximum early in life in heavily irradiated populations. Tumours arose earlier in irradiated mice and then advancement in onset corresponded to reduction in mean age at death of the entire population. As regards the influence of age at the time of irradiation, diverse effects

have been seen. Osteogenic sarcomas and tumours of the gastro intestinal tract have shown a higher incidence in animals irradiated when young, whereas the reverse occurs with leukaemias and tumours of the mammary gland.²⁶¹

Relation to radiation dose

147. The relation between tumour incidence and dose varied from one neoplasm to another. The incidence of some increased with increasing amounts of irradiation (e.g., thymic lymphoma), the incidence of others was maximal at intermediate dose-levels (e.g., hepatoma, ovarian tumour, pituitary adenoma), and some usually common, decreased in frequency with increasing dose (e.g., non-thymic lymphoma, sarcoma of breast, adenoma of lung).²⁶⁰ In no instance did tumour incidence vary as a simple linear function of dose, and extrapolation, therefore from the high doses in this experiment to doses near those from natural environmental radiation is not possible, and the question of whether or not very low doses of radiation cause some slight increase in the over-all risk of malignancy (so-called threshold) remains unsettled. As a general rule, single-dose irradiation is more effective in producing cancer than greatly protracted exposure with the same dose.

Mechanisms of carcinogenesis

148. Of the various neoplasms induced by radiation some may be caused indirectly without irradiation of the tumour-forming cells themselves. Thus in certain strains of mice, presence of the thymus is necessary for induction of lymphomas²⁶² although the thymus itself need not be irradiated. Strong evidence that induction is indirect is given by the neoplasm arising in a normal thymus transplanted to an irradiated host.²⁶³ In other strains, thymectomy shifts the site of origin of the tumour to other lymphoid tissue.²⁶⁴ Repeated radiation in proper sequence causes a higher incidence of lymphoma in mice than do single exposures to the same total dose.^{237, 264, 265} Inoculations of normal bone marrow or spleen,¹⁹⁵ partial shielding^{265, 267, 268} and certain radiation-protective agents,⁷⁰ decrease incidence. There is dose-rate dependence in response^{269, 271} that, together with the incidence after various radiation dosages²⁶⁵ suggests a curvilinear relationship between dose and response.

149. Indirect carcinogenesis also appears responsible for the development of thyrotrophic pituitary tumours in mice thyroidectomized by I¹³¹.²⁷² Such tumours may possibly be more readily induced if the pituitary is also irradiated.^{273, 274} Other pituitary tumours are as readily induced by local radiation of the pituitary as by TBR, suggesting that their pathogenesis is direct.²⁷⁴ For these as for many other types of radiation-induced tumours, the relative importance of direct and indirect causes is not yet understood. In certain instances, both causes seem to operate; e.g., the induction of ovarian tumours depends on destruction of ovogonia and oocytes by direct irradiation and on gonadotrophic stimulation of remaining ovarian stroma by pituitary hormones.²⁷⁵

150. Studies on radiation-induced mammary gland neoplasia in the rat^{276, 280} have shown that a single sublethal dose of X- or γ -irradiation in young male or female rats results in an increased incidence of mammary gland neoplasia. The dose-effect relationship appears linear over 25-400 r, and the curve within limits of error, extrapolates to zero. No data are obtained below 25 r; above 400 r, etc., the curve was either flattened or declined, since

the greatly increased incidence at 400 r depends on intact ovarian function and direct radiation injury to the breast is necessary for an increased incidence of radiation-induced neoplasia. These results indicate that primary radiation damage to the breast tissue is necessary, but this primary damage can be dormant and not result in neoplasia unless an additional mechanism is operative.

Somatic mutation theory

151. Under a broad definition of mutation, generally used by geneticists, as including all sudden heritable changes in a cell line, the somatic mutation theory of carcinogenesis can embrace almost all currently proposed mechanisms (e.g., gene mutation, chromosome breakage or loss, mutation or loss of cytoplasmic particles, or even virus infection). Under such circumstances the theory is reduced to a truism and merely serves to describe well-known characteristics of malignant disease. As a special case of this, simple gene mutations or other single-hit changes have often been invoked as a single basis for radiation-induced neoplasia, and incidentally as a basis for predicting effects under conditions that preclude direct observation. The simple point mutation hypothesis remains to be substantiated, as does the theory that naturally occurring point mutations cause "spontaneous" cancer.^{281, 282} A widely held view has been that, if a single hit on a gene or other cellular structure were the basis for radiation-induced neoplasia, then the dose-effect relationship might well be linear with no-threshold. The rat mammary tumour data and others indicate both a primary and secondary mechanism in this type of radiation-induced neoplasia. The neoplasms themselves were seen only when both mechanisms were operative. The secondary mechanism in the present situation (normal ovarian function) could not reflect a somatic mutation. Even if the primary event were a somatic gene mutation (or a single-hit chromosome break), the dose-effect curve²⁷⁸ would not have been linear with no-threshold unless the secondary mechanism were operative. It follows therefore that lack of linearity and of an apparent threshold does not rule out somatic mutation as the primary event. Lack of such a response might simply indicate a non-operative necessary secondary mechanism.

152. Furth³³⁰ concludes from the findings of several authors that radiation-induced rat mammary gland neoplasia "are best interpreted by supposing that radiation causes a subtle, irreversible change in the mammary gland which remains latent until the organ is subjected to proliferative stimuli".

153. The demonstration of a two-stage mechanism in the induction of some neoplasms throws doubt on the use of dose-response curves as arguments for or against the point mutation theory (or any simple one-hit theory). No "one" experiment even if the animals are numerous can settle this question for all types of malignancy and all circumstances. If the dose-effect curve is not linear, nothing would have been necessarily proved about the primary mechanism. If a linear no-threshold response obtained down to the lowest doses, the somatic mutation interpretation, if it could be made under these circumstances, would apply only for the particular neoplasm in the particular strain and species. Extrapolation would not be valid.

Chromosomal changes and carcinogenesis

154. The role of chromosomal changes as an intermediate cause in carcinogenesis has been widely de-

bated.^{284, 285} Malignant tumours often have aberrant (usually aneuploid) chromosome numbers and a high degree of instability in chromosomal constitution.²⁸⁶ It by no means follows that the chromosomal changes are the cause of the malignancy; inaccuracy in the transmission of genetic information may be merely the price of proliferation at unrestricted speed. Association of chromosomal variation with tumours therefore does not of necessity imply any cause-effect relationship.

155. Chromosomal aberrations can be induced in normal human and monkey cells cultured *in vitro* by X-ray in doses as low as 25 r^{287, 288} and such aberrations (presumably of mixed 1-hit and 2-hit origins) in *in vivo* monkey bone marrow cells show a rough proportionality with doses from 50-100 r. Blood cells cultured from two patients given radiation for ankylosing spondylitis showed numerous chromosome structural abnormalities but these rapidly declined in number.²⁸⁹ Similar changes have been seen in patients with chronic myeloid leukaemia after X-ray treatment.

156. The persistence of chromosome aberrations in peripheral blood leukocytes ~ 2½ years after accidental whole-body irradiation of eight men by mixed gamma and fission neutrons has recently been reported.⁷⁸¹ Five men received doses > 230 rad; three others, < 70 rad. The frequency of cells with chromosome counts differing from 46 ranged from 4-23 per cent in the irradiated compared to 2 per cent in controls. In the five cases with high doses, there were grossly altered chromosomes such as rings, dicentric, and minutes; these were often in cells with abnormal count with a frequency of 2-20 per cent. No polyploidy was seen. A detailed karyotype analysis of some normal-looking cells from irradiated individuals revealed the presence of pericentric inversions, translocations, and deletions. A comparison of the frequency of induced chromosome breaks in tissue culture preparations suggests that the frequency of aberrations diminishes with time, and that polyploid cells are eliminated more quickly.

157. There is increasing evidence of an association of specific types of leukaemia with chromosomal anomalies. In many cases of chronic myeloid leukaemia there is a specific abnormality (possibly a deletion) in one of the chromosomes of pair-21 or pair-22 (the Philadelphia chromosome). Variations in the proportion of cells with this Philadelphia chromosome in blood-cell cultures from different patients with myeloid leukaemia and its absence in skin cultures from the same patients strongly suggest the presence of a somatic chromosomal anomaly in these patients' leukaemic cells. Moreover, the incidence of acute leukaemia is greatly increased in mongolism, a disease²⁹¹ now known to be associated with trisomy-21. These observations suggest that either a deficiency or excess of genetic material of chromosome pair-21 may result in different types of leukaemia. For other types of leukaemia, no such consistent associations have been established as yet.^{290, 782, 783, 784}

158. These chromosomal aberrations and especially the possibility of a specific chromosome abnormality in myeloid leukaemia and the hereditary nature of the neoplastic change in subsequent cell generations suggest that cancer reflects a genetic change in the cell. But the course of evolution of malignancy in certain tumours argues against a one-stage cause, such as single point mutation or chromosomal aberration.^{285, 292, 293} Moreover, induction of neoplasia by indirect effects on the host cannot be due to the mutagenic action of radiation on the cancer-forming cells, since the cells themselves are not

irradiated. Here radiation probably merely favours selection of spontaneous carcinogenic mutants, possibly by excessive growth stimulation during recovery.

Radiation leukaemogenesis

159. Studies of radiation leukaemogenesis use the mouse because of ease of leukaemia induction and the availability of different leukaemias associated with various inbred strains. Mouse leukaemia is not a single disease; much confusion arises because precise classification is often lacking.^{294, 295} The most studied mouse leukaemia is lymphatic arising in the thymus, classified variously as thymic leukaemia, thymic lymphosarcoma, malignant lymphoma, and "mouse leukaemia". In the mouse, the thymus normally atrophies in early adult life instead of in early childhood as in man. Extensive studies by Upton *et al.*²⁹⁴ show that factors inducing this neoplasm differ from those inducing myeloid or granulocytic leukaemia. Since most radiation-induced leukaemias in man are granulocytic, thymic leukaemia of mice have little relevance to man.²⁹⁴ Myeloid leukaemia in mice, possibly more analogous to human radiation-induced leukaemia, has been studied less.

160. In spite of these reservations about the comparability of human and murine leukaemias, the leukaemia responses of the two species share certain features.²⁹⁶ Both species show an increased incidence of leukaemia after TBR. In mice, the leukaemia incidence in irradiated groups returns to or near control levels 18-20 months after exposure.^{228, 297} The Hiroshima and Nagasaki survivors²⁹⁸ had still some excess leukaemia mortality over their unirradiated controls by 1959. By adjusting time scales, human and murine experiences can be superimposed; for comparable radiation exposures, the factor of increase in age-specific leukaemia mortality over control is nearly identical for the two species.²⁹⁹

161. Data of Kaplan *et al.*²⁹⁸ indicate that lymphomata in thymectomized irradiated mice can appear at the site of transplantation when the thymus from non-exposed mice is transplanted into the irradiated animal. The origin of the neoplastic tissue has been studied^{263, 299, 301} and although in some instances the cells may be derived from the donor cells, in others they are derived definitely from recipient cells.

162. Radiation-induced myeloid leukaemias of the mouse are uninfluenced by the thymus but are reduced by splenectomy.²⁹⁴ They are more effectively induced by relatively lower radiation dosages than is the thymic form and their induction is apparently not similarly enhanced by fractionation of the exposure.²⁶⁴ Partial shielding reduces incidence²⁹⁴ as does prophylactic administration of mercaptoethyl guanidine,³⁰² a radio-protective agent. The incidence reaches plateau at radiation doses above 150 r.²⁶⁴ The shape of the dose-response curve is not definitely known, but data after doses of 16 and 32 r⁷² and after 128 or more^{294, 303} suggest curvilinearity in the low-dose range. In rats and mice injected with strontium-90, more differentiated forms of leucosis predominate when the accumulated dose to the bone marrow is small and less-differentiated forms when the dose is large, i.e., of the order of 6,000 rep or above.³⁰⁴

163. Variables besides radiation dose affect the probability of an animal developing leukaemia, e.g., strain, age at time of irradiation, sex, and endocrine status. Leukaemia incidence can be modified by endocrine status and genetic inheritance (by selection, hybridization, etc.) or by removal or implantation of tissues.^{294, 305-311}

Virus theory

164. Evidence that viral agents cause various types of cancer in mice³¹²⁻³¹⁶ stimulated the search for filtrable leukaemogenic agents in mice with radiation-induced leukaemias.³¹⁰⁻³¹⁸ Results as yet are not conclusive, but they suggest viruses as possible etiologic agents in radiation-induced leukaemia.²⁹⁸ Depression of host immunity by radiation may promote infection by an exogenous carcinogenic virus or radiation may activate a latent carcinogenic virus infection analogous to the induction of lysogenicity in bacteria. To these hypothetical mechanisms must be added the possibility of viral transduction of carcinogenic substances from one cell to another.^{312, 319}

Risk of carcinogenesis from low doses

165. Carcinogenesis is the most important late effect of radiation. Knowledge of the mechanism of radiation carcinogenesis is a prerequisite for the accurate assessment of risk at low doses. Since the mechanisms of carcinogenesis are unknown, any such assessment of risk must be purely speculative, although possibly of some value in estimating upper limits.

RECOVERY AND THE CONCEPT OF IRREPARABLE INJURY³²⁰

166. Radiation injury, like other injury, immediately sets off the classical reactions of homeostasis and repair; to some extent, radiation affects the repair processes themselves.

167. In the weeks after a single sub-lethal dose, damage gradually is repaired. Many, if not all, cells destroyed by radiation are replaced by regeneration from surviving cells. Irradiated organisms may resume a normal or near-normal appearance. With time there is recovery of resistance to lethality from further radiation. Most radiation injury from X- and γ -rays is thus frequently reparable. Animals, therefore, survive a prolonged dose several-fold larger than a single dose.

168. Despite apparent recovery residual damage (e.g., incomplete regeneration or residual defects in cells and tissues) and late effects seen after maximal recovery show that some injury is irreparable. Certain specific injuries associated with the formation of bone tumours caused by radiation are reparable. Recovery is more likely with injuries which are caused by β - than by α -radiation.^{261, 304, 321}

169. Life-shortening by radiation implies that an irreparable component of injury is detectable. This component is detectable as premature aging in an actuarial sense. But how closely this process parallels and contributes to that cumulative injury called natural aging is unclear in the quantitative sense. Likewise, it is not known whether the irreparable component represents abrupt aging at the time of injury or initiation of gradual aging. Limited observations in rodents, dogs, and swine indicate that irreparable injury is measurable, after an interval of presumed complete repair, as a reduction in acute lethal dose. This suggests that irreparable injury is at least partially sustained at the time of radiation and is potentially observable as a persisting tissue change; the distinction between reparable and irreparable injury has not yet been related to morphology.

EARLY AND LATE EFFECTS ON EMBRYOS AND FOETUSES

170. Ionizing radiations profoundly disturb development of embryos. Their susceptibility while very high may be

no higher than that of certain actively dividing and differentiating adult tissues. Irradiation of an embryo with 5-25 r causes evident changes; similar exposure of adult haemopoietic or epithelial tissues is likewise followed by morphological and functional disturbances. The difference between embryonic and adult response to low doses of radiation is that an over-all effect in embryos is even more extensive than in the adult probably because a minor irreversible injury in embryo, particularly after the blastomeres have lost totipotency, is amplified in development: morphogenetic relations are upset through death of cells in various precursor fields, and this leads to faults in the formation of adult structures.

171. Radiation effects in embryos may reflect two mechanisms: developmental alterations through cell destruction in the embryo and physiological disturbances in the mother.

The mammalian embryo

172. Mammalian pre-natal development can be divided into three periods with respect to radiation effects: (a) pre-implantation when early deaths are induced but survivors are mostly normal; (b) major organogenesis, yielding neonatal deaths and abnormalities; (c) the foetal period when sensitivity to death and gross malformations decreases. The general pattern in mice is given in figure 2.

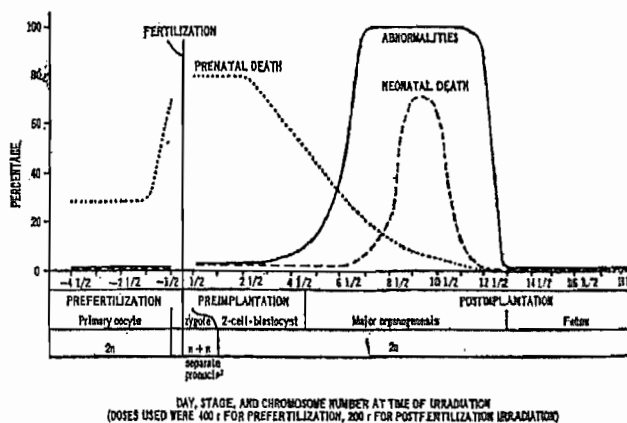


Figure 2. Incidence of pre- and neo-natal death and of abnormal individuals at term after irradiation at various intervals (separated by 24 hours) pre- and post-fertilization. Abnormal individuals may have more than one abnormality³²⁴

173. When females are irradiated after fertilization but before implantation, high and rapid mortality of the fertilized ovum is the main effect. Studies by the Russells^{322, 323} indicate that deaths are maximal for radiation given during the first two post-copulation days, and that one-third of total deaths are in the pre-implantation period. Most deaths, especially among embryos irradiated later after fertilization and closer to the expected implantation time, ensue shortly after implantation. No deaths in excess of controls occurred after day 10 1/2.

174. Survivors of irradiation in the pre-implantation period were free of obvious defects³²² had normal birth- and post-weaning heights, exhibited normal fertility and showed no evidence of decreased survival throughout life.¹⁵³ The all-or-none response to irradiation during cleavage stages which has also been observed in rats and guinea pigs³²³ has led Russell to suggest that mammalian blastomeres are totipotent.^{323, 324} On the other hand, Rugh and Grupp³²⁵ showed that a dose as low as 50 r to a pre-

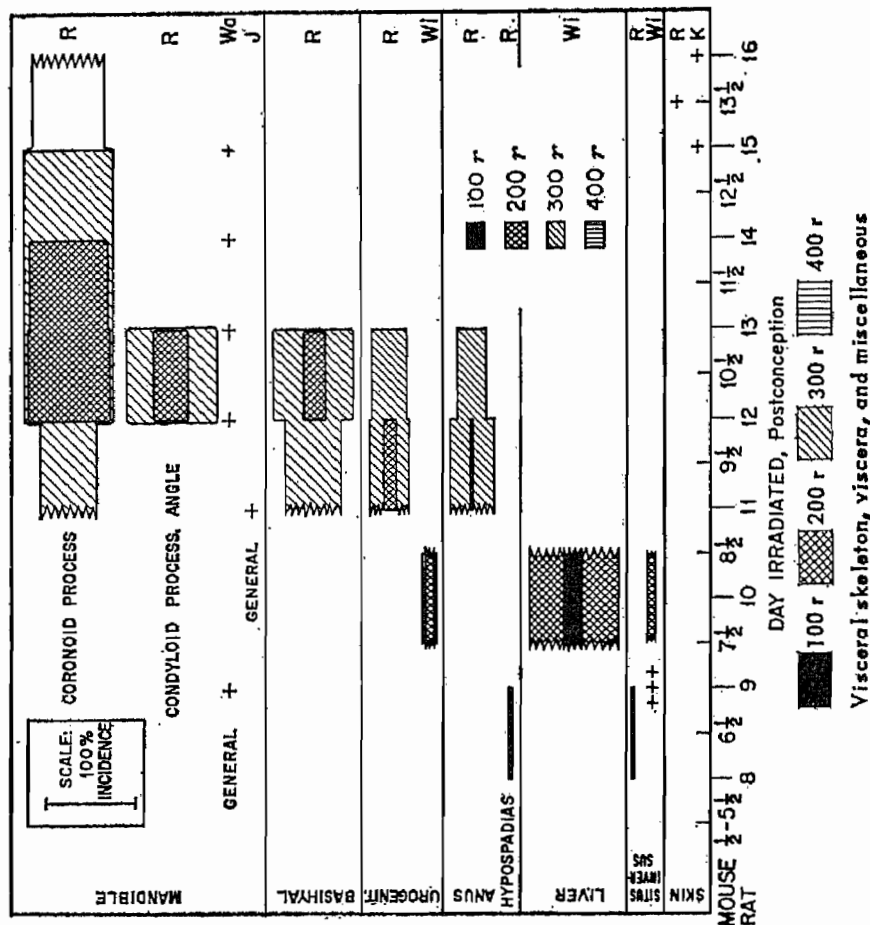
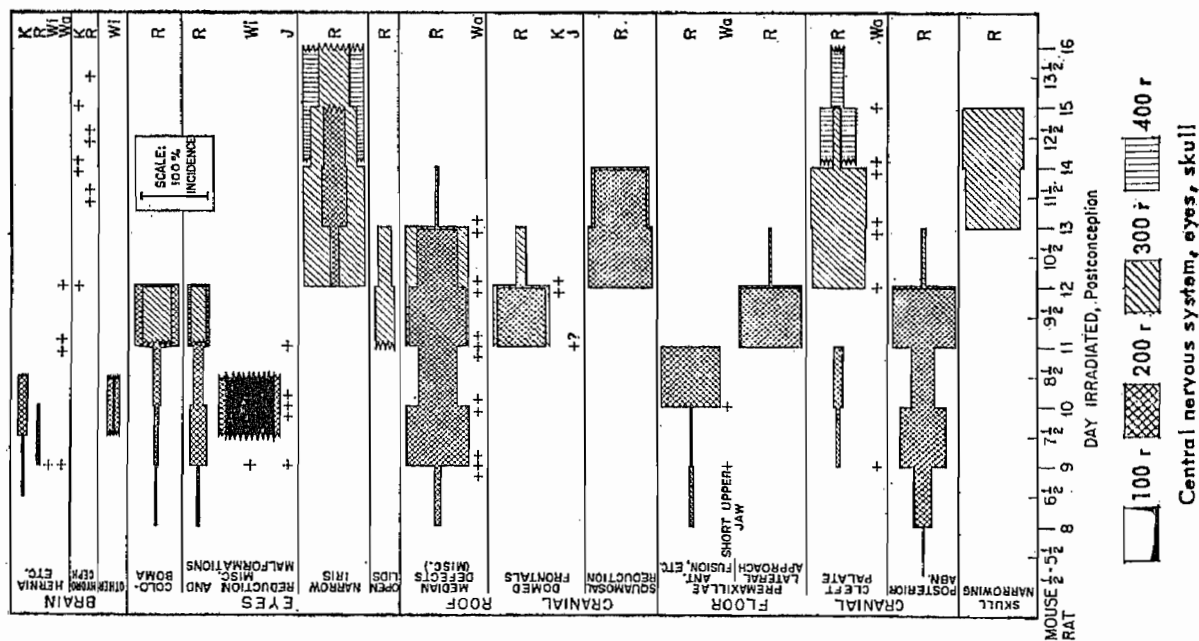


Figure 3 (continued)

implantation embryo might induce cerebral abnormalities. This result has not yet been confirmed by other investigators.

175. The pre-implantation mouse embryo is highly radio-sensitive. Earlier studies indicated that 200 r prevented about 80 per cent of all embryos from reaching the tenth day of gestation. It was recently shown that 25 r killed 38 per cent of embryos exposed before first cleavage. A dose of 5 r increased resorption.³²⁵ However, the degree of radio-susceptibility of an embryo may be species specific: the rat embryo before implantation can withstand a dose of 300 r.³²³

176. Mouse embryos given 200 r or more between gestation days 6.5-13.5 developed but had a high incidence of abnormalities. A certain proportion of the abnormal foetuses died at birth. The proportion of pre-natal deaths was much lower than in animals exposed in the pre-implantation period. The LD₅₀ for neo-natal death was > 200 r for irradiation in the pre-implantation period and through day 8.5; decreased to between 100-200 r for days 9.5 and 10.5 and then increased to 200-300 r for day 11.5 and finally to > 300 r for later periods in development.^{323, 324} With 200 r the incidence of grossly abnormal new-borns is 100 per cent for irradiation of most stages during major organogenesis. Doses as low as 25 r have been shown to be effective in causing morphological changes.³²⁶

177. Neo-natal mortality is greatest in embryos irradiated between gestation day 8½ to day 12. Exposure in the same period decreased the weight of new-born mice^{124, 323, 324} comparable quantitative studies have not been made in other mammals but there are frequent reports of marked decrease of size among rats and rabbits irradiated during development.

178. Several investigators have tried to decide whether specific developmental abnormalities depend on the stage of development at which radiation is given. Early work by Kosaka³²⁷ indicated that the brain and spinal cord are the most sensitive tissues at the beginning of major organogenesis, while at later stages thymus and, to a lesser degree, liver and spleen, become the most sensitive. A more detailed description of "critical periods" has been given by Job *et al.*³²⁸ The peak incidence of abnormalities was reached with embryos irradiated between gestation days 8-11. Hydrocephalus was easily induced in embryos irradiated at day 9, eye defects at day 10, jaw defects at day 11. According to Kaven³²⁹ the structure of the tail was most affected in embryos exposed on day 11, brain hernias on day 8, and skin defects on days 13-14. The results of Russell^{124, 330} and others on critical periods are given in figure 3. Maximum susceptibility to defects was between days 7-13, the beginning coinciding with the appearance of many differentiating centres. Irradiation at day 9 caused anencephaly, at day 10 eye defects, at day 11 hydrocephalus and spinal anomalies, and at day 12 anomalies in the fore-brain.

179. Embryonic neuro-blasts are particularly susceptible to radiation. Within two hours after 100 r, there are scattered areas of necrosis, and necrotization of individual neuro-blasts after doses as low as 40 r. With increasing exposures, more areas of developing neural tissues are affected. Intermitotic neuro-blasts are more susceptible to radiation than those in mitosis.³³¹ Cells during active differentiation may well be more sensitive than completely differentiated cells. Further studies are needed, and the radio-sensitivity of erythro-blasts, myelo-

blasts, and spongio-blasts should be compared with corresponding mature cells.

180. The existence of "critical periods" in development has thus been demonstrated, but the use of the term must be properly qualified.³²⁴ For some anomalies, the critical period is greatly extended, e.g. exencephaly can be induced by radiation at any time before neural differentiation.³³² Sometimes induction of a specific anomaly does not coincide with an apparent period of increased developmental activity, e.g. induction of polydactyly.¹²⁴ Also, the limits of periods of sensitivity seem to depend on the dose^{323, 324} and how it is fractionated;¹⁵³ however, stage of maximum sensitivity is usually revealed by the use of low-dose single exposure.

The human embryo

181. The first harmful effects of ionizing radiation on human embryos were recorded in 1901-1904. Soon afterwards, reports drew attention to serious hazards in irradiating pregnant women. Earlier clinical literature has been reviewed extensively.³³²⁻³³⁶ Table III summarizes observed malformations. Malformations specifically reported for human embryos are marked with an asterisk. The most frequent abnormalities are in the central nervous system, then eye defects and skeletal malformations.

182. Malformations among children irradiated *in utero* have been reported. In a 1929 survey of 75 children born of 106 irradiated women, 38 were abnormal, and in 28 of those the likeliest cause of malformation was radiation.³³⁷ The dose was estimated to be 30-250 r.

183. The frequency of malformations in man, as in other animals, depends upon developmental stage.

184. The marked qualitative similarities between radiation-induced abnormalities in man and other mammals make extrapolation of experimental studies to man apropos. For that purpose, a graph correlating development of mouse and human embryos constructed by Otis and Brent is useful³³⁸ (figure 4). The correlation between the appearance of some morphological features in the mouse and in the human embryo is given in table IV. Since mouse experiments have shown that

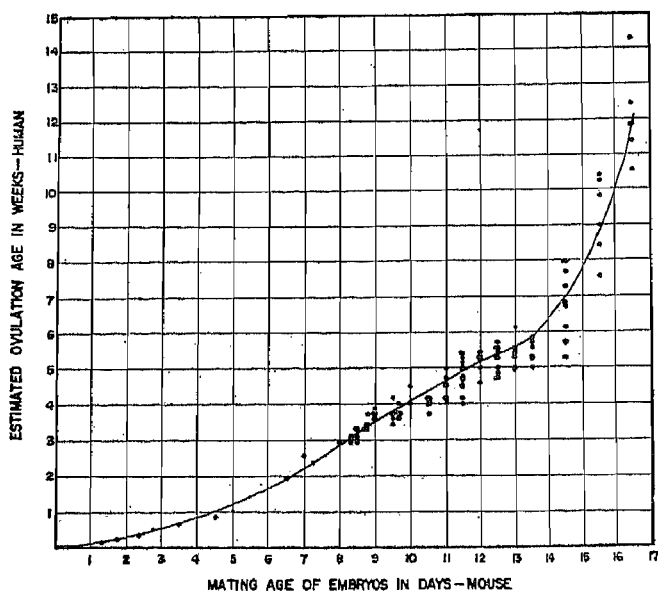


Figure 4. Graph of the time of appearance of structures in mouse and human embryos³³⁸

irradiation during the period of major organogenesis is potentially most hazardous and since part of that period occurs at a time when pregnancy may still be unsuspected Russell and Russell have suggested that whenever possible pelvic irradiation of women of child-bearing age be restricted to the two weeks following the menses.^{339, 340}

185. Besides abnormalities in embryos, fetuses, and in early childhood, several effects of irradiation during gestation have been reported, appearing at a later age in children. Stewart and collaborators³⁴¹ concluded that there was an increased incidence of leukaemia and cancer among children irradiated *in utero*, and also an increased incidence of mongolism.³⁴² Children of Japanese mothers exposed, during gestation, to atom bomb radiation tended to show stunting³⁴³ and some mental retardation, especially among boys,³⁴⁴ but neither observation has been supported by other studies.^{345, 346} Among children who, while *in utero*, had received an average of 3-5 rad during maternal diagnostic X-ray, 15 of 1,101 had phenotypic changes involving colour sectors in the iris of the eye. The incidence was only 11 in approximately 7,092 non-irradiated control siblings and parents. The difference is highly significant. This somatic effect is only seen in the children of women irradiated at 6 to 6½ months of pregnancy. It is not yet known whether the effect is due to genic chromosomal or other changes. These studies are discussed further in section V under the heading "Late effects".

Recovery and protection in irradiated germ cells and embryos

186. In the sea-urchin egg, as time elapses between irradiation and fertilization, there is the increased proportion of cleavages pointing the possibility of recovery.³⁴⁷ The effect was described by Miwa³⁴⁸ for *Pseudocentrolus depressus* irradiated with α - or γ -rays. This does not imply recovery to pre-irradiation stage.³⁴⁹ The delay between irradiation and fertilization counteracts the delaying effect of irradiation upon cleavage, but does not increase the number of embryos capable of normal development. In frogs Rollason³⁵⁰ found no evidence for this kind of recovery.

187. Recovery was seen when an organ from an irradiated embryo was transferred to a normal one. The irradiated organ, e.g. of a frog³⁵¹ or chick embryo³⁵² developed further and survived longer than it would have in its original environment. This does not necessarily denote recovery; it is perhaps better explained by assuming that the transfer of the organ removes it from the noxious environment of a dying embryo.

188. Recovery in embryonic tissues has been postulated by several authors from the observation that irradiation of embryos at an early stage brings early death, but survivors develop normally. Recent experiments³⁵³ have shown that exposure to radiation, even almost immediately after fertilization, caused marked abnormalities (brain hernia); survivors that developed without big abnormalities nevertheless showed stunting and some impairment of the ability to learn.³⁵⁴

189. After radiation-injury the embryo as a whole may show a certain recovery in that survivors of radiation continue to develop despite morphological damage.³⁵⁴ This does not imply that the injured tissues have recovered; the survivors are usually stunted and there is some topographical reorganization of undamaged tissues, which might indicate that the maintenance of viability and shape is due to some of the cells from

surrounding areas invading the lesion.³⁵² Recovery of an embryo is more the outcome of a regenerative process, aided by the remarkable powers of reorganization of embryonic tissues and scavenging activities of macrophages, than recovery of the cells actually damaged.

190. Expected radiation injury may be prevented to some extent by several factors; hypoxia, lowered temperature, and various thio compounds. Lowering the ambient temperature protects against immediate radiation effect in frogs, an effect lasting only as long as a low temperature is maintained;³⁵⁵ in salamander larvae, protection appears to persist.³⁵⁶ Also in chick embryos Goffinet³⁵⁷ protected against radiation by lowering temperature.

191. The effects of hypoxia were studied by Russell and collaborators:^{324, 358} mouse embryos exposed to doses 100-400 r had a lower percentage of abnormalities if irradiated in 5 per cent oxygen in helium. Allen, Schjeide and Piccirillo³⁵⁹ showed that the proportion of cells injured by radiation was reduced if irradiated cells were maintained afterwards in mildly anoxic conditions; anoxia reduces cell division.

192. Cysteamine as well as several other compounds protects to some extent against radiation if given before irradiation. The survival of chick embryo was improved after giving cysteamine, cystamine, and methylamine; the efficacy of these compounds was highest when the circulatory system began to function.^{357, 360} It has been observed that mercaptoethylamine can protect the rat foetus if irradiated on days 15-18,³⁶¹ and that cysteamine and similar compounds permit mouse foetuses to maintain a higher growth rate and lower mortality than irradiated untreated controls.^{362, 363}

IV. Acute radiation injury in man

ACUTE RADIATION SYNDROME

193. The acute radiation syndrome differs from ordinary injuries since there are integrating patterns of symptoms after higher doses, or a latent period at lower doses during which hidden histological changes are taking place from the time of exposure until the recrudescence of symptoms and frank danger of death. Recovery from the initial symptoms does not signify real recovery. Review of reactor accidents (see below) emphasizes the problem of inhomogeneous irradiation of the body in man and the influence of the part irradiated upon the symptoms that follow. Effects of localized irradiation on individual organs are discussed in earlier sections of the present annex.

Sources of information

194. There are four sources of information on acute radiation effects in man: (a) the largest, but studied under obvious difficulties, is the experience of the Japanese at Hiroshima and Nagasaki; (b) the less serious and smaller experience of the Marshallese, American servicemen, and Japanese fishermen to fall-out radiation during atomic tests in 1954; (c) exposure of a few people to reactor and radiation accidents in the United States, the USSR and Yugoslavia; (d) exposure of patients to therapeutic radiation. Some shortcomings of such information have been discussed earlier in paragraphs 43-45 above. Information on atomic bomb, fall-out, reactor accident, and whole-body radiation injuries has been summarized.^{50, 364, 372, 373, 388, 393, 702}

195. The total body response in man to radiation in sufficient doses includes: (a) radiation sickness beginning during or very soon after acute exposure, and overlapping with other responses; (b) degeneration and repair of proliferative tissues; (c) local and generalized toxæmia; (d) changes in homeostasis; (e) deterioration in physical and mental fitness.

Radiation sickness

196. After a single dose of radiation of 50 rad and above given to whole-body, symptoms have appeared in 1-2 hours. The onset, duration and severity of all symptoms varies depending largely on dose and partly on susceptibility.³⁶⁶ Symptoms may include:³⁶⁷ (a) general: headaches, vertigo, debility and abnormal sensations of taste or smell; (b) gastro-intestinal: anorexia, nausea, vomiting, diarrhoea; (c) cardiovascular: tachycardia, arrhythmia, fall of blood pressure and shortness of breath; (d) haematological: leukopenia, thrombopenia, and increased sedimentation rate; and (e) psychological: increased irritability, insomnia, and fear.

197. The incidence of radiation sickness is affected by the part of body irradiated.^{368, 369} Exposure over the whole trunk and partly over the upper abdomen causes more radiation sickness than does exposure of comparable tissue volumes in the extremities. Explanations for radiation sickness include: (a) release of toxic substances from disintegrating cells;³⁷⁰ (b) disturbance of pituitary-adrenal cortical function;³⁷¹ (c) tissue destruction giving rise to histamine and mildly toxic histamine-like products.

General clinical picture

198. Although the different organs have widely different radio-sensitivities for the acute radiation syndrome in man, three are important:^{63, 872, 873} the central nervous system (CNS), small intestine, and bone marrow, together with lymphoid tissue (table V). The acute radiation syndrome may therefore take three primary forms—cerebral, gastro-intestinal, and haematopoietic, depending on the dose. To induce acute effects in the central nervous system requires several thousand r; damage is seen within minutes to hours. The dose for the acute small intestine form is 300-500 r, with a latent period of ~ 5 days. For severe haematopoietic changes, the dose is > 200 r and the effect takes ~ 3 weeks to develop.

CNS form

199. The clinical picture of the CNS form must be extrapolated from animals and a few accidents in man. The onset is prompt and death may occur in minutes to hours. After the initial phase of radiation sickness, there is swift progression from listlessness, drowsiness, and anguish to severe apathy, prostration, and lethargy probably caused by small non-bacterial inflammatory foci appearing throughout the brain in 1-2 hours; this development of vasculitis or encephalitis gives rise to cerebral oedema. After > 5,000 r, one deals with seizures ranging from generalized muscle tremor to epileptoid convulsions similar to grand mal. This convulsive phase lasts a few hours and is followed by ataxia from vestibulocerebellar disturbance. Convulsions and ataxia probably result from the degenerative pyknosis in the granule layer of the cerebellum within two hours after exposure, concomitant with brain oedema. TBR causing the CNS syndrome is fatal.

200. The gastro-intestinal form predominates with lower doses (500-2,000 r). The prodromal nausea and vomiting begin promptly and do not subside. For some people these symptoms develop within 0.5 hours after exposure; in others not for several hours. Gastro-intestinal symptoms may continue (anorexia, nausea, vomiting, and diarrhoea). Sometimes these symptoms disappear after 2-3 days and recur ~ day 5 just when the patient's condition seemed to have improved, owing to injury of intestinal epithelium, leaving bare villi. Rather abruptly, malaise, anorexia, nausea and vomiting prevent normal food and fluid intake, leading to serious electrolyte imbalance. Simultaneously high fever and persistent diarrhoea—rapidly progressing from loose to watery to bloody stools—appear. The abdomen is distended and peristalsis is absent. Rapid deterioration leads to severe paralytic ileus. Exhaustion, fever and perhaps delirium follow; dehydration and haemoconcentration develop; the circulation fails, and the patient becomes comatose and dies a week or so after exposure from circulatory collapse.

201. After doses where regeneration is possible, fluid replacement during days 4-6 keeps dogs alive.⁷⁴ The epithelium regenerates and vomiting and diarrhoea subside. This is only a temporary respite as evidence of marrow aplasia and pancytopenia begin within 2-3 weeks. After doses that cause this severe intestinal damage, marrow regeneration is unlikely, so that even if there is spontaneous recovery or successful treatment, individuals have yet to experience the effects on haematopoiesis.

Haematopoietic form

202. In the haematopoietic form, after lower doses of radiation, e.g., < 500 r, the haematopoietic symptoms are due to different origins and appear in two successive phases. Leucopenia, thrombocytopenia and haemostatic abnormalities are a direct consequence of lesions of the haematopoietic organs. Symptoms such as haemorrhage and anaemia may be secondary to the visceral lesions and associated with ulceration of mucous membranes. Anorexia, apathy, nausea, and vomiting, and some diarrhoea are maximum 6-12 hours after exposure. The symptoms may subside so that by 24-36 hours individuals feel well, but their bone marrow, spleen, and lymph nodes are atrophying. The patient enjoys apparently normal health until ~ days 19-20 (many Japanese soldiers returned to work only to die later in the pancytopenic phase), when the patient has chills, malaise, and fever, headache, fatigue, anorexia and dyspnoea on exertion, and at this time partial or complete loss of hair is likely. Within a few days the general condition worsens, hospitalization is needed. The patient then develops sore throat and pharyngitis, accompanied by swelling of gingiva and tonsils and petechiae in the skin with a tendency to bruise easily, followed by bleeding from gums and ulcerations on gingiva and tonsils. Similar ulceration in the intestines causes a renewal of diarrhoea. The patient has high fever with complete anorexia. Weeks 5-6, with agranulocytosis, anaemia, and infection, are critical. The increased susceptibility to infection is caused by the dose dependent decrease in circulating granulocytes and lymphocytes, impairment of antibody production, impairment of granulocyte and RES function, lessened resistance to diffusion in subcutaneous tissues, and haemorrhagic ulceration permitting entrance of bacteria. Thereafter, if the patient recovers, fever, petechiae and

ecchymoses subside; ulcerations heal and convalescence begins about the end of the second month after exposure. These symptoms tend to merge into one another.

Prognosis

203. Early symptomatology in the diagnosis of radiation injury is a useful guide to management.^{44, 375, 376} Subjects with intractable nausea, vomiting, and diarrhoea will generally die—the *survival-improbable* group. Those in whom nausea and vomiting is brief, 1-2 days, followed by well-being, have a good chance to survive.

204. After initial symptoms, the effects of haematopoietic damage predominate. The *survival-possible* group are in the lethal dose range. The *survival-probable* group includes those with no initial symptoms or only mild and fleeting ones disappearing within a few hours. Practical experience on the Marshallese, Los Alamos, Argonne, Y-12, Vinca and Lockport accidents demonstrate that physical measurements to compute probable doses take more time than do several haematological procedures. The dose must be judged on the basis of symptoms. This is especially important in determining management and prognosis when physical measurements are not available, or when radiation exposure has been non-uniform.

(a) Nausea and vomiting

In general, if nausea and vomiting are absent, it may be assumed that the dose was relatively low. Nausea and vomiting warrant hospital admission for observation. The rapidity of onset of nausea and vomiting provides some notion as to the severity of the exposure: usually, the earlier the onset and more protracted the vomiting, the higher the dose.

(b) Erythema

Much depends on the type of radiation as to whether erythema will result. It is difficult to make judgements of the dose on the basis of erythema but its presence is evidence of a serious exposure.

(c) Haematopoietic and bone-marrow picture

Where casualties are few it is simple to carry out all haematological procedures and other studies that might be of value. In a radiation disaster, extensive studies would be impossible, although many leukocyte counts would be practical with modern electronic counting devices:

(i) Lymphocytes are valuable as an early criterion for judging radiation injury. In normal individuals, a fall in lymphocytes is seen within the first 24-48 hours. If at 48 hours the lymphocyte count is 1,200 or above, it is unlikely that the individual has received a fatal exposure; if the lymphocyte count is in the 300-1,200 range, a dose in the lethal range may be suspected; counts below 300 indicate an extremely serious exposure;

(ii) Early bone marrow examination is advisable for determining whether the patient was haematologically normal at the time of exposure and might give some insight to the extent of damage. Some workers consider that multiple bone marrow examinations would be no more helpful than peripheral blood examinations and have the disadvantage of being potential sources of infection. Cronkite and Bond have proposed a determination of the mitotic index in bone marrows on day 4 as a measure of dose exposure—a mitotic index of zero indicates an exposure of 200 rad or more.

(iii) The total white-cell count is of particular value for following the patient throughout the course. In general, the drop in neutrophils will reflect the degree of

exposure; a fall in white count beginning within the first week denotes a rather high exposure whereas late falls, such as observed in Marshallese, indicate a less serious exposure;

(iv) The platelet count, while being of some prognostic value, is of more importance in the general management of the patient. In general, the fall in platelet count would parallel the change in neutrophils, although occurring somewhat later, and the neutrophil count is more readily available, particularly in accidents away from hospital centres;

(v) The reticulocyte count would serve as a guide as to the extent of erythropoietic damage. Fe^{59} turn-over studies would be of little value; to be meaningful, they would have to be done serially and even then would add little information beyond that derived from the reticulocytes.

(d) Recovery potential

The type and extent of injury following radiation represents a spectrum and it is not possible to divide injury into clear-cut syndromes. In general, however, at higher doses, the predominant injury would be cerebral and the outcome uniformly fatal. With doses lower than this, the major injury would be to the gastro-intestinal and haematopoietic systems. Judicious use of fluid, electrolytes, and treatment of the haematopoietic injury as outlined below provide hope for recovery. In the so-called lethal dose ranges with X- and γ -radiation, the injury is primarily to the haematopoietic system. At doses of approximately 50-100 rad, symptomatology is mild, and below 50 rad, symptoms are virtually absent even though there is some injury, particularly to haematopoietic tissues.

Prognostic value of the leukocyte count

205. At Operation Crossroads depression in leukocyte count correlated with distance from the bomb.³⁷⁷ At Operation Greenhouse³⁷⁸ there were four groups of dogs with mortalities of 100 per cent, 100 per cent, 80 per cent, and 10 per cent. In the group given 800 rad, the total leukocyte count fell to zero; all the animals were dead by day 10. Group 2, given about 500 rad, had a smaller fall in leukocyte count. Group 3, with 80 per cent mortality, received ~400 rad, and group 4, given 200 rad with 10 per cent mortality, had a smaller decrease in leukocyte count.

206. Extrapolation to man directly is difficult, because the rate of change in leukocytes in man as shown in the Marshallese and various clinical experiences is much slower.^{44, 372, 373} Jacobs, *et al.*,³⁷⁹ re-analysed the leukocyte counts done in Hiroshima and Nagasaki after the explosion; despite the limitations of the data depression in total leukocyte count at different times correlates well with survival. The treatment of the acute radiation syndrome in man is discussed in section VIII.

ANALYSIS OF PAST ACCIDENTS

207. There have been at least eight major radiation accidents:

Los Alamos I21 Aug. 1945	Criticality (experimental assembly)
Los Alamos II21 May 1946	Criticality (experimental assembly)
Argonne2 June 1952	Criticality (reactor)
USSR?	Criticality (reactor)
Oak Ridge16 June 1958	Criticality (processing)
Yugoslavia15 Oct. 1958	Criticality (reactor)
Los Alamos III30 Dec. 1958	Criticality (processing)
Lockport, New York	..8 Mar. 1960	Radar X-radiation

The Idaho SL-1 reactor accident on 3 January 1961 is not discussed because the three fatalities were caused by blast from the nuclear excursion. The immediate dose calculations in the above accidents were of necessity very uncertain and probably not too meaningful. In the study of reconstituted accidents more accurate dosimetry has been obtained particularly from the point of view of non-uniformity of the exposure. Even here, there are important practical difficulties in assessing exposure when with the neutron component significant dosimetry is further complicated by considerations of distribution and RBE. In the present state of knowledge the doses presented should be considered as approximate orders of magnitude rather than exact measurements.

First and Second Los Alamos accidents

208. The first nuclear accident occurred at Los Alamos on 21 August 1945 and the second on 21 May 1946.^{380, 381} The accidents occurred during experiments with critical assemblies of a fissile core surrounded by neutron reflector material. In the first accident the reflector was tungsten carbide; in the second beryllium. In both accidents the man doing the experiment was touching the reflector at the time of the reaction. Exposure of these two fatally injured operators was non-uniform; hands and arms received the largest dose, abdomen and chest somewhat less, and head and legs the smallest. All others were presumed uniformly exposed, except for case 4, whose body from mid-chest down was partly shielded at the time of the second accident. The head, upper chest, and left arm of this patient received the highest dose.

209. Dose calculations are uncertain and probably not particularly meaningful; e.g., if 5 per cent of neutrons had an energy exceeding 5 mev the dose would have been increased by 45 per cent; the choice of RBE was critical. With these reservations, five cases received an estimated dose of less than 100 rem of soft radiation and less than 10 r of penetrating radiation. Case 6 (dose unavailable) had no symptoms of any kind after exposure. The only laboratory findings of significance were an initial rise in granulocyte count and a lymphopenia of less than 1,000 cells/mm³ from day 40. The lymphocyte count remained low for two years. In 1959 the patient retired, aged 68, with no signs of injury and a normal blood count.

210. Case 1, received an estimated average body dose of 840 rem of soft radiation and almost 500 r of γ -rays. His hands and arms, especially the right, received many thousand r. His hands and arms were tensely swollen 30 minutes after the accident, and soon thereafter he began to vomit and retch almost continuously for \sim 24 hours. His temperature rose gradually reaching 41.7° C rectally on the day of death 24 days after exposure. His pulse increased abruptly on day 6 and remained high with an episode of acute paroxysmal tachycardia on day 15 following a blood transfusion. Cardiac symptoms, abnormal electro-cardiograms, low blood pressure, enlargement of heart with friction rub were related at the time to his known congenital defect (Wolfe-Parkinson-White syndrome). The patient had extreme necrosis of the tissues of hands and arms, and extensive third-degree burns of the body extending to the pre-cardial region. The underlying heart undoubtedly received a high dose. At autopsy, the heart showed extreme fibrinous pericarditis with no microscopic evidence of damage to cardiac muscle. At the time this response was related to his known cardiac defect but in retrospect this probably represented radiation injury to the heart.

Several isolated cases of pericardial effusion and constrictive pericarditis have been reported in patients given radiation therapy to the chest.³⁸⁰⁻³⁸²

211. The second fatality received an estimated average dose to his torso of about 2,000 r of soft and 150 r of penetrating radiation, with considerably greater exposure of his hands. The patient vomited on his way to the hospital. Both hands were swollen within an hour after the accident. His temperature, pulse, and respiration rose abruptly on day 6 and increased until death on day 9. His hospital course was characterized by severe intestinal symptoms, with almost complete paralytic ileus and extreme abdominal distention. Continuous gastric suction was required. He had no diarrhoea. Both arms, packed in ice, were in effect amputated. The most striking features of the patient's blood count were the initial high white count, the complete disappearance of all lymphocytes from the peripheral blood by day 2, and the abrupt fall of the total white count on day 6. These findings are similar to those in the first case. At autopsy, among other findings, there was severe damage to intestines.

212. Case 4, a 34-year-old man, received an average estimated dose to the entire body of 400 r of soft and 40 r of penetrating radiation. His head and upper chest are believed to have received a larger dose than the rest of his body. On day 5 he developed fever, along with lethargy and somnolence for no clear cause at the time. The fever may possibly have been associated with damage to the CNS like that in the Lockport accident. His lymphocyte count fell to below 1,000 cells/mm³ by the sixth hour after exposure.

213. This patient had severe fatigue 15 days after exposure on discharge from hospital, and at first had 16 hours bed rest per day, improved gradually and was back to normal in 10 weeks. Although completely aspermic for several years after exposure, he recovered completely, lived an active normal life, and became the father of an additional two normal children. The patient had mild hypertension at the time of exposure. In the next several years his blood pressure rose but was treated successfully with reserpine. In 1955, aged 43, the patient had a severe posterio-lateral cardiac infarction. (It is difficult to relate this to his radiation exposure. The patient's coronary vessel probably received a relatively small dose. Patient's father died of a heart attack in his early 40's.) Within a year after the heart attack a diagnosis of acute myxedema was made. From clinical findings and laboratory tests this condition had undoubtedly been present for several years, and contributed to the coronary thrombosis. Whether radiation exposure to the neck was responsible for the thyroid damage is uncertain.

Argonne accident

214. A reactor criticality accident occurred at Argonne Laboratory on 2 June 1952. Four persons were exposed to a mixed field of radiation, γ -neutron dose ratio \sim 10 : 1. Clinical and dosage details were reported.^{374, 385} There were no deaths. The calculated doses range from 10.8-159 rad.

USSR accident

215. One reactor accident has been reported in the USSR causing "short general external exposure" of two people to neutrons and γ -rays.³⁸⁶ Doses of 300 r and 450 r were assigned but no γ -neutron ratio was given. Since fuller data are not available these dosages are uncertain.

216. A criticality accident occurred on 16 June 1958 in the Y-12 plant at Oak Ridge. Enriched uranium component was drained inadvertently into a waste drum³⁸⁷ causing a chain reaction. Eight persons received significant TBR; five were exposed to 236-365 rad including a neutron component of slightly more than one quarter. There was no associated trauma, the whole body was fairly uniformly exposed, and the radiation dose was rather accurately determined. Three persons received between 20-70 rad. In the five higher-dose patients the haematological values emphasized that TBR in man causes clearly defined symptoms. Blood and bone-marrow changes appeared over several weeks in well-defined stages: early and persistent lymphopenia and variable transient leukocytosis; mild leukopenia during the first ten days; abortive rise in white cells, and some increased erythropoiesis at about two weeks; severe depression of neutrophils and platelets greatest at weeks 4-6; rapid recovery of platelets and neutrophils; and anaemia maximal at week 7, with recovery accompanied by reticulocytosis. This sequence is uniform in different persons and similar after radiation over a wide range of dose. The patients showed the greatest depression of leukocytes and platelets between days 24-37. All five patients recovered from the early post-radiation effects and have now no visible damage.³⁸⁸⁻³⁹⁰

Yugoslavian accident

217. On 15 October 1958, the zero-energy reactor at the Boris Kidrich Nuclear Science Institute, Vinca, Yugoslavia, became super-critical, injuring eight people. The reactor was constructed with natural uranium rods suspended in a large tank that could be filled to various depths with heavy water. Six received significant doses of neutrons and γ -rays.³⁹¹⁻³⁹³ Following a brief hospitalization in Belgrade, the six patients were transferred to the Fondation Curie in Paris under the care of Dr. H. Jammet. The early dose estimates described by Jammet, *et al.*,³⁹¹ on the basis of local information from Vinca were 1,000-1,200 rem for the highest exposure and 300-500 rem for the lowest, placing five of the six in a range considered to be above the LD₅₀. All six had the acute TBR syndrome: nausea, vomiting, anorexia, asthenia beginning after the first hour and lasting 2-3 days; thereafter their general condition was relatively good, in contrast with the progressive evolution of haematological and cutaneous changes: fall in lymphocytes, then granulocytes, thrombocytes, and erythrocytes. Towards the end of the fourth week and during the following weeks there was a worsening in general condition with fever and clinical evidence of haemorrhagic disease. The individual originally believed to have received the highest dose was given foetal bone-marrow on 11 November, and the four patients having the next highest exposure were given homologous bone-marrow from adult donors at various times between 11 and 20 November. The man who received the foetal bone-marrow died as a result of radiation with no immunological reaction. Extensive clinical studies have been detailed.^{391, 394}

218. Comparison of the haematological and other clinical effects of the four Yugoslavian accident victims who survived after bone-marrow infusion with the five men exposed to 236-365 rad at the Y-12 plant, leads to the following conclusions:³⁹⁵ (a) the effects of injury suggest a somewhat higher dose in the Yugoslavian than in the Y-12 accident; (b) haematological patterns in the two groups of patients are remarkably similar, the Yugo-

slavs showing generally more severe injury; (c) haematological recovery occurred at about the same time after exposure in the two groups of patients; this and the fact that the bone-marrow was given just at this time to the Yugoslavs, makes evaluation of its therapeutic effect difficult.

219. An international group under the auspices of the International Atomic Energy Agency studied the dosimetry of the Vinca accident in a reconstitution of the accident.³⁹⁶ The recalculated doses, still under discussion, were between ~ 320 to 440 rad in the five treated.

220. In the follow-up³⁹⁷ on the Yugoslavs the patients continued to have slight reticulocytosis, 0.5-1.7 per cent, for several months. Electro-encephalograms showed slight abnormalities characterized by low voltage and instability; the tracings lacked the usual individuality of patterns expected in five patients and all looked remarkably alike. At 2 years, basal metabolic rates are normal. Lens opacities developed, decreased, and are no longer present. The female patient has had persistent menstrual difficulties with excessive bleeding. In the male patients sperm counts are still very much depressed 2 years later. The peripheral blood shows light lymphopenia. The patients complain of fatigue and neuro-circulatory instability—evaluation of both symptoms is difficult.

Third Los Alamos accident

221. A third radiation accident at Los Alamos on 30 December 1958 of a critical excursion, during a routine plutonium salvage operation caused massive over-exposure of one man.^{398, 399} The average TBR exceeded 3,000 rad; the dose to the anterior chest was $\sim 12,000$ rad, that to the front of the head $\sim 10,000$ rad. The victim went into a state of profound shock within minutes. The outstanding finding was right-sided heart failure with resulting renal ischemia and nitrogen retention. The patient died 35 hours after injury.

222. Less than 30 seconds after the accident the patient was ataxic and disoriented, needing support to remain erect. He complained of "burning up" and appeared flushed at this early time. Within 5 minutes he was virtually unconscious and was admitted to hospital 25 minutes after the accident. At this time, he was semi-conscious but disoriented and clearly in general shock with depression of blood pressure. Vigorous efforts to return the patient's blood pressure to a satisfactory level and to maintain it were made by giving pressor amines in heroic doses. Five hours after the accident the patient appeared to be in a satisfactory condition, he was relatively comfortable and mainly at ease. By this time it was obvious from dosimetric studies that his radiation exposure had been supra-lethal. His leukocyte count rose steadily to a peak of 28,000/mm³ but lymphocytes had virtually disappeared from the circulating blood in < 6 hours. He had marked oliguria, voiding a total of < 600 ml of urine over 22 hours with a total fluid intake of 14 litres in the same period. More than 30 hours after the accident the patient abruptly became worse, developed increasing abdominal cramps, became more cyanotic, and despite oxygen, lapsed into coma. His heart, that had received nearly 12,000 rad, stopped 34 $\frac{3}{4}$ hours after the accident.

223. At autopsy, the picture was that of acute right heart failure caused by right-side myocarditis complicated by excessive fluid intake. The most striking histological findings were in heart muscle: severe oedema and beginning degeneration of muscle fibre with cellular

exudate between fibres showing the presence of true interstitial myocarditis. In short, this could be termed a cardiac death. It should not be regarded as representative of all kinds of radiation injury to the heart, as in a slightly different position he could have received most of his exposure to the left side of the heart. In other accidents, other parts of the body might receive the greatest dose and other mechanisms of quick radiation death are possible.

Lockport accident

224. On 8 March 1960 nine technicians were exposed to pulsed X-radiation from an unshielded klystron tube at Lockport, New York.⁴⁰⁰ Two of the exposed were seriously injured, five others less seriously damaged, while two remained asymptomatic during observation. Shielding of greater or lesser areas of the body in men working closest to the tube was critically important in determining the outcome. To date, satisfactory integrated dose estimates of the entire body in any of the men are not available. Clinical exposure appeared to have been greatest over the right side of the head, right arm, and axilla of A, the man most seriously injured. Exposures of the nine varied with their individual activities. The best present estimates are that doses to A could have been as high as 1,200-1,500 r over certain parts of the body. Since even a few inches back and forth would result in major changes in exposure there is considerable uncertainty. B's exposure is slightly less than A's due to his smaller stature and slightly different position. C's position on the floor limited his exposure largely to head and upper chest. The next four, D, E, F, and G, were exposed over greater portions of their bodies for 60-120 minutes at 6 inches at 4-6 feet, and I and J were minimally exposed for ~120 minutes at 8 feet. Nevertheless, because of the pulsed nature of

the radiation, the actual exposure time was only 7.2 seconds/hr.

225. A was exposed from head down to mid-thigh, B from head to pubic symphysis. C was exposed largely above the shoulder level. Throughout exposure the men were unaware that they were being irradiated. Nevertheless, symptoms appeared during exposure, severe enough to make B and C seek medical aid on their way home. Headache was the first complaint, beginning during exposure and described as severe, deep within the centre of the head, and unlike any headache ever experienced before; even walking around caused intolerable pain. The headache persisted for several hours after exposure. Nausea and vomiting began in the most seriously injured shortly after the beginning of the headaches. Vomiting persisted throughout the first day; nausea subsided very slowly. The most seriously injured man continued to have morning nausea for a week after exposure and sporadically for several weeks. Of all the symptoms, nausea and fatigue were the most persistent. With the exception of F all the exposed developed conjunctival reddening. In A conjunctivitis and acute eye pain was followed by the development of haemorrhage and exudates in both eyes, with severe interference of vision in the right eye due to macular involvement. His eye difficulty has continued to be present and has changed only in that the acute symptoms have subsided. Vision in the right eye did not improve and that in the left eye remained stationary. Parotid swelling was the most severe in A. Both A and B had temporomandibular tenseness and pain on moving the jaw. Treatment was conservative throughout the patients' hospital course. In A an initial wave of erythema was present during the first 7 days after exposure, a second wave between days 13-19, and a third wave, also seen in B, D and C, between days 24-29. These waves are shown in figure 5 that also

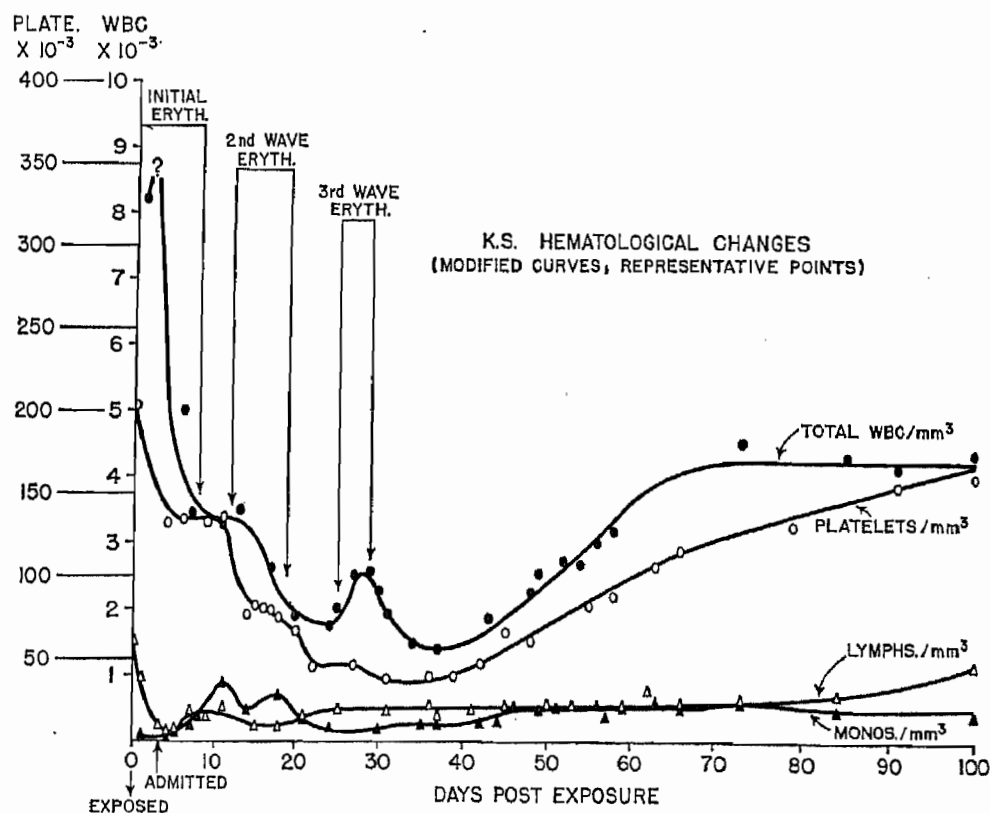


Figure 5. Graph showing the periods of erythema and levels of leucocytes, platelets, lymphocytes, and monocytes in K. S. (A) injured in the Lockport accident⁴⁰⁰

shows changes in the total white count, platelets, lymphocytes, and monocytes.

226. A's total leukocyte count fell from the time of admission until approximately the sixth post-exposure week. At that time minimal counts of $\sim 1,400/\text{mm}^3$ were seen. Monocytosis was a prominent feature of the peripheral blood during acute stomatitis present days 7-15. Lymphopenia was severe in this patient and was an important indication that A had sustained major radiation injury. Platelets reached minimal level of 35,000-40,000/ mm^3 during the fifth post-exposure week. There was no evidence of abnormal bleeding, with the exception of a few petechiae on the palate and one foot during the fourth post-exposure week.

227. At day 38, A became febrile, somnolent and mentally depressed; these symptoms increased, so that at day 44 he was moderately ataxic with transient paresthesias of the right arm and left hand, and mild transient reflex changes. These neurological symptoms varied over 12 days. Electro-encephalograms showed multiple, large and small focal abnormalities. The records improved gradually, until a normal record was first obtained on 12 September 1960. Mild fatigue with improvement in over-all symptoms continued at day 210.

228. In A there was complete aspermia by the sixth month, with complete return to better than normal values at the end of one year. Sperm samples of the others showed at most only the minimal depression during the acute phase.

229. Follow-up examinations on A, B and D at one year showed all observations on B were normal, progressive deafness in D—apparently traumatic—but no other significant findings, continuation of the eye symptoms in A, complete correction of aspermia, secondary loss of hair over the right temple and eyebrow, and mild asthenia.

ASSESSMENT OF INJURY

230. At present, the severity of illness following radiation damage can only be assessed by comparing the response of the patient with that of others previously exposed under similar conditions, who have survived or have been fatally injured. For this reason, detailed information concerning radiation dose, exposure conditions, and the clinical course of each patient injured by radiation should be available to all likely to be concerned with these conditions. There is need for further biological indicators of radiation damage, other than the existing methods, of which the early rate of fall and ultimate depression of lymphocytes appears the most sensitive. A number of patients from reactor accidents showed a high urine level of amino acids^{380, 401} and it was hoped that this might serve as an index of tissue breakdown.³⁸¹ The metabolism and re-utilization of amino acids by the body is so rapid that their release from proteins being quickly broken down after irradiation can be shown only by the use of special research techniques^{402, 403} not yet applicable to clinical diagnosis.

231. Creatine excretion in the urine is a good indicator of muscle break-down. Patients with muscular dystrophy excrete large amounts of creatine. It is possible that the weakness of irradiated patients might also be reflected in excretion of excess creatine. Radiation-induced creatinuria has been studied.⁴⁰⁴⁻⁴⁰⁸ There is a correlation between large integral doses of radiation to muscle and creatinuria. Since creatine estimations are simple and accurate this would appear to be a promising

line for further study. Similarly the excretion of beta amino isobutyric acid is an index of the break-down of cell nuclei but the analytical method is less simple.

V. Late effects of irradiation in man, including carcinogenesis

LIFE-SHORTENING

Effect of long-term radiation on life-span in man

232. The problem of extrapolation of animal life-shortening data to man is difficult because of the lack of data on life-shortening for large animals with life-spans intermediate between man and rodents. TBR of rodents shortens life-span; this effect has not been shown unequivocally in man. Three studies have compared mortality of radiologists with other physicians or with the general male population.

233. Dublin and Spiegelman⁴⁰⁰ investigated 2,046 deaths of United States medical specialists age 35-74, 1938-1942. Mortality in all specialist groups was less than that for all physicians, but mortality of radiologists and dermatologists was 16 per cent and 25 per cent respectively above that of all specialists combined. From their data, the mortality of radiologists and dermatologists, combined or separated, differs from that of specialists not using radiation routinely by an amount bordering on statistical significance. Dublin and Spiegelman did not calculate occupational risk in differences in life expectation, but estimated from their data and life tables for physicians that the difference between radiologists and dermatologists and other specialists is 1-3 years.

234. Warren⁴¹⁰ used 82,441 obituaries of physicians reported 1930-1954 in *Journal of the American Medical Association* to compare the mean age at death of United States radiologists (60.5 years) to that of other physicians not exposed occupationally to radiations (65.7 years); he concluded that radiologists died 5.2 years earlier.

235. Court Brown and Doll^{411, 412} compared the mortality of British radiologists 1897-1957 with those of all physicians and of men of equivalent social class (defined by the Registrar-General). Correcting for age distribution and various biases in vital statistics, they concluded that British radiologists show no evidence of life-shortening. They attribute this to early adoption of effective safety measures.

236. These studies suffer from uncertainties and limitations that bedevil evaluations in man. Dublin and Spiegelman did not intend an analysis to apply to mortality in radiologists specifically. For this purpose their work suffers from small sample size. Warren's data were not corrected for age distribution of groups at risk. Seltzer and Sartwell⁴¹³ found "the difference between radiologists and other physicians as to average age at death can be accounted for simply by differences in age composition between the two groups". The differences found by Dublin and Spiegelman included consideration of age distributions. These data were analysed in annex G of the 1958 report.⁴¹⁴

237. Warren has compared the survival of radiologists averaged over five-year periods with survival of the general population.⁴¹⁵ The latest report giving survival of the general population and radiologists (Warren, personal communication) suggests that the slope of the

radiologists group is approaching that of the general population, i.e., the survival of radiologists has increased from 1930 to 1957 at a more rapid rate than that of the general population. This suggests in retrospect that the evidence of life-shortening in American radiologists should not be dismissed out of hand. The fact that no life-shortening was found among radiologists in the United Kingdom probably reflects not only differences in safety procedures, but also in practice. In the United Kingdom, most radiology is done in hospitals, and therefore many examinations are made by radiographers rather than radiologists themselves. In the United States the private practice of radiology is much more extensive, and the radiologist tends to do this himself. Fluoroscopy is much more extensively practised in the United States than in the United Kingdom and probably the number of X-ray films used in radiographic examinations is likewise greater.

238. A lower limit can be set for life-shortening of United States radiologists by considering leukaemia incidence only. A statistically significant excess of leukaemia among those radiologists has persisted for years, decreasing recently.⁴¹⁶⁻⁴²⁰ This is equivalent to a life-shortening of 3-12 months, depending on assumptions.

239. In conclusion, occupational exposure of United States radiologists increased mortality in past decades, but the radiation doses and distribution are unknown. The exposures must have been heterogeneous with hands, arms, and upper body receiving the most. A life-shortening effect in man after substantial TBR is to be expected from animal data. Despite uncertainties, data on radiologists and other medical specialists represent one of the best available means for studying late effects of radiation in man.

CARCINOGENESIS IN MAN

240. It was early known that skin cancers were common in radiologists and dermatology patients. Later, radiation-induced tumours were seen in haematopoietic tissue, bone and thyroid. Increased leukaemia has been reported in United States radiologists, in Japanese atomic bomb survivors, in children irradiated in infancy for benign conditions (usually thymic enlargement) and in ankylosing spondylitis patients. Some retrospective studies have reported that a greater proportion of children with leukaemia and other malignancies were exposed to X-ray *in utero* than selected controls without malignant disease.

Leukaemogenesis

Situations in which a relationship between radiation and leukaemia has been established

241. Single doses of external radiation to whole body at ~ 100 rad or more and irradiation of an appreciable portion of the bone marrow with ~ 500 rad or more, slightly increase the incidence of leukaemia in man. There is no evidence of an increase in the first fifteen months after exposure. In the Hiroshima data, limited to 2 km from hypocentre, the incidence increased to a maximum between years 4-7, declined thereafter but was still above the expected incidence in 1959. The Japanese data⁴²⁰⁻⁴²⁶ shows that with short-term exposures to doses greater than ~ 100 rad, the incidence of leukaemia integrated over fifteen years increases with dose. The exact quantitative relationship between dose and incidence of leukaemia is unknown. Assuming proportionality, the increase over the natural incidence, averaged over the

fifteen-year period, is about 100 cases per 10^6 persons per 100 rad for each year at risk. This estimate is probably too low in children and too high in adults. Additional data are needed for selected age groups.

242. Large amounts of external radiation, protracted over a long time given to the entire body or a large segment of bone marrow, are leukaemogenic in man. Nevertheless, present uncertainties about the influence of dose rate, fractionation and total dose make it impossible to estimate the probability of leukaemia other than under short-term exposures to high doses. Moreover, long-term exposure is probably less leukaemogenic than short-term exposure for the same total dose.

243. I^{131} given in high doses, e.g., therapy of carcinoma of the thyroid has in some cases caused leukaemia.⁴⁵⁵

244. Cases of leukaemia in which a relationship to radiation exposure was shown^{427, 428} indicate that with few exceptions the leukaemia was either acute or chronic granulocytic. In the United States and United Kingdom, the commonest chronic leukaemia is lymphocytic; its increasing incidence has not been correlated with irradiation.

Situations in which a relationship between radiation and leukaemia has been suspected but not established

245. It is not known whether short-term exposure to doses of less than ~ 100 rad given to the entire body or a portion is leukaemogenic. In particular there is a question about an increased incidence of leukaemia among children exposed *in utero*, during diagnostic pelvimetry of the mother.⁴²⁸⁻⁴³⁷

246. There are no documented cases of leukaemia as a late effect of radio-isotopes such as $Sr^{90, 90}$ and radium at any body burden. With thorium while there are nine recorded cases, the relationship between thorium and leukaemia is hard to gauge because of scarce clinical and dosimetric information.

247. Since leukaemia has been seen after irradiation in Japanese, British and sporadically in other nationalities, there is no reason to believe there is any outstanding racial sensitivity to radiogenic leukaemia.

Leukaemia in the Japanese survivors of the atom bomb

248. The increased leukaemia incidence in Japanese, exposed to nuclear explosions in Hiroshima and Nagasaki, is inversely related to the distance from the hypocentre. Dose-estimates are uncertain even after the results of recent tests which simulated an actual nuclear explosion with extensive shielding. Heyssel *et al.*,⁴²⁶ summarizes studies by the Atomic Bomb Casualty Commission since 1951 on the increased leukaemia in the Hiroshima survivors and relate incidence to calculated dose from γ -rays and neutrons combined in the open air at various distances from the hypocentre. In these calculations, they used an RBE of 1 for neutrons. They estimated that 60 per cent were indoors at the time of the explosion, reducing the air dose by 30-70 per cent. With leukaemia cases diagnosed up to 1957 they postulated a linear relationship between incidence and calculated open-air dose of 177 rad or more. The point, representing the leukaemia incidence of 3,605 persons receiving a mean estimated air dose of 77 rad, falls almost on the line drawn through points at higher doses. No cases of leukaemia were seen in 3,512 and 1,305 persons receiving an average estimated air dose of 34 and 19 rad respectively.

249. These authors also show that the latent period between exposure and development of leukaemia depends on dose. They report that nearly all cases in the exposed and non-exposed persons were acute leukaemia or chronic granulocytic leukaemia. Among the Japanese, chronic lymphocytic leukaemia is very rare; a very few cases were found in exposed and unexposed groups and their significance, if any, is hard to evaluate. Heyssel *et al.*, estimate that radiation increased the incidence of leukaemia rather than accelerated the appearance of spontaneous cases.

250. For several reasons, individual dose values can be appreciably in error. At least 200 survived where the mean open-air dose was calculated to be 2,620 rad.⁴³⁸ Allowing for shielding and assuming that they were at the edge of zone, the doses received, by these calculations, must have been > 100 per cent lethal. In the low-dose region, the accuracy of the calculated doses may be seriously questioned since many victims in the 2,000-2,499 metre zone, where the calculated average dose was less than 10 rad, had symptoms (epilation, oropharyngeal lesions, and purpura)⁴²⁷ suggestive of severe radiation dosage. The calculated dose is far below that producing radiation sickness after TBR and it may be that the quoted doses are a serious underestimate because of the contribution of induced radio-activity. On the other hand, since victims even farther away were also said to have similar symptoms it is the consensus of opinion of the observers⁴³⁸ who interviewed these patients that their symptoms were complicated by malnutrition and factors other than radiation exposure.

251. These studies by Heyssel *et al.*,⁴²⁵ suggest a straight-line relationship between doses above ~ 100 rad and the incidence of leukaemia among bombed Japanese. Considering the large variation inherent in incidence and dose estimations, the data could also have been represented by a straight line with a different slope, or by a curved line.⁴²⁸ Although the data are not enough to say whether the relationship is linear over the entire dose range, they do allow a conservative estimate of the probable incidence of leukaemia in a population of all ages over the first 10-15 years after a single exposure to high doses. A reasonable estimate might be an average of 100 additional cases per 100 persons per 100 rad for each year at risk during that period.

252. It is not possible to demonstrate an age-incidence relationship because of the small number of cases of leukaemia in Japan although there is some indication of a higher rate among bombed children than bombed adults. Hence, prediction of incidence in selected age groups or calculation of the probability of leukaemia among the individuals exposed may be speculative.

253. There are some data which suggest an increase in leukaemia incidence in Hiroshima among persons who were not directly exposed to the atomic explosion but who entered the area very soon afterwards. These data should not be overlooked, although there is great difficulty, at the present time, in making any accurate calculation of the dose received from the induced radio-activity.⁴³⁹

Leukaemia in ankylosing spondylitis

254. Court Brown and Doll^{412, 440} in the United Kingdom reviewed 13,352 patients, presumed to have ankylosing spondylitis given X-ray treatment to their spines, from 1 January 1953 to 13 December 1954. They reviewed death certificates and clinical and pathological

data of all suspected of dying of leukaemia or aplastic anaemia; they calculated from dose records mean dose to spinal marrow and whole-body integral dose of a large sample. There were thirty-two proved and five probable cases of leukaemia and four cases of aplastic anaemia; the number expected from national vital statistics was 2.9 for leukaemia and 0.3 for aplastic anaemia, a significant increase in mortality from these causes.

255. They estimated the annual incidence of leukaemia for the general male population not therapeutically irradiated to be 50/10⁶. The annual incidence in man given a mean dose of over 1,750 rad to only spinal marrow was 1,600-1,700/10⁶. For all patients regardless of site of exposure, the annual incidence was 7,200/10⁶, with a mean spinal marrow dose of over 2,250 rad.

256. Classifying cases by mean spinal marrow and integral dose shows a correlation between dose and leukaemia incidence. The shape of the incidence-vs-dose curve depends upon whether mean spinal marrow or integral dose is used, and whether the cases given extra-spinal radiation are excluded. However, whatever the method of analysis, the relatively small number of cases of leukaemia and the dose parameter used make it impossible to decide whether the dose response relationship is or is not linear (figure 6).

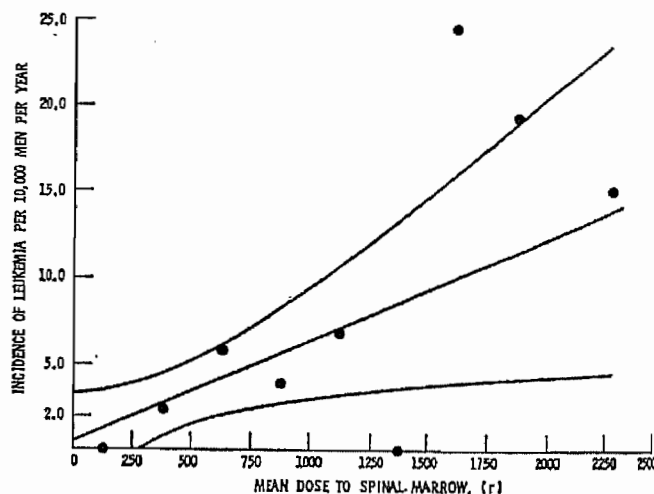


Figure 6. Incidence of leukaemia in relation to mean spinal marrow dose of therapeutic irradiation. The regression line was obtained after weighting the rates according to their reliability and is given by $Y = 0.00586X + 0.380$; the 95 per cent probability limits of the value of Y for each value of X are shown by the curved lines. Redrawn from Court Brown and Doll⁷⁸⁰

257. The single point below 500 rad is based on two cases of lymphatic leukaemia, one chronic that developed after a mean marrow dose of 471 rad, and the other in which the spine received 113 rad but extra spinal regions received additional larger doses.

258. There were ten cases of leukaemia within five years after a single course of therapy. Of the thirty-seven leukaemias, including those with multiple courses over years and those with a single course in a month, the diagnosis was made in thirty-five within five years of the last treatment. Of the fifty leukaemias in spondylitic patients after X-rays, including those reported by Court Brown and Doll, thirty-eight were acute and only eight were chronic—with only one of the latter being chronic lymphatic leukaemia. Data in the remainder were insufficient to establish clinical type.

259. Some leukaemia patients showed a sequence of pathological changes: a persistent damaged or aplastic marrow was a precursor rather than a consequence of leukaemia; other cases of aplastic anaemia were seen after the same dose range.

260. In attempting to extrapolate the incidence data to low doses, use of the incidence of spontaneous leukaemia in the general population as a control is questionable since there appears to be a strong hereditary factor in ankylosing spondylitis.⁴⁴¹ This is underscored by the report of Abbott and Lea⁴⁴² showing an association between untreated rheumatism and leukaemia. The only available control group of 399 untreated spondylitic patients is too small to be useful.

261. Because of limited data in the lower dose range and lack of an adequate control group, this study does not provide evidence on leukaemia incidence after doses below 500 rad.

262. Leukaemia is a rare disease; cases after radiation represent only a small portion of its incidence. Nevertheless, in a single case where the onset of leukaemia associated with radiation exposure occurs within an appropriate interval after a known single exposure to over 100 rad, the probability that the disease is due to radiation is high. It is possible to estimate this probability by considering the normal incidence in the population and the probable increase in the incidence of leukaemia after a single high dose.^{443, 444} This probability will increase to a maximum around the fourth-seventh year after exposure and thereafter decrease perhaps ultimately diminishing to the level of the incidence expected in the general population.

Leukaemia in children (table VI)

263. Some investigators found an increased incidence of leukaemia in children given radiation to the thymus; others have not. There is no satisfactory control group for a conclusive statistical evaluation. Simpson, Hempelmann, and Fuller,⁴⁴⁵ Simpson and Hempelmann⁴⁴⁶ and Simpson⁴⁴⁷ found in 2,393 such cases in upstate New York—87 per cent traced⁴⁴⁸—twenty-one cases of malignancy instead of 3.6 expected, and nine confirmed and one unconfirmed leukaemia deaths instead of one expected. Most other malignancies were thyroid carcinomas. There was no significant difference between expected and observed incidence of cancer or leukaemia in 2,722 untreated siblings of children in this study.

264. Exposures measured in air were known or calculated from radiation factors for all but 299 children. Four of the known leukaemias were in 1,050 children with a cumulative exposure of less than 200 r, 5 were in 1,025 children given 200-600 r. All other malignant neoplasias were among children given 200 r or more. Average survival between irradiation and death from leukaemia was 5.3 years.

265. Since the state of the thymus gland in the sibling group is unknown and is, in general, normal in children of the general population, this study does not differentiate between the association of leukaemia and (a) X-ray exposure, or (b) thymic enlargement. Because it is impractical if not impossible to get an accurate control group, (i.e., children with thymic enlargement at birth not treated with X-rays), children irradiated for other reasons must be studied.

266. Conti *et al.*^{448, 449} studied in 1948 1,564 children treated with X-rays in Pittsburgh—96 per cent had thy-

mus glands of normal size at birth. The radiation factors were uniform; 88 per cent were given 75-300 r (usually 150 r) to the manubrium; the remainder were restudied 11-18 years after therapy. Four cases of malignant disease, including one of leukaemia, were expected in this group; none was found. There was no significant difference between the number of expected and observed cases of cancer and leukaemia in untreated siblings.

267. The failure to find the four expected cases of neoplasia is not significant, since one-tenth of the group was not located. One can conclude, nevertheless, that there was no evidence of an increased cancer rate in treated children or of a greatly increased leukaemia frequency.

268. To avoid variables due to considering children given X-ray therapy to the mediastinal region only, a study was made of 6,473 children in Rochester, New York, treated with X-rays for various benign conditions in the past twenty-five years.⁴⁵⁴ The difference between the eight leukaemia cases observed and the two expected is significant. There were five leukaemia deaths in 2,750 children treated for thymic enlargement; two were in seventy-five children treated for pertussis and one in 1,073 children given X-rays to the head and neck region, mainly for lymphoid hyperplasia of the nasopharynx. There were no leukaemia deaths in 2,460 children treated with superficial X-rays for benign skin lesions.

269. Similar surveys of children treated for thymic enlargement and other benign lesions are now being made in the United States. Latourette and Hodges⁴⁵⁰ reported the incidence of neoplasia in 861 children treated for thymic enlargement, 1932 to 1951. Most children were treated with 200 r or less, through a large 10 x 10 cm port. The two cases of lymphoma (one being leukaemia) were more than expected, but not significantly so. One child had a carcinoma of the thyroid and others had various benign tumours. Snegireff⁴⁵¹ found two thyroid tumours in 148 children followed out of 1,131 children treated for thymic enlargement; Moloney, in a discussion of Simpson's work⁴⁴⁷ mentions seven cases of thyroid neoplasias including two malignancies in 125 of 700 children so treated.

270. Saenger *et al.*⁴⁵² reported on 1,644 out of 2,230 children treated for various benign conditions. Of 675 given treatments exclusively to the chest, mainly for thymic enlargement, only 124 received more than 200 r. Eighteen cases of thyroid neoplasia (eleven diagnosed as malignant) and one case of leukaemia were found in the entire group. They also report a striking incidence of morbidity of all types of non-fatal illnesses in these children, indicative of the selected nature of the group.

271. From these studies it is clear that an association between radiation exposure and subsequent leukaemia has been established only in one group of children treated with X-rays for thymic enlargement. Further epidemiological studies are needed to establish the true incidence of leukaemia in children given thymic irradiation, and especially the relation of incidence to dose, port size, and part of body treated.

272. Numerous studies of children given radiation to the thymic region showed an increased incidence of thyroid neoplasia; in contrast, an increased leukaemia incidence was found only in one study.

273. Long-term exposure to radiation will increase slightly the incidence of leukaemia in man. This opinion is based mainly on the reported increased incidence of

leukaemia in United States radiologists and the appearance of sporadic cases following long-term exposure from diverse sources.⁴²⁸ Since information on dose and other data are poorly documented, this evidence is not as good as that for short-term radiation. Data are inadequate to allow even a guess as to relationship between dose and induction of leukaemia after long-term exposure. Experiments in animals indicate that the leukaemogenic effects of cumulative doses are less in long-term than in short-term exposure.²⁶⁹ Whatever the dose rate in long-term radiation, it is likely that the cumulative dose exceeds ~ 100 rad in those cases where leukaemia is believed to have been induced by radiation.

Leukaemia in radiologists

274. Among United States physicians the ratio of leukaemia deaths to total deaths between radiologists and non-radiologists was 10.3:1, 1929-1943,⁴²⁰ 6.7:1, 1944 to 1948⁴²⁷ and 3.6:1, 1952-1955.⁴²⁸ The downward trend probably reflects better precautions by radiologists and possibly an increase of leukaemia among non-radiologists. From 1938 to 1952, there were seventeen leukaemic deaths in United States radiologists (35-74 years of age) — an average annual rate, after correction for age distribution, of $610/10^6$ compared with the population average, $121/10^6$.⁴²⁹ The ratios vary, depending upon time and corrections for age distribution.

275. Braestrup⁴²³ estimates that radiologists working with old-type X-ray equipment and few protective measures received as much as 100 rad per year; that exposure before 1930 was considerably higher; and that at present it averages considerably less than 5 rad per year. His estimates of accumulated total exposure of a radiologist using old-type X-ray machines was about 2,000 rad during forty years of practice. Lewis⁴²⁰ assumes the average exposure of all radiologists to be 30 rad per year or 1,200 rad in forty years. However, these estimates and assumptions of dose must be treated with great reserve in view of the uncertainty involved in their derivation, and it also has to be recognized that the distribution of radiation dose throughout the body was far from uniform.

276. In contrast, British radiologists who began practice after 1921 have had no increase in leukaemia; the only two known cases were among those in practice before this time,⁴⁵² probably for reasons previously discussed in the differences in life-shortening.

Pelvic irradiation and leukaemia in children (table VII)

277. In an extensive retrospective survey, Stewart, Webb and Hewitt⁴³⁰ interviewed mothers of: (a) 677 of 792 children under ten certified as having died of leukaemia in England and Wales, 1953 to 1955; and (b) 739 of 902 children under ten certified as dying in the same period from other cancer. They also interviewed a control group of mothers whose children were still alive and who were matched with the study children for age, sex, and locality. They found a higher frequency (13.7 per cent) of diagnostic X-ray pelvimetry in mothers of children dying from cancer than in mothers of control children (7.2 per cent). There was some correlation between size of the ratio between numbers exposed to abdominal irradiation and number of X-ray films reported to have been taken. The ratio was highest for mothers exposed during the first few months of pregnancy.

278. Four similar retrospective studies were made in different parts of the United States. Ford *et al.*⁴³¹ com-

pared seventy-eight leukaemic children and seventy-four children having other malignancies with 306 dead controls matched for colour, age and place of death in New Orleans. Their findings are in line with observations of Stewart *et al.*⁴³⁰ 26.9 and 28.4 per cent of the children with leukaemia and other forms of malignancy were irradiated *in utero*, compared with only 18.3 per cent of control children.

279. The three other studies, using other methods for selecting controls, do not show the same excess of foetal irradiation in leukaemic children. Polhemus and Koch⁴²³ found no significant difference in the history of pre-natal irradiation in 251 diagnosed leukaemic cases in the Children's Hospital of Los Angeles, compared with the same number of matched control children with non-orthopaedic diseases on the surgical service of the same hospital. In a current study of childhood leukaemia in California, Kaplan and Moses⁴³² found that the number of children with leukaemia having a history of pre-natal irradiation exceeded that of the group of siblings used as controls; such an excess was not seen, however, when the leukaemic children were compared with healthy playmates. Murray *et al.*⁴³⁴ found no significant difference in the history of pre-natal exposure of sixty-five children with leukaemia, sixty-five matched dead controls, and the 175 living siblings of both groups.

280. In these retrospective studies, the choice of the control group is crucial. The studies as presented do not differentiate clearly between the association of leukaemia and (a) the effect of the medical condition which prompted the diagnostic examination, or (b) the effect of X-rays.

281. In an extensive prospective study on the incidence of leukaemia after exposure to diagnostic radiation *in utero*, Court Brown, Doll and Bradford Hill^{435, 436} followed up 39,166 live-born children whose mothers had been subjected to abdominal or pelvic radiation during pregnancy, 1945 to 1956. Among their children nine were found to have died of leukaemia before the end of 1958, instead of the normally expected number, 10.5.

282. It is clear, therefore, that existing data on sequelae to irradiation *in utero* have led to conflicting conclusions. Stewart's data are very important for evaluating somatic effects in man as they are the only data pointing to low doses of radiation being carcinogenic. Because of their serious implications, the circumstances surrounding these data must be understood. If these data are not misleading for reasons yet unknown, one would have expected double the incidence of leukaemia in the Court Brown, Doll, Bradford Hill study just cited, i.e., twenty cases instead of the nine actually found. The data of Court Brown *et al.* thus put into doubt the conclusions of Stewart *et al.* On the other hand, if the ratio from Stewart *et al.*'s⁴²⁹ earlier report is used, 1.7:1 instead of 2:1, the difference between the expected figure of 17 ± 4 and 9 ± 3 is not such that a definite conclusion can be drawn.

283. The conclusion of Stewart *et al.*⁴³⁰ also implies that foetal haematopoietic tissue is much more susceptible to the leukaemogenic effect of irradiation than adult tissue. As previously stated, it is not known whether short-term exposure to doses less than ~ 100 rad to the entire body or a portion is leukaemogenic. Nevertheless to answer the question raised by the data about the incidence of leukaemia among children exposed to diagnostic pelvimetry *in utero* certain theoretical estimates can be made. Such estimates for the adult suggest that 1 rad to bone-marrow produces one case of leukaemia per million

persons per year for perhaps ten years of risk. Since the normal annual incidence of leukaemia in England and Wales under age ten is ~ 37 per million and the amount of radiation received by the foetus from irradiation of the mother's abdomen is estimated to be ~ 1 rad, it follows that if this dose were to double the incidence of leukaemia in children it would have to be ~ 40 times more leukaemogenic than the same dose in the adult.

284. Although foetal tissue appears more radio-sensitive than adult tissue, e.g., foetal nervous and thyroid tissues are more radio-sensitive than their corresponding adult tissues, there is no evidence that this holds for haematopoietic tissue. In fact, adult haematopoietic tissue appears to be the one adult tissue that is as radio-sensitive as embryonic tissue. From their study of patients irradiated for ankylosing spondylitis, Court Brown and Doll⁴¹² estimated the dose to marrow that doubles the expected incidence of leukaemia to be 30-50 r. Assuming that the leukaemogenic effect of radiation is the same in foetus and adult and that 40 r is the doubling dose, and that radiation to the foetus *in utero* is as high as 4 r, one would not expect to find more than a 10 per cent increase in leukaemia in children irradiated *in utero*, i.e., in the Court Brown, Doll and Bradford Hill study the increase to be expected over the estimated 10.5 would be one case.

285. Doubts about the controls in Stewart *et al.*'s study have been discussed.⁴³⁶ A probable bias is under-reporting of radiation exposures by the control mothers since it is reasonable to suppose that mothers of dead children would recall the events of pregnancy more completely than mothers of children who are alive and well. In the light of the study of Court Brown *et al.*⁴³⁶ the question of the effect on the foetus remains open. Clearly a further study of this problem is needed.

286. It has not been established whether internal emitters selectively deposited in bone (bone-seekers) but not delivering a uniform dose to the marrow are leukaemogenic in man. The apparent increase in leukaemia among patients with polycythemia vera treated with P^{32} is suggestive but not conclusive in the absence of an adequate control population. Leukaemia has followed giving I^{131} in high and repeated doses in patients treated for carcinoma of the thyroid. Leukaemia has also been reported after treatment of hyperthyroidism with relatively small doses of I^{131} . In the latter instance, since the number of cases is small and there are metabolic and other complicating factors in these patients, it is not possible to decide whether or not radiation alone at this dosage level is leukaemogenic in man. A recent extensive survey by Pochin⁴⁵⁶ gives no indication that this treatment induces leukaemia. Mouse leukaemia has been induced with bone-seekers,⁴⁵⁶ however, it is questionable whether this disease, or the conditions or irradiation and tissues irradiated, are comparable to those for man. An estimate of the probable incidence of leukaemia from deposition of Sr^{90} has been computed.⁴¹⁰ No confidence can be placed in such estimates because of lack of meaningful estimates of dosage to the marrow. Data obtained from external exposure studies^{420-426, 440, 441} are not directly applicable in the case of non-uniformly deposited isotopes.

MALIGNANT NEOPLASMS IN THE JAPANESE SURVIVORS OF ATOMIC BOMB

287. Harada and Ishida⁴⁵⁷ have recently reported on the incidence of neoplasms among survivors at Hiroshima during May 1957-December 1958. These are tumour registry figures and the data, not based on a

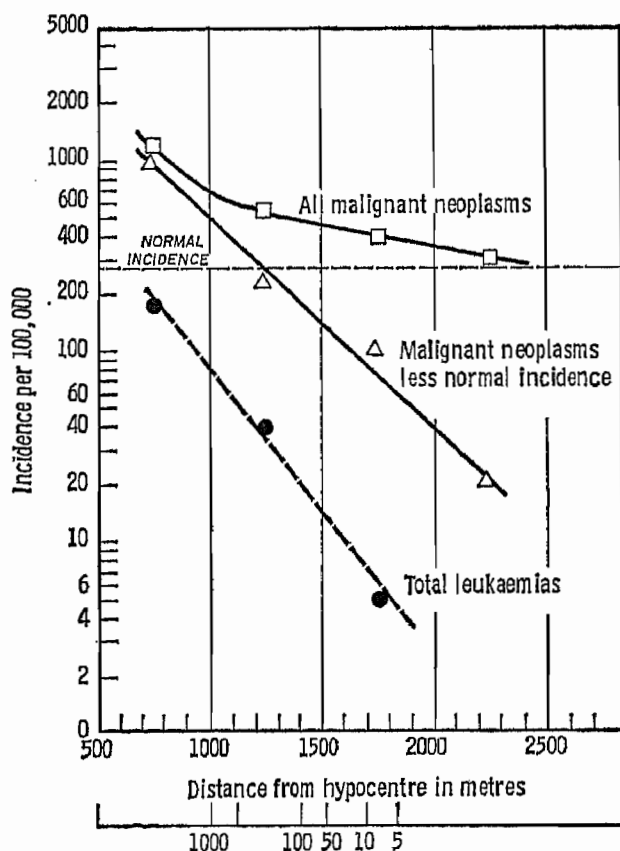
closed sample, are subject to the factors of selection that might enter into the admission of cases to this series. With this important reservation the incidence increased in inverse proportion to hypocentre distance. If the background incidence of all malignant neoplasms, i.e., 280 per 100,000 among the non-irradiated population is subtracted from the incidence of malignant neoplasms the curve is linear and parallels the incidence of leukaemia (figure 7). The incidence correlated to site was higher in all age groups (figure 8). Table VIII shows a significant difference between observed and expected cases of cancer of stomach and lung at the 1 per cent confidence level, while differences in cancer of the cervix and ovary are significant at the 5 per cent level, though the numbers are still small. These preliminary observations need extension in numbers and time so that the increased incidence of carcinoma developing only after many years of latency after irradiation can be correlated with dose and temporal occurrence.

288. Despite the numerical weakness of the data,⁴⁵⁸ the degree of initial leucocyte count depression in the first fourteen weeks after exposure correlated with the occurrence of late effects. The data indicate that the more severe the initial exposure as indicated by clinical signs and early laboratory work, the oftener late effects appear (figure 9).

LOCAL EFFECTS

Radiation cataract

289. Exposure of the optic lens to X-rays, γ -rays, β -particles and neutrons causes cataracts in man.



Air dose (rad), without consideration for individual shielding

Figure 7. All malignant neoplasms (including leukaemia) among atom bomb survivors, May 1957-December 1958, and total leukaemias, 1950-1957, by distance from hypocentre per 100,000 population per year. Modified from Harada and Ishida⁴⁵⁷

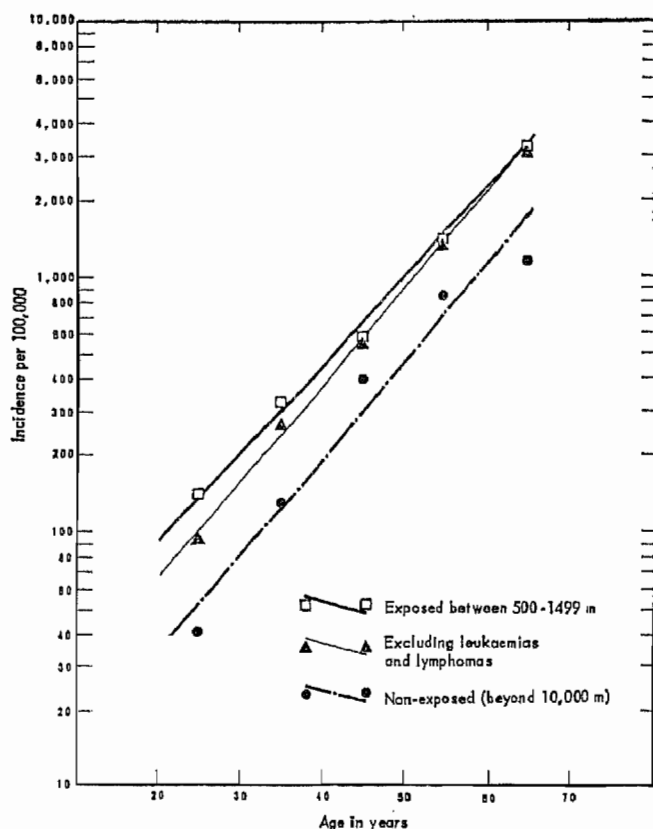


Figure 8. Malignant neoplasms (excluding lymphoma and leukaemia) per 100,000 per year by age and exposure status, May 1957-December 1958. Modified from Harada and Ishida⁴⁵⁷

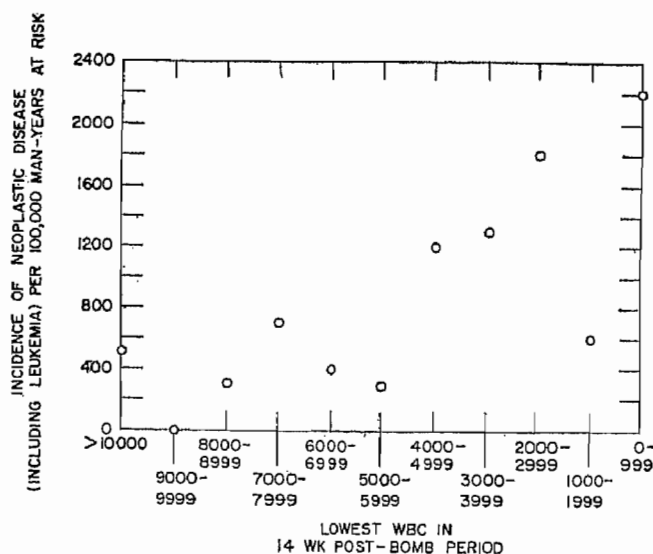


Figure 9. Incidence of late effects among Hiroshima atom bomb survivors, plotted against the lowest leukocyte count in the first 14 weeks after exposure⁴⁵⁸

Although changes in the optic lens have been detected after doses as low as 200 r, the minimal effective X-ray dose (200 kv) for the production of clinically significant cataract is 600-1,000 rad; this dose may be lower for infants or children and is highly dose-rate dependent. Neutrons are 5-10 \times more effective in causing cataracts than X-rays.

290. The characteristics of radiation cataract in early states of development are: an initial dot-like opacity, usually at the posterior pole of the lens, around which

small granules and vacuoles develop as it enlarges. The central opacity develops a relatively clear centre, giving it a doughnut appearance by the time the opacity is 3-4 mm in diameter. At this time, granular opacities and vacuoles may develop in the anterior sub-capsular region of the lens, usually in the pupillary area. The opacity may remain stationary at any stage. Often it shows a slow progression for a long time to the point described before it remains stationary. If the opacity progresses, it takes on a non-specific appearance and cannot be differentiated from cataracts from other causes.

291. X- or γ -radiation have caused ~ 200 cases of radiation cataracts in man.^{459,467} Most had latent periods but in many these were not related to radiation variables such as quality, dose, or duration of treatment. The dose and factors that might permit its calculation were not reported in many cases.

292. The problems of minimal cataractogenic dose—effect of dose and mode of exposure on incidence of stationary or progressive cataracts, influence of dose fractionation and dose or duration of exposure on the latent period, effect of radiation quality, and age on lens sensitivity—are still unsolved for man.

293. From animal studies, radiation cataract results from radiation destruction of the anterior epithelium, which supplies cells that differentiate into fibres of the lens. Young animals exposed pre- or early post-natally have greater lenticular radiation-sensitivity than older animals.

294. Merriam and Focht⁴⁶⁴ studied in man 100 cases of radiation cataract and seventy-three cases of irradiation to the head without subsequent cataract. Duplicating the radiation factors, they measured X- or γ -ray dose to the lens in a phantom. Any clinically recognizable characteristic opacity was regarded as a radiation cataract regardless of whether vision was affected. Numerous uncontrollable variables in this study made it impossible to determine the threshold dose.

295. The minimal effective doses were the least radiation producing some lenticular opacity. It was impossible to classify cases by dose and degree of lens opacity; they were classified by whether opacities were stationary or progressive and this was then related to dose.

296. Ninety-seven of the radiation cataract cases and seventy without radiation cataract were classified by timing of treatment: single, fractionation over three weeks, to three months, and fractionation > 3 months. The minimal doses for production of lenticular opacity in cases for each group were 200 r, 400 r, and 500 r respectively. These figures suggest that the threshold dose increases with duration of treatment.

297. Of thirty-seven cases irradiated in a single treatment (with radium plaques), all twenty with doses from 200-1,150 r developed lenticular opacities. The other seventeen received doses from 40-175 r to the lens without developing lens changes. There were only two cases of stationary lens opacities of minimal degree at an estimated dose of 200 r, first seen nineteen and twenty-two years after treatment. Because of the small number of cases (four) with doses from 200-350 r, the fact that there were none without cataracts does not prove that the lens cannot tolerate higher single doses. Further information on the effects at these dose levels is necessary to determine the upper limits of tolerance. The maximal non-cataractogenic dose in this treatment group was 175 r in a patient followed for 8½ years.

298. Of eighty-seven cases given multiple treatments for three weeks to three months, forty-nine developed lenticular opacities with X- or γ -ray doses of 400-6,100 r to the lens. Lens opacity after 400 r (one case) was first seen 2½ years after treatment and was stationary. The maximal non-cataractogenic dose in this group was

1,000 r with a treatment time of 2½ months and a follow-up period of 13½ years. The following table gives the incidences and types of lenticular opacities in patients after irradiation in various dose ranges for a three-week–three-month over-all time.

Dose range (r)	Cataract type			
	Cataract incidence	Stationary	Progressive	Indeterminate
40–350.....	0 of 18 patients	—	—	—
351–550.....	4 of 9 patients	3	0	1
551–750.....	6 of 10 patients	5	1	0
751–950.....	16 of 26 patients	7	6	3
951–1,150.....	2 of 3 patients	1	1	0
1,151–1,399.....	No cases	—	—	—
1,400–6,100.....	21 of 21 patients	2	18	1

299. Of forty-three cases irradiated over a period longer than three months, twenty-eight developed lenticular opacities after X- or γ -ray doses of 550-6,900 r to the lens. There were two cases of cataract after 550 r, one progressive and one stationary, first seen forty-four months and four years after treatment respectively. The maximal non-cataractogenic dose in this group was 1,100 r, with a treatment time of 1½ years and a follow-up period of twenty-two years.

300. The 100 per cent incidence level of lenticular opacities occurred at the lowest-dose level for the single treatment group (200 r) and at any greater dose. In the multiple treatment cases, the longer the duration of treatment, the lower the incidence at a given dose range below 1,150 r; the higher the dose for a given treatment, the shorter the time of appearance of the lens changes and the higher the incidence of progressive opacities with resulting decrease of vision. In general, fractionation of dose delays the time of onset of cataracts and decreases the incidence of severe opacities.

301. The lenses of children under one year of age seem to be more sensitive to radiation than those of older children and adults.

302. Cataract production by fast neutrons compared with X-rays increases significantly with protracted exposure; i.e., the RBE is about 2-4 for high-intensity and 9 or greater for low-intensity radiation, only because the dose of the "standard" radiation changes, not that for neutrons.

303. By December 1948, at least ten nuclear physicists of mean age thirty-one had incipient cataracts after cyclotron exposure.⁴⁶⁸ Three cases were severe with definitely impaired vision. Four were moderately severe, and three were minimal. It was estimated that over periods of 10 to 250 weeks, these men had received total doses of fast neutrons to the lens of 10 n-135 n with a median dose of 50.* At the time the cataractogenic exposures were received, periodic blood counts done on most showed no change in blood picture warning of over-exposure to radiation.

304. After the finding of radiation cataracts in the physicists, Cogan *et al.*^{469,470} found 10 heavily irradiated Japanese atom bomb survivors with radiation cataracts. In studies by Kimura in 1949, described by Fillmore,⁴⁷¹ 98 cases of lenticular opacity were reported, 85 among the 922 survivors in the high-dose region 1,000 metres or less from the hypocentre. The severity of the lesions was

not reported, but it is inferred that they were generally mild.

305. In 1955, Sinskey⁴⁷² reported an intensive investigation of 3,700 exposed and non-exposed Hiroshima Japanese from May 1951-December 1953: there were 154 survivors with posterior sub-capsular plaques in the lens large enough to be visible with the ophthalmoscope. Opacities not so visible in the greater percentage of survivors were not considered because they did not decrease visual acuity in standard tests. Because of the relatively negligible effect of the atom bomb on visual loss seven years after the bombing, the term cataract, associated with severe loss of vision or blindness, was avoided in this survey.

306. Sinskey found that of 425 survivors in Nagasaki between 400-1,800 metres from ground, 47 per cent had lens changes detected by slit-lamp examination, with or without history of epilation and shielding. Although most opacities were so insignificant as to be invisible with the ophthalmoscope, statistically significant lens changes were present in survivors with no other known early or late evidences of radiation damage.

307. Among ~ 8,000 exposed survivors of Hiroshima and Nakasaki examined by 1956 (eleven years after the atomic bomb explosions), ten cases of severe cataract were found. The relationship between these cases and radiation alone is not clear.

Radiation effects on fertility

308. The late pathological effects in gonads are chiefly a hastening in involutional changes associated with advancing age. In animals, there is little evidence of radiation-induced testicular tumours, but ovarian tumours are increased by radiation.

309. Histological sterility is complete absence of gametes and even gametogenic elements. It is difficult to predict its permanency by biopsy or from necropsy sections. Permanent and complete histological sterility requires large doses to the gonads; such doses would be lethal given in a short time to the whole body or a substantial part.

310. *Functional* sterility can be induced by smaller doses; this may be temporary or permanent depending upon size and intensity of dose. In the male, the rate of sperm production need only be reduced to where there are insufficient sperm in semen to be effective. An increase in abnormal sperm after irradiation also reduces the number of effective sperm. Since the number of nor-

* 1 n is equal to ~ 2 rad.

mal sperms per ejaculate necessary for reproduction is large, sub-fertility may be associated with considerable but subnormal spermatogenesis. These conditions can be induced by doses to the gonads sub-lethal if given as TBR.

Sterility doses for men and women

311. The long-term pathological effects of radiation on gonads have had little study with accurate dose estimates. From fragmentary data certain estimates are attempted.

312. Gonadal doses affecting fertility are probably similar for men and women: a single dose of ~ 150 rad to gonads may induce brief, temporary sub-fertility in many men and women; a single dose of ~ 250 rad may induce temporary sterility for 1-2 years, and 500-600 rad permanent sterility in many, especially in people with borderline fertility, with temporary sterility in others for several years; single doses of 800 rad or more would probably cause permanent sterility in all but a few most resistant men and women.

313. Gonadal doses causing only temporary alterations in fertility in fertile people are sub-lethal if given as TBR. Gonadal doses that permanently sterilize most fertile people are likely to equal the TBR lethal dose.

314. Limited experience with the Marshallese, exposed Japanese, and certain accident cases suggest that substantial fractions of the mid-lethal dose for man (400-600 rad) do not have a serious, permanent effect on fertility, but gonadal doses are not known with certainty; few people have been studied for this purpose for a long time after exposure.

315. Men may be sterilized permanently without prominent changes in interstitial sex cells, hormone balance or libido. Women sterilized by radiation undergo greater physiological changes since ovarian production of sex hormones is intimately related to development and discharge of ova. Radiation termination of production of ovarian follicles induces an artificial menopause in women similar to natural menopause, with amenorrhea, "hot flushes", diminished libido, and occasionally psychic depression. From experimental data, long-term radiation may seriously impair fertility in animals such as man with relatively poor gonadal regenerative ability.

Degenerative diseases and histopathological changes

316. Injuries of the skin, atrophy, dermatitis, epilation, and epidermal neoplasia were among the first recognized late radiation effects. In human skin, 500-700 rad may induce permanent epilation. Smaller doses cause temporary epilation, may decrease pigmentation or gray the new growth of hair in irradiated areas. This effect has not been reported in Japanese. Doses in the erythema range or higher may also increase pigmentation of skin, epidermal atrophy, and decrease sebaceous and sweat glands in irradiated regions. Hyperkeratotic areas in skin, and vascular sclerosis are also late effects of skin radiation. Surface doses of $\sim 1,600$ rad may cause considerable permanent dilation of capillaries (telangiectasia) in irradiated areas. In the past late changes were seen more commonly than today in the skin of hands and faces of persons occupationally exposed to radiation; radiation dermatitis and ulcers were often followed by epidermoid carcinomas.

317. Nephrosclerosis is long known as a complication of over-exposure of the kidneys in radio-therapy. Renal

hypertension may be induced in man within months or a few years by single localized X-ray doses of $\sim 3,000$. 5,000 rad or by fractionated doses of lesser size (e.g., a total dose of 2,300 rad to both kidneys in 35 daily doses).⁴⁷³ These conditions have been induced in experimental animals in a short time by local radition of the kidneys with large doses. More recently, nephrosclerosis with renal hypertension and associated generalized arteriosclerosis were induced in rats and mice as late effects of TBR with much lower doses (sub-lethal or LD₅₀ range). Although the pathogenesis of nephrosclerosis as a late effect is not clear, histopathological data indicate that changes in fine vasculature are important in early and late initiation and development.

318. Nephrosclerosis and related hypertension may appear as a late radiation effect in animals in which it has rarely or never been seen within the average lifespan (later periods are not well studied) or its onset may be advanced in animals in which the disease has appeared spontaneously. Renal hypertension, once established and progressive, increases vascular sclerosis throughout the body; progressive arteriosclerotic changes often induce progressive atrophy of parenchymatous organs. Consequently, when irradiation has induced or advanced nephrosclerosis with related hypertension in animals or man, the incidence of death from related causes (e.g., renal and cardiac failure, and cerebral haemorrhage) increases with corresponding reduction in death from other unrelated causes or from diseases having longer induction times. Irradiation of human brain or spinal cord with several thousand rad, given singly or in large fractions over a few weeks, may injure blood vessels, cause ischemic damage of tissues, and progressive sclerosis of blood vessels, with subsequent secondary degeneration of brain or spinal cord. Blood vessels may rupture one to several years after exposure.

319. Atrophic and fibrotic changes, often with arteriosclerosis, have been seen in human haemopoietic organs long after local radiation. Secondary anaemia has been associated with myelofibrosis after long-term radiation of bone marrow and also as a late complication of radiation therapy. Radiation osteitis is a late degenerative effect of intensive irradiation (a few thousand rad) of bone. The degenerative and destructive processes develop slowly, and after many years lead to necrosis, pathologic fracture, and osteogenic sarcoma.

320. The gastro-intestinal tract has shown some permanent and late effects after fractionated doses of several thousand rad; atrophic and fibrotic changes and sometimes late ulceration in mucosa, and permanently reduced secretion of acid and pepsin by the stomach.

321. Intensive irradiation of the lungs in radiation therapy causes slowly developing progressive fibrosis, with vascular damage and arteriosclerotic changes. Radiation fibrosis⁴⁷⁴ usually develops slowly, but there have been fatalities eight weeks after therapy. Lungs show fibrosis with thickening of alveolar walls and vascular system. The alveolar walls may be lined by cuboidal epithelium and the remaining alveolar sacs may be filled with cells. Cough and dyspnea are the principal symptoms. Roentgenographs are similar to those of pulmonary fibrosis from other causes. There is considerable unexplained individual variation in post-irradiation fibrosis but in general the incidence depends on dose. The degree of disability depends also on the amount of lung tissue irradiated; thus, treatment of intrathoracic neoplasms where a large part of pulmonary tissue is

exposed is apt to be more serious than treatment of carcinoma of the breast, where usually only part of one lung is exposed.⁴⁷⁵ Malignant neoplasms of the lung have been seen in miners who inhaled radio-active substances, and have been induced in animals by intra-tracheal injection and implantation of radio-active substances.

322. Substantial doses of radiation to actively proliferating mammalian tissues reduce their regenerative capacity. Failure of such tissues to regenerate parenchymal cells to normal numbers is often associated with increased connective tissue and vascular changes. In general, incomplete regeneration varies directly with size of the single dose or with dose rate in long-term radiation; in some tissues such as testis, fractionation may increase dose efficiency in damaging regenerative capacity. It is not clear to what extent the permanence of this effect is due to the direct effect of radiation on stem cells, or to damage of supporting tissue. Nor is it clear to what extent in each tissue incomplete regeneration is due to: (a) decreased reproductive capacity of existing stem cells, (b) decreased stem cells surviving, (c) asynchrony in regeneration of histological elements with increase in connective tissue, or (d) damage of fine vasculature, although any or all factors may be implicated depending upon dose. Little is known quantitatively about the reproductive capacity of individual stem cells or the numbers of primitive stem cells surviving in the post-recovery period after irradiation. Fibrosis of small blood vessels with general reduction in vascularity is often associated with subsequent reduction in number of parenchymatous cells and increase in connective tissue.

323. Changes in vascular and lymphatic systems, with destruction of radiation-sensitive parenchymatous cells, are important in the pathogenesis of many late radiation effects. Many late effects may come from metabolic and nutritional disturbances due to impaired blood supply that reduce function and reparative capacity, and increase susceptibility to traumatic damage, infection and disease in general.

Effects on growth and development

324. The regenerative processes of the body are fairly sensitive to radiation; their inhibition may be prolonged especially if vascular integrity is impaired. More quantitative study is needed after local and TBR.

325. Some quantitative studies in rats indicate that repeated TBR at 24 rad/wk inhibits growth. A significant decrease in growth can be caused by repeated TBR without decrease in haemoglobin or absolute neutrophils levels.

326. Localized irradiation of the epiphysis inhibits bone growth and shortens bones in man and animals, the effects being greatest in youngest animals. Localized irradiation of the jaws decreases tooth growth.

327. Studies in Japanese children after the atomic bomb indicate a statistically significant if slight retardation of growth and maturation. However, the effect of non-radiation factors has not yet been adequately evaluated. Extensive measurements on 4,800 children at 6, 7 and 8 years after exposure in Hiroshima showed generally that growth was retarded and maturation delayed.^{476, 477} In another study of several hundred children in Hiroshima and Nagasaki, in years 2, 4 and 5 after irradiation, physical growth and development were affected adversely, and retardation of height, weight, and skeletal development was still evident at the end of

1950.⁴⁷⁸ The investigators believed that factors other than radiation—e.g. malnutrition—may have contributed to these effects.

VI. Special features of internal and external contamination

PHYSICAL CONSIDERATION⁴⁷⁹

328. The hazards of exposure to radio-nuclides depend greatly on their physical and chemical properties; these determine their entry into the body and retention in various organs. The duration of radiation depends also on physical half-life and in some instances on complicated decay chains causing a shift of the emitter from one place to another as the isotope undergoes transmutation.

329. The nature of the emitted radiations may determine the range of exposure and hence the pattern of injury e.g., an energetic α -ray will penetrate no further than 0.07 mm. in tissue; β -rays deposit their energy largely locally; γ -ray energy will be absorbed in larger volumes or an appreciable portion of the energy will escape the body altogether.

330. The degree of damage depends to some extent on the concentration of ions along the path of ionization. For an equal energy, this is greatest with the shortest range emissions i.e., α -rays. For most types of response the effects are greater where ionization is dense.

331. In recent years, attention has centred on the long-term hazards of radio-nuclides of long half-life, e.g., Sr^{90} and Cs^{137} . But, intermediate and short-lived isotopes may be important, depending on circumstances. Possible accidental discharge of radio-active material from reactors, as nuclear detonations, may contaminate local areas with various fission and activation products. Even in global fall-out from the thermo-nuclear tests, fission products of intermediate half-life are a source of γ -radiation which, for a few months after detonation at high altitudes, has exceeded that from Cs^{137} .⁴⁸⁰ Among the short-lived isotopes the most interesting, especially in nuclear accidents is I^{131} .

332. The important isotopes of intermediate half-life include Ba^{140} , Ru^{108} , Ru^{106} , Co^{60} , Ce^{141} , Ce^{144} , Y^{91} , Zr^{95} , and Sr^{90} . Some are so poorly absorbed that for practical purposes they may be considered as external γ -ray sources; Ba^{140} and Sr^{90} are absorbed and must be considered with Sr^{90} as contributing dose to the skeleton.⁴⁸¹

333. In past weapon tests, studies of fall-out patterns have shown that the geographical distribution of isotopes depends on many factors, including the altitude of explosion and the nature and amount of surrounding material. Particle size and their solubility vary with distance as with other factors.⁴⁸² Any nuclear accident is likely to produce a unique pattern of variables, e.g., due to the features of the accidental discharge from the Windscale reactor in Great Britain the contaminating fission mixture had a lower content of radio-strontium relative to radio-iodine than might have been anticipated.

SPECIAL PROBLEMS ASSOCIATED WITH INTERNAL EMITTERS

Localization of radiation

334. Theoretical and experimental considerations suggest that the effects in tissues from uniformly applied radiation may differ from the effects of radio-active

particles aggregated into a "point source".⁴⁸³ In the latter, dose-rates close to the point source differ from those near the end of the range of the particles. Dose-rate near the origin is extremely high; these high rates may be important, if the relationship between injury and dose-rate is non-linear. Dose-rates are unimportant if the effects of radiation are related to dose in a linear non-threshold way. Then, the effect may reflect a single-event so that only total dose is important; dose-rate and spatial distribution are inconsequential. When the radio-element is diffusely deposited, the probability of the distribution of injury is the same for all cells in the tissue, whereas in discrete deposition, the probability of injury of cells close to the aggregate is increased but that of injury to the cells far away is reduced.

335. If the relation between dose and degree or probability of injury is not linear then spatial distribution is important. Also, different biological effects may show different relationships with dose. Present data are not adequate to define differences in hazard between focal and diffuse radiation.

Concept of RBE

336. Even with uniform irradiation the concept of RBE is by no means simple, as is discussed in other parts of the report, since the relative effectiveness of radiations of different quality may depend on many factors other than LET, including dose, dose-rate, biological end-point, and other factors. With many internal emitters and particularly with the bone-seeking isotopes, there is the additional problem of a very non-uniform distribution of radiation dose, which introduces further severe problems into the use of RBE factors, which have not yet been solved.

337. Because of the many difficulties, the concept of RBE can be applied only in a very general way, especially to internal emitters, and care must be taken when using it to establish standards of radiation safety for various types of ionizing radiations. In particular, it must be emphasized that an RBE established for one biological effect is not necessarily valid for another.

Modes of entry of radio-isotopes into animals and man

338. Among the fission products only few are of significance with regard to internal contamination. The uptake and metabolism in the organism depends on the nature of the materials and their chemical and physical properties. The routes of environmental contamination into the body are ingestion, inhalation, and skin absorption.

Ingestion

339. Gastro-intestinal absorption is the most important route of uptake of Sr^{90} and Cs^{137} from nuclear weapons tests. The levels of these isotopes in animals and man correlate with their levels in the diet; they are readily absorbed.

340. Ingestion is an important mode of entry only for soluble isotopes. The solubility of interest is solubility in body fluids rather than solubility in water. Many soluble compounds may be converted to relatively insoluble hydroxides at the pH of body fluids. Also, relatively insoluble compounds may be converted to soluble compounds in body fluids. Only those having intermediate or long half-lives can be absorbed by man in proportion

to fall-out levels except where rainwater is used for drinking and cooking because of the relatively long times in the ecological pathway.

341. Another factor is whether the isotope is a radio-nuclide of an element required by the body or of one chemically similar to a required element. The actinide and lanthanide rare earth series of elements have no chemically similar counterparts among required body constituents and are usually poorly absorbed by plants and animals. For these radio-nuclides, inhalation may be relatively more important than ingestion.

342. Although some generalizations are possible from the similarities of elements with families of the periodic table and from similarities to required body constituents, each radio-nuclide has its own metabolic properties. There is a continuing need, therefore, for data on gastro-intestinal absorption of all radio-nuclides that are potential contaminants of the environment.

Inhalation

343. In industry, inhalation has been found to be the most important route of entry of potentially hazardous materials. Inhalation of radio-active isotopes creates three potential hazards: absorption into the systemic circulation and subsequent deposition in a critical tissue or organ; irradiation of the lungs themselves from materials deposited on respiratory surfaces and picked up by bronchial lymph nodes; ingestion. Inhalation is generally the most important route of entry of short-lived radio-nuclides and of insoluble radio-active materials.

(a) Size of inhaled particles⁴⁸⁴

344. The relationship between size of radio-active particles and their deposition in the respiratory tract is complex, since retention and movement vary with particle size. In general, very small particles may be deposited throughout, freely entering the lower portions of the lung. As particle size increases, deposition throughout the respiratory tract decreases, and reaches a minimum at a particle size of $\sim 0.4 \mu$. With further increasing particle size, up to $\sim 10 \mu$, the fraction deposited in the total respiratory tract increases. Particles $> 10 \mu$ will not penetrate the passages to the alveoli, and are deposited mainly in the upper respiratory tract, where there is rapid clearance. As particle size increases further, the point of deposition is further up the respiratory tract, until the probability of inhalation of large particles becomes low because of the filtering action in the nostrils.

(b) Radio-activity of inhaled particles

345. Suspended radio-active materials may be very heterogeneous in particle size and in other physical and chemical properties. Compounds of several radio-elements can be attached to a particle of inert material, or a single radio-active compound can be the entire particle. Usually radio-nuclides become associated with inert materials during information or after subsequent agglomeration.

(c) Solubility of inhaled particles

346. Once a radio-active substance is deposited in the body, its fate—translocation and excretion—is partly determined by its solubility in body fluids. Solubility depends principally on chemical composition, but physical properties such as size, shape, and surface area are also important, especially of heterogeneous particles in which radio-active substances are adsorbed on the surfaces of inert nuclei.

Skin absorption

347. Absorption of radio-isotopes through the skin has not been sufficiently studied. The skin is not usually considered an actively absorbing organ, especially for inorganic substances. Animal experiments have been limited because anatomical and physiological dissimilarities between human skin and that of the more common laboratory animals lead to problems of interpretation. The skin does not appear to be an important route of entry of nuclides contaminating the general environment. However, skin absorption of radio-active materials should not be ignored, especially when large quantities may come in contact with the skin surface in industrial accidents. A specific example is tritium as tritium water (H_2O). The amount of atmospheric tritium water that exchanges with moisture on the skin surface and enters the circulation is about equal to that entering via inhalation of the same tritium-containing atmosphere.^{485, 486} Absorption of a few other radio-nuclides through human skin has been studied.⁴⁸⁷ When the skin is broken, e.g. in wounds, absorption of radio-nuclides is greatly accelerated and increased.

EFFECTS OF RADIO-ISOTOPES AFTER ABSORPTION

348. The effects of radiation from materials within the body are similar to those of external radiation. Important differences arise because (a) radio-isotopes are not distributed uniformly within the body; and (b) they serve as more or less continuous sources of radiation.

EARLY EFFECTS

349. In animal experiments, haematopoietic symptoms of acute radiation disease appear 7-10 days after lethal amounts of radio-isotopes given intravenously or parenterally.^{488, 489} Sub-acute effects, frequently seen 1-5 months later, may include haematopoietic symptoms as well as malfunction of those organs within which the radio-isotope is deposited most heavily, e.g., polonium leads to kidney damage, plutonium and the rare earths to liver damage, radio-iodine to thyroid damage, and radio-strontium to bone damage.^{489, 492} A recent paper on the accidental exposure of 103 luminous-dial painters to Sr^{90} gives data on its urinary excretion in man and gives some information on possible early haematological effects.⁴⁹³ A more complete account on urinary excretion of Sr^{90} in man is given in a report on a case of accidental inhalation.⁴⁹⁴

350. It is unlikely that many human cases of acute or sub-acute poisoning due to internal emitters will ever occur. In nuclear war or a reactor accident, the chance of serious damage from external radiation greatly overshadows that from radio-nuclides which might enter the body. On the other hand, the long-term effects of small amounts might become a serious problem.

Late effects

351. Experience with the long-term effects of internal emitters in man is essentially limited to radium, used therapeutically and in the dial-painting industry, to thorium used as a contrast medium for roentgenographic diagnosis, and to elements in the decay chains of radium and uranium to which miners have been exposed. Cancer has appeared in these groups.⁴⁹⁵⁻⁴⁹⁹ More recently, radio-phosphorus, radio-iodine, and other new nuclides have been used in treatment and diagnosis; scanty reports of tumour induction require verification.

Effects of internal emitters on the lung, including cancer of the lung

352. In 1939, Rajewsky reported a technician in a radium plant who died with pulmonary fibrosis similar clinically and anatomically to that after external irradiation.⁵⁰⁰ The technician was twenty-four years old and had worked three years in the plant. At death, his lungs contained $\sim 6.2 \times 10^{-2} \mu\text{c}$ of radium which would give a mean dose rate of ~ 0.2 rad per week. Most radium previously deposited had almost certainly been cleared from the lung at the time of death; therefore earlier dose rates must have been much higher. The lung cancers in the miners of Joachimsthal and Schneeberg, in Czechoslovakia, are familiar. The mines were first opened in 1410 for copper and iron; in 1470 silver and arsenic were discovered and mined, and later bismuth, nickel and uranium. Other metals found were tin, zinc, cobalt, manganese, magnesium and lead. At the beginning of the twentieth century, uranium was the principal element mined for the dye industry. Three surveys were made to establish the incidence and determine the cause of cancer of the lung among the miners.⁵⁰¹⁻⁵⁰³ The concentration of radon in the air of the mines^{504, 505} varied considerably in different shafts (0.36×10^{-6} — 47×10^{-6}) and averaged $2.9 \times 10^{-6} \mu\text{c/cc}$.

353. Although the exact role of radium in the etiology of the lung cancers is unknown, there seems little doubt that their incidence among the Schneeberg and Joachimsthal miners is at least 50 per cent higher than that in the general population. The cancers of the lung are morphologically similar to those in other groups of the population, with the possible exception of the absence of adenocarcinoma. The average latent period for the induction of lung cancer in these miners was ~ 17 years, and calculations have suggested that assuming uniform distribution the dose to the lung would have been $\sim 1,000$ r during this time.⁵⁰⁶

Long-term effects of internal emitters in animals

354. In animals, effects are generally measured in terms of tumour induction and life shortening. Tumours may appear in those tissues in which the isotope is located and also in adjacent tissues within the range of the radiation. Thus radio-strontium, which localizes in bone, induces in mice osteosarcomas and rarely epidermoid carcinomas of the oral and nasal mucosa.⁴⁹¹ In man radium has caused, in addition to the usual sequela of bone malignancy, epithelial tumours arising in the mastoid cavity and the accessory nasal sinuses.⁴⁹⁹ Other instances in which tumourgenesis is associated with the direct action of ionizing radiation on tissues include tumours of the liver, gastro-intestinal tract, lungs and skin. In the case of thorium, for example, hepatic carcinomas and hemangio-endotheliosarcomas have been noted abnormally often in patients given thorotrast intravenously for angiography.⁵⁰⁷ The incidence of these tumours increases with the quantity of incorporated radio-isotope, the dose up to a given point and may also depend on the dose-rate within the critical organ.⁵⁰⁴

355. In other instances, however, irradiation by radio-isotopes may lead to abscopal (other than local) effects. Neoplasia of endocrine glands and of sex organs (typified by the hypophysis and ovaries) are induced by various radio-isotopes irrespective of their organ distribution. Their incidence is not clearly related to dose or dose-rate, and may depend strongly upon such factors as strain and sex. Hormonal dysfunction induced by radiation plays an important role in their etiology.⁵⁰⁴

An intermediate position is occupied by mammary tumours and lymphomas, where the incidence is dependent on dose, but which are unaffected by the pattern of isotope distribution. In mice, lymphocytic neoplasms may arise where the primary target is bone, perhaps resulting from the TBR occurring while the isotope is circulating.⁴⁹¹

Effects of internal emitters on the lung in animals

356. More striking effects were seen after deposition of radio-active gases and particles in the lungs, e.g. high incidence of pulmonary tumours in mice inhaling radon.⁵⁰⁸ They were exposed continuously to air containing radon at 1.2×10^{-6} $\mu\text{C}/\text{cc}$, and lived 161-453 days. Ten or twelve animals had lung adenomas, and one an adenocarcinoma arising in a small bronchus. There was one adenoma in the controls. Tracheal administration of 50 mg of quartz and three-hour exposure to air containing 8×10^{-6} curies radon per litre retarded weight increase and changed the peripheral blood composition.⁵⁰⁹ Radon affected the silicotic process significantly inducing metaplasia of bronchial and alveolar epithelia, and in some cases, malignant tumours and bone tissue in the lung parenchyma and in blood vessel walls. Proliferation of bronchial epithelial cells along with atrophy and proliferation of the tubular epithelium of the kidney were seen in mice five months after an eighteen-hour exposure to 2.4×10^{-4} curie of radon per litre of air.⁵¹⁰ The carcinogenic action of radon is due to its disintegration products.^{511, 512} Pneumoconiosis does not play a decisive part in the pathogenesis of lung tumours due to the effect of radon.⁵¹³

357. Changes in pulmonary histology have been seen after various α - and β -emitting elements, Ru^{106} , Rh^{106} , Sr^{90} , Ce^{144} , Pu^{239} , Po^{210} and Co^{60} , were given to rodents, mostly by intratracheal injection.

358. Strontium-90 was given by transthoracic injection of glass beads⁵¹⁴ and in one study Ru^{106} was plated on a platinum cylinder introduced into a bronchus.⁵¹⁵ In most studies, squamous metaplasia of the bronchial epithelium was seen in many of the animals; fibrosis and pneumonitis were common. Because of the high frequency of lung pathology in rodents, it is unsafe to ascribe all changes to the radio-active elements. The tumours thought to be bronchogenic were unencapsulated and invasive. In studies with implants many of the tumours surrounded the implants.

359. Cember intra-tracheally injected up to 4.5 millicuries of S^{35} as BaSO_4 , in rats, and found no effects definitely attributable to the radio-active particles.⁵¹⁶ In another study after 375 microcuries of $\text{BaS}^{35}\text{O}_4$ given intra-tracheally to twenty-four rats once a week for ten weeks, two of sixteen rats surviving showed severe squamous metaplasia in the lung, and two had bronchogenic squamous cell carcinomas. The estimated average dose to the lung during ten weeks was 12,000-20,000 rad.⁵¹⁷

360. Cember also reported bronchogenic squamous cell carcinoma after pulmonary implantation of Sr^{90} glass beads.⁵¹⁴ Four squamous cell carcinomas, two lymphosarcomas, and one lymphoma were seen in rats carrying the Sr^{90} beads. Six tumours were intimately associated with the beads. The total dose given the lung ranged from 5×10^4 rad to $> 2 \times 10^5$ rad.

361. Warren and Gates⁵¹⁸ induced epidermoid carcinoma of the bronchus in mice with Sr^{90} glass beads and with Co^{60} implants. For Co^{60} the radiation doses were high, up to 400,000 rad in 200 days, to the nearest viable

bronchial epithelium, or 12,000 rad to epithelium one cm. from the source. They were unable to produce carcinoma in mice at doses $> 70,000$ rad to bronchial epithelium. For Sr^{90} the dose given bronchial epithelium to within five mm from the source was 13,000 rad after 200 days. Not all mice developed epidermoid carcinoma.

362. Other experiments with relatively insoluble particles retained in the lung for long times have shown an increase in malignant tumour incidence. Intratracheal $\text{Pu}^{239}\text{O}_2$, 0.06 to 0.16 microcurie, caused fibrosis, sterile pneumonitis, and benign papillary cystadenomas in 60-80 per cent of mice within 100 days.⁵¹⁹ Similar results were seen after intra-tracheal $\text{Ru}^{106}\text{O}_2$. Malignant lung tumours were seen in these mice. For various tumours a dose has been calculated assuming uniform distribution of radio-isotope in lung tissue and exponential loss from lung.⁵²⁰ The authors original estimate of dose to lung was used where reported (table IX).⁴⁸⁴ The smallest lung doses mean values associated with malignant tumours were 115 rad after 0.003 μC $\text{Pu}^{239}\text{O}_2$ and 300 rad after 0.15 μC $\text{Ru}^{106}\text{O}_2$.⁵²¹ However, the etiology of these tumours is uncertain because autoradiograms failed to show radio-activity in the area of the tumour.

363. In other studies, at least 2,000 rad was the estimated dose to lungs that developed tumours. The estimated dose is questionable in many cases because of the non-uniformity of the distributed radio-active materials. Autoradiograms showed that inhaled particulates were localized in discrete areas of the lung.⁵¹⁹ In these cases, dose to microvolumes of tissue could be considerably greater than that estimated by assuming uniform distribution. Therefore, from the dose estimates given in table IX one should not conclude that the dose required to induce lung cancer is necessarily as low as 2,000 rad; it may, indeed, be much greater. Lung carcinogenesis after inhalation of radio-active particles has not been very common; only a few studies have been completed. Lisco⁵²² has described epidermoid carcinoma, adenocarcinoma, and hemangio-endothelioma in 50-100 per cent of rats inhaling about 0.2 to 1 μC PuO_2 smoke. Recently, Temple *et al.*,⁵²³ in preliminary work, found a bronchiolar carcinoma in a mouse killed 500 days after deposition of 0.01 μC of $\text{Pu}^{239}\text{O}_2$ by inhalation. In most reports summarized in table IX, the authors also found significant metaplastic changes, some at doses lower than those given in the table. Other effects causing death of mice were seen after inhalation of $\text{Pu}^{239}\text{O}_2$.⁵²⁴ Ninety per cent mortality occurred within ten months after deposition of 0.34 μC . No increased mortality occurred after deposition of smaller quantities, although some lung pathology was present. Cember reported no increase in non-specific mortality after implantation of sufficient Sr^{90} in glass beads to produce bronchogenic carcinoma.⁵¹⁴

364. Although radio-isotopes accumulate in pulmonary or tracheobronchial lymph nodes, little is known of their effects. A tracheobronchial lymph node from a dog two years after 20 μC of intratracheal $\text{Pu}^{239}\text{O}_2$ showed characteristic radiation damage. The architecture of the node was destroyed and there was only limited regeneration of lymphatic tissue. In other dogs, possible histologic changes were seen within a year after inhalation of 2 μC $\text{Pu}^{239}\text{O}_2$.⁵²⁵

Effects of internal emitters on bone⁵²⁶

(a) Histological damage in bone

365. Whatever the source of radiation, external or from internally deposited isotopes, the general patterns of histological change are remarkably similar in different

species. Histological damage includes: (i) empty lacunae, (ii) vessel injury, (iii) irregular abnormal new bone, and (iv) varying degrees of fibrosis; in addition, in rats and mice where endochondral ossification continues in adult animals and in young rabbits there may be (v) unresorbed cartilage, (vi) abnormalities of cartilage in the epiphyseal plate, and (vii) severing of old and abnormal resorption of new spongiosa.

366. Bone damage takes two forms. First, bone may be injured probably by indirect destruction through vascular injury and by direct action on the osteocytes. The presence of osteotropic isotopes especially Sr^{90} during a chronic phase of injury (after 180-200 days and later) induces a sharp deterioration in the blood supply, as a result of the emptying of considerable sections of the vascular bed of blood forming and bone tissues with the disruption of vascular innervation.^{527, 528} The damage to osteocytes and vessels can be seen within a few days in animals given a large short-term radiation; but it is best seen as a late change in bones of patients with radium poisoning, as well as in experimental animals. Secondly, radiation having damaged osteoblasts and osteoclasts, can initiate abnormal activity in osteogenic connective tissue. Short-range α -emitters, radium, mesothorium, radio-thorium and plutonium affect the osteogenic connective tissue lining endosteal surfaces and resorption cavities of bone trabeculae, inducing marked terminal fibrosis, especially when the dose injected is high. The longer-range β -emitters, Sr^{90} and P^{32} , and external irradiation affect loose connective tissue in the bone marrow spaces between bony trabeculae as well as on the surface of the trabeculae. They induce variable degrees of active cellular fibrosis often characterized by proliferation of pleomorphic spindle cells with conspicuous numbers of mitotic figures and abnormal giant cells.

367. At higher dose levels most changes are seen in different species. Their severity decreases considerably with time, especially with an isotope of relatively short half-life, e.g., P^{32} , where irradiation is short compared with that of longer-lived isotopes. With decrease in dose or end of radiation, these changes become less severe, and at sufficiently low doses, the initial damage is repaired so that no histological evidence of damage remains; bone has a considerable capacity for repair.

(b) Histogenesis of bone tumours

368. Gross damage causing dead bone and repair may occur without malignant change. Tumours do not necessarily arise at the site of maximum damage. In fact, it is possible that, in very heavily irradiated bone, the tumour incidence decreases, since the capacity of the tissue to proliferate will be greatly influenced. There is no obvious correlation between incidence of sarcoma and degree of radiation damage. Thus external irradiation of the knee joint and adjacent ends of the femur and tibia of rats damages and induces tumours in the epiphysis and metaphysis of both long bones; but not in the patella, where energy absorption is lower. In the long bones of rats given P^{32} and of rabbits given Sr^{90} , the earliest microscopic tumours appear as small foci of proliferating cells amongst spindle cells of osteogenic connective tissue that show fibrosis in rats. In rabbits fibrosis is less evident. This does not mean that the tumour arises from cells responsible for fibrosis—only that it arises in the same region of bone. To have a reasonable chance of seeing microscopic tumours when animals are killed, one must use a radiation dose large enough to give high tumour incidence. The types of cells giving rise to tu-

mours cannot be defined morphologically because of the extremely abnormal environment in damaged tissue. The histological characteristics of tumours seen in various species show that the cells at risk are the "osteogenic" connective tissue cells. There is no precise evidence as to whether all these cells are equally susceptible to irradiation, though it appears unlikely that the osteocyte is. The cell may be an undifferentiated "reticulum cell"; if so, it is surprising that there is no evidence of myeloid leukaemia unless there are at least two different types of undifferentiated "reticulum cell". The increased leukaemia in mice after Sr^{90} was always lymphatic.

369. The sequence of bone tissue changes in rats from the moment of introduction of the radio-isotope (Sr^{90} , Sr^{89} , Ce^{144}) to the appearance of the primary tumour nodule, postulated by Kraevsky and Litvinov³²¹ is:

(i) 1st to 20th day: initial unspecific response of the bone in the form of development of endosteal tissue and intensified remodelling of bone;

(ii) 20th to 80th day: inhibition of bone modelling. Slowing down of osteogenesis. Abrupt dystrophic changes in the osteogenic tissue. Reduction in the number of osteoblasts and vessels. Coarsening of the basic material. Onset of atypical bone formation—the background for subsequent tissue malignancy;

(iii) 80th to 120th day (first pre-tumour phase): onset of redundant and degenerate bone formation. Intensified formation of pathological bone structure in a radically changed environment;

(iv) 120th to 150th day (second pre-tumour phase): growth of polymorphous osteogenic tissue among pathological bone structures. Appearance of accumulation of atypical, free, intensively-dividing, osteogenic cells;

(v) 150th to 180th day (third pre-tumour phase): proliferation of atypical osteogenic and immature bone tissue;

(vi) 180th day and later: tumour-appearance of primary tumour nodules and their subsequent growth.

370. Whether antecedent histological bone damage is always found in a bone having a radiation-induced tumour must be left undecided at present.

(c) Relationship between the pattern of radiation dose in space and time, histological bone damage, and bone tumour induction

371. The radiation dose, i.e., the absorbed energy expressed in rad, is important in relation to histological damage. Some investigators have considered only the dose given or retained in μc without attempting to calculate rad, since there are many difficulties in calculating a meaningful dose in rad. Calculations in rad should be encouraged since it is only in this way that a quantitative relationship between radiation and biological effect can be obtained. The relationship between dose, dose-rate and the formation of bone tumours has been studied in experiments with Sr^{90} , Ce^{144} , Pu^{239} , Pm^{147} , Y^{91} , Sm^{153} , Eu^{154} , Gd^{153} , Dy^{161} , Ho^{166} , Er^{169} , Tm^{170} , Yb^{176} , Lu^{177} , Hf^{181} , Ta^{182} , W^{187} , Re^{188} , Os^{192} , Ir^{192} , Pt^{198} , Au^{198} , Hg^{201} , Tl^{203} , Pb^{210} , Bi^{212} , Po^{210} , At^{210} , Rn^{222} , Ac^{227} , Th^{232} , Pa^{233} , U^{238} , Np^{237} , Pu^{239} , Am^{241} , Cm^{244} , Bk^{247} , Cf^{252} , Es^{253} , Fm^{257} , Md^{258} , No^{259} , Lr^{262} , La^{138} , Ce^{140} , Pr^{141} , Nd^{144} , Pm^{145} , Sm^{147} , Eu^{151} , Gd^{155} , Terbium^{159} , Dysprosium^{163} , Ho^{165} , Er^{167} , Tm^{169} , Yb^{173} , Lu^{175} , Hf^{178} , Ta^{180} , W^{182} , Re^{186} , Os^{190} , Ir^{194} , Pt^{196} , Au^{197} , Hg^{200} , Tl^{204} , Pb^{208} , Bi^{214} , Po^{214} , At^{214} , Rn^{220} , Ac^{228} , Th^{232} , Pa^{234} , U^{238} , Np^{240} , Pu^{244} , Am^{248} , Cm^{250} , Bk^{262} , Cf^{266} , Es^{270} , Fm^{274} , Md^{278} , No^{282} , Lr^{286} , La^{138} , Ce^{140} , Pr^{141} , Nd^{144} , Pm^{145} , Sm^{147} , Eu^{151} , Gd^{155} , Terbium^{159} , Dysprosium^{163} , Ho^{165} , Er^{167} , Tm^{169} , Yb^{173} , Lu^{175} , Hf^{178} , Ta^{180} , W^{182} , Re^{186} , Os^{190} , Ir^{194} , Pt^{196} , Au^{197} , Hg^{200} , Tl^{204} , Pb^{208} , Bi^{214} , Po^{214} , At^{214} , Rn^{220} , Ac^{228} , Th^{232} , Pa^{234} , U^{238} , Np^{240} , Pu^{244} , Am^{248} , Cm^{250} , Bk^{262} , Cf^{266} , Es^{270} , Fm^{274} , Md^{278} , No^{282} , Lr^{286} .

372. Most difficulty in interpreting the response of bone to bone-seeking isotope arises from the considerable spatial and temporal non-uniformity of dose, and from the changing spatial relationship between cells and radiation source, especially in young growing animals. The difficulty is knowing which of the many variables predominates in inducing histological changes. Two variables are: (i) accumulated dose and (ii) dose-rate to the site. The incidence of osteosarcomas increases with dose

and dose-rate. Accumulated dose and dose-rate are inter-related: a great problem with accumulated dose is the time over which it should be integrated. The dose accumulated up to the time of tumour induction is useful, but a proportion of radiation given in the later stages may be "wasted" for tumour induction. Attempts have been made to relate accumulated dose and dose-rate to damage and tumour production in studies in space and time with Sr^{90} and P^{32} in rats and rabbits. Information on dose and bone damage with other isotopes is far less detailed.

(d) *Accumulated radiation dose to the site*

373. With isotopes that emit long-range β -rays, e.g., Sr^{90} , Y^{90} and P^{32} , maximum dose-rates in different parts of the skeleton of rats and rabbits varies considerably from one bone to another, mainly because of variation in bone size. In a small bone, contribution to dose-rate from cross-fire in neighbouring deposits is less than in a larger bone. This causes variation in the maximum accumulated dose in different bones. When maximum accumulated dose is compared with distribution of osteogenic sarcomas in the skeleton with Sr^{90} , sites of maximum accumulated dose correlate with sites of osteogenic sarcomas. However, other factors must also be important: sites of maximum accumulated dose (usually the ends of the long bones in young animals) are also the areas of maximum growth and therefore of actively proliferating tissues; they are also the largest volume of irradiated bone.

374. Where damage was compared with dose-rate in time and accumulated dose in the upper half of the tibia of young rabbits, given Sr^{90} (i) as a single intravenous injection or (ii) as daily pellets by mouth, the bone volume given maximum dose-rate and accumulated dose correlated with the sites of tumour origin. In animals given a single injection, maximum dose-rate and accumulated dose and site of tumour origin were confined to a small length, ~ 5 or 6 mm., of bone. In fed animals, maximum dose-rate and accumulated dose were along a 3-cm length of bone along which abnormal bone tissue appearing to be the tumour origin was wide-spread.

375. The injection of P^{32} at different time intervals (fractionated doses) shows that the rate at which tumours appear can be altered for a given total injected dose. The maximum accumulated dose was approximately the same in groups of rats injected at different intervals; this indicates that factors other than maximum accumulated dose also influence the induction of bone tumours.

376. From a comparison of the dosages in mice given Ca^{45} and Sr^{90} causing the same incidence of bone tumours, the conclusion was that cells on the surface of the bone and bone trabecules (osteoblasts and connective tissue cells) were the cells at risk and not osteocytes. This conclusion is not necessarily unique. In this comparison, two difficulties are: (i) at the dose levels compared there were fewer tumours in long bones with Ca^{45} than with Sr^{90} ; and (ii) dosimetry of Ca^{45} is subject to error. These data suggest that after Ca^{45} and Ra^{226} "hot spots" might soon become buried in bone and hence unimportant in giving significant radiation to bone surfaces. The "diffuse component" with these isotopes, may be the more important in giving the effective dose.

377. Several workers have reported complete histological recovery in bones of young animals of all species with maximum accumulated dose (to time of sacrifice) 2,000 rad. However, since this dose still induces a sig-

nificant incidence of tumours, a more detailed histological search or a new indicator might reveal persisting damage. Pre-tumour proliferations of immature osteogenic tissue can be resorbed if the dose-rate (Sr^{90} , Y^{90}), is reduced, thus demonstrating that repair of "carcinogenic" injuries is possible.³²¹

(e) *Radiation dose-rate to the site*

378. A range of dose-rates from 50 rad/min. for X-rays, 0.2 rad/min. for P^{32} and 0.05 rad/min. for Sr^{90} induced similar tumour incidence, i.e., 30-60 per cent for maximum accumulated doses of 3,000-8,000 rad. In a small group of rabbits a maximum dose of $\sim 20,000$ rad over 6-8 months gave 100 per cent tumour incidence. Over this relatively high range, the dose-rate may not be important in carcinogenesis.

379. At the relatively high radiation dose levels maximum accumulated radiation dose correlates with bone damage and tumour incidence with Sr^{90} in rabbits; this relationship is less clear with P^{32} in rats. Data are not yet available from which to plot the relationship of radiation dose to damage with short-range β -emitters or α -emitters.

380. Many other variables, such as volume and oxygen supply of tissue, proliferative activity, and irradiated movement of cells at risk must be important in determining the effect of dose-rate and accumulated dose; their relative importance is unknown.

Dose and dose-rate in carcinogenesis by internal emitters

381. The relationship between tumour induction and absorbed dose of radiation is obscured by a series of problems. The basic difficulty is that internal irradiation, unlike external irradiation, continues indefinitely, but at an ever-changing intensity. Consequently, questions such as the relative importance of dose-rate and total dose in time and space are difficult to attack experimentally.

382. Several lines of evidence indicate that dose-rate is a major factor in the induction of osteosarcomas by bone-localizing isotopes. In mice, tumour incidence has increased as the second or third power of the dose expressed in terms of amount of radio-activity given, and tumour incidence has varied with the time pattern of administration.

Internal emitters and leukaemia

383. An increased incidence of leukaemia after internal emitters have been seen in mice but it is overshadowed by far greater induction of bone tumours.³²¹ An increased incidence of leukaemia induced by incorporated isotopes was obtained in rats with Sr^{90} , Cerium-144, Niobium-95, Caesium-137 and other isotopes and in dogs with Sr^{90} .^{322, 323} The disease has been reported in radium patients, but only in those exposed occupationally also to much external γ -irradiation.³²⁴ In studies of tumour induction by radium in dogs, no leukaemias or allied conditions have been seen under conditions that induce a high incidence of bone sarcoma.³²⁵

Internal emitters and life-shortening

384. Reduction in life expectancy is an important consequence of radiation from internal emitters; this response has been seen in mice irradiated at low levels that failed to show an increased incidence of neoplasms. At such levels of radiation it has not been possible to attribute reduction in life span to any specific degenerative or infectious disease. The animals die with the same pathological conditions seen in control populations.

Alkaline earths (calcium, strontium, barium, radium)

385. These nuclides are metabolized qualitatively like calcium: they are rapidly and almost exclusively deposited in the skeleton, where they are retained very tenaciously. Unless the physical half-life of the isotope is short, the significant residence time of these bone-seeking radio-elements may cover the life span of man. Like calcium, they are readily absorbed from the intestine, provided they are in soluble form.

Radium-226

386. Radium-226 is of special significance since its toxicity in man is well established. It has, therefore, been used for estimating the potential toxicity of other bone-seeking radio-elements. The value for maximum permissible burden was established without reference to the time of exposure. The symptoms of radium poisoning and body burdens alluded to earlier were found in people ~ 20-30 years after their exposure to radium. During the early part of the post-exposure period, the amount of radium in the body was certainly considerably higher than that finally measured. The best estimates are that an individual retaining 0.1 μg Ra^{226} 30 years after a single exposure must have initially absorbed about 10 μg .⁵³⁸

387. Many dial painters, who provided much of the information on Ra^{226} toxicity, were also exposed to other emitting elements, specifically Ra^{228} and Th^{232} . Thus they received a much greater radiation dose than is estimated from Ra^{226} burdens alone. Such a single exposure, or exposures of reasonably short duration, produce heterogeneous deposition patterns in bone. Continued exposure, as shown for Sr^{90} , causes a much more uniform pattern. This further complicates definition of the effective dose. There has been no work showing how the effects of Ra^{226} in the adult may differ in children.

Strontium-90

388. The general qualitative similarities in the distribution and metabolism of the alkaline earths have been shown from single-dose studies after strontium, radium and calcium in several species, although their rates of transfer are not identical. Thus knowledge of the metabolism of the other alkaline earths assists in understanding the fate of Sr^{90} in the human body. This information, combined with tracer experiments with strontium and studies of stable strontium, enables reliable estimates to be made of the body burden after a given intake of Sr^{90} , but some uncertainties remain in estimates made on newborn and young children.

389. Sr^{90} is found universally in the biosphere, and its primary source in man is from calcium-rich foods, especially milk. It follows calcium qualitatively in the biosphere and its absorption into plants varies somewhat with availability of calcium. This may be partly true also of animal uptake of Sr^{90} ; however, there is evidence that the absorption of Sr^{90} from the intestine proceeds independently of calcium to some extent. Growing animals retain Sr^{90} more efficiently than adults, reflecting the more active calcium deposition in young animals.⁵³⁷

390. The metabolic patterns of the alkaline earths differ quantitatively, e.g., preferential absorption of calcium over strontium from the gastro-intestinal tract and faster renal excretion of strontium.

391. Recent work with Sr^{85} retention in normal adults shows results similar to those in animals.⁵³⁸ The retention of the alkaline earths, including Sr^{90} , can be described by a power function of the form

$$R_t = At^{-b}$$

where R_t is retention at time t , in days after injection, A is equal to R_t at one day, and b is the slope of the log-log line. The slope, b , for strontium in man is about half that estimated for Ra^{226} in man, i.e., the rate of excretion of Sr^{90} at time t is considerably less than that rate of excretion of Ra^{226} at the same time after exposure. However, experiments with rats and dogs indicated qualitatively the opposite; this further complicates direct comparisons between Ra^{226} and Sr^{90} .

Lanthanide and actinide rare earths (including yttrium)

392. The lanthanide rare earths are produced in high yields in fission reactions: the parent materials in such reactions are members of the actinide rare earth series. These elements behave similarly in their chemical and biochemical reactions. However, differences in chemical behaviour within these groups (particularly the lanthanides) are reflected in changes in their biological behaviour.⁵³⁹

393. Members of both classes are distributed over the earth from nuclear devices; they have not as yet been identified in appreciable quantity in mammals and man. This is undoubtedly because of their extremely low solubility and correspondingly low absorption from the intestine. In animals, less than 0.01 per cent of an ingested dose is absorbed. Very young animals may be exceptional since suckling mice absorbed 2-3 per cent of plutonium given orally in milk or as citrate.⁵⁴⁰ Distribution studies suggest concentration of plutonium in bone, liver and ovary. In the latter organ, auto-radiography has shown a selective uptake in certain follicles.⁵⁴¹

394. These materials, put directly into the blood stream, behave like colloids and are rapidly taken up in the reticulo-endothelial system and in the more superficial parts of the skeleton. In the skeleton retention is very tenacious, but movement from the reticulo-endothelial system is appreciable over a few months.⁵⁴²

395. Locally injected solutions of the uncomplexed ions tend to remain at the site of injection. The complexed ions are removed from the site fairly rapidly and follow the pattern of the intravenously injected material.

396. Attempts to damage the intestinal mucosa by repeated high doses of the rare earths (yttrium and plutonium) have shown that the susceptibility of rats to such an exposure is low. Considerable energy is absorbed within the contents of the large intestine, while passage through the small intestine is quite rapid.

Caesium-137

397. Caesium-137 is present in the biosphere. Early spectrographic studies failed to detect radio-caesium in any animal. More recently, it has been found in mammalian and other vertebrate species. In man, the concentration of stable caesium is about 1×10^{-10} g/g wet tissue. Cs^{137} from nuclear debris has now been measured in food and man.⁵⁴³

398. The amount of Cs^{137} in the body reflects the quantity of isotope in the diet in turn affected by the degree of radio-active contamination. As a result of the relatively short residence time of Cs^{137} in man (the bio-

logical half-time is about 140 days)⁵⁴⁴ attention is being focused on this isotope as a means of studying fall-out rates and mechanisms.

399. The major portion of the Cs^{137} burden of the United States population is probably derived from milk, and meat products are the second most important source.⁵⁴⁵ The 1959 mean Cs^{137} burden of a United States resident is estimated at $0.01 \mu\text{C}$.⁵⁴⁶ This burden contributes a dose of $\sim 1 \text{ mr/yr.}$, i.e., ~ 2 per cent of natural radiation background.

400. Because of the chemical similarity of caesium, potassium and rubidium, their metabolism is similar. Caesium, like potassium, occurs chiefly intracellularly, with low concentrations in body fluids and bone. Tissue distribution studies have shown that muscle mass contains the largest part (perhaps 60 per cent) of body caesium, with visceral organs, brain, blood, bones and teeth following in that order.⁵⁴⁷ Radio-autographic studies in mice have confirmed the high accumulation in muscles and also indicated a rapid and high uptake of Cs^{137} in cartilage.⁵⁴⁸

401. Caesium salts are quite soluble, and are quickly and completely absorbed, more or less independently of route of administration. The ion is excreted through the kidney, except in ruminants where a considerable portion is excreted by way of the gut. Tracer studies in the cow show that about 13 per cent of a single dose will find its way into the milk within 30 days.⁵⁴⁹

Iodine-131

402. I^{131} is produced abundantly in fission and being volatile is readily liberated. Therefore, under special conditions, I^{131} may constitute a problem. Whenever such a situation arises, the concentration of iodine in the small volume of the thyroid gland is the primary hazard.

403. The Windscale reactor incident in England in 1957⁵⁵⁰ is an example of this. An accident during reactor operation released fission products from the reactor stack. The fission products escaping through the filters were predominantly I^{131} . Significant downwind contamination covered an area of 518 square kilometres. The only major vector for human intake of I^{131} was milk. The adult thyroid tolerates at least 4,000 rad with no demonstrable ill effects. However, evidence from young children given 200 r of X-rays to the neck suggests that this dose may produce carcinoma of the thyroid in ~ 3 per cent.⁴⁴⁹ This comparison of the carcinogenic effects at high levels (thousands of rad) of irradiation with I^{131} in the adult thyroid and effects of lower levels (hundreds of rad) of external radiation with X-rays should not be taken to mean that the child thyroid is more susceptible than the adult to the carcinogenic effect of radiation. Evidence of a carcinogenic effect of external X-irradiation on the adult thyroid is still most scanty, but very limited data suggest that irradiation of the neck of young adults treated for tuberculous adenitis has induced thyroid cancer.⁵⁵¹ Moreover, the very low incidence of thyroid carcinoma in patients with hyperthyroidism⁵⁵² and the well-documented experimental evidence that carcinogenic dose response curves eventually reach a maximum and decline at high levels with many types of neoplasm, and particularly in the induction of thyroid tumours by I^{131} in rats, (figure 10),⁵⁵³ presumably due to complete thyroid destruction at higher dose levels, casts considerable doubt on the significance of the apparent resistance of the adult, and usually hyperthyroid thyroid,

to the carcinogenic effect of large doses of I^{131} . In the child's thyroid weighing $\sim 5 \text{ gm}$, $1 \mu\text{C}$ of I^{131} per gramme of thyroid was estimated to yield an integrated dose of about 130 rad. After the Windscale incident, milk samples from nearby farms contained more than $1 \mu\text{C/litre}$. To limit radiation to the thyroids of children to 20 rad, it was necessary to prohibit consumption of milk containing more than $0.1 \mu\text{C}$ of I^{131}/l of milk. This meant discarding much milk for six weeks.

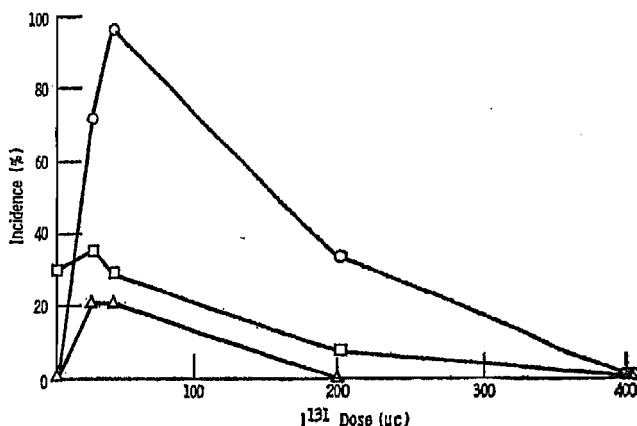


Figure 10. Incidence of thyroid tumours in male Long-Evans rats given injections of various doses of I^{131} 779, 790

○ Follicular adenoma
□ Alveolar carcinoma
△ Papillary and follicular carcinoma

404. Two problems in radio-isotope metabolism are of special concern: (a) estimation of body content from excretion data; (b) acceleration of excretion of a deposited radio-isotope by therapeutic measures. Where total body counting methods are inapplicable, due to the radiation characteristics of the isotope, measurement of radio-isotope levels in excreta offers the only method for estimating body content. The relationship between body content and excreta levels as a function of time after exposure and route of exposure is therefore an important study in large animals and in man after exposures giving rise to detectable radio-isotope excretion. Efforts to promote the excretion of deposited radio-isotopes are discussed in paragraph 525 below.

VII. Dose-effect relationships

EARLY EFFECTS

Immediate

405. At very high doses, usually $> 10,000 \text{ r}$, mammals die in minutes or hours probably due to brain injury. Typical central nervous symptoms develop soon after irradiation (acute ataxic phase), similar to irradiation of the head only.⁵² An experimental exponential relationship has been established for mice⁵⁴ between dose and survival time: $\log (\text{median survival time, hrs}) = a - b \text{ dose}$ (figure 11).

Early death

406. Between 1,200-10,000 r, the survival time of animals is $\sim 2-6$ days. Death is caused by "intestinal syndrome". No dependence of survival time on dose within this range was found (according to Cronkite⁵⁷⁵ the range is even broader, up to 30,000 r), but this may be fortuitous: injury to intestines might be decreasing

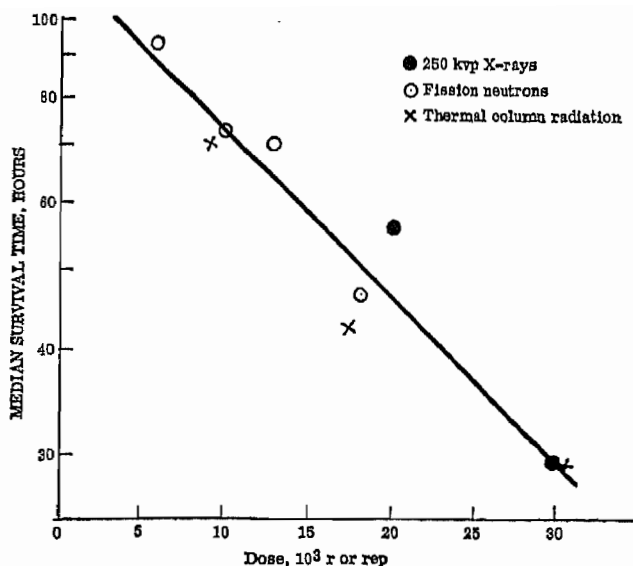


Figure 11. Relationship between high dose and survival time in irradiated mice⁶⁴

with decreasing dose, and the effects of the "bone marrow" or other injury might become more pronounced. Autopsies of animals always show changes in many organs.

407. From 1,000 r down to 50 per cent of the LD₅₀ dose survival time is increased. Death after weeks is due to bone marrow injury accompanied by secondary infection. Survival *vs.* dose follows the familiar sigmoid curve, often seen with delayed toxicity. From such curves, conveniently after probit transformation, the mean lethal dose can be calculated. The mean lethal dose, LD₅₀ for mammals, is ~ 200-900 rad (table I).

Body weight loss and organ atrophy

408. Irradiated animals lose body weight; this loss is dose dependent, and represents atrophy of different organs and a general deterioration of nutrition of many

tissues. Damaged metabolism and lowered food intake contribute to weight loss.

409. Voluntary food and water intake by an irradiated animal can be used for plotting dose-effect curves; no doubt other indices would serve also.

410. Unfortunately assessment of atrophy has usually been limited to weighing the organ. Some components of tissues decline rapidly after radiation; biochemical descriptions are lacking. In mouse spleen after TBR, concomitant atrophy of some elements and hyperplasia of others result in a complex dose relationship.⁵⁶⁴

External irradiation

411. Smith and Tyree⁵⁵⁵ irradiated rats with 250 kVp X-rays and showed that three responses to radiation increase with dose—weight loss, time required to regain pre-irradiation weight and limitation of food and water intake. The linear relationship was obtained (24 hours after radiation) for percentage of weight lost or percentage of food intake against log of dose over 25-1,000 r,¹¹⁷ (figure 12). Weight loss of rats increased linearly with dose over 100-1,200 rad.⁵⁵⁶ When weight loss of irradiated rats was compared with that of starved and dehydrated rats, no linear relationship was found within 50-1,400 rad for X-rays and thermal column radiation.¹¹⁷

Internally-deposited radio-isotopes

412. Pregnant rats were injected with P³² and embryos weighed days 6-10 after fertilization to measure weight loss due to internally-deposited radio-isotopes. Weight loss of 6-day-old embryos correlated linearly with dose but was curvilinear for older embryos.⁵⁵⁷

Intestinal atrophy

413. The weight of intestines decreases sharply after irradiation; correlation between dose and effect is linear.

414. The weight of intestines (expressed as percentage of control) of rats given 250 kVp X-rays and thermal column irradiation depended linearly on dose

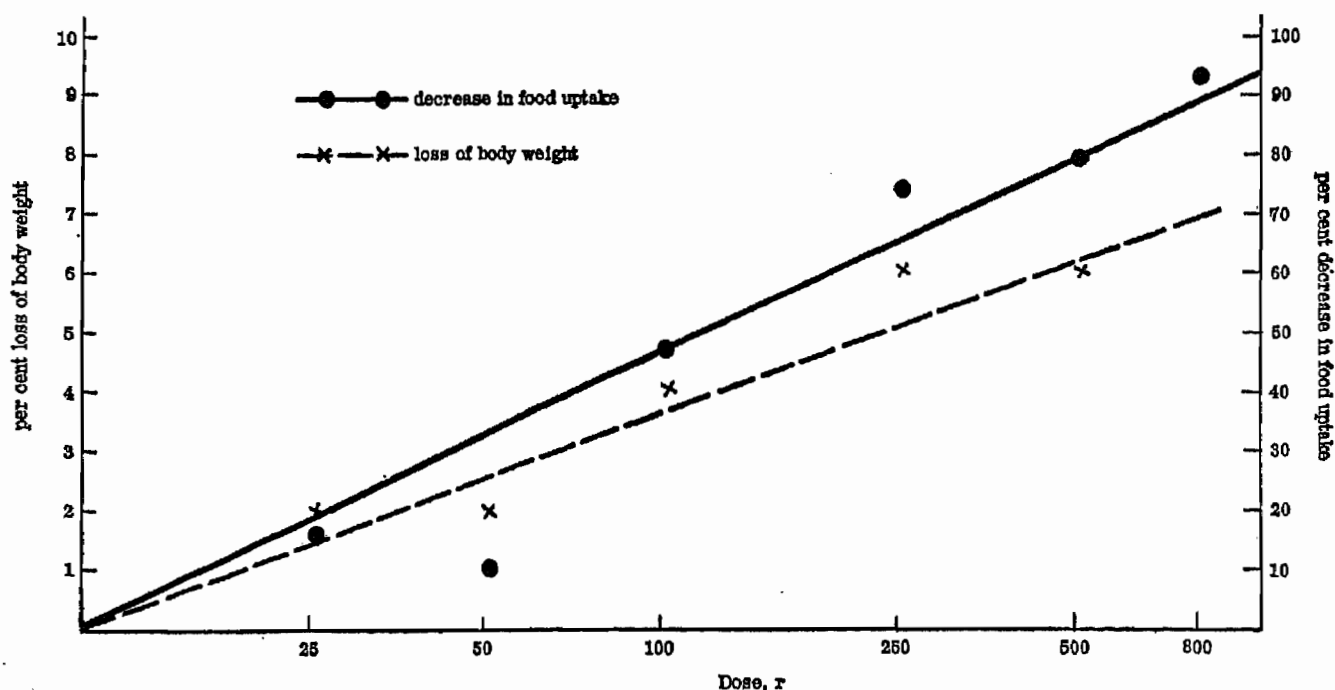


Figure 12. Relationship between body weight lost or decrease in food intake in rats plotted against dose¹¹⁷

over 100-400 rad.⁵⁵⁰ The equation of the regression line was: intestinal weight (per cent of control) = $102.1 - 0.075 \text{ dose (rad)}$.

415. The method, although simple and rapid, is not convenient for studying dose-effect relationships because the change is small: even at high dose (about 400 rad) no more than 30 per cent weight reduction of intestines was found. This is because the radio-sensitive component of intestines, the epithelium, forms only a part of the total weight, the rest being radio-resistant muscle.

416. DNA content as an index for measuring radiation atrophy of intestines was recently suggested by Mole and Temple⁵⁵⁸ but detailed studies have not yet been published.

The atrophy of spleen and thymus

417. Thymus and spleen weight decrease in irradiated animals. This effect has been used to correlate dose and effect, and to estimate the RBE of various radiations.

External irradiation

418. Weight loss of spleen and thymus in mice exposed to various radiations was related linearly to the log of dose. With 250 kVp X-rays, organ weight decreased 10 per cent after 50 rad; no experiments with other radiations have been done at doses < 100-150 rad, at which a 20-30 per cent weight loss was found with Co⁶⁰ γ -radiation, 4 MeV γ -radiation, thermal, 14 MeV, and fission neutrons.⁵⁵⁹

Internally deposited radio-isotopes

419. The dependence of organ atrophy on dose from internal sources of radiation suffers from uncertainties in dose estimation and chemical toxicity. In mice given tritium-water the rapid equilibration of water enables dose to be calculated on the assumption of an even distribution of tritium. The percentage reduction in spleen and thymus weight was linear with log of dose over 150-600 rad; the corresponding weight loss was 30-70 per cent.

420. Correlation between organ atrophy and radiation from internally deposited fission products (plutonium plus products of neutron irradiation of plutonium deposited in tissues) showed a linear relationship between reduction of spleen weight and log of the concentration of radio-active isotopes in tissue. The dose-range was ~ 400-1,600 rad. The thymus did not incorporate any isotope and could not be used as an index.

421. Thymus is useful for correlating dose and atrophy because of its relatively simple cellular composition. However, there are two competing processes in thymus atrophy: (a) decrease of mass, predominating in the lower-dose range, and (b) weight gain predominating at higher doses especially > 1,000 r.⁵⁵⁰ Perhaps measurement of ribonucleic acid (RNA) would be a more useful index of radiation injury to thymus. Concentration of RNA⁵⁶⁰ (per wet weight of tissue) correlated linearly with dose; RNA decreased 10-80 per cent within 100-600 r. Activity of nucleopolymerases in thymus was also dose-dependent, varying from 40-60 per cent with 40-160 r.⁵⁶¹

Testicular atrophy

422. Testes weight (expressed as log of percentage control) of mice, rats and hamsters irradiated with 250-kVp X-rays varied with dose, but with important species

differences.⁵⁶² The dose-effect curve in mice indicated at least two components; in hamsters and rats only one. The first component was highly radio-sensitive: after 75 r, testes weight was ~ 75 per cent of control. The over-all equation of the dose-effect curve, over 0-1,500 r, was:

$$W = Ae^{-kaD} + Be^{-kbD}$$

in which W = weight, D = dose.

423. In mice irradiated with 250-kVp X-rays, Co⁶⁰ γ -rays, thermal-column neutron, and α -particles together with Li⁷ recoil nuclei dose dependence was entirely different. The relationship was exponential, over 50-300 rad with 20 per cent weight loss at the lowest dose and 55 per cent at the highest. The computed equation was: $W = a - b \log D$. This discrepancy cannot be resolved at present.

424. The exponential equation of Kohn and Kallman⁵⁶² suggests that a single event inactivates one biological unit in testes; the effect appears independent of dose-rate.

425. However, this interpretation is questionable in the testis containing various cells, ranging from diploid to haploid, with numerous intermediates. One type of spermatogonia is extremely radio-sensitive; their number is significantly reduced after 20 r. Testes atrophy is due to loss of mature cellular components, along with inhibition of differentiation of earlier stages.

Lymphatic tissue

426. Recently in rabbits given 35 r-1,000 r with 220 kVp X-rays sensitivity of lymphatic tissue was measured by the volume of the appendix *in vivo* and *in vitro*.⁵⁶³ The appendix volume decreased 55-75 per cent. The percentage decrease of appendix *vs.* dose has two components; from 35-100 r linear and > 100 r exponential (figure 13).

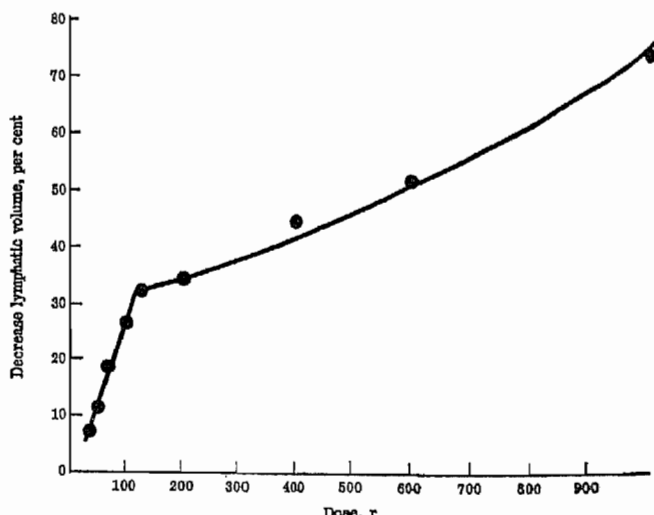


Figure 13. Decrease in volume of appendix irradiated *in vivo* in rabbits plotted against dose⁵⁶³

Depression of mitotic activity

427. Suppression of mitotic activity is a prominent effect of ionizing radiation.

428. With isolated single cells, e.g. grasshopper neuroblast, mitosis and the influence of radiation may be followed directly. Radiation given in late prophase

shortly before dissolution of the nuclear membrane is more efficient in inhibiting mitosis (in grasshopper neuroblast) than if given later.⁵⁶⁴

429. The numerous mitoses in irradiated animal tissues make quantitative evaluation more difficult; results depend not only upon irradiation but also upon the stage of mitosis at the time of irradiation. The general picture from many studies is that irradiation decreases the number of prometaphases, metaphases, anaphases and telophases. This is probably because cells irradiated in one of these phases complete mitosis regularly while cells in interphase are prevented from entering mitosis. The decrease in prometaphase-through-telophase cells correlates with dose. If the dose is sufficient to reduce mitotic cells to zero, the time of their reappearance also directly relates to dose.⁵⁶⁵ (figure 14).

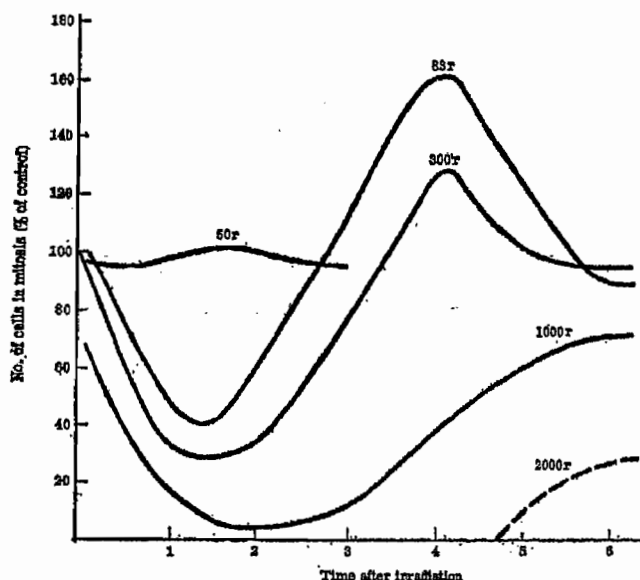


Figure 14. Relationship of dose to time of reappearance of mitosis⁵⁶⁵

430. The effect of radiation upon mitotic activity of animal somatic cells has been studied quantitatively on chick fibroblasts, rat retina cells, grasshopper neuroblast and epidermal and lymphatic cells of mice.

431. The doses of X-rays in chicken fibroblasts were 80-450 r; the smallest depression of mitotic index was ~ 60 per cent.⁵⁶⁶ The relationship between dose and percentage of normal mitotic index was curvilinear, but lack of data at lower doses precludes extrapolation of the curve. A similar curve was obtained with rat retina cells;⁵⁶⁷ their radio-sensitivity was higher than chicken

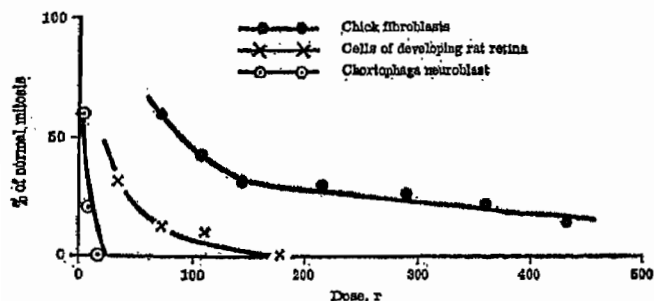


Figure 15. Relationship between dose and percentage of normal mitosis in chicken fibroblasts,⁵⁶⁶ cells of developing rat retina,⁵⁶⁷ and grasshopper's neuroblast

fibroblasts: ~ 30 r reduced the mitotic index ~ 70 per cent, and doses of 180 r decreased the mitotic index to zero. Grasshopper neuroblast was still more sensitive; the dose-effect curve was similar (figure 15).

432. Doses as low as 5 r of X-rays depressed by 50 per cent the mitotic activity of the adrenal glands, jejunum, lymph node and epidermis of mice (figure 16).⁵⁶⁸ Log of dose vs. percentage reduction of mitosis was approximately linear. Some curves showed a threshold effect; others did not.

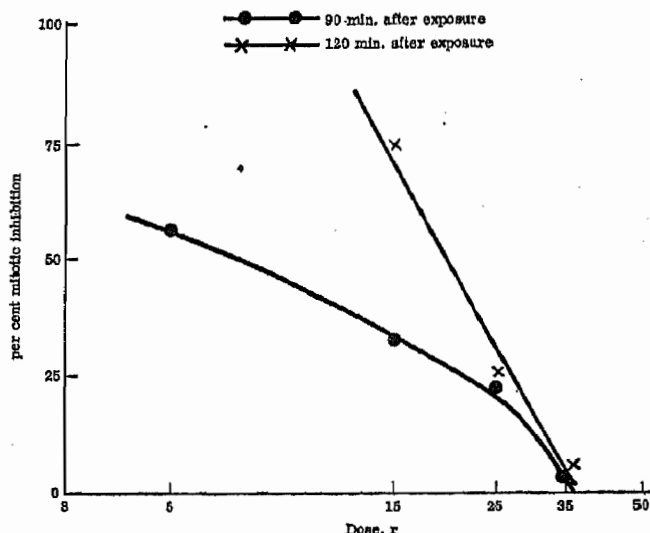


Figure 16. Relationship between dose and mitotic activity of the adrenal glands, jejunum, lymph node and epidermis of mice⁵⁶⁸

433. Probably a more useful method of following dose-effect relations is by measuring the time for the mitotic index to return to normal. This method used to study the mitotic index of mouse ear epidermis cells irradiated with thermal neutron or X-rays over 5-55 rad showed a linear relationship between log of duration of depression of mitotic activity and dose.⁵⁶⁹

Depression of iron uptake by erythrocytes and erythrocyte-forming tissues

434. The functional state of erythrocyte-forming tissue is usually gauged from incorporation of ^{59}Fe . More extensive studies usually measure ^{59}Fe in erythrocytes simultaneously with isotope content in isolated bone-marrow cells and various other tissue compartments, e.g., spleen, liver and plasma. Irradiation depresses iron incorporation.⁵⁶⁹

Quantitative studies

435. Iron incorporation by bone-marrow of animals (mice) irradiated with X-rays (250 kvp), γ -rays (4 MeV Co^{60}), neutrons (14 MeV fission and thermal column), and tritium β particles over 40-300 rad⁵⁶⁹ was depressed 10-80 per cent. Correlation between dose and effect followed the exponential equation; effect = $a - b$ log dose.

436. A different dose-effect was found in rats irradiated with Co^{60} gamma-rays and with thermal neutron (with RBE equal about 1) over 40-500 rad (figure 17).⁵⁷⁰ iron-uptake decreased steeply with increasing dosage; it was significantly lowered at 60 rad and reached about 30 per cent of control value at 150 rad; further increase in dose had less effect on iron uptake. The two-

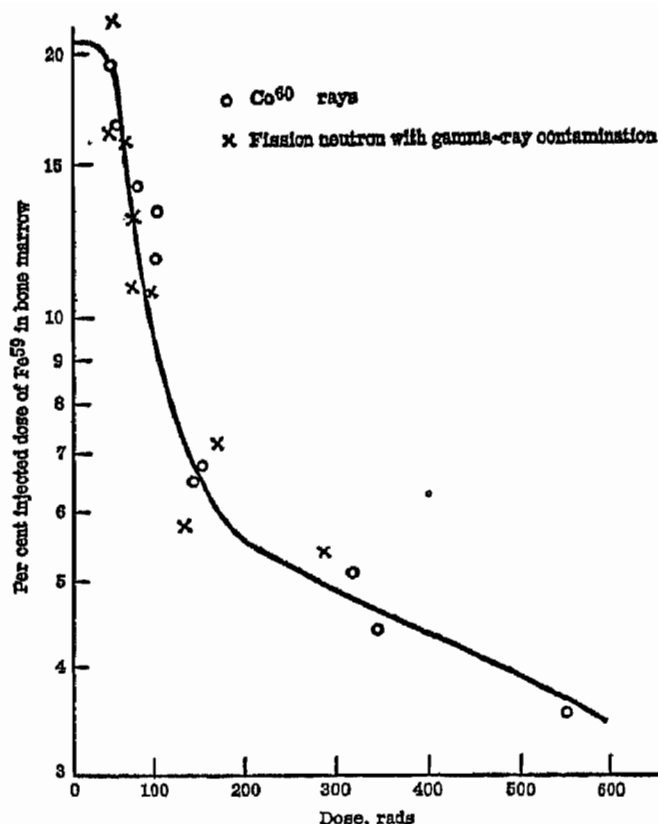


Figure 17. Depression of Fe^{59} -uptake in bone-marrow of rats irradiated with Co^{60} γ -rays and thermal neutrons⁵⁷⁰

component character of the curve corresponds probably to two main systems of iron incorporation in blood marrow (a) in dividing and differentiating cells of normoblast series, (b) in surviving, less sensitive cells (e.g. reticulocytes), and perhaps the iron-protein storage complexes in bone-marrow.

437. A plot of log percentage iron uptake *vs.* dose over 40-150 rad gave a straight line. The graph shows that doses below about 40 rad have very little if any influence on iron uptake by bone-marrow. The equation derived is $\log\text{-effect} = a - b \text{ dose}$ (figure 18).

438. Results obtained by various authors disagree, possibly due to differences in experimental methods. Storer's and Rambach's studies show a threshold dose for iron incorporation at 30-40 rad while others found an impairment of bone-marrow erythropoietic function at 5 rad. A still more pronounced difference is apparent between dose-effect function of the two groups of investigators: in Storer's results effect varies proportionately to log-dose; in Rambach's data, log of effect varied with dose. Experimental differences were considerable; the incorporation time for iron in one group was 6 hours, in the other, 72 hours; the amount of radioactive iron given controls was five times larger in Rambach's work than in Storer's.

439. The high sensitivity of erythropoietic tissue and the ease and precision with which its functional status can be followed make it one of the most suitable for work on the sensitivity of mammalian cells. It is doubtful whether single dose experiments will solve the problem, as fast division leading to numerous cell types at each moment in bone marrow implies a mixed population of presumably different radio-sensitivities. Long-term irradiation, preferably at very low levels, might be more

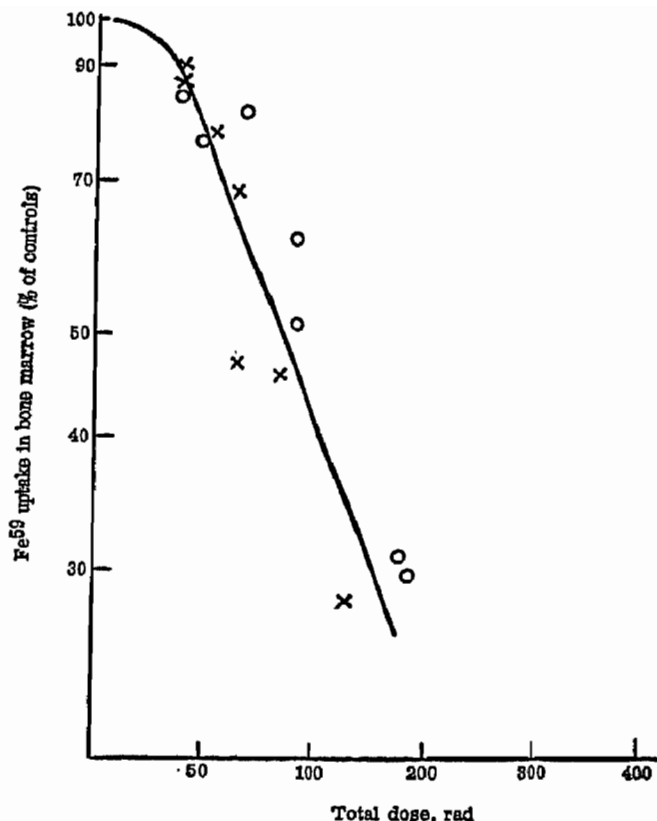


Figure 18. Effect of dose on Fe^{59} -uptake in bone-marrow of rats after 40-150 rad⁵⁷⁰

useful in evaluating the effects of radiation on erythrocyte-forming cells. Unfortunately no satisfactory experiments have been done. In some reported so far, long-term irradiation has been given as repeated single irradiation and this, obviously, might permit recovery between irradiations; also, the time between the last irradiation and the assay of the iron uptake was in some experiments 10-11 days—ample to make injury negligible by repair. Some injury persists as shown by experiments of Baum and Alpen⁵⁷¹ who computed the exponential correlation between number of exposures and decrease of Fe incorporation into erythrocytes. In long-term exposure, this irreversible or very slowly reversible injury might accumulate and become a noticeable injury.

Suppression of immunological mechanism

440. TBR damages the immune response of the body: production of antibodies is suppressed, susceptibility to infection increased and transplanted heterologous tissues survive in the host for a long time. Neither antibody production nor susceptibility to infection is a convenient index of the effect of radiation. However, the incidence of successful tissue transplants has been used to study the dose-effect relationships.

Leukaemia transplantation

441. The incidence of successful transplants of mouse leukaemia into another strain increases with dose over 100-500 r. A straight line can be plotted of probit of percentage of leukaemia *vs.* log of dose.

442. In mice irradiated with X-rays or neutrons 100-600 r or rep-log of dose was linearly related to percentage of successful leukaemia transplants (after probit transformation).⁵⁷² Different strains of mice showed marked

differences. The mean dose producing 50 per cent leukaemia deaths ranged from 327 ± 20 r- 470 ± 41 r for X-rays, and from 258-363 rep for thermal column irradiation. The slope of the probit percentage incidence *vs.* log dose line varied 5-10 for various strains.

LATE EFFECTS

Induction of lens opacity

443. Cataract formation is not understood; but opacity of the lens is due to radiation damage of lens epithelium that has a relatively high mitotic activity. The mitotic index decreases to ~ 0 after $\sim 1,500$ r, followed after a time (dose-dependent) by recovery with a typical overshoot in mitotic index. Abnormal cells are formed: some showing increased size, decreased transparency and multiple nuclei. Similar abnormal cells can also be seen in many other tissues of high mitotic activity, but they cannot be shed from the lens as they can from bone-marrow. They remain inside the lens structure (probably because of the restricting tough capsule surrounding the lens) and form centres of opacity. Recent data indicate that slight recovery of the lens is possible.⁵⁷³

444. Cellular homogeneity along with inability to slough the injured cells make the lens useful for studies on dose-effect correlation, only limited by the methods for assaying the injury and by difficulties in estimating the dose.

Methods

445. The degree of injury (i.e. the degree of opacity) is estimated by an ophthalmoscope or slit lamp; this necessarily subjective method has a rather high threshold of resolution. Comparison of the effect of radiation in various animals is more difficult because of variation in susceptibility among species and dependence on age. Lastly, estimation of the dose to the lens has a large margin of uncertainty, especially with neutron-irradiation.

446. Reduced glutathione decreases in an irradiated lens, as does the activity of the enzymes of glutathione metabolism.⁵⁷⁴ Irradiation also decreases the weight and RNA content of the lens, even when no opacity is seen.⁵⁷⁵

Human studies

447. The lowest dose for lens opacities formation has been estimated from experimental as well as human accident studies. The slow formation of cataract makes the outcome difficult to interpret.

448. Notwithstanding these reservations, a number of estimations of the critical dose for cataract formation have been made. Among Japanese survivors up to 1950, 100 people with radiation cataract have been found among those who received an estimated dose of 5-15 rep in neutrons and about 600 r of γ -rays.

449. In 10 cases of nuclear accidents, August 1945-September 1946, cataract formation was seen in only one person who received whole body dose of 15 rep neutrons and 26 r of γ -rays; the calculated dose to the eye was 45 rep. The critical dose for cataract formation appears to be ~ 20 -45 rep.

450. The data on radiation-induced cataract in man are hard to analyse quantitatively. Dosage is often very uncertain and the follow-up time of patients not long enough. A report of Cogan and Dreisler⁴⁶⁰ shows that

one out of three patients given 600 r of 200-kvp X-rays developed a cataract; with increased exposures the time for appearance of opacity was shortened. A survey of 100 cases of radiation cataract and 73 cases of patients given radiation to the head was made by Merriam and Pocht.⁴⁶⁴

451. The patients were grouped according to the time-schedule of irradiation. For the cases given a single dose, the minimum cataractogenic dose was 200 r, for the cases given doses spread over 3-12 weeks the cataractogenic dose was 400 r, while for those whose treatment spread over more than three months the dose was 550 r. The greater the dose the less the time for the appearance of cataract. In figure 19, incidence of cataract is shown as a function of dose among patients irradiated with doses given over more than three weeks.

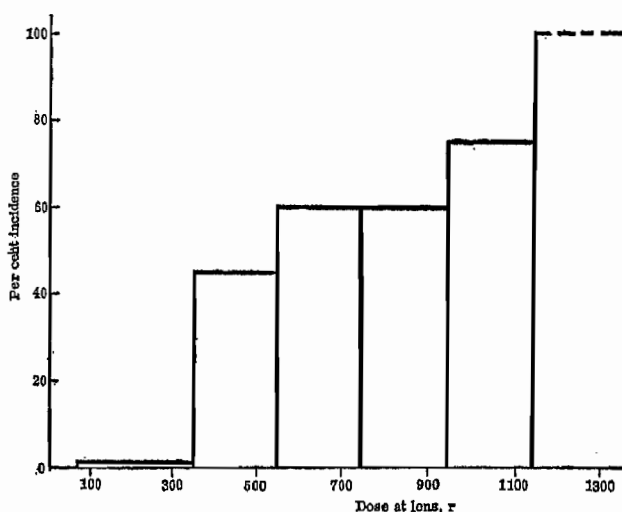


Figure 19. Relationship of cataract incidence to dose given over more than three weeks⁴⁶⁴

Experimental studies

452. A number of experimental studies permit rough estimation of the lowest dose for cataract formation. Storer⁵⁷⁶ found that any doses of 250-kvp X-rays, 12.5 r and up increased the incidence of cataract in mice (lower doses were not tested); this agrees well with the increased incidence of lens opacities after 15 r of X-rays.^{174, 577} The lowest dose for rabbits for hard X-rays (1,200 kvp) was ~ 250 r.

RBE

453. Neutrons have a higher efficiency in inducing cataract: their RBE for purposes of human protection has generally been taken as 10 by ICRP (A). Some earlier studies on neutron-induced cataracts employed cyclotron-produced beams, i.e. neutrons together with hard γ -rays: Evans⁵⁷⁸ found that 80 rep of fast neutrons produced lens opacity in 100 per cent of mice. Storer⁵⁷⁶ found the RBE of neutrons was 15 relative to 250 kvp X-rays; 2.9 rep of fast neutrons produced lens opacities in 50 per cent of exposed mice.

454. During Operation Greenhouse, mice receiving 1-10 rep of fast neutrons (together with about 1 r of hard gamma-rays) all showed cataracts. In rabbits, Cogan *et al.*⁵⁷⁹ estimated the threshold dose of 14 MeV neutron for cataract induction to be ~ 10 rep (RBE of neutrons ~ 220).

Dose-effect correlation

455. Cataract formation is dose and dose-rate dependent: the RBE of different radiations is perhaps more diverse than with other radiation injuries and does not permit setting up an equation for dose *vs.* effect. The dose dependence of cataract formation for neutrons⁵⁸⁰ and for γ -rays¹⁷⁴ shows a clear correlation between dose, energy of neutrons, and degree of opacity (figures 20-21). Constants cannot be derived.

Shortening of life-span

456. Continuous exposure to low doses of radiation does not cause the dramatic effects seen at high doses. The symptoms are not specific to radiation. The effects of long-term exposure necessitate study of life-span and comparison of causes of death between exposed and non-exposed populations. Observations have to continue until the death of irradiated subjects. Experiments are limited,

therefore, to short-lived animals. Exclusion of multiple intercurrent factors, e.g. infections which in long-term experiments might affect any group is essential. Moreover, for adequate study of the cause of death, large numbers of animals are needed, especially when the main interest lies in a rare effect, e.g., as in studying the incidence of tumours. Strains with higher incidence of this effect may be selected but this may restrict the validity of the results. Usable results are therefore still rather meagre.

457. The life of animals exposed to continuous irradiation is usually shortened. Survival plotted against time gives sigmoid curves; the median survival time is shortened with exposure. Different strains of mice differ in sensitivity to radiation as measured by LD₅₀'s²⁸ and in different life-span shortenings linearly related to their life expectancy.²²⁴

458. If shortening of life-span is plotted against dose-rates, the relationship is linear for γ -rays and fast neu-

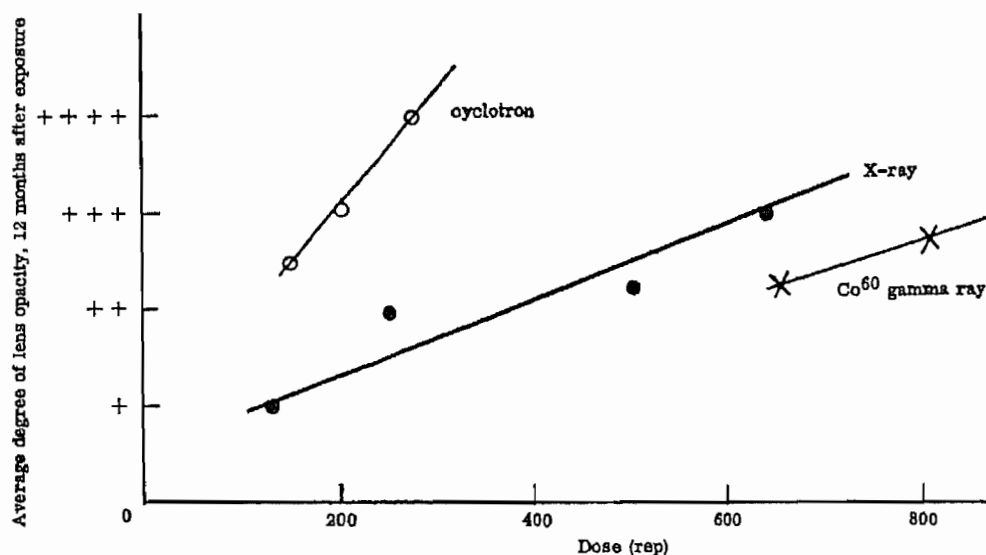


Figure 20. Relationship between dose and degree of opacity¹⁷⁴

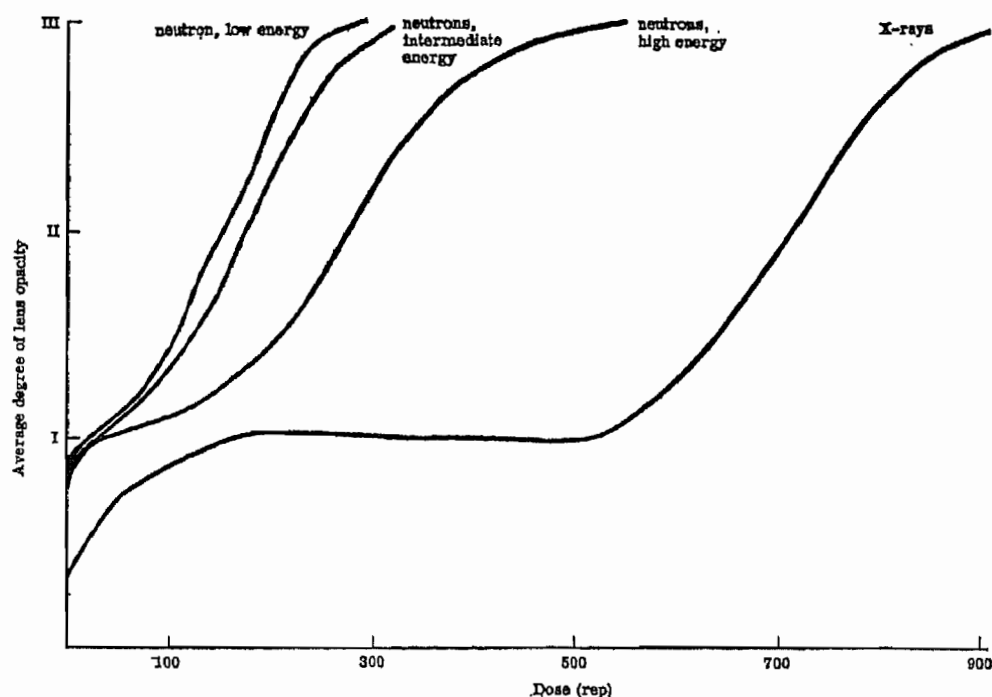


Figure 21. Relationship between dose and degree of opacity⁵⁸⁰

trons within the range of dose rates shown in figure 22.⁵⁸¹

459. When irradiated animals are given a second course of irradiation, the LD_{50} depends on the time between the first and second exposure, and increases asymptotically with time.⁵⁸²

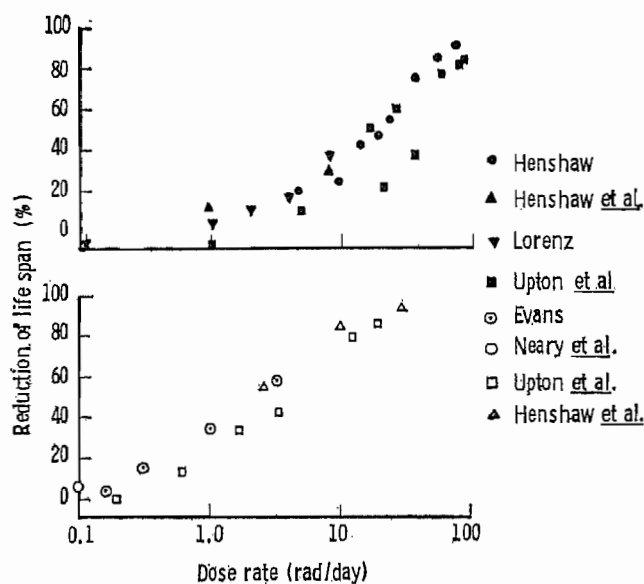


Figure 22. Reduction of mean or median survival time in mice exposed daily for the duration of life (solid symbols, X- and γ -rays; open symbols, fast neutrons). Redrawn from Upton⁵⁸³

460. From these data, Blair formulated a theory on the shortening of life-span by irradiation:²⁵⁷

- (a) The total injury caused by radiation is proportional to the dose;
- (b) The injury is partly reparable;
- (c) Recovery from reparable injury is exponential;
- (d) Irreparable injury accumulates in proportion to total dose;
- (e) Reparable and irreparable injury are additive and death occurs when their sum reaches a level inversely related to the age of exposed animals.

461. Blair's theory has stimulated design of experiments and many results fit its predictions.⁴⁸ Blair's postulates have been challenged. Radiation damage is made up of many individual injuries,⁵⁸⁴ mostly unidentified, and the pattern varies from strain to strain.²²⁴ Accordingly any simple recovery mechanism is over-simplification. Recovery also differs according to kind and manner of irradiation.⁶⁸ That the lethal threshold is inversely related to life expectancy is doubtful, since the LD_{50} varies with age but less simply than as proposed by Blair.⁵⁸⁴⁻⁵⁸⁸

462. Demographers have long known that the log of age-specific death rate of a population ("the force of mortality") plotted against age at death, is roughly linear beyond early childhood. This relationship, Gompertz' law, applies to irradiated populations. Force-of-mortality curves for exposed animals parallel control curves at a distance directly related to dose for single exposure, whereas for constant long-term irradiation, the slope of the curve increases by a factor depending on dose rate.²⁸⁵

463. These observations have encouraged analogies between chronic irradiation injury and aging. Aging, while familiar to everyone, is difficult to define. What is

observed statistically is not aging but mortality—something related to it and which measures it. The analogy is supported by the pathology of irradiated animals, showing histological damage resembling lesions of senescence.

464. Sacher^{281, 258} has stated that the physiological state of an individual fluctuates around some central value and any individual leaves the population when his state reaches a limit called the lethal boundary. It is assumed that such a limit is a fixed one, common to all individuals of the population. The physiological state of the individual decays with time, approaching asymptotically the lethal boundary. From mathematical argument Sacher asserted that log rate of mortality follows linearly the mean physiological state of a homogeneous population. If it is assumed that the physiological state decays linearly with age, as seems the case for many physiological characters, the force of mortality will also be linearly related to age. This is indeed observed for most animal populations. A corollary of Sacher's theory is that impairment of the physiological state brings it closer to the lethal boundary, so that the probability of transgressing it through random fluctuations increases. Irradiation would shift the physiological state so that the force-of-mortality curve of the exposed population would coincide with the curve for some later age.

465. Sacher's brinkmanship theory is closely related to the information approach to lethality and radiation damage. Although cloaked in different language and using different mathematical conventions, this theory as expounded by Quastler²⁵² and by Yockey⁵⁸⁷ leads to a parallel with Gompertz' law.

466. In their present state these theories are so all-inclusive that they are not concerned with the nature of the radiation injuries or with the recovery processes; physiological state (or degree of orderliness according to Yockey) is largely undefined, as is the death to which the theories refer. Accidental deaths are not considered by them; it is less clear whether the only relevant deaths are not those ascribable to senility—the observed causes of death are dependent on diagnostic accuracy. Radiation studies have been confined mostly to recording the overall mortality, thus lumping specific and "senile" causes of death; but as the experiments are expanding, consideration of the causes of death becomes unavoidable.

467. Differences among strains disappear for males when deaths from leukaemia are excluded. On the other hand, when animals dying from leukaemia or females carrying ovarian tumours are excluded, even differences between sexes disappear.²²⁴ Larger numbers of animals might well have brought out further differences ascribable to the differential incidence of other conditions. Something of the kind is seen in human populations where Gompertz' law holds, but only approximately and over a limited age range. However, on plotting the force of mortality for individual causes against age, linearity of most of the resulting graphs is strikingly improved and can be carried down to a much earlier age.

468. Although nothing is known about the lesions shortening life-span in multi-cellular organisms, knowledge that irradiation is powerfully mutagenic has incited speculation about the role of somatic mutation.

469. Somatic mutation has been invoked by Szilard⁵⁸⁸ as the cause of aging. He thinks a cell dies when both homologous genes of a pair responsible for an essential cell function are impaired by mutation. Mutation can be inherited, when it is called a fault, or be spontaneous, and

called an aging hit. The number of faults carried by an individual is fixed at birth, whereas the aging hits accumulate randomly with time, so that at any moment the number of surviving cells carried by an individual depends on his hereditary load and on his age. Death occurs when the number of surviving cells carried by the individual approaches a critical limit. Szilard calculated the average number of faults carried by the individual in human populations, and predicted the shortening of life-span by radiation in man. His results cannot be checked in our present state of ignorance about the life-shortening effect of radiation in our species. The theory in its present state does not predict the expected parent-offspring correlation in life-span; if it did it would prompt a not too difficult test on human populations.

470. Besides Szilard, Failla²⁵⁵ also interpreted aging as a mutational effect, and showed that Gompertz' law can be derived by assuming that the change in mortality rates with time is a one-hit process. It is none the less premature to attribute such a complex phenomenon as aging to somatic mutation which in vertebrates has been studied mainly in cell cultures. There is little knowledge about possible repair and recovery mechanisms of mutational effects. Even in unicellular organisms, radiation damage is not confined to the genome and it would be surprising if this were not true for the cells of higher organisms. Attempts to shorten life-span by giving chemical mutagens were unsuccessful,⁵⁸⁹ but more recent work in two laboratories has confirmed the radiomimetic effects of chemical mutagens for life-shortening.^{210, 590}

Induction of tumours

471. In man the induction of leukaemia at present provides a basis for inferences about the dependence of incidence on dose, and data being accumulated as to the induction of bone tumours by radium is adding valuable information to this.⁶⁰¹ Animal data prove that ionizing radiation induce benign and malignant tumours. If tumour incidence increases with dose, taking into account the statements made later on threshold, studies on dose-effect relationships are by their nature inconclusive about what the mechanism is.

472. Knowledge on tumour growth is limited and experimental difficulties abound. The long latent period in the appearance of tumours impedes work at higher doses, since other radiation-induced pathological disturbances may cause death before tumours appear. At low level of irradiation animals have to be kept a very long time; intervening infections often vitiate experiments. Moreover, the incidence of tumours is low; low-level irradiation studies require unwieldy numbers of animals.

473. As a further complication, radiation is not necessarily the direct cause of tumours: lymphoma in mice and mouse ovarian and pituitary tumours are an indirect effect of irradiation.

474. The role of co-carcinogens is almost completely unknown in radiation carcinogenesis. In chemical carcinogenesis, with a co-carcinogen, the amount of carcinogenic agent was related linearly to tumour incidence; carcinogen alone has a threshold.⁵⁰² Croton oil after radiation increased the incidence of benign tumours in skin.⁵⁰³

475. Combined radiation and methylcholanthrene were synergistic in inducing leukaemia, P³² and methylcholanthrene⁵⁰⁴ in inducing skin tumours, and mechanical irritation and X-rays in inducing sarcomas.⁵⁰⁵

476. Change in susceptibility with age of animals is still another complication in studies on tumour-induction.⁵⁹⁶ This and the long latent period for tumour-induction make correlation of injury with accumulated dose difficult in animals exposed to long-term low-level irradiation.

Quantitative studies

477. The rate of tumour development and amount of strontium-89 injected into mice were related linearly, after a latent period which increased with diminishing dose.⁵⁹⁷ However, the plot of the number of tumours at any time after treatment becomes curvilinear and appears as a higher power of the dose.²⁸⁵

478. Dose-response curves for mouse lymphomas,²⁹⁷ ovarian tumours and myeloid leukaemia were non-linear.³⁰⁸ Bone tumour induction in mice by strontium-90 is not proportional to incorporated radio-isotope and may be described as proportional to the square or cube of the dose.⁵⁹⁸

479. Data on the influence of dose-rate in the induction of neoplasm by ionizing radiations are as yet fragmentary. In most instances a given dose is substantially less carcinogenic absorbed over a long period at low dose-rates than it is absorbed in a single short exposure.^{539, 599} Blum,⁶⁰⁰ from skin-cancer induction in mice by ultraviolet light, suggests that the time for the appearance of tumours is inversely proportional to the square root of the dose-rate; the dose-effect curve would have a rising inflection with increasing dose-rate, and a threshold, if any below limits of observability.

Radiation-induced leukaemia in man

480. Radiation-leukaemia surveys may examine a population of exposed and non-exposed people and observe directly the incidence of leukaemia in the two groups. In retrospective studies, groups of leukaemic and non-leukaemic populations are selected, the frequency of irradiated and non-irradiated individuals calculated, and the risk of leukaemia estimated.

481. Retrospective studies, beginning with people selected without prior knowledge of their radiation history, are likely, in the present state of radiation records, to misestimate exposure; the reliability of information about past radiations depends largely on memory.

482. Three major prospective studies are the Hiroshima and Nagasaki atom bomb survivors,⁴²⁰⁻⁴²⁶ children treated with X-rays for thymus enlargement,^{438, 445} and adults treated with X-rays for ankylosing spondylitis.^{412, 440}

The Hiroshima and Nagasaki surveys⁴²⁰⁻⁴²⁶

483. The Hiroshima and Nagasaki explosions offer a unique and most important opportunity to study the radiation-leukaemia problem. They should answer the question about the long-term effects in child and adult. The irradiation dose was large and the population exposed substantial: ~ 1,000 survivors received an LD₅₀ dose, and 10,000 a dose over the greater part of the body of ~ 100 rad or more. Important effects could hardly be missed. Overlooked effects could only be those produced from prolonged exposure to smaller doses or those requiring intense radiation to a restricted part of the body. Such effects would be observed most readily among people occupationally exposed and among patients given large doses of therapeutic radiation.

484. Data from the Hiroshima and Nagasaki populations will be less clear about dose-effect relationships. The irradiation was instantaneous; the results cannot tell what is likely to happen where the dose is spread out in time or intermittent. Great efforts are being expended to make exposure history as accurate as possible; nevertheless, how people were shielded is, in many instances, uncertain and hence there will always be some uncertainty about the exact irradiation received. Therefore, information about dose-effect relationships must also be sought elsewhere. Here data from hospital patients or persons occupationally exposed should prove useful. The dose-effect relationship is discussed in paragraphs 248-253.

Children irradiated for thymus enlargement^{430, 438, 445}

485. The data are too scanty to warrant conclusions about the relationship between dose and incidence of leukaemia or thyroid cancer among children given radiation to the thymus (see paras. 263-272).

X-ray treated ankylosing spondylitis^{412, 440}

486. An extensive survey on irradiated ankylosing spondylitis in England by Court Brown and Doll gave special attention to dosage expressed as maximal bone-marrow dose, mean bone-marrow dose, and whole-body integral dose for every leukaemic, and for every patient belonging to a random sample of the whole exposed population. The results are familiar. As there were only two leukaemic female patients, the quantitative study was limited to males. Age distribution ranged from fourteen years onwards.

487. The clinical treatment of ankylosing spondylitis consists usually in irradiating the affected bones with a dose of $\sim 1,000$ r. If the symptoms recur, re-treatment is often given. This is the explanation in this study of the positive correlation between cumulative mean bone-marrow dose, and the time between the first treatment and death of the patient. One possible explanation of the findings not excluded by the data could be that patients with ankylosing spondylitis, irrespective of the method of irradiation, are more likely to develop leukaemia than healthy people.

488. With these limitations in mind, the incidence of leukaemias was plotted against maximal bone-marrow dose, mean bone-marrow dose, mean bone-marrow dose among patients whose spine and sacroiliac regions only were exposed, and whole body integral dose. The incidence in all depends on dose and the dose-response curve bends upward. This suggests a non-linear relationship between exposure and incidence.

489. Owing to the fewness of cases on which it is based, the ankylosing spondylitis survey only proves that there is a dependency of incidence on dose but gives little information as to quantitative relationship. Further details on the dose-effect relationship are given in paragraphs 254-262.

Concept of threshold

490. Thresholds have been observed for many somatic effects, but it is a question whether radiation and leukaemia incidence are related below a certain dose. Whatever the dose-response curve, a critical exposure level might be required before irradiation brings about the cellular derangements responsible for inducing leukaemia and other tumours. Experimental and clinical data on tumours and leukaemia considered as demonstrating the linear character of the dose-effect curve are all ob-

tained in the higher dose-range, 100 rad and above. The nature of this relationship has not been studied for lower dose levels. Kamb and Pauling⁶⁰¹ have expressed the view that the existence of a very low threshold or its absence cannot be feasibly determined by studies in animals. A. V. Lebedinsky's⁶⁰² conception may prove to be correct: he believes that for initial changes in any structures of an organism at the molecular level there is no threshold dose at which the various types of ionizing radiation begin to have an effect, whereas a threshold does exist at the level of the cell, the tissue, the organs and the organism due to compensatory responses and regenerative processes. The ankylosing spondylitis and the Hiroshima surveys hint that at the lowest doses no difference can be shown between the observed incidence of leukaemia and the incidence expected in the general population. In such circumstances a search for a threshold is futile. It cannot be taken as axiomatic that if at moderate or large doses an effect is proportional to dose it is justifiable to extrapolate the same relationship to lower doses. Recent evidence neither proves nor disproves the existence of a threshold for radiation effects in inducing tumours in man. To avoid the danger of under-estimating the probability of radiation-induced leukaemia and other malignancies, it seems reasonable to assume that the observed cases of malignancy will not exceed the number predicted, if the relationship between incidence of malignancy and dose were considered linear (no threshold) for all doses.

VIII. Protection and modification of radiation injury

INTRODUCTION

491. This chapter discusses the physiological, biochemical and biological methods that have been developed to protect against and modify the injury of living organisms by radiation. Although to date work on radiation protection and recovery has found few practical applications to the survival of higher organisms, this is a rapidly developing field and more recent ways of promoting recovery by transplanting blood-forming cells may develop practical significance.

PROTECTIVE AGENTS

Anoxia

492. That anoxia reduces radiation mortality was first shown by Lacassagne⁶⁰³ in newborn mice. Also, rats exposed to 800 r in 5 per cent O₂ + 95 per cent N₂ were alive 30 days after exposure; all controls died.⁶⁰⁴ At 1,200-1,400 r, 50 per cent of treated animals survived 30 days. Results with mice in 7 per cent O₂ + 93 per cent N₂ were less impressive; ~ 80 per cent of the treated animals survived 800 r, lethal to all controls. Similar results were obtained in chicks,⁶⁰⁵ rats,⁶⁰⁶⁻⁶⁰⁷ and mice.^{608, 609} Some symptoms, e.g., desquamation, can be alleviated by hypoxia.⁶¹⁰ Lamson *et al.*^{611, 612} studied long-term effects, such as life-shortening, tumour incidence, hypertension, and nephrosclerosis, in rats surviving 1,000 r of hypoxic TBR. Carbon monoxide also reduced the radio-sensitivity of mice,^{613, 614} guinea pigs, rabbits, and rats.⁶¹⁵ CO₂ was ineffective.⁶¹⁶ Correlation of anoxia with various responses has been reviewed⁶¹⁷ and the mechanism discussed.⁶¹⁸⁻⁶²⁰ Cyanide-induced anoxia was particularly effective in mice;⁶²¹ other workers have had difficulty in getting similar re-

sults.^{95, 98, 622, 623} Nitrate also reduced radiation mortality somewhat.^{624, 625} P-aminopropiophenone, a methaemoglobinemia-producer, gave 72 per cent survival in mice given an LD₁₀₀ radiation exposure.^{626, 627} Another way of lowering O₂ tension, hypothermia, increases survival rate in newborn mice⁶²⁸ as confirmed in mice and rats.^{629, 630} On the whole, this approach, while illuminating the mechanism of protection, offers few practical possibilities.

493. Radiation response may be modified in two ways: (a) preventing injury to vital parts of the organisms; (b) aiding recovery of the affected system. Injury can be prevented by supplying cells with chemicals interfering with or limiting formation of free radicals or making the cell constituent less susceptible to interaction with the radical; the protective chemical might even reverse actual damage, e.g., oxidized thiol groups. A pharmacological drawback of preventive chemicals is that they must be given immediately before irradiation so as to be at the target site during irradiation. Biological entities—cells or tissues—introduced after radiation can replace affected cells and tissues and thus permit recovery. Modifying factors in irradiated organisms may be transient or permanent.

Protective chemicals

494. Serious study of protective chemicals began after Barron's demonstration that sulfhydryl compounds protect many enzyme systems *in vitro*.⁶³¹ Patt⁶³² first used a sulfhydryl compound for protection of animals, and was soon followed by others.⁶³³

495. Table X⁶³⁴ lists many varied compounds tested for protective effects.

496. The way in which protective compounds work is controversial. Table X shows how widely different chemical entities offer varying degrees of protection. Presumably, no single theory encompasses all substances.

497. Protective chemicals may act in the following ways:

- (a) Inactivation of radiation-induced free radicals;
- (b) Minimizing free radicals formed by induction of hypoxia;
- (c) Induction of metabolic changes;
- (d) Reversion of injury in the primary target.

498. Inactivation of free radicals formed in water by radiation is the most widely accepted theory of chemical protection.

499. Thiol compounds are known to react rapidly with free radicals⁶³⁵ thereby scavenging intra-cellular free radicals. Some sulfur-containing compounds are protective *in vivo* through the formation of a thiol, e.g., alkyliso-thioureas rearrange into mercaptoalkylguanidines.^{636, 637}

500. The radical-scavenging hypothesis does not account for several facts in radiation protection. Marked differences in protection are given by structurally closely related compounds (e.g., N-diethylcysteamine and N-methylphenylcysteamine);⁶³⁸ reaction products of thiols with free radicals in irradiated serum are a minute fraction of the total free radicals formed;⁶³⁹ also, it does not explain protection against the direct action of ionizing radiation which is probably responsible for most damage.⁶⁴⁰

501. Differences in activity of closely related compounds might reflect inability of some to enter the cell. Protection against the direct action of radiation might be explained by assuming that thiol compounds restore enzymes to the —SH condition needed for their function—an hypothesis suggested by Pihl and Eldjarn.⁶⁴¹ Proteins form mixed disulfides easily, e.g., insulin fragments.

502. Compounds containing the labile —SH group protect molecular structures against direct and free radical-mediated action of radiation. Undoubtedly, an additional action is lowering intracellular O₂ tension and reducing number of free radicals;⁶⁴¹ thiols share the latter property with several other chemicals e.g. choline derivatives.⁶⁴² Several thiols protect animals against O₂ poisoning; this supports the belief that lowering of O₂ tension is important in the action of protective chemicals.⁶⁴³

503. These theories of the action of protective chemicals cannot account for the protection given by certain pharmacologically active substances, e.g., reserpine⁶⁴⁴ which can protect rats if given as early as 24 hours before irradiation; its action correlates with obvious changes in tissue metabolism. Similarly, the effects of parathyroid hormone and EDTA could be related to the effects of calcium on cell permeability that prevent the loss of intracellular constituents due to the radiation-induced increase in permeability.^{645, 646}

Modifying treatments

504. Death of an animal exposed to the lower range of lethal doses is mainly due to bone-marrow injury. This suggested treatment with viable bone-marrow cells that might permanently or temporarily take on the function of the destroyed cells. The feasibility of repairing radiation-induced damage by biological means was suggested from the prevention of thrombopenia in X-irradiated guinea pigs by shielding of bones in the early experiments of Fabricius-Moller⁶⁴⁷ and by the shielding experiments of Jacobson *et al.*⁶⁴⁸ The success of bone-marrow therapy depended on genetic similarity between irradiated host and donor animals. Isologous marrow gave many more survivors than homologous marrow, and heterologous grafts were even less effective.⁶⁴⁹⁻⁶⁵¹ Proof of cellular colonization was given by Lindsley, Odell and Tausch in 1955,⁶⁵² using as index antigenic differences between cells of host and donor. Ford *et al.*,⁷⁶ distinguished host and donor cells by means of marker chromosomes.

505. The survival of transplanted bone-marrow is determined by the compatibility of its antigenic pattern with that of the recipient. As a rule, only bone-marrow from a uniovular twin or from another individual of the same highly inbred strain (isograft), persists; transplants from another individual from the same outbred species (homograft) or from another species (heterograft) are rejected. If the immunological mechanism of the host is suppressed, the graft may take. One way of suppressing the immunological mechanism is irradiation; this is why animals exposed to much radiation accept marrow transplants. However, if the suppression of immunological mechanisms in the recipient is transient, as may happen if the dose of radiation is not high enough, the graft will eventually be rejected. If the dose is high enough, the graft will take, but owing to the immunological competence of the transplanted marrow, a reverse immunological reaction will take place, i.e. reaction of

the grafted tissue against the host. This reaction, called "secondary disease", is a wasting syndrome characterized by atrophy of the host's lymphatic tissues, which frequently results in death.

506. The antigenic pattern of tissues is determined by isoantigens. Two broad groups of isoantigens are distinguished: (a) the so-called H-antigens evoke production of humoral antibodies; (b) the other type, T-antigens, produces tissue immunity by accelerated rejection of grafts, but does not elicit the appearance of antibodies in blood plasma and body fluids.

507. The chemistry of H-antigens is understood, mainly from studies by Morgan and Kabat.⁶⁵³ H-antigens are polysaccharides in which an amino-acid or lipid moiety is firmly bound but does not contribute to immunological specificity. Immunological specificity is determined by a small segment of the polysaccharide molecule. Several more-or-less distinct molecules of the same immunological specificity may be found in the same individual: blood-group substances in erythrocytes are lipopolysaccharides, while blood-group substances in tissue fluids are polysaccharide-amino-acid complexes; the latter show broad polydispersity.

508. The chemistry of T-antigens is largely unknown. The relatively insensitive and imprecise tests available for assessing their activity, along with the inherent difficulty in isolating them from living mammalian cells, made it appear that "T-antigenicity" is the property of living cells only. However, R. B. Billingham, L. Brent and P. B. Medawar⁶⁵⁴ isolated an antigenically active substance in a DNA-containing fraction of disintegrated lymphoid cells. Activity was destroyed by DNA-ase treatment, by periodate oxidation, and by digestion with crude enzyme preparation known to be mucolytic and capable of destroying the activity of blood-group substances. Current information shows that T-antigen may again be mucopolysaccharide,⁶⁵⁵ and therefore not unlike H-antigens.

509. Even though repeated skin-grafts do not cause the appearance of precipitating or cytotoxic antibodies in the blood of recipient animals,⁶⁵⁶ several studies indicate an association between tissue transplantation and the appearance of cytotoxic, haemagglutinating or other antibodies;⁶⁵⁷⁻⁶⁵⁹ H-antigens and T-antigens may be different complex molecules but with the same haptenic-groups in their structure.⁶⁶⁰ The antigenic potency as well as chemical stability depend on molecular components not directly determining immunological specificity. Morgan⁶⁶¹ has shown that purified somatic hapten of *Sh. shigae* may acquire full antigenic potency if coupled with protein derived from the same or other bacterial species; human blood-group substance A from erythrocytes (lipopolysaccharide) is resistant to hot alkali, while blood-group A substance from body fluids (an amino-acid-polysaccharide) is easily hydrolyzed by the same treatment.⁶⁶² If the T-antigens were lipopolysaccharide, then their lesser potency compared with H-antigens in eliciting the production of humoral antibodies, and their liability to lyophilization and other procedures, would be explicable. The T-antigens and the H-antigens might well be a diverse group of substances upon which the histo-incompatibility genes have imprinted specific antigenic configuration, probably in their polysaccharide components.

510. The ability of transplanted bone-marrow cells to persist in irradiated animals has been variously demonstrated. Erythrocytes and platelets were identified by

specific agglutination.⁶⁶²⁻⁶⁶⁵ Identification of donor's granulocytes was carried out by demonstrating alkaline phosphatase in the circulating cells, alkaline phosphatase being present only in the rat's (donor) granulocytes and not in the mouse's (recipient) granulocytes.⁶⁶⁶⁻⁶⁶⁷ The repopulation by rat's lymphoid cells in irradiated mice has been shown by finding rat's chromosome number and structure in dividing lymph node cells of the recipient⁷⁶ and by employing cytotoxic sera with cell-culture technique.⁶⁶⁸

511. When animals, irradiated with doses sufficient to cause acute death due to bone-marrow syndrome, are injected with living erythropoietic cells, they survive. The 30 days' median lethal dose is roughly doubled if bone-marrow transplantation is used to protect mice; with other types of irradiation the results are less consistent, but at certain dose levels of γ -rays and 14-MeV neutrons marked protection has been shown.⁶⁶⁹

512. Many authors confirmed the protective action of bone-marrow transplantation in acute radiation syndrome in various species. Homologous bone-marrow protected rats,⁶⁷⁰ hamsters,⁶⁷¹ rabbits,⁶⁷² dogs,⁶⁷³ and guinea pigs.⁶⁸¹

513. The feasibility of bone-marrow transplantation in man has been studied to a limited extent. An exchange of bone-marrow cells can occur between non-identical twins before birth.⁶⁷⁴⁻⁶⁷⁶ The phenomenon can be explained as acquired immunological tolerance, due to transplantation of immunologically immature cells, as seen by Owen.⁶⁷⁷

514. In studies on man, suppression of immunological defence of the host has been achieved by "acquired tolerance". Attempts at homo-transplantation of bone-marrow into donors whose immunological mechanism has been suppressed by radiation or by radiomimetic drugs have met with little success, and indeed contraindications seem clearer. The studies may be divided into two groups: (a) patients accidentally exposed to high doses of radiation; (b) patients deliberately irradiated to replace diseased with normal marrow. Thomas *et al.*⁶⁷⁸ have shown that transplanted marrow functioned temporarily in leukaemic patients given TBR: the donor cells in some cases persisted for two months in the recipient though they disappeared completely after ~ 3 months. In another study,⁶⁷⁹ 9 patients with acute leukaemia irradiated with 300-500 r were given marrow (obtained from excised human bones) containing about 5×10^9 viable cells without evidence of a successful transplant. Bone-marrow given to patients with bone-marrow aplasia, without irradiation, gave similar results. There is evidence of a temporary acceptance of bone-marrow in irradiated leukaemic patients.⁶⁸⁰⁻⁶⁸² In most studies, the percentage of donor's type blood cells in the recipient's circulation was low at the beginning and steadily decreased; a notable exception is a patient with bone-marrow failure due to chemotherapy of Hodgkin's disease⁶⁸² given bone-marrow taken from her sister. The difference in blood groups between donor and recipient was marked, and skin grafts were rejected. Nevertheless, bone-marrow transplantation was successful, the donor's blood cells, low at first, began to increase in the recipient's circulation at about the sixth month after transplantation and were still present after nine months. The success in this case is probably due not only to pre-treatment with radio-mimetic drugs but also to Hodgkin's disease: a patient with Hodgkin's disease⁶⁸³ may tolerate a skin graft for a prolonged period. Hodgkin's disease is accompanied by a production of abnormal

γ -globulins and a marked decrease of immunological reactivity; proliferation of abnormal and immunologically incompetent cells may be taking place at the expense of normal lymphoid cells.

515. Bone-marrow was given five men accidentally irradiated in Yugoslavia on 15 October 1958. Of six exposed, the five who received the higher doses were given marrow. The man in most serious condition was injected at first with foetal bone-marrow (4×10^9 cells), and then with adult bone-marrow. There was no evidence of improvement after foetal marrow; after adult marrow the number of blood cells, mainly platelets and granulocytes, increased sharply. Nevertheless, the patient eventually died with symptoms of delayed intestinal damage and haemorrhages from the respiratory tract. The remaining four patients were given bone-marrow a month after the accident from donors of a similar blood-group pattern; about 10^{10} marrow cells were injected. Soon after transplantation of marrow, the number of circulating blood cells increased. However the initial number of donor's cells, ~ 20 per cent of the total, dropped to negligible values in 3-4 months.⁵⁹⁴ It appears that for a short time the transplanted bone-marrow assumed normal haemopoietic activity, although the evidence supporting this has been challenged by Fliedner⁷⁸⁵ and it was certainly ultimately rejected. The relatively low percentage of the donor's type blood cells, and their rapid disappearance demonstrates that the recipient's bone-marrow maintained its activity although diminished throughout the period of acute radiation sickness. Furthermore, as discussed earlier in paragraphs 217-220, the haematological recovery patterns were similar to those of patients recovering spontaneously from lesser amounts of radiation.

516. The transplantation of foreign bone-marrow in experimental animals prevents acute death; the same is presumably true for man. Survivors usually die later, the mortality beginning usually in the fifth week post-irradiation, but sometimes earlier. Death of animals is preceded by diarrhoea, loss of weight and dermatitis; at autopsy a generalized atrophy of lymphoid tissue is visible. The syndrome is usually called *secondary disease*, but sometimes also homologous disease or foreign bone-marrow disease. The main cause of secondary disease is reaction of grafted tissue against the host, the latter having been rendered immunologically incompetent by irradiation. Minor factors influencing both time of onset of secondary disease and its final outcome include late radiation effects in the host and decreased resistance to infection.⁶⁸⁴

517. Evidence for the immunological pathogenesis of secondary disease is based mainly on genetical studies, F_1 -hybrids do not usually react against grafted tissues of either parental strain but may in certain circumstances react immunologically against inbred parental strain tissue. However, when irradiated hybrids received parental tissue, fatal secondary disease ensued. In the reverse case, i.e. irradiated parental strain grafted with hybrid tissues, the survival was almost complete. In the first case, parental tissue encounters foreign antigens in the host, derived from the other parent and produces antibodies to histo-incompatibility antigens; in the other case, the specificity of transplanted tissue is broader than that of the host and no antibody production is possible.^{685, 686}

518. Secondary disease can be potentiated if transplantation of bone marrow is accompanied by even a small amount of the donor's lymph-node cells.⁶⁸⁴

519. These two lines of evidence indicate that the immunological reaction of grafted tissues against the host form the basic pathogenetical factor in secondary disease; several other factors enter. Delayed radiation effects in the host is one^{687, 688} and the delayed reaction of the hosts' recovering immunological system against grafted tissue is another.⁶⁸⁴ Transient decrease in resistance to infection, at a time when the host lymphoid system has not yet recovered and the grafted bone-marrow is not potent enough, contributes considerably to the mortality due to secondary disease.

520. The indications for transplantation of bone-marrow in cases of radiation damage are limited. It may be useful when the patient's bone-marrow remains viable even though seriously affected: the implanted tissue may in this case help the organism through the most dangerous period of haemopoietic failure; eventually the foreign tissue will be rejected and the danger of fatal secondary disease will disappear. In serious cases, grafting bone-marrow, substituting for the patient's haemopoietic cells, may eventually cause death by secondary disease.⁶⁸⁹ The dangers in bone-marrow treatment of acute radiation disease influenced the decision not to use it in the Y-12 accident in June 1958.³⁸⁸

521. There are at least three possibilities of increasing the usefulness of bone-marrow treatment: (a) pre-treatment of the recipient with "enhancing antibody"; (b) use of foetal marrow; and (c) antigenic adaptation of transplanted marrow to the hosts' antigenic pattern.

522. Enhancement might be useful when the host's immunological reaction is not completely abolished and is sufficient to cause speedy rejection of the graft before it might exert supportive action. Enhancement supports the growth of transplanted tissues by inducing the immunity status in the host, before transplantation. It can be effected by injection of the lyophilized tissue to be implanted⁶⁹⁰ or by passive immunization with a serum containing anti-implant tissue antibodies.⁶⁸⁸ The latter but not the former method might be useful clinically.

523. The persistence of grafted bone-marrow could be improved if its antigenic pattern was made compatible with the antigenic pattern of the host. Very little work has been done in this direction. From the studies on the transplantation of neoplastic tissues, it is known that tumours after passage through F_1 -hybrids (strains of tumour origin and some others) have more takes when tested in backcrosses with the same two strains.⁶⁹¹ This finding is open to more than one interpretation: Klein⁶⁹² showed that the increased frequency of takes in backcrosses is due to antigenic adaptation of tumour tissues and not to selection of more resistant cellular clones during the passage. The phenomenon resembles the changes by parameria of their antigenic pattern to suit unfavourable environments containing specific antibodies, in which the newly-acquired character is inherited cytoplasmically.^{693, 694} In tissue transplantation, some preliminary experiments aimed at inducing antigenic compatibility have been carried out:⁶⁹⁵ parathyroid embryonic tissue was cultured in media containing increasing concentration of recipient sera before implantation. The evidence for the successful grafting was clinical improvement. No analogous experiments have been done on marrow cells, but with modern techniques of marrow cultivation, it should be possible to assess the probability of increasing takes and survival time in donors.

524. On the basis of the immune tolerance theory, foetal marrow, theoretically, might lead to the creation

of a permanent chimera where there has been total destruction of lymphoid tissues. The grafted marrow cells would not be rejected and in time should acquire tolerance to the host's antigens. If foetal cells are used, as has been shown, immunological interaction between donor and recipient is reduced.⁶⁹⁶⁻⁶⁹⁸ Similar experiments in man are limited and very preliminary. Mathé *et al.* injected foetal marrow in one of the victims of the Yugoslav reactor accident but found no evidence of haemopoietic activity of implanted tissue; the patient, however, was apparently in the preterminal stage with intestinal symptoms.⁶⁹⁴ In toxic bone-marrow failure, injection of foetal liver cell suspensions produced circulating blood cells characteristic of the donor's for about three weeks.⁶⁹⁹

INTERNAL DECONTAMINATION

525. Recent efforts to promote the excretion of deposited radio-isotopes, such as plutonium, thorium, yttrium and the rare earths, have been encouraging. For these elements, the chelating agent, diethylenetriaminepentaacetate (DTPA) has proved much superior to the earlier studied ethylenediaminetetraacetate (EDTA) and should be a practically useful agent for the prompt treatment of accidental exposure to these radio-isotopes.⁷⁰⁰ Prolonged treatment with DTPA is effective in removing substantial fractions of firmly deposited plutonium from bone.⁷⁰¹ The removal of strontium or radium appears less hopeful; no practically useful treatment can be recommended for radio-isotopes of these elements. Increasing the level of dietary calcium deserves to be studied further as a possible means of delaying the uptake of strontium-90. However, the benefits to be obtained therefrom must be large enough to justify any risks entailed in greatly increasing the intake of calcium,

TREATMENT OF ACUTE RADIATION SYNDROME^{702, 703}

526. The management of radiation injury is governed by the same considerations that influence the management of any other clinical problems, namely the history, clinical picture, laboratory data, and estimated magnitude of exposure to the injurious agent. In most instances, it is not possible to estimate dose accurately. Even if it were possible, knowledge of the dose would be of limited value in governing the management of the patient since there is individual variation in the response to a given dose as well as great uncertainty about the dose-effect relationship in man. Experience with the Japanese atom bomb casualties, the Marshallese exposed to fall-out radiation, reactor and critical assembly accidents, and other accidental exposures to radiation, have shown that some estimate of biological effects can be made from careful clinical and haematological data. Such continuing scrutiny should determine therapy.

527. The conservative medical management of the acute radiation syndrome is recommended,^{44, 888, 704} reserving for desperate situations those therapeutic measures that carry a high intrinsic risk to the patient.

Summary

528. Biological effects depend not only on total dose (energy absorbed) but also on type of radiation; distribution of dose in time and space and on the physical state of the organism and species. Determination of bio-

logical effects of small dose irradiation should now be based primarily on an analysis of functional changes and not only on morphological changes as in the past.

529. While the mechanisms of radio-sensitivity have not yet been clarified, the radio-sensitivities of cells, tissues, and organs can be arranged in order, and show a remarkable similarity in all mammalian species.

530. The clinical course of the acute radiation syndrome in man is well known through observation on Japanese and Marshallese exposures, criticality accidents, and radio-therapeutic experience. However, largely because of uncertainties as to the physical factors, the exact relation between dose and effect is not well understood. The best estimate of the median lethal dose for man is 300-500 rad, short-time TBR.

531. At low doses, functional changes appreciably outweigh permanent somatic damage. Among the more sensitive of these are transient changes in gametogenesis, neural function, and haematological responses, especially in the lymphocytes. However, evidence of permanent damage becomes apparent only with larger doses approaching the lethal range.

532. Life-shortening in animals has been well established as a consequence of long-term and of short-term irradiation. Life-shortening in man is probable, however, results are still inconclusive.

533. The development of neoplasia may follow short-term or long-term exposures of both animals and man. Apparently, leukaemia is the earliest neoplastic change that has been observed in man. Leukaemia induced in the Japanese and in other groups of exposed human beings has usually been of the chronic myeloid type or of the acute type, and the incidence has increased roughly with dose.

534. There is some evidence of an increased incidence of some malignant tumours other than leukaemia in Japanese survivors, but the evidence so far is inadequate to permit reasonable inferences as to dose-effect relationships.

535. There is no satisfactory evidence as to the concentration-effect relationships in man as regards carcinogenesis from internal emitters. No tumours have thus far appeared with residual radium of less than 0.7 μg .

536. Consideration of possible mechanisms of radiation carcinogenesis, including a number involving the genetic apparatus of somatic cells, indicates a wide divergence in possible dose-effect relationships as a consequence, and indicates further that the question of these mechanisms may be amenable to experimental testing. Further analysis of carcinogenic action of radiation will require careful study of the dependence of such action on the type of radiation (alpha, beta, etc.) and its physical properties (quantities of energy, ionization density, etc.) and, in particular, a study of the role of dose-rate. These data will provide the key to an understanding of the relevant mechanisms. However, elucidation of this problem will require an equally careful study of the processes of regeneration, particularly in relation to dose rate and the temporary characteristics of irradiation. An analysis must be made of the types of mutation which result in the formation of tumours, and their probable character. Lastly, there must be a stage-by-stage analysis of data to establish a scale of effects related to the conditions of irradiation.

537. The embryo, at least in certain stages, is more susceptible to radiation than the adult.

538. Radiation protection can be achieved in animals by a variety of chemical and physical procedures, none of which has yet been established as of value in man

except possibly in instances of localized therapeutic irradiation.

539. Many investigations are under way to determine the value of general supportive and specialized therapy for the treatment of acute radiation injury in man and for decontamination.

TABLE I.⁸⁵ LD₅₀ VALUES FOR MAMMALS*

Species	Radiation used	Radiation factors	LD ₅₀ value		Ref. No.
			Air dose (r)	Absorbed dose (rad)	
Mouse.....	250 kvp X-ray	0.5 mm. Cu, 1 mm. Al HVL 1.6 mm. Cu	362+ to 443+	521+ to 638+	(705)
	200 kvp X-ray	0.25 mm. Cu, 1 mm. Al HVL 0.8 mm. Cu	405	558+	(706)
	Bomb gamma	High energy and dose rate	759	666+	(707)
Rat.....	200 kvp X-ray	0.45 mm. Cu, 1 mm. Al HVL 1 mm. Cu	665	815+	(708)
	200 kvp X-ray	0.5 mm. Cu, 1 mm. Al HVL 1.05 mm. Cu	640	796+	(709)
Ground squirrel.....	250 kvp X-ray	0.25 mm. Cu, 1 mm. Al HVL 0.9 mm. Cu	700	> 700+	(710)
Hamster.....	2,000 kvp X-ray	HVL 5 mm. Pb	800	> 800+	(711)
	250 kvp X-ray	0.5 mm. Cu, 1 mm. Al HVL 1.6 mm. Cu	460+	586+	(712)
	200 kvp X-ray	0.25 mm. Cu, 0.5 mm. Al HVL 1.5 mm. Cu	700	> 700+	(671)
Guinea pig.....	200 kvp X-ray	0.25 mm. Cu, 1.0 mm. Al HVL 0.8 mm. Cu	337	400+	(42)
	186 kvp X-ray	0.25 mm. Cu, 1.0 mm. Al HVL 0.8 mm. Cu (crossfire exposure)	400	380+	(649)
	Co ⁶⁰ gamma	Multiple sources	500	490+	(43)
	1.10 Mev (50%) 1.33 Mev (50%)	Dose rate 70 r/min (4 π exposure)			
Rabbit.....	200 kvp X-ray	0.5 mm. Cu, 1.0 mm. Al HVL 0.98 mm. Cu (bilateral exposure)	800	735+	(24)
	250 kvp X-ray	3.25 mm. Cu HVL 3.4 mm. Cu (multiport exposure)	805	751+	(713)
	250 kvp X-ray	Parabolic filter HVL 2.0 mm. Cu (crossfire exposure)	700+	680+	(714)
	Co ⁶⁰ gamma		1,094	911+	(715)
	1.10 Mev (50%) 1.33 Mev (50%)	HVL 5.1 cm. Al Dose rate 50 r/hr (multiple sources)			
Monkey.....	250 kvp X-ray	HVL 1.6 mm. Cu Dose rate 3 r/min. (bilateral exposure)	760+	546+	(65)
	250 kvp X-ray	0.5 mm. Cu, 1.0 mm. Al HVL 1.0 mm. Cu (animals rotated)	550	522+	(716)

TABLE I.⁸⁵ LD₅₀ VALUES FOR MAMMALS* (continued)

Species	Radiation used	Radiation factors	LD ₅₀ value		Ref. No.
			Air dose (r)	Absorbed dose (rad)	
Dog.....	250 kvp X-ray	0.5 mm. Cu, 1.0 mm. Al HVL 1.5 mm. Cu (bilateral exposure)	281	244 ⁺	(717)
	1,000 kvp X-ray	HVL 2.0 mm. Pb (bilateral exposure)	304	250 ⁺	(38)
	2,000 kvp X-ray	HVL 4.3 mm. Pb (bilateral exposure)	312	260 ⁺	(37)
	Co ⁶⁰ gamma	HVL 5.1 cm. Al (bilateral exposure)	465 ⁺	303 ⁺	(718)
	1.17 Mev (50%)				
	1.33 Mev (50%)				
	250 kvp X-ray	14.2 mm. Al Parabolic filter, 0.5 mm. Cu HVL 2.15 mm. Cu (unilateral exposure)	450	322 ⁺	(38)
Swine.....	Bomb gamma	High energy and dose rate	271	250 ⁺	(378)
	1,000 kvp X-ray	HVL 2.0 mm. Pb (bilateral exposure)	510	247 ⁺	(38)
	2,000 kvp X-ray	HVL 4.3 mm. Pb (bilateral exposure)	388	237 ⁺	(719)
	2,000 kvp X-ray	HVL 4.3 mm. Pb (unilateral exposure)	500	305 ⁺	(719)
	Bomb gamma	High energy and dose rate	225	187 ⁺	(720)
	Co ⁶⁰ gamma	HVL 5.1 cm. Al Dose rate 50 r/hr (multiple sources)	618	242 ⁺	(721)
	1.17 Mev (50%)				
Sheep.....	1.33 Mev (50%)				
	Nb ⁹⁵ and Zr ⁹⁵ gammas	HVL 3.9 cm. Al Dose rate 20 r/hr (multiple sources)	524	205 ⁺	(722)
	0.73 Mev (93%)				
Goat.....	0.23 Mev (7%)				
	200 kvp X-ray	0.5 mm. Cu, HVL 0.98 mm. Cu (bilateral exposure)	350	237 ⁺	(723)
	Co ⁶⁰ gamma	HVL 5.1 cm. Al Dose rate 50 r/hr (multiple sources)	784	306 ⁺	(721)
Burro.....	1.17 Mev (50%)				
	1.33 Mev (50%)				
	Ta ¹⁸² gamma	HVL 4.3 cm. Al Dose rate 20 r/hr (multiple sources)	651	256 ⁺	(724)
	1.22 Mev (57%)				
	1.13 Mev (37%)				
	0.2 Mev (6%)				
	Nb ⁹⁵ -Zr ⁹⁵ gamma	HVL 3.9 cm. Al Dose rate 20 r/hr (multiple sources)	585	229 ⁺	(722)
Man.....	0.73 Mev (93%)				
	0.23 Mev (7%)				
	Fall-out gamma	Dose rate variable (plane field)	350 (?)	300 (?)	(53)
	1.5 Mev (19%)				
	0.75 Mev (57%)				
	0.1 Mev (24%)				

* See text for additional explanatory material relating to the table.

⁺ Value not given in work cited. Calculated or estimated from data given.

All dose-rates used were of the order of 5 to 60 r/min., and all exposures were unilateral unless otherwise noted. The LD₅₀ values in rad represent the absorbed dose in soft tissue at the centre (midline) of the animal. The dose in rad was estimated as follows: the tissue dose in r was first estimated, if not given, from the air dose by estimating all scattered radiations and taking into account the geometry of the exposure conditions used.⁸⁸ Scatter can be approximated from standard depth-dose data.^{38, 708, 726, 728} The present authors duplicated as nearly as possible many of the experimental conditions and used the air/tissue dose ratio thus obtained. The tissue dose obtained represents the dose a dosimeter would indicate if it were embedded in tissue (or phantom material). The tissue dose in r was converted to absorb dose in rad, using the appropriate soft-tissue conversion factor.^{727, 729} The conversion from air to tissue dose is an approximation made in many cases from incomplete physical data, and the conversion factors from tissue dose to rad are still open to question (see above). Additional details of the conversion used for any of the situations will be furnished on request. Total scatter varied with essentially full scatter, from less than 5 per cent of the air dose

with Co⁶⁰ gammas to approximately 45 per cent with 250 kvp or lower energy X-rays.^{85, 726, 730} Ellinger quotes the LD₅₀/14-day value for guinea pigs, which is not significantly different from his LD₅₀/30-day value. Depth-dose measurements under the unusual geometrical conditions of the Oak Ridge multicurie γ -ray exposure field were made by the present authors in collaboration with Col. Bernard Trum. The large ratios, air dose-midline absorbed dose, obtained for burros, sheep, and swine result principally from geometrical factors.³⁸ In most positions, occupied by the exposed large animals, over 50 per cent of the dose is received from a target to skin distance of less than 1.5 m.; thus inverse square fall off is appreciable. Large animals standing in the field receive much of the dose at the midpoint in the animal from the anterior or posterior directions, as opposed to the transverse (shorter) axis with bilateral irradiation in the laboratory (this would not apply to an upright man). All midline doses probably are maximal for an acute LD₅₀ value, since if the data for the effect of dose rate on LD₅₀ in the rat⁷³¹ apply to the larger species, the values should be further reduced by a factor of approximately 0.8 to allow comparison with radiation delivered in the course of minutes. The values should be also reduced further for comparison with X-ray LD₅₀ values because of the apparently reduced effectiveness of γ -radiation relative to X-radiation.⁴⁷ The LD₅₀ value for man can be considered only a rough approximation, since the dose is poorly known and there was no mortality in the exposed group (see below).

TABLE II. DISEASES OF MAJOR FREQUENCY IN γ -IRRADIATED MICE (OPERATION GREENHOUSE)²⁶⁰

Disease	Percentage observed incidence in mice receiving indicated γ -ray dose									
	Control		223 rad		368 rad		578 rad		697 rad	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
None.....	4.25	0.97	1.90	0.94	3.16	0	1.96	1.68	4.07	2.63
Pneumonia.....	9.48	12.01	6.19	3.77	7.91	6.21	5.23	4.36	5.56	3.76
Nephrosclerosis, mild.....	1.31	2.60	2.38	2.36	2.85	3.79	3.59	6.71	3.70	4.51
Nephrosclerosis, moderately severe.....	0.33	0.33	0	0.47	0.63	1.38	1.63	3.02	3.33	7.14
Nephrosclerosis, severe.....	0	0.65	0.48	0.47	1.58	3.45	10.13	18.79	21.48	37.22
Nephrosclerosis, severity unspecified.....	0.33	1.95	3.81	2.36	7.59	4.48	24.51	17.79	28.52	15.79
Enteritis and colitis.....	4.58	2.27	3.33	2.36	1.90	2.41	4.90	3.36	1.85	1.88
Dermatitis.....	10.78	1.95	10.48	2.36	8.86	0.69	4.90	0.67	3.70	0.38
Emaciation.....	0.65	1.62	0	0	1.27	1.03	0.65	1.68	5.56	3.38
Cyst, liver.....	2.61	1.30	1.90	2.83	0.95	2.07	1.96	4.36	1.11	1.88
Cyst, kidney.....	0.65	0	1.43	0	0.95	0	2.94	1.01	1.48	0.75
Cyst, ovary.....		1.30		1.42		1.72		1.34		1.50
Cyst, all sites.....	3.60	3.25	3.33	4.25	2.53	4.83	4.90	9.06	2.96	4.89
Atrophy, bone marrow.....	0	0.32	0.48	0.47	0.32	0.69	0	1.68	1.48	0.75
Atrophy, testis.....	0.65		1.90		0.95		0.95		1.11	
Atrophy, adrenal cortex.....	0.33	8.12	1.43	8.96	1.27	7.93	1.63	8.72	2.96	10.53
Dental defects.....	8.83	1.63	7.15	1.42	8.86	2.07	6.86	1.68	1.48	1.13
Volvulus.....	0.98	0.65	3.33	0.47	0.63	1.03	0.65	0.34	1.11	1.50
Abscess, all sites.....	7.52	2.92	8.10	1.42	3.48	1.72	1.31	1.34	1.11	0.75
Hyperplasia, endometrium.....		1.95		1.89		1.38		0.67		0.38
Hyperplasia, adrenal cortex.....	0	0.97	2.86	3.77	2.12	3.45	3.92	3.36	5.18	6.01
Hyperplasia, Harderian gland.....	0.98	0	0.95	0	2.85	2.07	1.31	1.01	0.74	0.75
Hyperplasia (myeloid), bone marrow.....	0.33	0	0	0.94	1.27	0.34	4.58	2.35	4.44	3.01
Hyperplasia (myeloid), spleen.....	0.33	1.30	1.43	3.37	1.90	4.48	6.21	6.38	7.41	15.41
Hyperplasia (lymphoid), spleen, lymph nodes.....	0	0.32	0	0.47	1.27	1.03	1.63	1.01	2.59	2.26
Haemorrhage, testis.....	0		0		0.63		2.29		1.11	
Haemorrhage, brain.....	0	0	0	0	0.63	0.34	0.33	1.68	1.85	1.13
Haematoma, testis.....	0.65		0.95		0.95		1.31		1.85	
Haematoma, ovary.....		13.31		10.38		12.76		13.42		7.52
Haematoma, adrenal.....	0	0	0	0	0	0	0	2.01	0.37	2.63
Thrombosis, auricle.....	0.65	1.62	1.90	0.47	2.85	2.41	1.96	2.35	0.37	1.13
Infarct, all sites.....	0.65	0	1.43	0.47	1.58	0.69	2.94	2.01	1.48	2.63
Angiitis, all sites.....	0.65	0	0.95	0.47	1.03	2.98	6.71	5.04	7.04	13.91
Hepatoma.....	7.84	3.25	7.62	10.38	11.71	14.83	8.82	8.05	4.44	1.79
Luteoma.....		1.30		16.51		19.66		17.11		15.41
Granulosa-cell tumour, ovary.....		0.32		3.30		4.14		4.36		2.26
Tubular adenoma, ovary.....		0.32		5.19		4.48		2.68		1.50
Mixed tumour, ovary.....		0.32		10.85		10.69		7.05		5.64
Supcapsular cyst, ovary.....		19.16		2.36		2.41		1.68		0.38
Cystadenoma, ovary.....		0		2.83		2.76		0.67		2.26
Adenoma, pituitary.....	0.98	3.57	1.43	4.25	0.95	7.59	1.96	12.42	0.74	3.38
Adenoma, lung.....	9.48	9.42	9.05	8.49	11.08	7.59	7.19	6.04	2.96	2.26
Adenoma, kidney.....	1.96	0	1.43	0	1.90	1.72	1.63	1.01	1.11	0.38
Adenoma, adrenal.....	0	0.97	2.86	0	2.22	3.10	3.27	3.69	1.48	1.88
Cytadenoma, lung.....	2.29	3.25	3.33	1.89	4.75	4.48	3.59	2.01	1.48	1.13
Cystadenoma, Harderian gland.....	0	0.32	0.95	1.42	1.27	1.38	0.33	2.01	0.37	0
Squamous-cell carcinoma, stomach.....	0.98	0.65	2.38	1.42	1.58	1.38	0.65	0.34	0	0
Squamous-cell carcinoma, skin.....	0.33	0	0	0.94	0.32	0	0.98	0.67	0	0.38
Adenocarcinoma, lung.....	2.94	0.97	0.48	2.36	1.27	1.38	0	1.01	0.74	0
Adenocarcinoma, breast.....	0	0.97	0	3.77	0.32	3.79	0	3.02	0	1.88
Adenocarcinoma, Harderian gland.....	0	0	0	1.42	1.58	1.38	0.33	0.34	0.74	0
Sarcoma, voluntary muscle.....	0	0	0.48	0.47	0.63	0.69	0.33	0.67	0.37	0
Sarcoma, breast.....	0	6.82	0	3.77	0	4.14	0.65	2.01	0	0.38
Sarcoma, bone.....	0	0.65	0	0	0	0	0.33	2.01	0	0.75
Lymphoma, thymus.....	1.64	3.24	2.86	5.66	2.85	4.13	6.86	11.08	13.07	10.15
Lymphoma, abdomen.....	7.52	20.22	12.38	14.62	13.30	8.64	3.92	6.72	2.60	3.63
Lymphoma, other.....	10.14	18.52	7.21	10.85	12.34	16.21	9.14	9.06	4.81	4.89
Myeloid leukemia, all sites.....	0.33	0.65	0.48	1.42	0.95	1.03	1.31	0.34	1.11	0.38
<i>Number of neoplasms per mouse</i>										
Neoplasms, all sites.....	1.08	1.15	1.37	2.21	1.46	2.26	1.11	1.73	0.66	1.07

TABLE III.⁷³² MAJOR ABNORMALITIES INDUCED IN MAMMALS BY FOETAL IRRADIATION

Brain	Exostosis on proximal tibia
Anencephaly	Metaphysis
Porencephaly	Amelogenesis*
Microcephaly*	Sclerotomal necrosis
Encephalocele (brain hernia)	
Mongolism*	Eyes
Reduced medulla	Anophthalmia
Cerebral atrophy	Microphthalmia*
Mental retardation*	Microcornea*
Idiocy*	Coloboma*
Neuroblastoma	Deformed iris
Deformities	Absence of lens and/or retina
Narrow aqueduct	Open eyelids
Hydrocephalus*	Strabismus*
Rosettes in neural tissue	Nystagmus*
Dilation of 3rd and 1st ventricles	Retinoblastoma
Spinal cord anomalies*	Hypermetropia
Reduction or absence of some cranial nerves	Congenital glaucoma
	Partial albinism
Skeleton	Cataract*
General stunting	Blindness
Reduced skull dimensions	Chorioretinitis*
Skull deformities*	Ankyloblepharon
Head ossification defects*	
Vaulted cranium	Miscellaneous
Narrow head	Situs inversus
Cranial blisters	Hydronephrosis
Cleft palate*	Hydroureter
Funnel chest	Hydrocoele
Congenital dislocation of hips	Absence of kidney
Spina bifida	Degenerate gonad*
Reduced and deformed tail	Abnormalities in skin pigmentation
Overgrown and deformed feet	Motorial disturbance of extremities
Club feet*	Increased probability of leukaemia
Digital reductions	Congenital heart disease
Calcaneo valgus	Deformed ear*
Abnormal limbs*	Facial deformities
Syndactyly*	Pituitary disturbances
Brachydactyly*	Dermatoma and myotoma necrosis
Odontogenesis imperfecta*	

* These anomalies have been found in humans exposed *in utero* to radiation and are attributed to the action of radiation.

TABLE IV.⁷³² CORRELATIONS IN DEVELOPMENT: MOUSE AND MAN DEVELOPMENTAL STAGE IN HUMAN: ORGAN PRIMORDIA

Age in days		Embryo mm	
Mouse	Man		
5	6		Implantation
	14	0.15	Germ layers, extra emb. membranes
	16	0.40	Primitive streak
8	20.5	1.5	Neural groove, blood islands, notochord
9	25.5	2.4	Cephalization, extensive vascularization, neural folds meet, primordia of sense organs, thyroid, limbs, muscles, pronephros, branch, arches, somites
10.5	28.5	4.2	Prim. brain w. vesicles, complete circulation, GI tract and derivatives, mesometanephros, vertebrae, 31 somites, yolk haemopoiesis
11.5	33.5	7.0	Genital ridge, heart, liver, mesonephros protuberant, limb and lung buds, 5 brain vesicles, all sense organs, cardiac septa and 38 somites
12.5	36.5	9.0	Heart chambered, nerves and ganglia differentiating thyroid anlagen bilobed
13.5	38.0	12.0	Sexless gonad primordia, liver haemopoiesis, brain flexures, limbs, thymus, GI tract actively differentiating
14.5	47.0	17.0	Cerebral hemispheres, corpora striatum, thalamus, blood vessels all actively differentiating, endocrine glands, peripheral and sympathetic nerves, eyes well formed
15.5	65.0	40.0	Cerebral cortex, intest, villi, thyroid follicles, first ossifications, sex differentiation with sex cords and germinal epithelium

TABLE V.⁷³³ EFFECTS OF IONIZING RADIATION ON MAN—SCHEMATIC SURVEY

	<i>Acute radiation syndrome, form</i>		
	<i>Cerebral</i>	<i>Gastro-intestinal</i>	<i>Haematopoietic</i>
Determining organ.....	Central nervous system	Small intestine	Bone-marrow
Threshold dose, r.....	2,000	500	100
Latent period.....	½-3 hr.	3-5 days	3 weeks
Characteristic signs and symptoms	Lethargy, convulsions, ataxia	Diarrhoea, fever, disturbance of electrolyte balance	Leukopenia, purpura, infection
Underlying pathology.....	Inflammatory reactions in central nervous system, brain oedema	Denudation of gastro-intestinal mucosa	Atrophy of bone-marrow
Time of death (if occurring)...	Within 2 days	Within 2 weeks	Within 2 months
Cause of death.....	Respiratory arrest	Circulatory collapse	Haemorrhage, generalized infection
Prognosis.....	Hopeless	Poor	Good
Source of information	Animal experiments	Animal experiments, bomb casualties, nuclear accidents	Bomb casualties, nuclear accidents, radio-therapy

TABLE VI. EPIDEMIOLOGICAL STUDIES OF THYROID NEOPLASIA AND LEUKAEMIA IN CHILDREN TREATED IN INFANCY ON THYMIC REGION: SUMMARY OF PUBLISHED DATA

<i>Reference</i>	<i>Reason for irradiation</i>	<i>Dose range in r</i>	<i>Number of irradiated children</i>	<i>Control</i>	<i>Thyroid carcinoma</i>	<i>Leukaemia</i>	<i>Expected number</i>
Conti <i>et al.</i> ⁴⁴⁸ Pittsburgh	Prophylactic thymus irradiation	75-300	1,564	2,923	0	0	3 cases of malignancy 1 leukaemia
Simpson-Hempelmann-Fuller ⁴⁴⁶	Thymic enlargement	(1) 200	2,393 (80% traced)	2,722	21	9	3.6 cases of malignancy
Simpson-Hempelmann ⁴⁴⁶		(2) 200-600					1 leukaemia
Simpson ⁴⁴⁷							
Latourette and Hodges ⁴⁵⁰	Thymic enlargement	Average 200	861		1	1 lymphoma 1 leukaemia	0.1 carcinoma 1 lymphoma and leukaemia
Murray <i>et al.</i> ⁴⁴⁴	Various benign diseases (45% chest)	Average 400	6,473			8	2 leukaemia
Snegireff ⁴⁵¹	Thymic enlargement	Average 400	148	162	0	0	
Cronkite-Moloney-Bond ⁴²⁸	Thymic enlargement		125		2 (out of 7 neoplasias)	0	
Saenger ⁴⁵²	Chest—mainly for thymic enlargement	50-1,200 r	1,644	3,777	11	1	0.12 carcinoma
Stasek <i>et al.</i> ⁷²⁴	Cervical lymphadenitis	100-300 r	52		1		

TABLE VII.⁴³⁵ FREQUENCY OF ABDOMINAL IRRADIATION DURING PREGNANCY OF MOTHERS OF CANCER CHILDREN AND MOTHERS OF CONTROL CHILDREN: SUMMARY OF PUBLISHED DATA

Reference	Cancer children		Control children	
	Description of group	Proportion of mothers who received abdominal irradiation during pregnancy	Description of group	Proportion of mothers who received abdominal irradiation during pregnancy
Kjeldsberg ⁴³⁶	Children with leukaemia seen at Riks-hospitalet, Oslo, 1946-56	5/55 (9.1%)	Healthy children	8/55 (14.5%)
Kaplan ⁴³⁷	Children dying of acute leukaemia in California, 1955-56	37/150 (24.7%) 34/125 (27.2%)	(a) Closest Sib (b) Most habitual playmate	24/150 (16.0%) 27/125 (21.6%)
Polhemus and Koch ⁴³⁸	Children with leukaemia seen at the Children's Hospital, Los Angeles, 1950-57	72/251 (28.7%)	Children attending the Children's Hospital, Los Angeles, 1950-57 with other selected conditions	58/251 (23.1%)
Ford <i>et al.</i> ⁴³⁹	Children dying of leukaemia under 10 years of age in Louisiana, 1951-55: (a) White (b) Coloured	20/70 (28.6%) 1/8	Children dying of causes other than cancer under 10 years of age in Louisiana, 1951-55: (a) White (b) Coloured	48/247 (19.4%) 8/59
MacMahon ⁷³⁰	Children dying of cancer under 10 years of age in New York City, and born in a specified maternity hospital, 1947-57	8/114 (7.3%)	1% sample of children born in one of 11 specified maternity hospitals, 1947-57, residents of New York City only	173/2,520 (7.3%)

TABLE VIII.⁴³⁷ COMPARISON OF OBSERVED AND EXPECTED INCIDENCE OF MALIGNANT NEOPLASMS IN SELECTED SITES AMONG SURVIVORS IN HIROSHIMA EXPOSED WITHIN 1,500 METRES FROM THE HYPOCENTRE, APRIL 1957-DECEMBER 1958

	Observed	Expected	Ratio	Test result
Cancer of stomach, sexes combined	24	12.41	1.93	*
Cancer of lung, sexes combined	10	2.32	4.31	*
Cancer of breast	5	2.49	2.00	N.S.
Cancer of cervix uteri	8	3.67	2.18	**
Cancer of ovary	4	1.01	3.96	**

N.S. Not significant.

* Significant at the confidence level of 1%.

** Significant at the confidence level of 5%.

TABLE IX.⁴⁷⁹ OBSERVED TUMOURS AND CALCULATED DOSE FROM RADIO-ACTIVE MATERIALS DEPOSITED IN THE LUNG

Material and radiation ^a	Species	Results	No.	Calculated dose (rad) ^b	Remarks	References
Po ²¹⁰ (alpha)	Rat	Squamous cell carcinoma	2/15	2,500	5 and 15 months after 5 μ C/Kg	510
Pu ²³⁹ O ₂ (alpha)	Mice	Fibrosarcoma ^c	1/21	115	500 days after 0.003 μ C	521
	Mice	Squamous cell carcinoma	2/17	2,300	400 days after 0.06 μ C	523
	Mice (inhalation)	Bronchiolar carcinoma	1	600	500 days after 0.1 μ C	523
	Rats (inhalation)	Epidermoid carcinoma	—	—	Between 50 and 100 per cent surviving 250 days after deposition of 0.2 to 1 μ C developed malignant tumours	522
BaS ⁹⁰ O ₄ (beta)	Mice	Bronchiolar carcinoma	1/41	4,000	100 days after 0.16 μ C	523
	Rat	Squamous cell carcinoma	2/16	12,000 to 20,000	300 days after 375 μ C/week for 10 weeks	517
Ru ¹⁰⁶ O ₂ (beta)	Mice	Lymphosarcoma ^c	1/23	300	340 days after 0.15 μ C	521
		Alveolar cell carcinoma	1/10	4,000	422 days after 2 μ C	
		Non-differentiated tumour	1/11	9,000	350 days after 4.5 μ C	
Ru ¹⁰⁶ (metal cylinder) (beta)	Rat	Bronchogenic carcinoma	5/26		224 to 337 days after implantation of 2.1 to 14 μ C (dose calculated at 100 microns from source)	515
				2-9 $\times 10^4$		
Sr ⁹⁰ (glass beads) (beta)	Rat	Lymphosarcoma Carcinoma	4/23	50,000	131 to 375 days after implantation of 1.1 to 59 μ C	514
				70,000		
Ce ¹⁴⁴ F ₃ (gamma)	Rat	Carcinoma	1/27	2,200	127 days after 5 μ C	736
			1/23	5,500	48 days after 15 μ C	
			7/28	8,900	93 days after 25 μ C	
			4/15	15,000	83 days after 50 μ C	
Co ⁶⁰ (gamma) (wire)	Mice	Epidermoid carcinoma of bronchus	—	12,000 to 400,000	200 days after implantation	518

^a All materials administered intratracheally or otherwise as indicated.

^b Assuming uniform distribution and exponential loss unless otherwise indicated.

^c Classed as incidental by author because autoradiogram showed no radio-activity in area of tumour.

TABLE X.⁷³⁷ CHEMICALS USED FOR PROTECTIVE EFFECTS

Thiols related to cysteine and cysteamine

Compound	Animal	Dose mg/kg	Protective effect ^a	References
<i>N-Alkyl and N-aryl derivatives of cysteine and cysteamine</i>				
Cysteine.....	Mice, rats	950-1,200 i.p.	3	738, 739, 632
Cysteine.....	Rats	1,900 per os	2	740
Cysteamine.....	Mice, rats	75-250 i.p.	3	741, 738, 742, 363, 743
Cystine.....	Mice, rats	240-280 i.p.	0	744, 745
Cystamine.....	Mice	150-300 i.p.	3	744, 746, 747, 363
Cystamine.....	Mice, rats	400-600 per os	2	748, 749, 750, 751
N-Monomethylcysteamine.....	Mice	60-120 i.p.	2	638
N-Dimethylcysteamine.....	Mice, rats	40-70 i.p.	2	752, 638
N, N'-Tetramethylcystamine.....	Rats	60 i.p.	2	638
N-Diethylcysteamine.....	Mice	50-60 i.p.	2	752, 638
N-Piperidylcysteamine.....	Mice	25 i.p.	0	638
N-Methylphenylcysteamine.....	Mice	250 i.p.	0	638
N-Phenylcysteamine.....	Rats	150 i.p.	0	638
S,2-Aminoethylisothiuronium bromide HBr (AET)....	Mice	240-480 i.p.	3	753, 636
S,2-Aminoethylisothiuronium bromide HBr.....	Mongrel dogs	100 i.p.	0	754
S,2-Aminoethylisothiuronium bromide HBr.....	Macaca mulatta monkeys	200-250 i.p.	3	755
S,2-Aminoethyl-N-methylisothiuronium chloride HCl..	Mice	150 i.p.	2	637
<i>N-Acyl derivatives of cysteine and cysteamine</i>				
Glutathione.....	Mice, rats	800-1,000 i.p.	3	744, 756, 757, 745
Glutathione.....	Rats	2,000 per os	0	745
N-Acetylcysteamine.....	Mice, rats	120-250 i.p.	2	752, 638, 747
N-Acetoacetylcysteamine.....	Mice	240 i.p.	0	637
Alaethine.....	Mice	250-300 i.p.	1	752, 738
Pantetheine.....	Mice	350-550 i.p.	0	746, 752, 738
N-Acetylmethylcysteamine.....	Mice	150 i.p.	0	638

TABLE X.⁷³⁷ CHEMICALS USED FOR PROTECTIVE EFFECTS (continued)

Compound	Animal	Dose mg/kg	Protective effect*	References
<i>Compounds with covered sulfur function</i>				
α -Homocysteine thiolactone.....	Mice	—	+	758
N,S-Diacetylcysteamine.....	Mice	280–320 i.p.	0–1	339, 636, 752, 738
S-Methylcysteamine.....	Mice	850 i.p.	0	744
S-Benzylcysteamine.....	Mice	160 i.p.	0	738
Methionine.....	Mice	500–1,500 i.p.	0	738
S,2-Dimethylaminoethylisothiuroniumchloride HCl....	Mice	350 i.p.	0	637
S,2-(1-Morpholyl) ethylisothiuronium bromide HBr...	Mice	150 i.p.	0	637
Di(ethylaminoethyl)sulfide.....	Mice	140 i.p.	0	752
<i>Compounds with branched or prolonged carbon chain</i>				
3-Mercaptopropylamine.....	Mice	90 i.p.	3	752
3-Mercaptopropylguanidine.....	Mice	125–250 i.p.	3	637
Homocysteine.....	Mice	450 i.p.	2	738
1-Mercapto-5-diethylamino pentane.....	Mice	35 i.p.	0	638
1-Mercapto-7-aminoheptane.....	Mice	40 i.p.	0	638
α -Methylcysteine.....	Rats	100 i.p.	0	638
<i>Thiols with alcoholic or carboxylic acid groups</i>				
Thioglycolic acid.....	Mice	180 i.p.	0	744, 738
Mercaptosuccinic acid.....	Mice	350 i.p.	0	744
2,3-Dithiopropanol (BAL).....	Mice, rats	150–200 i.p. and s.c.	0–1	82, 752, 737
Dithiopentaerythrit.....	Mice	75 i.p.	0	759
<i>Thiophenols</i>				
2-Mercaptothiazoline.....	Mice	100 i.p.	0	637
1 (-)-2-Thiolhistidine.....	Mice	420 i.p.	0	759
Ergothioneine.....	Mice	500 i.p.	0	744
4,6-Dimethyl-2-mercapto pyrimidine.....	Mice	270 i.p.	0	759
o-Aminothiophenol.....	Mice	50 i.p.	0	759
<i>Miscellaneous sulfur-containing substances</i>				
Ammoniumdithiocarbonate.....	Mice	500 i.p.	3	760
Diethyldithiocarbamate.....	Mice	600 i.p.	3	760, 761
Thiourea.....	Mice	2,500 i.p.	2	762, 763, 738, 760, 764
Thiocyanide.....	Mice	200 i.p.	0	744
Thiacetamide.....	Mice	150 i.p.	0	744, 759
Sodium tetrathionate.....	Mice	150 i.p.	0	750
Sodium sulfide.....	Rats	5 i.v.	0	745
<i>Compounds with pronounced pharmacological and toxicological activity</i>				
Histamine.....	Mice	220–350 i.p. 500 i.p.	2 0	744, 746 765
Tryptamine.....	Mice	75–95 i.p.	3	744, 746, 765
Serotonin.....	Mice	95 i.p. 25 i.v.	3 3	746 766
DOPA.....	Mice	95 i.p.	2	746
Tyramine.....	Mice	80–275 i.p. 80 i.p.	3 0	744, 746 765
Hydroxytyramine.....	Mice	50 i.p. 75–300 i.p.	0 3	765 744, 746
Arterenol.....	Mice	3–5.5 i.p. 2.75 i.p.	2 0	746 765
Epinephrine.....	{ Mice Chickens	0.7–1.4 i.p. 5 i.m.	1 1	767, 768 605
Amphetamine.....	Mice	1 i.p.	1	766
Ephedrine.....	Mice	78 i.p. 6 i.p.	0 0	746 766
Oxytocine.....	Rats, mice	23–40 units/kp i.p.	3	767, 769
Reserpine.....	Mice	4 s.c.	3	644
Sodium cyanide.....	Mice	5 i.p.	2	744
Malononitrile.....	Mice	6.5 i.p.	3	744
p-Aminopropiophenone.....	Rats	15–30 i.p.	3	770
Apresoline.....	Mice	10 i.p. 10 s.c.	2 2	771 771
Amine oxides.....	Mice	250 or.	2	772

TABLE X.⁷³⁷ CHEMICALS USED FOR PROTECTIVE EFFECTS (continued)

Compound	Animal	Dose mg/kg	Protective effect*	References
<i>Various metabolites and "inert" compounds</i>				
Fructose.....	Mice	13,500 i.p.	2	744
		5,000 i.v.	0	608, 773
Glucose.....	Mice	13,500 i.p.	1	744
		5,000 i.v.	0	773
Propylene glycol.....	Mice	3,000 i.p.	3	744
Glycerol.....	Mice	185 i.p.	0	744
Formic acid.....	Mice	92 i.p.	2	744
Pyruvic acid.....	Mice	700 i.p.	1	744
		250 i.v.	2	608, 773
Lactic acid.....	Mice	180 i.p.	0	744
		250 i.v.	0	608, 773
β -Ketobutyric acid.....	Mice	250 i.v.	1	773
Caprylic acid.....	Mice	290 i.p.	2	744
Salicylic acid.....	Mice	275 i.p.	2	744
Succinic acid.....	Mice	950 i.p.	1	744
α -Ketoglutaric acid.....	Mice	250 i.v.	1	773
Ethylenediaminetetraacetic acid.....	Mice	580 i.p.	2	744

* *Protective effect.* The grading of the optimal protective effect has been carried out according to the following arbitrary scale: 0 = no protective effect; 1 = slight or dubious protective effect (e.g., α -ketoglutaric acid); 2 = moderate protective effect (e.g.,

formic acid); 3 = strong protective effect (e.g., cysteamine, AET). i.p. = intraperitoneally; i.v. = intravenously; i.m. = intramuscularly; s.c. = sub-cutaneously; or. = orally.

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ANNEX E

RADIATION FROM NATURAL SOURCES

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Introduction

1. The radiation from natural sources at any specific location remains relatively constant with time; it does, however, vary from place to place. Natural radiation arises from two sources—cosmic rays and naturally occurring radio-active materials. While cosmic rays are predominantly an external source of irradiation, naturally occurring radio-active materials give rise to both external and internal irradiation of the human body. A distinguishing characteristic of irradiation by natural sources is that the entire world population has been exposed to it since the beginning of time and will continue to be exposed to it in the future.

2. The biological effect of ionizing radiation varies with the type of radiation, and, in order to take this into account, a weighting factor is used to obtain the tissue dose in rem from the corresponding absorbed dose in rad. This factor is known as the relative biological effectiveness (RBE) and the usual definition is given in annex A. However, the RBE factor for a particular type of radiation is not a constant, and varies with a number of other parameters such as dose-rate, dose fractionation, type of biological effect, oxygen tension and temperature.

3. The RBE values given in annex A are those pro-

posed for radiation protection purposes^{1,2} and are generally thought to be rather conservative, particularly in the case of α -particles and neutrons. For the estimation of biological damage it is quite probable that lower values are more applicable. For instance, the 1959 ICRP Committee II report³ states the following with regard to the RBE for α -particles:

"Many experiments⁴ indicate that (RBE) α is much smaller than 10 for biological damage resulting from acute exposure—perhaps as small as 1.4—but for chronic exposures, much higher applicable values have been reported.⁵ Therefore, until more data for chronic exposures are available, it would be unwise to use a value of (RBE) $\alpha < 10$."

For low energy electrons of ≤ 0.03 MeV, Shtukkenberg⁶ suggests that the RBE is 2.8-3.0 (i.e., greater than the usual value of 1.7), when one takes into account the smaller biological effect produced by chronic irradiation when compared to a single exposure. In the light of all the uncertainties, it is thought prudent to use the RBE values given in annex A in order to estimate the exposure pattern in man, but to keep in mind that in general these values will be too high (see also annex H). Where possible in the present annex, tissue doses will be given in rem as well as in rad.

I. Cosmic rays

NATURE OF RADIATION

4. Primary cosmic radiation may be divided into three categories: galactic cosmic radiation, geomagnetically trapped radiation, and solar cosmic radiation.

(a) Galactic cosmic radiation presents a more or less constant space environmental factor, and its particle composition has been quite well determined. Outside the atmosphere at latitudes above 55° , primary cosmic rays of galactic origin consist of 87 per cent protons, 12 per cent alpha particles, and 1 per cent heavier nuclei (C, N, O, Mg, Ca, Fe).⁷⁻¹⁰

(b) Geomagnetically trapped radiation is the second category. At higher altitudes, in regions symmetrical with regard to the magnetic equator, there exist two radiation belts containing electrons and protons which have been captured by the magnetic field of the earth.¹¹⁻¹⁴ The inner belt begins at about 1,000 km altitude, reaches a maximum intensity at about 3,000 km and extends from 30° N to 30° S. The outer belt begins at an altitude of about 12,000 km, passes through a maximum intensity at about 15,000 km and extends from 60° N to 60° S. The energy spectrum of the particles in each belt differs considerably but has not been investigated fully enough to give an accurate estimate of the radiation dose-rate in these regions. The dose-rates will be dependent on the amount of shielding assumed and, for the inner radiation belt, values of 10 and 120 rad per hour have been suggested^{18,19} for 1 and 2 g per cm^2 shielding respectively. Dose rates in the outer belt may be of the order of 10^4 rad per hour²⁷ owing to soft electron bremsstrahlung, but this can be reduced considerably by shielding. A further high intensity field of low energy electrons^{18,19} is to be found at high latitudes ($> 60^\circ$) and altitudes (> 25 km) and is associated with auroral processes.

(c) Solar cosmic radiation is the third major radiation phenomenon. Large fluxes of protons are observed to reach the vicinity of the earth following severe solar flares which occur on the surface of the sun. Because of the potential danger of space travel and because of the relationships to solar physics, magnetic fields, and many geophysical events, this radiation is under intense study. Solar cosmic ray events may be divided into two classes: "high energy" and "low energy". During high energy events a significant number of particles have energies high enough to produce effects observable by ground level neutron monitors, whereas high altitude measurements or riometer measurements are necessary to detect the low energy events. The high energy events appear to be much less frequent than those of low energy. Only five such events were detected during the twenty years preceding 1959; however, an additional five events have been detected during 1959 and 1960, three of which occurred in one month, November 1960. The low energy events, on the other hand, have been observed to occur at the rate of ten per year since 1957. The most intense high-energy outburst of solar protons recorded to date was observed following the great solar flare of 23 February 1956. Shortly after the beginning of the flare, solar particles with energies of several Bev began striking the ionosphere. Data available from a number of flare events seem to indicate that the initial flux reaching the vicinity of the earth may be monodirectional with the flux, then becoming isotropic after about the first hour. There is also some evidence that the spectrum of the initial particles may be considerably harder than that of those arriving later. Measurements

made with the Pioneer V space probe have been somewhat enlightening on the behavior of solar protons in free space. The probe encountered outbursts of solar protons at a distance of about 5 million km from the earth during the period from 27 March to 6 April 1960. Unlike the radiation belts, the solar particles are not restricted to a small region of space that could be avoided or traversed rapidly, but would apparently be encountered throughout the solar system. Consequently, steps will have to be taken to shield directly against these particles in order to achieve manned missions of any appreciable time duration.

5. The primary particles interact with nuclei of the upper atmosphere, producing secondary radiation, which consists of mesons, electrons, photons, protons and neutrons—all with a very wide range of energies. Electrons and photons constitute the soft component of the secondary radiation, protons and neutrons the nucleonic component. The primary radiation intensity gradually decreases with decrease in altitude and at about 20 km it has practically disappeared, so that below this altitude cosmic radiation is almost entirely secondary in nature. In the altitude region above 20 km, the proportion of secondary radiation rapidly decreases until, at about 50 km, the radiation dose-rate is due predominantly to the primary component, except in the case of the auroral regions and the inner and outer radiation belts (para. 4). The increase in cosmic radiation dose-rate with altitude is such that above about 2 km, cosmic radiation becomes the major dose-rate contributor in man.

RADIATION DOSE-RATES

6. The radiation dose-rate due to the ionizing component of cosmic rays is generally estimated by measuring the number of ion pairs per cm^3/sec , using an energy independent ionization chamber, and then converting this value to the rate of absorption of energy assuming that 34 eV are required to form 1 ion pair. Many measurements of this type have been made. These measurements, however, do not take into account the radiation dose-rate due to the neutron component of cosmic rays, and this must be measured separately. Many measurements of cosmic ray neutron flux have been made but there are relatively few estimates of the resulting tissue dose-rate. This is due to the fact that the tissue dose-rate is very dependent on the neutron energy spectrum²⁰ which is extremely difficult to determine. The cosmic radiation dose-rate often used as a "base level" is that at sea level for high altitudes ($\sim 70^\circ$). There are indications^{21,22} that the most reliable figure for the ionizing component in this region is 1.90-1.96 ion-pairs per cm^3/sec , which gives a soft tissue and gonad dose-rate of about 28 mrad/y.

7. The cosmic ray neutron component results in a tissue dose-rate which, at sea level for middle latitudes, has been estimated by Patterson *et al.*²³ using three different type neutron detectors, which could respond to different ranges of neutron energy. Patterson's calculations show that the dose-rate from the neutron component of cosmic rays at sea levels is 25 mrem/y. This estimate is the dose-rate at the skin using the values of RBE established by the United States National Committee on Radiation Protection and Measures and ignores the absorption of neutrons in building structures and the body itself. It has been assumed that there is an average of 10 cm of building materials in roofing materials, timbers and ceilings, and that the average depth of the gonads and bone-marrow is 4 cm. By applying corrections for the

absorption of the various energies of neutrons, assuming these materials to be tissue equivalent, and assuming that the average time spent out of doors is seven hours a day, the resultant tissue dose-rate is 13 mrem/y. (These data are based on the depth dose curves for neutrons given in reference 24.) This is probably more reliable than the value of 18 mrem/y for sea level at 51° N given by Tobias¹⁰ whose estimate was based on measurements using a single type neutron detector which did not give a direct measurement of fast neutron flux, the most critical portion of the neutron energy spectrum with regard to dose-rate considerations. According to Shtukkenberg's²⁶ calculations, the cosmic radiation fast neutron (> 10 MeV) tissue dose-rate at sea level is approximately 10 per cent of the total dose-rate. He suggests that the total dose-rate resulting from cosmic radiation is 88 mrem/y, if an RBE value of 10 is assumed for densely ionizing particles with energies up to 15 MeV, and 57 mrem/y, if a value of 6.5 is used.

8. It is therefore suggested that 50 mrem per year be taken as a typical value for the total cosmic radiation tissue dose-rate for sea level at middle latitudes. The value is subject to variations with a number of parameters, as discussed in paragraphs 9-18 below.

VARIATIONS WITH LATITUDE AND LONGITUDE

9. Cosmic ray intensity exhibits a latitude effect which is due to the earth's magnetic field preventing the incoming primary particles below a certain critical minimum energy from reaching the earth's atmosphere. This critical cut-off energy decreases with increasing latitude, the net result being that the cosmic ray intensity at the geomagnetic equator is lower than at other latitudes. The intensity remains relatively constant between 15° N and 15° S, then shows a rapid increase until about 50° latitude, after which it remains practically constant again. The latitude effect is generally expressed as the percentage increase at 50° over the intensity at the equator.

10. The average value²⁶ for the latitude effect of the ionizing component of cosmic radiation at sea level is 10 per cent. The percentage increases slowly to a value of about 30 per cent at an altitude of 5 km and then much more quickly to a value of about 350 per cent at the transition region (about 20 km) of the atmosphere (para. 15).

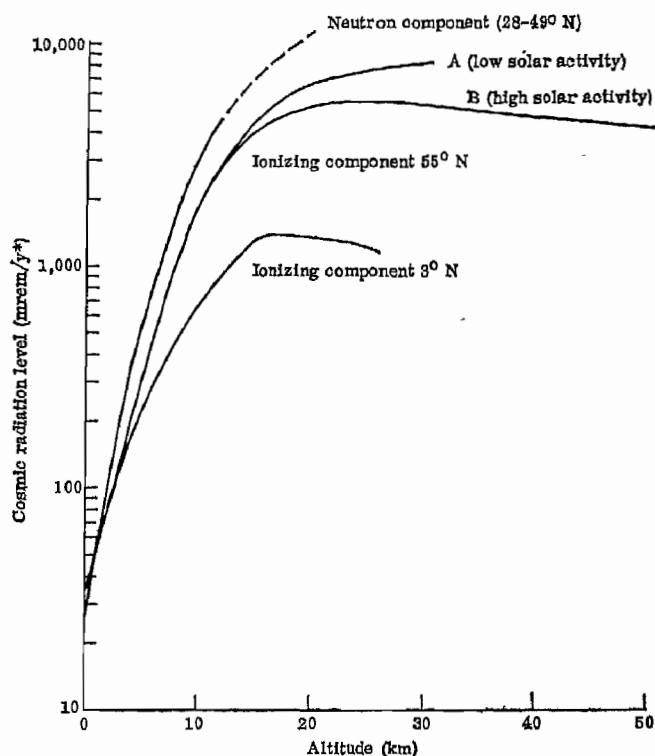
11. Since the neutron component of cosmic radiation includes neutrons produced by interaction with the atmosphere, it also exhibits a large latitude effect.²⁷ At altitudes from sea level up to about 3 km, the latitude effect is about 150 per cent and at 9 km, is about 250 per cent.

12. Changes in cosmic ray intensity with longitude are expected to occur²⁸ since the magnetic centre of the earth and the geometrical centre do not coincide, the magnetic centre of the earth being approximately 300 km from the centre of the earth along a line passing approximately through 10° N geomagnetic latitude and 160° E longitude. The intensity of the ionizing component at sea level has been found to vary about 5 per cent along the geomagnetic equator,²⁹ the effect diminishing at higher latitudes.³⁰ The nucleon intensity shows similar but larger intensity variations with change in longitude.^{27, 31}

VARIATIONS WITH ALTITUDE

13. The variation in composition of the cosmic radiation with altitudes up to 50 km has been described in

paragraph 4. Figure 1 gives the measured variation of cosmic radiation dose-rates in mrem per year with altitude for the ionizing component³² at 3° N and 55° N, and for the neutron component²⁸ in the latitude range 28-49° N. The significance of curves A and B is explained in paragraph 15.



* See annex A for comment on RBE values used.

Figure 1. Variation of cosmic radiation level with altitude

14. Typical values for the total cosmic radiation tissue dose-rates for various altitudes at the equator, 30° and 50° latitude, have been estimated, assuming that Patterson's²⁸ results for the neutron component at various altitudes apply to a latitude of 50° and that the latitude variations are as suggested in paragraphs 10-11 (table I).

VARIATIONS WITH TIME

15. Time variations of cosmic ray intensity result from a number of causes including solar flares, the 11-year solar cycle, the 27-day lunar period, temperature changes in the upper layers of the atmosphere, barometric pressure changes and air fronts. The modification in cosmic ray intensity which is associated with the 11-year cycle³³ of solar activity is most pronounced for the lower part of the energy spectrum of the primary cosmic radiation and is therefore only evident at high altitudes where it results in a minimum intensity at the period of maximum solar activity. This is illustrated by curves A and B in figure 1 which show³² the total ionization as a function of altitude in 1954 (curve A) when the sun was at its lowest ebb in twenty-two years, and in 1937 (curve B), a year of high solar activity.

16. Further variations associated with the sun are the so-called cosmic ray storms which are of short duration, one day up to a couple of weeks. They start with a sudden decrease, or series of decreases, in cosmic ray intensity and are followed by a slow recovery. These storms and decreases in intensity are correlated with the

number and size of sun spot groups as well as the appearance of solar particles.³⁴ Therefore they also follow the 11-year solar cycle.

17. The sun also acts as a powerful source of cosmic radiation during prominent flares. The spectrum of protons produced by these flares is much more enhanced in the low energy portion than that for the primary cosmic radiation³² and in most cases moderate amounts of shielding will be effective. The largest flares, for example the giant flares of 4 May 1960 and of 23 February 1956, may, however, produce dose-rates which are quite high at altitudes of the order of 10-20 km and their effect is considerable even at sea level. Calculations for the February 1956 increase show³⁵ that the integrated exposure over the duration of the increase was 5 to 10 rad at an altitude of 15 km. Solar particles produce a strong influx at high latitudes of protons having energies from a few tens to many hundreds of MeV. As these protons continue to bombard the earth's atmosphere for days they may represent a major radiation problem in the stratosphere especially as they may produce dose-rates of the order of 10 rem/hr at 20-25 km altitude.³⁶ During years of high solar activity a dozen or more such events may occur per year.

18. The neutron intensity would also be expected to exhibit a dependence on solar activity corresponding to the solar modification of primary cosmic radiation. Short-term variations at high altitudes and latitudes and associated with periods of high sunspot activity have also been observed. For instance, Simpson²⁷ reports increases in intensity of at least 30 per cent at 9 km altitude which persist for the order of days. Further variation in the neutron component will also occur near the earth's surface due to alterations in the moisture content of the soil, and it is also affected by the moisture content of dense cloud formations.³⁷

II. Natural radio-activity in the earth's crust

NATURALLY OCCURRING RADIO-ACTIVE NUCLIDES

19. Naturally occurring radio-active materials are widely distributed throughout the earth's crust and the resulting gamma ray dose to mankind varies from a value somewhat less than that due to cosmic rays to values many times higher. Some of the more important of these nuclides are the long-lived U^{238} , Th^{232} and Ra^{226} (and their shorter-lived daughter products), K^{40} and the cosmic ray produced isotopes C^{14} and H^3 . Other isotopes such as Rb^{87} , La^{138} , Sm^{147} and Lu^{176} also exist in nature but their abundance is so low as to make a negligible contribution to the dose received by mankind. The physical characteristics of some of these isotopes are given in table II.

CONCENTRATION IN COMMON ROCKS

20. In general, natural radio-nuclides are found to be more concentrated in granitic rocks than in basaltic rocks.^{38,39} Limestones and sandstones are low in radio-activity, but certain shales are more radio-active, especially those containing organic matter.⁴⁰ Marine sediments appear to be more radio-active than either non-marine or estuarine deposits.³⁸

URANIUM AND THORIUM

21. Uranium ore has been found in large quantities in Australia, Canada, Czechoslovakia, Republic of the Congo (Leopoldville), South Africa, the United States,

the Soviet Union and other areas. Large deposits of monazite, the principal thorium-bearing mineral, are found in Brazil, the United Arab Republic, China, India and the United States. Although thorium is more abundant than uranium, uranium is found in a much greater variety of chemical combinations. Table III shows their concentration in various rocks, as determined by a number of workers, expressed as $\mu\mu\text{c/g}$.

RADIUM-226

22. Ra^{226} is one of the daughter products of U^{238} but, because of leaching and weathering, it is not necessarily in equilibrium in soil with its long-lived parent. There is a considerable range of concentration in various rocks, as indicated by table III. Particularly high concentrations are found in alum shales in Sweden.^{41,42} The Ra^{226} concentration in the soil in various parts of the United States has been found by measurement to vary between 0.09 and 0.8 $\mu\mu\text{c/g}$ soil.²⁰

POTASSIUM

23. Potassium is relatively abundant in nature. Its radio-active isotope K^{40} constitutes 0.0118 per cent⁴³ of the total amount of potassium and contributes⁴⁴ 28 β -dps per g K and 3.45 γ -dps per g K. The K^{40} content of various rocks is given in table III. It has been estimated that the potassium content of soil is about 10^{-3} to 3×10^{-2} g K/g soil⁴⁵ (1 to 30 $\mu\mu\text{cK}^{40}$ /g soil.)

Rn^{222} AND Rn^{220} IN THE EARTH'S CRUST

24. Since uranium and thorium are almost universally distributed, their respective short-lived gaseous daughter products, Rn^{222} and Rn^{220} , accumulate in soil and rocks. The daughter products of this trapped Rn^{222} and Rn^{220} contribute over half the observed gamma activity of uranium minerals.⁴¹ The Rn^{222} and Rn^{220} in the soil diffuse into the air at a quite variable rate, depending on a number of factors including moisture content of the ground,⁴⁶ presence of snow,⁴⁷ amount of rainfall,^{48,49} conditions in soil and atmosphere, particularly atmospheric turbulence and pressure.

DOSE-RATES FROM THE EARTH'S CRUST

25. The gamma dose-rates in air over radio-active rocks and soils can be calculated from the energies, absorption factors and relative abundances of the various component gamma rays, allowance being made for scattered radiation. The expressions obtained by Hultqvist⁴² and O'Brien *et al.*⁵⁰ for the gamma dose-rates in air above ground containing uniform concentrations of U^{238} , Th^{232} and K^{40} agree to within 10 per cent. The average of their expressions gives the following relations between the dose-rate in air (D , mrad/y) at a height of one metre above ground containing uniform concentrations (S , $\mu\mu\text{c/g}$) of U^{238} , Th^{232} (both in equilibrium with their daughters) and K^{40} :

$$\left. \begin{aligned} D_U &= 17.8 \times S_U \\ D_{Th} &= 25.5 \times S_{Th} \\ D_K &= 1.56 \times S_K \end{aligned} \right\} \quad (1)$$

26. The β -particle emission of these naturally-occurring radio-nuclides can contribute an external dose to the human skin. These skin dose-rates have been calculated by O'Brien *et al.*⁵⁰ for β -emission from U^{238} , Th^{232} and K^{40} in soil assuming homogenous distribution and complete equilibrium between the U^{238} and Th^{232} and their decay products. The external contribution to the dose-rate delivered to susceptible organs (such as

gonads, bone, etc.) resulting from β -emission, must be regarded as negligible.

27. Typical estimates of the average dose-rates in air at a height of one metre above limestone may be of the order of 20 mrad/y and that for granite areas may be of the order of 150 mrad/y. It is obvious, however, that there will be quite large variations in these values, and this is borne out by the measured terrestrial dose-rates in air reported for areas in various countries as given in table IV. Further, much higher values are reported for some areas, e.g., monazite sands, where the uranium and thorium contents are very high (see section VII below).

28. The terrestrial gamma dose-rate inside buildings will, generally, be different from the value out of doors owing to the different radio-active content of the building materials and also the attenuation effect of the walls for the radiation from sources outside the building. A further small increase in dose-rate may be produced by the accumulation of Rn^{222} and Rn^{220} as a result of poor ventilation in the buildings (see section IV below). Reported terrestrial dose-rates in air inside buildings in various countries are given in table V.

29. In order to obtain tissue dose-rates to specific organs due to external gamma sources, allowance must be made for attenuation by intervening portions of the body. O'Brien *et al.*⁵⁰ have calculated the dose-rates in man at various depths as fractions of the free-air gamma dose-rates. Assuming that the testicles, ovaries and bone-marrow are at depths⁵¹ of 1, 7 and 4 cm, the resulting screening factors are 0.68, 0.58 and 0.62, respectively. These are in very good agreement with the average experimentally determined screening factors obtained by Spiers⁵² using a water-filled model—0.70, 0.56 and 0.64 respectively. It is, therefore, suggested that a value of 0.6 be used as the screening factor for gonads and bone-marrow in the case of terrestrial radiation. (F III, 18)

30. The estimation of mean dose-rate to a population should be made by a carefully planned series of measurements of dose-rates both indoors and out of doors and then weighting the measurements according to time spent in each place. A very good example of such a survey is one which was recently made in four areas in the United Kingdom.⁵³ The mean values of local gamma-radiation dose-rates obtained are given in table VI. In computing the mean dose-rates to the gonads and bone marrow, screening factors of 0.63 and 0.64 respectively were used and it was assumed that an average of six hours per day per person was spent out of doors.

31. Insufficient measurements have been made to enable a reliable estimate of the mean dose-rate to the world population to be made. It should be pointed out that the major part of most people's lives in most areas of the world is spent inside buildings. With this in mind, consideration of tables IV and V seems to indicate that, except for certain regions of high activity, the average terrestrial gamma dose-rate in air is of the order of 30 mrad/y, i.e., a mean gonad and bone dose-rate to the world population from terrestrial gamma radiation is only about 50 mrad/y (para. 29).

III. Natural radio-activity in water

32. An extremely wide range of natural radio-activities exists in various types of water, depending largely upon their origin. The levels of natural activity originat-

ing from uranium and thorium series are found to be high in certain natural springs which are found in areas where there are high concentrations of uranium and thorium in the soil. Similarly, drinking water exhibits wide variations of activity depending upon its origin and on the treatment it receives before it becomes available for consumption. High levels of natural potassium-40 activities are found in sea-water.

PUBLIC WATER SUPPLIES

33. Public water supplies are of interest since drinking water is one of the modes of entrance of natural radio-activity into the body. Table VII gives concentrations of Ra^{226} and Rn^{222} present in various public water supplies. It should be pointed out that the radium content of water is reduced by the introduction of filtration and/or softener systems, so that the intake of radium from a particular supply may be modified in the case of some individuals by the use of domestic water softeners. Lucas⁵⁴ quotes a case where one of these units (ion-exchange type) removed 98 per cent of the Ra^{226} present in the normal water supply.

34. Many drinking water supplies will also contain naturally occurring Th^{232} and/or its decay products. Krause⁵⁵ has investigated the Ra^{226} content of twenty-six samples of well-water from the Illinois (United States) sandstone area and has compared them with the Ra^{226} contents of the same samples which had been previously measured by Lucas.⁵⁶ The Ra^{228}/Ra^{226} ratio covered an extremely wide range of values, 0.04 to 2.43, with an average of 0.60. The Ra^{228} concentrations ranged from 0.9 to 7.9 $\mu\text{C}/\text{l}$, whilst Ra^{226} went from 3 to 36 $\mu\text{C}/\text{l}$.

OCEAN WATER, RIVERS AND NATURAL SPRINGS

35. Typical concentration of U^{238} , Th^{232} , Ra^{226} and K^{40} in sea-water are respectively 0.2-9 $\mu\text{C}/\text{l}$,⁵⁷ 0.1-1.10⁻³ $\mu\text{C}/\text{l}$,⁵⁸ 0.02-0.3 $\mu\text{C}/\text{l}$ ⁵⁹ and 300 $\mu\text{C}/\text{l}$.⁶⁰ Table VIII gives the concentrations of U^{238} , Ra^{226} and Rn^{222} present in various natural waters and springs. Spring-waters may exhibit extremely high radio-active concentrations, particularly of Rn^{222} , but as they are consumed regularly only by a very small percentage of populations, and since Rn^{222} ingested from drinking water probably has a mean life of about one hour in the body,⁶¹ the resulting mean dose to the world population from spring-water is negligible.

SKELETAL Ra^{226} CONTENT DUE TO DRINKING WATER

36. The skeletal content of Ra^{226} is determined by its introduction into the body through food, water and, to a lesser extent, air. Muth *et al.*⁶² have shown that under normal environmental conditions only about 10 per cent of the Ra^{226} enters the human body through water and about 90 per cent from food. When the Ra^{226} concentration in water is relatively high and the intake from water exceeds the intake from food, some correlation is found to exist between the skeletal concentration and the concentration in water.⁶⁴ With relatively low (normal) Ra^{226} concentrations in water, no such correlation is observed as the skeletal Ra^{226} content is then basically determined by its intake from food.

IV. Natural radio-activity in the lower atmosphere

Rn^{222} AND Rn^{220} AND THEIR DECAY PRODUCTS

37. Wherever there are uranium or thorium bearing minerals present in the soil, the gaseous decay products

Rn^{222} and Rn^{220} are injected into the atmosphere by diffusion (para. 24). The rate of injection varies considerably with seasonal and meteorological conditions. Measurements of Rn^{222} and Rn^{220} and/or their daughter product activities is often carried out by a combination of filtration and ionization chamber or scintillation methods.⁶³ The daughter products, in the form of ionized atoms, attach themselves to the aerosols and dust particles which are always present in the air. The collection efficiency of filter papers for these particles is often very uncertain and depends on the linear air velocity through the paper and the size range of the dust particles in the air.^{64,65} Thus, in low dust atmospheres such as those of air-conditioned rooms, the retention of the daughter products by filter papers may be very low. Ion collection efficiency may, however, approach 100 per cent by the application of a suitable electric field.⁶⁶ In addition, the Rn^{222} and Rn^{220} present in the atmosphere are not necessarily in equilibrium with their daughter products and will also contain varying fractions of uncombined atoms of daughter products, both of which affect the dose-rate to the lungs upon inhalation (para. 42). The concentration of Rn^{222} and Rn^{220} will also vary with height, for instance the average value at a height of 10 m for Rn^{222} is 90 per cent of that at ground level.^{26,67,68} Rn^{220} , by virtue of its very short half-life, will virtually have disappeared at heights of 10-20 m. The average concentrations of Rn^{222} and Rn^{220} present in free air at ground level in various regions are given in table IX. Values are particularly dependent upon the length of time the air mass spends over continental land masses.^{67,69,70} Also, in areas of high radio-activity and under special meteorological conditions, e.g. smog and temperature inversion, values may be higher by several factors of ten.

38. As the majority of the people spend a large part of their time in buildings, the average natural radio-activity concentration in air which refers to the world population is more dependent upon the level in buildings than in free air. In general, the level indoors is higher than that out of doors and it is dependent upon the building construction materials and the ventilation conditions. The level out of doors will determine the concentration that will be reached by very efficient ventilation of the building. The results of measurement by Hultqvist⁴² in three types of buildings in Sweden for conditions with and without ventilation are given in table X. A ventilation rate of 10^{-3} /sec was used, i.e., the air in the building was renewed every seventeen minutes.

39. Reported Rn^{222} content of the air indoors at various localities is given in table XI. Consideration of these data indicates that the best estimate of a "world average" concentration of Rn^{222} in air may be of the order of $0.5 \mu\text{C}/\text{l}$. The corresponding figure for Rn^{220} may be of the order of $0.02 \mu\text{C}/\text{l}$.

40. The external gamma dose-rate in air (D) produced by a concentration of $C \mu\text{C}/\text{l}$ of Rn^{222} or Rn^{220} in equilibrium with their decay products per litre of air can be calculated by Hultqvist's relation:⁴²

$$D = 14C \text{ mrad/y}$$

In obtaining the dose to various body organs allowance must be made for body shielding. The screening factor of 0.6 used previously for terrestrial radiation (para. 29) will again be used here. Hence, for "average" air concentrations of Rn^{222} and Rn^{220} (para. 39), the total body tissue dose-rate will be of the order of 4.5 mrem/y. It should be pointed out, however, that this contribution to the tissue dose-rates will have been included in any

measurement of local gamma-radiation dose-rates that have been made and so is allowed for in the average local gamma dose-rate given in paragraph 31.

41. There will also be a further total body tissue dose produced by the Rn^{222} and Rn^{220} in the air resulting from that portion which is transferred via the blood from contact with the alveolar air. Using Spiers⁵⁸ results, the total dose-rate to soft tissues due to the inhalation of air containing $0.5 \mu\text{C}/\text{l}$ of Rn^{222} in equilibrium with its daughter products, is of the order of 3 mrem per year. Ruzer's results⁷¹ indicate that the whole body dose-rate due to the inhalation of $0.5 \mu\text{C}/\text{l}$ of Rn^{222} is of the order of 0.01 mrem per year.

42. The dose-rate to the lungs from Rn^{222} and Rn^{220} and their decay products occurs as a result of deposition and/or passage back and forth through the tracheo-bronchial tree of these decay products⁷² and depends largely on their size, specific activity and percentage of uncombined atoms,⁷³ since these determine the amount of radio-activity retained in the lungs. Rn^{222} and Rn^{220} , being gases, are retained only to a very small extent, and so do not make a very large contribution to the dose-rate. Stannard⁷⁴ gives the mass deposition of small particles in the respiratory tract (figure 2), derived from the results given by Hultqvist.⁴² Values for dose-rates to the lung for exposure to Rn^{222} or Rn^{220} in equilibrium have been calculated by various workers. For instance, using the expressions of Hultqvist,⁴² Morgan,⁴² Ruzer,⁷¹ Shapiro,⁷⁶ and Schraub,⁷⁰ values are obtained of 20 mrad (200 mrem), 90 mrad (900 mrem), 10 mrad (100 mrem), 10 mrad (100 mrem), 250 mrem, respectively, for the annual dose to the lungs from a continuous concentration of $0.5 \mu\text{C}/\text{l}$ Rn^{222} in equilibrium. The variations in these estimates are chiefly due to the differences in the assumption regarding time spent in the relevant locale, respiration velocity and the weight of the irradiated lung tissue. Hultqvist⁴² has estimated the dose-rate

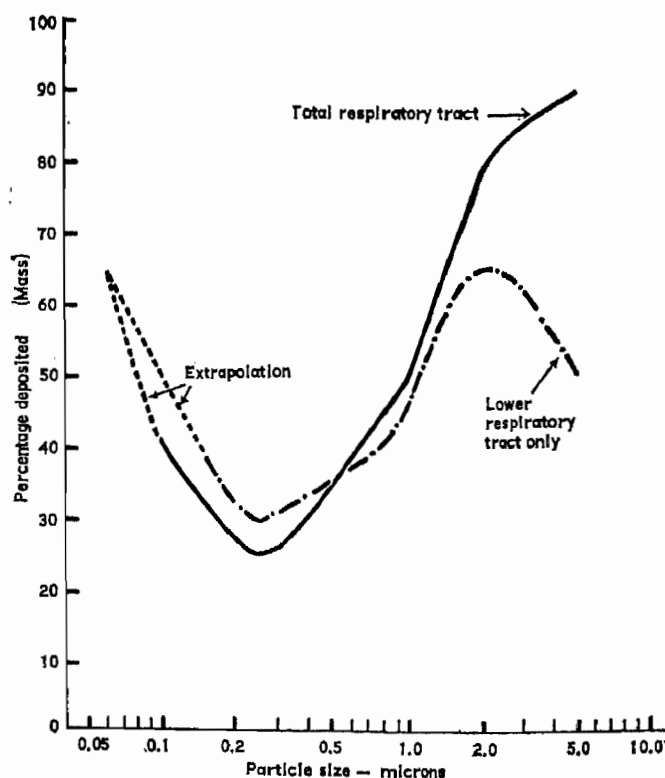


Figure 2. Percentage mass deposition of small particles in the respiratory tract

to the lungs from Rn^{222} and its decay products and from Rn^{220} and its decay products in the case of radio-active equilibrium and also where this equilibrium has been greatly disturbed by a high ventilation rate ($10^{-3}/\text{sec.}$). The dose-rates to the lungs along with the average concentrations of Rn^{222} and Rn^{220} in air for three types of buildings in Sweden are given in table X. It is apparent that the lungs receive a higher irradiation from natural sources than any other body tissue.

Pb^{210} , Bi^{210m} AND Po^{210}

43. The daughter products, Po^{218} , Pb^{214} , Bi^{214} and Po^{214} , because of their short half-lives, are normally not very far from secular equilibrium with the parent Rn^{222} , but the concentrations of Pb^{210} , Bi^{210m} and Po^{210} will be relatively much lower at ground level than their equilibrium values, as they will be washed out of the atmosphere long before equilibrium has been reached. Measured levels of Pb^{210} , Bi^{210m} and Po^{210} in the air at ground level are given in table XII. These concentrations are insignificant with respect to dose considerations.

CARBON-14*

44. Carbon is one of the elements that are essential to all forms of life and thus is involved in most biological and geochemical processes on the earth. Associated with the stable isotopes of carbon (C^{12} and about 1.1 per cent C^{13}), there is always a very small but variable amount of C^{14} , a pure β -emitting ($E_{\text{max}} = 0.165 \text{ MeV}$) radioactive isotope of carbon with a half-life of 5760 ± 50 years.⁷⁷

45. C^{14} is formed upon absorption of neutrons in the nitrogen nuclei of the atmosphere. When the neutrons involved are of cosmic ray origin, the C^{14} formed is referred to as "natural", and when the neutrons originate from nuclear testing, the resulting C^{14} is "artificial".

46. Due to isotopic fractionation in most processes in which carbon is involved, small variations occur in the relative amounts of the three isotopes of carbon found

$$\begin{aligned} \text{Specific activity of } C^{14} &= \frac{\text{Production rate of } C^{14} \text{ (atoms/cm}^2/\text{min)}}{\text{(disintegrations/min/g carbon) Carbon in exchangeable carbon cycle (g/cm}^2\text{)}} \\ &= \frac{2.2 \times 60}{8.1} \text{ dpm/g} \sim 16 \text{ dpm/g} \end{aligned}$$

51. Experimental determinations of the specific activity of natural C^{14} in the biosphere have ranged from 12.9 to 15.3 dpm/g carbon,⁸⁰⁻⁹³ the most recent measurement being 14.46 dpm/g.⁸⁰ The absolute disintegration rate for C^{14} in pre-1900 biospheric carbon may thus be taken to be 14 ± 1 dpm/g, which corresponds to a C^{14}/C^{12} ratio of 1.20×10^{-12} .

52. The constancy of the cosmic ray flux with time is of considerable interest, and three independent types of experiments have been carried out to give further information on this question. These three methods, which cover different time periods, are:

(a) Measurement of the C^{14} activity in biospheric samples of known age (time range of several thousands of years).^{82, 94-96}

(b) Comparison of radio-carbon and ionium ages of ocean sediments (time range of a few thousands to tens of thousands of years).⁹⁷

(c) Comparison of observed activities of various cosmic ray induced radio-isotopes in meteorites (time range of hundreds to millions of years).⁹⁸

* For discussion on C^{14} see also annex F, part I.

in nature. Thus, for example, the C^{13}/C^{12} ratio in plant material is 1.7 per cent less than that in the atmosphere^{78, 79} and the change for the C^{14}/C^{12} ratio is twice this amount.^{80, 81}

Production of natural C^{14}

47. The C^{14} produced in the atmosphere owing to absorption of cosmic ray neutrons may be estimated from flux-energy data and the neutron cross-sections of the various constituents of the atmosphere. These cosmic ray neutrons are entirely secondary in nature.

48. The neutrons are slowed down by collision and all ultimately undergo neutron capture by nuclei present in the atmosphere. It is generally assumed that virtually all of the cosmic ray neutrons result in C^{14} production,⁸² i.e., the $N^{14}(n,p)C^{14}$ is the only reaction of importance. However, Hess *et al.*⁸³ conclude that only 67 per cent of cosmic ray neutrons are captured by this process, 16 per cent are captured by other processes, 17 per cent leak out of the atmosphere, and 0.2 per cent are captured by the earth.

49. The short-term variation of cosmic ray neutron flux with time, altitude and latitude is considerable (paras. 7, 11, 12, 14, 18), making it quite difficult to obtain an average value for neutron production to be used for the estimation of C^{14} production. The computation of the cosmic ray C^{14} production rate has been carried out by several workers⁸²⁻⁸⁸ who have obtained values ranging from 1.3 to 3.1 atoms/cm²/sec. (i.e., average 2.2 atoms/cm²/sec which is equivalent to 3.4×10^{26} atoms C^{14} /y/earth's surface).

50. If the average value of the cosmic ray flux has been constant over the last tens of thousands of years (several C^{14} half-lives), the C^{14} activities in the carbon cycle would be in a "steady state" situation, for production of C^{14} would be balanced by decay of C^{14} . The specific activity of C^{14} would then be given by the following relation:

53. All these data support the basic premise that the average cosmic ray flux has been essentially constant for hundreds of millions of years, and that any variation over the time period of interest for natural C^{14} (100-50,000 years) is less than a few per cent. It has been pointed out by Stuiver¹⁰⁰ that available evidence on sunspot activity (which is known to affect the cosmic ray level in the upper atmosphere) suggests some correspondence between sunspot activity and the C^{14} concentration in the atmosphere, as indicated by tree ring measurements.^{95, 100} Recent measurements of C^{14} variations in an 800 year old Kauri tree show¹⁰¹ a gradual increase in the C^{14} content of the atmosphere over the last 850 years which could be attributed to an increase in the cosmic ray flux.

54. This natural C^{14} in the biosphere results in a negligible external dose-rate to man, and a larger, but still quite small, dose-rate due to its presence in the body tissues (para. 82).

TRITIUM

55. Tritium, H^3 , a radio-active isotope of hydrogen with a half-life of 12.26 years, is, like C^{14} , continuously being produced in the atmosphere by cosmic rays, thus

giving rise to concentrations of tritium in nature. These natural tritium levels have, since 1952, been modified by the addition of tritium to the atmosphere by nuclear weapons tests, especially by high yield fusion devices.

56. The tritium content of molecular hydrogen in the troposphere of the middle latitude regions of the northern hemisphere in 1949-1951,¹⁰² 1954-1956¹⁰² and mid-1959¹⁰³ respectively was about 30, 300 and 1500 $\mu\mu\text{c/g H}$. The resulting tissue dose-rate due to the incorporation of tritium in the body is considered in paragraph 84.

BERYLLIUM-7 AND OTHER COSMIC RAY-PRODUCED NUCLIDES

57. Other radio-active nuclides known to exist naturally owing to the interaction of cosmic ray neutrons with the atmosphere include Be^7 , Na^{22} , P^{32} and S^{35} . Of these, Be^7 , with a concentration of the order of $2 \times 10^{-5} \mu\mu\text{c/litre}$,^{104,105} has the highest concentration. The tissue dose contribution from each of these nuclides is negligible.

V. Natural radio-activity in foodstuffs

58. The natural radio-activity in soil and water becomes transferred to man via the food-chain cycle. Study of this aspect requires measurement of activity levels in plants, some of which are used directly as human foods, while others, such as grasses, form the principal food of animals which in turn themselves become human food (F II). There is a wide range of activities in vegetation and there appears to be no simple correlation with the corresponding activities in soil for which the range is smaller. As there is not much information regarding the discrimination factors for the soil-food and food-man processes, the dose-rates to particular body organs are best related to measured concentrations in the particular organs.

TOTAL ALPHA ACTIVITY

59. A number of measurements have been reported of total α -activity in various dietary materials, but as the various daughter products in both the U^{238} and Th^{232} radio-active series may exist in different degrees of non-equilibrium, the individual isotopes should be identified in order to obtain the maximum information.

60. An extensive set of data on the total α -activity of foods has been published by Turner *et al.*,¹⁰⁶ and values vary from less than 1 up to $1.7 \times 10^4 \mu\mu\text{c/kg}$ of food. In general, their measurements show low activities in milk products, fruit and vegetables, but higher values in cereals and nuts. They estimate that an adequate diet will not contain less than 2 $\mu\mu\text{c}$ total α -activity per day, but it is obvious from the large range of values of activity in the different foods that small changes in eating habits can result in a large change in the intake of radio-activity. Mayneord¹⁰⁷ estimates that an adequate Western diet is not likely to contain less than 5 $\mu\mu\text{c}$ of α -activity per day.

RADIUM-226

61. Regular three-monthly measurements¹⁰⁸ of the Ra^{226} content of the various foods in the average diet of three areas in the United States are being carried out by the Atomic Energy Commission's Health and Safety Laboratory and their results are given in table XIII. By using the Department of Agriculture's food con-

sumption figures for the United States, Hallden and Fisenne¹⁰⁸ conclude that the average daily intake of Ra^{226} for the two surveys in New York City, Chicago and San Francisco is 2.4, 1.9 and 1.7 $\mu\mu\text{c}$ respectively. Measurements of the Ra^{226} in the diet of infants in New York City¹⁰⁹ indicate that if the August 1960 samples are typical, then the intake of infants during the first year of their life is 212 $\mu\mu\text{c}$ (0.6 $\mu\mu\text{c/d}$) of which about one-third comes from milk and one-half from cereals.

62. Muth *et al.*⁶² have reported the Ra^{226} content of a wide variety of foods in Germany which give a range of activities 0.1 to 6 $\mu\mu\text{c/kg}$. Their values, some of which are given in table XIV, agree very well with the United States figures in table XIII. Muth *et al.* estimate that the daily intake of Ra^{226} is about 3 $\mu\mu\text{c}$, of which about 10 per cent is contributed through intake of Ra^{226} in water.

63. In addition to total α -activities for different foods, Turner *et al.*¹⁰⁶ reported the Ra^{226} activities for a few of the same samples. Some of these values are given in table XV for purposes of comparison with the United States and German results. It is thought¹¹⁰ that the high values for cereals might be due to a contribution from Australian wheat for which total α -activity content has been reported for some samples to be higher than that for wheat from the United Kingdom and Canada.¹¹¹

THORIUM

64. No evidence has yet been found of the presence of Th^{232} in dietary materials. Mayneord and Hill¹¹² have published the α -spectrum of a sample of breakfast cereal made from whole wheat. This shows the two long-lived α -emitters, Ra^{226} and Th^{232} and their daughters. U^{238} and Th^{232} are absent and the Th^{232} may therefore be presumed to originate from Ra^{226} (a β -emitter which therefore does not appear in the spectrum) rather than by metabolic uptake of the element thorium. Later evidence¹¹³ on the α -activities of leaf ash indicates uptake of Ra^{226} in preference to thorium. Turner *et al.*¹⁰⁶ reported both Ra^{226} and Th^{232} contents for twenty-three different food samples, and the average $\text{Th}^{232}/\text{Ra}^{226}$ activity ratio for these was 0.9.

Pb^{210} , Bi^{210m} AND Po^{210}

65. It has been observed^{112,113} that the α -activity observed in certain samples of grass is mainly due to the presence of Po^{210} , accompanied by its parent Pb^{210} (β - γ emitter). Hill¹¹⁴ suggests that this largely originates from a process in which Pb^{210} , resulting from the decay of atmospheric Rn^{222} , together with a fraction of the equilibrium amount of its descendant Po^{210} are deposited by rainfall directly on to the foliage. This fractionation is probably explained by the fact that both nuclides arise from the decay of a gaseous precursor. It is evident that Po^{210} or one of its precursors, such as Rn^{222} or Pb^{210} , may also be taken up directly from the soil. Since snow and even moderate rainfall can restrict the rate of escape of Rn^{222} from the surface of the soil (para. 24 above), it is clear that these factors could result in concentration of Pb^{210} , and in turn Po^{210} , being produced in the top layer. The relative uptake by vegetation from the soil and from direct deposition on the foliage probably varies from site to site, depending on parameters such as species of plant, soil drainage characteristics, depth of water table below the surface, etc.

POTASSIUM-40

66. K^{40} is present in a fixed proportion (0.0118 per cent) of total potassium in all natural materials. The

potassium content of food varies considerably—for example, in the United Kingdom¹¹⁵ values given for a very large number of samples of different types of food range from 0.1 per cent up to about 5 per cent (0.76 $\mu\mu\text{c}$ K^{40}/g up to about 38 $\mu\mu\text{c}$ K^{40}/g). Consequently potassium intake will be very dependent on diet and may show large variations between countries. For instance, Scott Russell¹¹⁶ has pointed out that in the United Kingdom 23 per cent of the total potassium in diet originates from dairy produce and 35 per cent from potatoes, while in the United States the figures have been given as 38 per cent and 19 per cent respectively. The potassium intake for the United States based on per capita food consumption has been calculated to be approximately 2300 $\mu\mu\text{c}/\text{d}$.^{117, 118}

VI. Natural radio-activity in the human body

67. The extremely low levels of naturally occurring radio-activity normally present in the human body make measurement of the individual radio-isotopes very difficult. *In vivo*, measurement of gamma rays is often used to measure the body potassium content. The total body Ra^{226} content can be estimated by measuring the rate of exhalation of radon and assuming a general value for the fraction of the total radon formed which escapes in the breath. This fraction is not accurately known and may indeed vary under different conditions. Ra^{226} and other nuclides can also be estimated by the analyses of autopsy samples.

TOTAL ALPHA-ACTIVITY

68. Turner *et al.*¹¹⁹ measured the total α -activity of bones of persons native to Cornwall, London and Cumberland. The average value is 0.38 $\mu\mu\text{c}/\text{g}$ ash, but individual results show large variations (figure 3). There appears to be a significant difference between values for Cornish bones and those from the London area or from Cumberland. The total α -activity in 10 Eskimo bones¹⁰⁷ showed a range from 0.18–0.97 $\mu\mu\text{c}/\text{g}$ ash with an average of 0.61, and the rib of an Egyptian¹⁰⁷ who died almost 4,000 years ago gave a value of 0.34 $\mu\mu\text{c}/\text{g}$ ash. Figure 3 indicates that for persons not occupationally exposed to α -activity, the concentration does not vary with age, but as the weight of the skeleton increases from birth to adult so the total α -activity in the skeleton increases in this period and then stays constant.

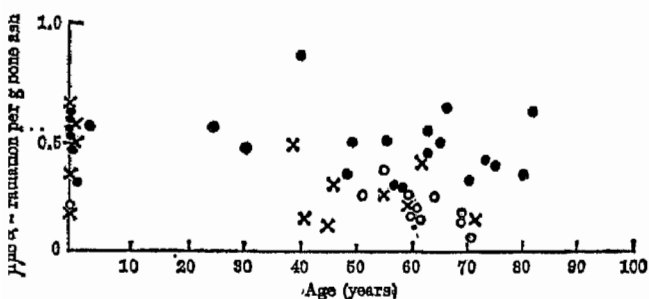


Figure 3. Human bone ash, total α activity. ●, Cornwall; ×, London; ○, Cumberland

69. Mayneord¹²⁰ finds a large variation of activity for different soft tissues, 0.15 to 1.00 $\mu\mu\text{c}/\text{g}$ ash, but the average value of 0.52 $\mu\mu\text{c}/\text{g}$ ash agrees very well with that obtained for skeleton ash. This leads Mayneord to conclude that in the normal human being, about 25 per

cent of the α -emitting radio-active material is in the soft tissues.¹⁰⁷

RADIUM-226

70. Ra^{226} is taken into the body through food, water and, to a lesser extent, air (para. 36). The total Ra^{226} content of normal human bodies has been determined by a number of workers, and values ranging from 3–1400 $\mu\mu\text{c}$ obtained. These results are summarized in table XVI, along with data regarding the number of samples measured, and the average Ra^{226} content of drinking water in the area from which the samples were obtained. Where results are reported in terms of activity per gram ash, and individual total ash values are not given, it is assumed that a 70 kg man produces 2600 g skeletal ash and 400 g tissue ash. The results show⁶⁴ some correlation with the Ra^{226} content of drinking water when this source is predominant.

71. Walton *et al.*¹²¹ measured the Ra^{226} concentrations in samples from up to 11 bones from each of 11 bodies in order to determine the variation within the skeleton. They concluded that there is no systematic difference in the radium content of the various bones of the average skeleton, at least to within ± 15 per cent. Departures from the mean of up to 50 per cent do occur in a few specimens. However, this degree of consistency within the various bones was not confirmed by Holtzman¹²² in his measurements of both the Ra^{226} and Pb^{210} content of five bones from each of three persons who had been born in different states in the United States. These results are given in table XVII.

72. There is a distinct possibility that measurements on teeth may be used as an indicator of Ra^{226} bone levels, particularly if water concentrations are constant in the area. Lucas⁶⁴ found a value of 0.10 $\mu\mu\text{c}/\text{g}$ ash for the average of Ra^{226} levels in teeth for nine persons which was almost identical to the 0.11 $\mu\mu\text{c}/\text{g}$ ash found for bone from residents from the same city. The total α -activity levels in teeth obtained from the Royal Dental Hospital were also very similar to those in bones from persons who had lived in London.¹⁰⁷ Further, the activity of teeth from the inhabitants of Niue Island,¹²³ an area of high natural radiation (see section VII below), is of the order of ten times that of teeth from the inhabitants of normal areas.

73. The relative concentrations of radium in the skeleton and body tissues is uncertain. Muth *et al.*⁶² suggest that 25 per cent of the total body radium is contained in the skeleton, whereas Hursh *et al.*¹²⁴ give a figure of 78 per cent and Lucas⁶⁴ 80–85 per cent. Results given by Hill¹²⁰ also tend to support this higher figure. The results for bone and muscle ash and wet tissue are given in table XVIII. No explanation has been given for the relatively high tissue values obtained by Muth, but total α -activity values in bone and soft tissue (para. 69) favour a skeletal content of about 80 per cent of the total body value.

74. Consideration of the above information indicates that the world average for the Ra^{226} total body burden is likely to be closer to 50 $\mu\mu\text{c}$ than 100 $\mu\mu\text{c}$. In subsequent considerations, we will assume a conservative value of 75 $\mu\mu\text{c}$, of which 80 per cent (60 $\mu\mu\text{c}$) is in the skeleton.

THORIUM

75. The presence of Th^{232} in human tissues¹²⁵ has been demonstrated by means of α -ray spectroscopy, but, as

with plant tissues (para. 64), the parent isotope of the thorium series, Th^{232} , has not yet been detected. It is therefore thought¹²⁵ that the Th^{228} originates from the metabolic uptake of radium in the form of Ra^{226} rather than uptake of thorium. Because the half-life of Ra^{228} is considerably less than that of Ra^{226} , it may be expected that the $\text{Ra}^{228}/\text{Ra}^{226}$ activity ratio will be a maximum in newly formed bone and will be less than this value in older bone. The magnitude of this effect is not known and, indeed, it does not appear to be sufficient to introduce an age effect into the total α -activity content of bones (figure 3). Mayneord *et al.*¹²⁵ suggest that 40 per cent of the total α -activity in adult bone is due to radiothorium, i.e., $\text{Th}^{228}/\text{Ra}^{226}$ series activity ratio is approximately 0.7. Measurements reported by Stehney¹²⁶ on ashed bone samples from six subjects (average Ra^{226} skeletal content of about 90 $\mu\mu\text{c}$) gave an average $\text{Th}^{228}/\text{Ra}^{226}$ series activity ratio of 0.4. This value is rather uncertain owing to the large fractional errors in the Th^{228} measurements. Using thoron in breath technique, Cullen¹²⁷ has found indications of much higher Th^{228} content of normal persons. It will be assumed that the world average Ra^{228} total body content is 50 $\mu\mu\text{c}$, of which 40 $\mu\mu\text{c}$ is in the skeleton.

Pb^{210} , $\text{Bi}^{210\text{m}}$ AND Po^{210}

76. Various workers have determined Pb^{210} , $\text{Bi}^{210\text{m}}$ and Po^{210} concentrations in human bone in excess of that expected from the Ra^{226} content. Holtzman¹²² made measurements on samples of individual bones from forty-four humans and found an average skeletal Pb^{210} content of 360 $\mu\mu\text{c}$ (corresponding mean Ra^{226} content was 100 $\mu\mu\text{c}$). He concluded that the origin of this Pb^{210} was mainly from food, to a slightly smaller extent from the atmosphere and a minor contribution only from drinking water. Hursh¹²⁸ obtained a value of 105 $\mu\mu\text{c}$ for the mean skeletal Pb^{210} content of eighteen cadavers obtained in the New York area (average Ra^{226} content was 120 $\mu\mu\text{c}$). Hill and Jaworowski¹²⁹ measured the Pb^{210} content of bone samples from six subjects and found an average skeletal content of 160 $\mu\mu\text{c}$. It will be assumed that 200 $\mu\mu\text{c}$ Pb^{210} is the skeletal content of an average person.

DOSE-RATES FOR NATURALLY OCCURRING U AND TH SERIES

77. From the available data on natural radio-activity in humans, the average skeletal content of Ra^{226} , Ra^{228} and Pb^{210} , each in various states of equilibrium with its daughter products, has been chosen as 60 $\mu\mu\text{c}$, 40 $\mu\mu\text{c}$ and 200 $\mu\mu\text{c}$ respectively (paras. 74-76). The range of values for individuals is extremely large, e.g. for Ra^{226} it may be higher or lower than the average value by a factor of at least 25 (table XVI). However, for a population in a given small area, the range is likely to be much smaller.

78. The dose-rate to bone due to the naturally occurring uranium and thorium series is mainly due to the alpha-emitting components, and hence the irradiation pattern is extremely variable and depends on the size of the particular tissues being considered, their relation to the radio-active deposit and the ranges of the alpha particles. Spiers¹³⁰ has calculated the dose-rates to the osteocytes, the connective tissue lining the walls of the Haversian canal and the bone marrow originating from the Ra^{226} and Ra^{228} content of bone on the assumption that 35 per cent of the Rn^{222} and Rn^{220} formed is retained in

the bone. The results for the average Ra^{226} and Ra^{228} contents, suggested in paragraph 77 and assuming 35 per cent and 100 per cent equilibrium respectively, are given in table XIX. Also included in the table are the estimated dose-rates to the same tissues resulting from a skeletal Pb^{210} content of 200 $\mu\mu\text{c}$ (50 per cent equilibrium). The average dose-rates to the body tissues other than bone, assuming that the Ra^{226} , Ra^{228} and Pb^{210} activity is uniformly distributed and that the activity levels are 25 per cent of the values assumed for the skeleton of an average individual, are about 0.5, 0.8 and 0.3 mrem/y respectively from each of the above radio-isotopes.¹³⁰

POTASSIUM-40

79. *In vivo* measurements of total body potassium content have been made by a number of workers. The results of measurements by Anderson *et al.*¹³¹ for 1,590 males and females as a function of age of the subject are given in figure 4. The concentrations vary considerably with age, and above an age of twelve years, a sex difference appears. Beyond twenty years of age, the percentage content in both males and females decreases in a similar manner but the male level is about 20 per cent higher than the female.

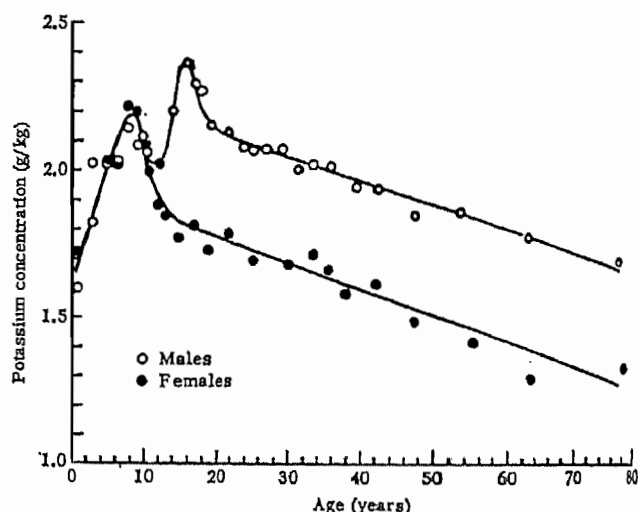


Figure 4. Average body potassium concentration of males and females as a function of age of subject

80. The potassium content of the various body organs varies considerably from about 0.05 to about 0.31 per cent, and the average for the whole body is about 0.2 per cent.¹³² There is evidence that the potassium content of gonadal tissue is close to 0.20 per cent by weight, and using this figure, Rundo¹³³ estimates that the dose-rate to the testes is 17 and 2 mrem per year from the β - and γ -radiation respectively. This is in good agreement with the values of 16.5 and 2.3 mrem/y given in the 1958 report of the Committee and 18 and 2 mrem/y by Spiers.²¹

81. In trabecular bone, Spiers⁵³ quotes the potassium content as being between a value of 0.05 per cent for mineral bone and a value near to 0.2 per cent for bone-marrow, and gives the mean dose-rate as 15 mrem per year.

CARBON-14

82. The tissue dose rate due to natural C^{14} has been given as 1.0 mrem/y,⁶² 1.5 mrem/y¹³⁴ and 1.6 mrem/y,¹³⁵ the difference between these values being essentially due to the values assumed for the specific disintegration rate

of natural C^{14} and the average beta energy per C^{14} disintegration. Taking 14 dpm/g carbon as the specific disintegration rate (para. 51), 50 keV as the average C^{14} beta energy¹⁸⁸⁻¹⁸⁸ 18 per cent¹ as the average carbon content of the whole body of 70 kg weight, RBE equal to 1, then the average dose throughout the human body due to natural C^{14} is 1.06 mrem/y. The corresponding average dose-rate to soft tissue, with a carbon content of 12 per cent,¹⁸⁹ is 0.71 mrem/y, and to bone, with a carbon content of 27.8 per cent,¹⁸⁹ is 1.64 mrem/y.

83. Owing to the Suess Effect (F I 68) the dose reduction during the period 1850-1954 was approximately one mrem (about 0.01 mrem/y). If the use of fossil fuels up to year 2000 is as has been estimated,¹⁴⁰ the Suess Effect will then be nearly 10 per cent and the dose reduction over the period 1850-2000 would be approximately four mrem.

TRITIUM

84. The natural level of tritium in water in the middle latitude regions prior to the introduction of tritium due to weapon testing was of the order of 0.005-0.02 $\mu\mu\text{C/g H}$.¹⁴¹⁻¹⁴⁴ Assuming soft tissue to be 100 per cent water, and that the average energy of tritium beta rays is 6 keV, this implies an average dose-rate to soft tissue of about 0.003 mrem/y (RBE = 1.7) or 0.006 mrem/y if an RBE of 3 is used (para. 3).⁶

VII. High natural radiation areas

85. In a small number of areas the dose-rate from natural background radiation is considerably higher than that experienced by populations in the major portion of the world. This high radiation background is due to the presence of larger than normal amounts of naturally occurring radio-active materials in the soil, drinking water, air, building materials, etc., and also to the cosmic ray altitude effect (paras. 13 and 14). It is considered¹⁴⁵ that studies of the populations in these areas are likely to contribute to the fund of biological knowledge and the ultimate specification of the genetic risks accruing from increasing exposure to ionizing radiation. This type of study is one of the few ways of studying the effects of ionizing radiation on human hereditary material.

HIGH NATURAL RADIO-ACTIVITY IN THE EARTH'S CRUST

86. There are five known major inhabited areas where there is increased radiation from soil or rock—these are in Brazil, France, India, Niue Island and the United Arab Republic. Data on the size, population and dose-rates of these areas are given in table XX.

87. The Kerala radiation measurements¹⁴⁶ were made inside three main types of houses in ten villages in the area. The results did not show any clear relation between radiation levels and structural differences in these houses. The average gamma dose-rates in the villages included in the survey revealed a twenty-fold variation (131-2,814 mrad/y), and the average value of 1,300 mrad/y is obtained by weighting values for each village according to its population.

88. There also exists the possibility of an additional significant radiation dose to the populations in these areas due to internal deposition of radio-active material. No published material on this aspect is available at present.

89. Certain natural springs have a very high natural radio-activity content and some of these are listed in table VII. However, these springs are not generally used as a permanent source of drinking water and so do not

represent a continuous source of radiation exposure to large populations.

90. In those areas where the drinking water is of higher than normal activity, the populations are receiving additional radiation exposure and may be of interest for study of possible biological effects. One such area where a detailed survey is currently being made is in the Middle West region of the United States. Some of the drinking water in this area originates from wells which penetrate the deep sandstone formations and the water has concentrations up to 37 $\mu\mu\text{C Ra}^{226}/\text{l}$. Results reported so far¹⁴⁷ indicate that drinking water containing more than 1 $\mu\mu\text{C Ra}^{226}/\text{l}$ is consumed by approximately 800,000 people, of whom about one half consume water containing more than 4 $\mu\mu\text{C Ra}^{226}/\text{l}$. Of these, about 30,000 people consume water with activity in the range 10-37 $\mu\mu\text{C Ra}^{226}/\text{l}$. The resulting range of Ra^{226} skeletal burdens⁶⁴ in people who have been consuming this water for long periods of time is given in table XVI.

HIGH NATURAL RADIO-ACTIVITY IN THE AIR

91. The Rn^{222} and Rn^{220} content of air will generally be higher in areas of higher than normal natural radio-activity. For instance, the average Rn^{222} concentration at Bad Gastein,¹⁴⁸ which is situated in a deep valley containing many radio-active springs, is about 1 $\mu\mu\text{C}/\text{l}$ compared with the average value of about 0.1 $\mu\mu\text{C}/\text{l}$ for the European continent. Also, concentrations in confined volumes such as buildings will be considerably higher if ventilation is poor or absent. Under certain meteorological conditions, e.g., during fog, the natural radio-activity concentration in the air may increase by several factors of ten.

HIGH NATURAL RADIO-ACTIVITY IN BUILDINGS

92. Aside from high radiation in buildings due to the increased Rn^{222} and Rn^{220} content of the air (para. 91), dose-rates may be increased owing to the high natural radio-activity of the construction materials. Granite and light-weight concrete containing alum shale are common building materials which often result in particularly high radiation levels inside buildings, as can be seen from the dose-rates given in table V.

HIGH ALTITUDE AREAS

93. As discussed in paragraphs 13 and 14, the cosmic ray intensity increases markedly with altitude. This raises the possibility of study of populations living at altitudes of the order of 3,000 metres where the total cosmic ray dose-rate due to the neutron and ionizing components may be of the order of 50-150 mrem/y. Table XXI gives some of the high altitude areas in the world along with their altitude, latitude, population¹⁴⁹ and cosmic ray contribution to tissue dose-rate estimated on the basis of the figures given in table I.

VIII. Summary of exposure data

94. The mean gonad and skeletal dose-rates from natural sources of irradiation under "normal" conditions are given in table XXII. (For information on high natural radiation areas, reference should be made to section VII above.) The suggested typical value for the total cosmic radiation tissue dose-rate, 50 mrem/y, is the value at sea level for middle latitudes (para. 8 and table I). The terrestrial gamma-radiation results from the gamma activities present in the soil, buildings and air, and the average tissue dose-rate of 50 mrem/y takes into account absorption of radiation by the outer tissues

and also the relative time spent indoors and outdoors. Internal irradiation of man arising from the presence in the body organs of naturally occurring radio-active nuclides— K^{40} , C^{14} , H^3 and various decay products of the uranium and thorium series—is extremely dependent on geometrical considerations and average dose-rates in various tissues are given in table XXII. The dose-rate to the lungs due to the natural radio-activity content of the air is not presented in table XXII but, as mentioned in paragraph 42 above, this dose-rate is higher than that to any other body tissue. The dose-rates due to H^3 are very small in comparison with those due to the radio-nuclides given.

95. The total dose-rates in the body tissues given in table XXII may be considerably in error owing to uncertainties of the individual components. These uncertainties are discussed in the text of the present annex, and it is anticipated that more truly representative values will become apparent as further investigations are made. It is felt that where a representative value for the natural background dose-rate to individuals in "normal"

areas is required, the best value which can be recommended at the present time is about 130 mrem/y.

TABLE I. VARIATION OF TOTAL COSMIC RAY CONTRIBUTION TO TISSUE DOSE-RATE WITH ALTITUDE AND LATITUDE

Altitude (km)	Total cosmic radiation tissue dose rate in mrem/y*		
	Equator**	30°**	50°**
0.....	35	40	50
1.....	60	70	90
2.....	100	130	170
3.....	170	220	300
4.....	260	360	500
5.....	400	580	800
10.....	1,400	2,300	4,500
15.....	3,000	5,000	11,000
20.....	3,500	6,000	14,000

* See annex A for RBE values used.

** Distinction between geographical and geomagnetic latitudes is not justified.

TABLE II. PHYSICAL DATA FOR RADIATION FROM CERTAIN NATURALLY OCCURRING RADIO-ACTIVE NUCLIDES¹⁴⁸

Nuclide		Radio-active half-life	Particle energies in MeV and percentages where known*	γ energies in MeV and percentages where known*
Symbol	Common name			
H^3	Tritium	12.26 y	β^- 0.0186(100)	No γ **
Be^7	Beryllium-7	53 d	EC	0.477(12)
C^{14}	Carbon-14	5,760 y	β^- 0.165(100)	No γ
Na^{22}	Sodium-22	2.58 y	β^+ 0.54(90)EC(10)	1.28(100)
P^{32}	Phosphorus-32	14.3 d	β^- 1.71	No γ
S^{35}	Sulphur-35	87 d	β^- 0.167	No γ
K^{40}	Potassium-40	1.3×10^8 y	β^- 1.32(89)EC(11)	1.46(11)
Rb^{87}	Rubidium-87	4.8×10^{10} y	β^- 0.27	No γ
La^{138}	Lanthanum-138	1.1×10^{11} y	EC(70), β^- 0.20(30)	1.43(70), 0.81(30)
Sm^{147}	Samarium-147	1.2×10^{11} y	α 2.20	No γ
Lu^{176}	Lutecium-176	2.2×10^{10} y	β^- 0.42(100)	0.31(100), 0.20(100), 0.088(100)
U^{238}	Uranium I	4.51×10^9 y	α 4.19, —, CE, SF	0.048(23)
Th^{234}	Uranium X_1	24.1 d	β^- 0.19(65), 0.10(35)	0.092, 0.063, 0.029
Pa^{234m}	Uranium X_2	1.18 m	β^- 2.31, —(99), IT(1)	0.043, 0.23—1.83
U^{234}	Uranium II	2.50×10^5 y	α 4.77(72), 4.72(28), —, SF	0.053, 0.118
Th^{230}	Ionium	8×10^4 y	α 4.68(76), 4.61(24)	0.068, 0.142—0.254
Ra^{226}	Radium	1,620 y	α 4.78(95), 4.59(4), —	0.187(4), —
Rn^{222}	Radon	3.823 d	α 5.49(99+), 4.98(0.08), 4.83	0.51(0.08).
Po^{218}	Radium A	3.05 m	α 6.00(99+) β^- (0.02)	No γ
Pb^{214}	Radium B	26.8 m	β^- 1.03(6), —	0.352, 0.295, 0.053—0.259
Bi^{214}	Radium C	19.7 m	β^- 3.18, —(99+) α 5.51, —(0.04)	0.61, 1.12, 1.76, 0.45—2.43
Po^{214}	Radium C'	1.6×10^{-4} s	α 7.68	No γ
Pb^{210}	Radium D	20 y	β^- 0.017(85), 0.063(15)	0.046(15)
Bi^{210m}	Radium E	5.0 d	β^- 1.16(99+) α (0.02)	No γ
Po^{210}	Radium F	138.4 d	α 5.30, —	0.80(0.001)
Th^{232}	Thorium	1.41×10^{10} y	α 4.01(76), 3.95(24)	0.059(24)
Ra^{228}	Mesothorium I	6.7 y	β^- < 0.02	No γ
Ac^{228}	Mesothorium II	6.13 h	β^- 1.11(53), 0.45—2.18	0.057, 0.10, 0.91, 0.078—1.64
Th^{228}	Radiothorium	1.91 y	α 5.42(71), 5.34(28), —	0.084, 0.212, 0.137, 0.169
Ra^{224}	Thorium X	3.64 d	α 5.68(95), 5.44(5)	0.241(5)
Rn^{220}	Thoron	55 s	α 6.28(99+), 5.74(0.3)	0.54(0.3)
Po^{216}	Thorium A	0.16 s	α 6.78	No γ
Pb^{212}	Thorium B	10.64 h	β^- 0.34(84), 0.58(12), —	0.239(84), 0.30, 0.115—0.41
Bi^{212}	Thorium C	60.5 m	β^- 2.25, —(64), α 6.09, —(36)	0.040(25), 0.73(6), 1.62, 0.124—22
Po^{212}	Thorium C'	3×10^{-7} s	α 8.78	No γ
Tl^{208}	Thorium C''	3.1 m	β^- 1.80(47), 1.0—2.38	2.61(100), 0.58(77), 0.51(30), 0.040—1.09
U^{235}	Uranium-235	7.1×10^8 y	α 4.18—4.56, SF	0.185(55), 0.143(12), 0.095(9), 0.074—0.38
Np^{237}	Neptunium-237	2.2×10^6 y	α 4.52—4.87	0.087(14), 0.029(14), 0.057—0.200
Pu^{239}	Plutonium-239	24,300 y	α 5.15(72), 5.13(17), 5.10(11), —, SF	0.013(17), 0.051, 0.038—0.42(< 0.001)

* Beta and gamma energies (MeV) are limited to four plus a range, given in order of decreasing intensity. When known, the percentage of disintegration (intensity) giving a particular energy appears in parenthesis following the energy. The dash between two energies indicates that there are three or more radiations in that range of lesser intensities than those already given. A dash following several energies indicates additional energies of lesser intensity. Percentages applied to gamma energies are transition

intensities rather than photon intensities; they also include conversion-electron intensities.

** "No γ " means that gammas have been searched for but not found (excepting perhaps X-rays from electron capture).

CE = conversion electron.

EC = electron capture.

IT = isomeric transition.

SF = spontaneous fission.

TABLE III. U^{238} , Th^{232} , Ra^{226} AND K^{40} CONTENTS IN $\mu\mu\text{C/g}$ IN VARIOUS ROCKS (MEAN VALUES)

Type of rock	U^{238}	Th^{232}	Ra^{226}	K^{40}	Reference
Igneous rocks.....	0.5				38
	1.4	1.3	1.3	22	150
		3.5	3.7	25	151
		2.3	3.1	29	41
Granites.....				30	57
	1.4		2.6		152
	3	13			153
		1.0	1.1	11	154
Basalts.....				8	41
			0.5		57
Volcanic rocks:					153
Basic lavas.....	0.9	~ 3			
Acidic lavas.....	5	~ 15			155
Sedimentary rocks.....			0.25		153
Sandstones.....	0.4	0.7	0.7	9	150
Sandstones.....			0.3		41
Limestone.....	0.5	0.15	0.4	2.3	150
Limestone.....		0.1	0.7	2.5	41
Limestone.....			1	2.5	42
Alum shales, Sweden.....		0.1	60		41
Alum shales, Sweden.....		0.17	60	29	42
Shales.....	0.5	0.14	0.4	2.3	150
Bituminous shale, U.S.A.....	22				152
Phosphate rocks, Florida.....	40				152
Phosphate rocks, Nauru.....	20	0.8			156
Phosphate rocks, N. Africa.....	4	1.0			153
Phosphate rocks, N. Africa.....	8				57

TABLE IV. MEASURED TERRESTRIAL GAMMA DOSE-RATES OUT OF DOORS IN VARIOUS COUNTRIES

Country	Dose rate in air mrad/y	Comment	Reference
Austria.....	47-56		157
France.....	45-90	Limestone	
	180-350	Granites and shales	158
Japan.....	23-37	Kanto loam	159
	79-119	Granite areas	159
Sweden*.....	70-100	Stockholm street	160
	60-120	Igneous rocks	160
	50	Clay	160
UK.....	18-61	Sedimentary rock or clay	53
	77-155	Granite areas	53
USA*.....	45-130	Measurements in 23 States	161

* Values obtained by subtraction of an experimentally determined value of 28 mrad/y to allow for cosmic radiation at sea level and appropriately larger quantities at various altitudes.

TABLE V. MEASURED TERRESTRIAL GAMMA DOSE-RATES IN AIR INSIDE BUILDINGS IN VARIOUS COUNTRIES

Country	Dose rate in air mrad/y	Comment	Reference
Austria.....	47-56	Wooden house	157
	65-75	Brick or concrete	157
	75-112	Granite	157
Japan.....	48-68	Concrete	162
	29-41	Wooden (Tokyo)	159
	80-100	Wooden (Kyoto)	159
Sweden*.....	48-57	Wooden	42
	99-112	Brick	42
	158-202	Light weight concrete (containing alum shale)	42
UK.....	85-300	Granite	163
	32-57	Other than granite	163
USA.....	29-90	17 houses in New York area	161

* Values obtained by subtraction of 28 mrad/y to allow for cosmic radiation (but this correction is probably too large in the case of multistorey buildings).

TABLE VI. MEAN DOSE-RATES FROM TERRESTRIAL GAMMA-RADIATION ONLY
IN FOUR LOCALITIES IN UNITED KINGDOM⁵³

Locality	Mean dose-rate in air mrad/y		Mean dose-rate in human tissues mrad/y	
	Out of doors	In houses	Gonads	Bone-marrow
Edinburgh.....	48.5	60.0	36	37
Dundee.....	63.0	67.2	42	43
Aberdeenshire.....	69.5	81.5	50	51
Aberdeen.....	104.0	85.3	57	58

TABLE VII. NATURALLY OCCURRING RADIO-ACTIVITY IN PUBLIC WATER SUPPLIES

Water source	Ra ²²⁶ concentration $\mu\text{C}/\text{l}$	Rn ²²² concentration $\mu\text{C}/\text{l}$	Reference
Austria Bad Gastein.....	0.6		167
Germany, 7 cities.....	0.03-0.3	Up to 220	62
Sweden, 2 cities.....	0.2-1		169
UK, ground and surface water.....	Up to 0.7	Up to 200	61
Cornish waters.....	Up to 2.4	Up to 3,000	61
Devon waters.....		Up to 13,000	170
USA, tap water for 41 cities.....	Up to 0.2 (average 0.04)		171
Deep sandstone well, Ill.*...	Up to 37		172
Surface water, Ill.....	< 0.2		56
USSR, freshwater (mean).....	1		173

* See section VII.

TABLE VIII. NATURALLY OCCURRING RADIO-ACTIVITY OF NATURAL WATERS AND SPRINGS

Water source	U ²³⁸ concentration $\mu\text{C}/\text{l}$	Ra ²²⁶ concentration $\mu\text{C}/\text{l}$	Rn ²²² concentration $\mu\text{C}/\text{l}$	Reference
Germany, river water.....		0.07-0.8		62
UK, river water.....		0.01	0.2-0.3	164
USA, river water.....	0.005-0.01	0.03 (1-3) ²¹		57
Lake water.....	1.7			57
Ground water.....	Up to 40	Up to 22		165
Austria, springs.....	Up to 4		Up to 10 ⁵	166, 167
France, springs.....		Up to 139	Up to 10 ⁶	158
Germany, springs.....		0.07-18	Up to 10 ³	62
Japan, springs.....	Up to 0.3 ⁵⁷		Up to 7 \times 10 ⁴	153
Lebanon, springs.....			Up to 6 \times 10 ³	39
UK, springs.....		Up to 12	Up to 7 \times 10 ³	61
USA, springs.....			Up to 3 \times 10 ⁵	153
USSR, springs and brooks.....	Up to 3			168

TABLE IX. CONCENTRATIONS OF Rn²²² AND Rn²²⁰ IN FREE AIR
AT GROUND LEVEL IN VARIOUS REGIONS

Average concentration in $\mu\text{C}/\text{l}$

Country	Rn ²²² (radon)	Rn ²²⁰ (thoron)	Reference
Austria.....	0.1-0.3		157
Czechoslovakia.....	0.03	0.002	69
France.....	0.2	0.006	158
Holland (Amsterdam).....	0.13		174
Sweden.....	0.1		42
UK.....	0.3		53
USA.....	Up to 3 (smog conditions)		175
		0.004	175
USSR.....	0.005-0.5	0.05	173

TABLE X. AVERAGE CONCENTRATIONS OF Rn^{222} AND Rn^{220} IN AIR OF VENTILATED AND UNVENTILATED SWEDISH APARTMENTS AND THE CORRESPONDING CALCULATED AVERAGE DOSE RATES TO LUNGS⁴²

Outer wall construction	Average concentration in $\mu\text{Ci}/\text{l}$				Average dose rate to lungs in mrem/y			
	Rn^{222}		Rn^{220}		Rn^{222}		Rn^{220}	
	A*	B**	A*	B**	A*	B**	A*	B**
Wood.....	0.527	0.537	0.0278	0.136	263	73	185	52
Brick.....	0.909	0.913	0.0910	0.450	453	128	582	173
Light weight concrete (containing alum shale).....	1.86	1.86	0.0959	0.461	930	262	640	178

* Condition A: Assuming equilibrium.

** Condition B: High ventilation rate, 10^{-3} sec.⁻¹.

TABLE XI. AVERAGE Rn^{222} CONTENT INDOORS AT VARIOUS LOCALITIES⁴²

Country and locale	Average Rn concentration $\mu\text{Ci}/\text{l}$	Country and locale	Average Rn concentration $\mu\text{Ci}/\text{l}$
Canada, laboratory.....	0.05-3	Brick apartments.....	0.9
UK.....	0.08	Concrete apartments.....	1.9
		USA, laboratory.....	0.9-1.0
		USA, laboratory.....	<0.1
Sweden: Wooden apartments.....	0.5	USA, laboratory.....	0.13

TABLE XII. AVERAGE CONCENTRATION OF Pb^{210} , Bi^{210m} AND Po^{210} IN AIR AT GROUND LEVEL IN VARIOUS REGIONS

Region	Rn^{222} daughter product	Average concentration in air $\mu\text{Ci}/\text{l}$	Reference	Region	Rn^{222} daughter product	Average concentration in air $\mu\text{Ci}/\text{l}$	Reference
UK.....	Pb^{210}	3×10^{-8}	176	USSR.....	Bi^{210m}	4×10^{-8}	173
USA.....	Pb^{210}	10^{-8}	70	UK.....	Po^{210}	0.4×10^{-8}	176
USSR.....	Pb^{210}	5×10^{-8}	173				

TABLE XIII. RADIUM-226 IN FOODSTUFFS (μCi Ra^{226} PER KG ORIGINAL MATERIAL)

Food type	New York City		Chicago		San Francisco	
	Survey 2 June 1960	Survey 3 Oct. 1960	Survey 1 May 1960	Survey 2 Sept. 1960	Survey 2 Aug. 1960	Survey 3 Jan. 1961
Whole wheat bread.....	3.2	1.2	3.5	2.9	2.8**	2.8
White bread.....	3.2	1.5	3.3	2.0	2.9	2.5
Flour—white.....	2.7	1.7	2.4	2.0	1.34	0.83
Milk—liquid.....	0.25	0.24	0.24	0.22	0.22	0.2
Potatoes.....	2.0	2.5	1.4	0.77	1.0*	2.0
Macaroni.....	2.1	1.8	1.6	1.9	1.2	1.7
Dried beans.....	6.1	3.2	7.0*	2.5	2.3	4.1
Canned vegetables.....	2.2	0.54	1.8	1.1	0.91	1.0
Fresh vegetables.....	2.4	1.2	2.2	0.57	0.66	0.84
Root vegetables.....	3.4	2.3	2.0*	1.8	2.6*	2.4
Canned fruit.....	0.37	0.37	1.2	0.26	0.5	0.73
Fruit juices.....	1.6	0.49	0.68	0.86	0.71	0.62
Fresh fruit.....	1.5	2.8	1.4	0.57	0.91	0.65
Rice.....	1.5	1.0	0.7	0.37	0.63	0.8
Eggs.....	4.1	7.9	2.7	2.7**	2.6	1.9
Fresh fish.....	1.2	0.68	0.71	1.0	0.8	1.2
Shellfish.....	1.2	1.1	2.5	1.7	2.0	1.0
Meat.....	0.44	0.47	0.45	0.64	0.81	0.55
Poultry.....	0.73	0.86	0.79	1.4	1.9	0.49

* Data corrected by barium recovery as well as strontium recovery.

** Missing sample. Paired value used for computing sums.

TABLE XIV. Ra^{226} CONTENT OF VARIOUS FOODS IN GERMANY⁶²

Food	$\mu\text{Ci}/\text{kg}$ food	food	$\mu\text{Ci}/\text{kg}$ food
Bread.....	2.6	Carrots	1.6, 1.7, 6.1
White bread.....	1.7, 3.3	Apples	0.9
Wheat flour.....	2.7	Eggs	3.1
Milk.....	0.3	Fish	2.8, 4.0, 4.0, 6.3
Potatoes.....	0.6, 1.0	Pork, beef	0.8, 1.5, 0.8, 0.8
Cabbage.....	1.0, 2.4	Tap water	0.03-0.34 (av 0.19)

TABLE XV. Ra^{226} CONTENT OF VARIOUS FOODS IN UNITED KINGDOM¹⁰⁸

Food	$\mu\text{C/kg food}$	Food	$\mu\text{C/kg food}$
Cereal.....	25, 62, 68	Fresh fish (plaice).....	1.5
Tinned pears.....	1.1	Cockles and mussels.....	18.2, 5.7
Egg.....	2.0	Veal, Sausage.....	0.9, 2.0

TABLE XVI. TOTAL BODY Ra^{226} CONTENTS

Sampling locality	Number of bodies	Concentration Ra^{226} in tap water $\mu\text{C/l}$	Ra^{226} body content μC		Type of sample	Reference
			Range	Mean		
USA, Rochester, N.Y.....	20*	0.04	38-353	118	Whole body ash	177
USA, Rochester, N.Y.....	14*	0.04	47-130	87	Whole body ash	178
USA, Rochester, N.Y.....	9	0.04	15-65	30	Body organ ash	124
USA, Northwest Pacific area.....	50	0.001	13-139	47	Whole body ash	179
Germany, Frankfurt on Main.....	15	0.14-0.31	130-790	330	Body organ ash	180
Germany, Frankfurt on Main.....	Up to 56	0.2	—	130 (35 in skeleton)	Body organ ash	62
USA, New York.....	140	0.04	3-150	24	Whole skeleton ash	121
Six different countries.....	21	—	—	40	Single bone ash	121
13 different countries.....	499	—	—	33	Bone ash—	
	15 samples				composite sample	121
USA, Prisoners, 4 mo. detention.....	11	3.4	—	100	<i>In vivo</i> , radon in breath	181
USA, Prisoners, 7.6 yr. detention.....	8	3.4	—	202	<i>In vivo</i> , radon in breath	181
USA, Prisoners, 19.7 yr. detention.....	11	3.4	—	236	<i>In vivo</i> , radon in breath	181
USA, Lockport boys.....	8	8	—	368	<i>In vivo</i> , radon in breath	181
USA, Chicago boys.....	7	0.03	—	36	<i>In vivo</i> , radon in breath	181
USA, low activity water.....	42	< 0.1	15-81	36	Single bone ash	54
USA, high activity water.....	34	0.1-10.5	36-1400		Single bone ash	54

* Check series using different methods of measurement.

TABLE XVII. Ra^{226} AND Pb^{210} IN BONES OF SUBJECTS FROM ROCHESTER, N.Y., USA¹²³

	Concentration in ($\mu\text{C/g ash} \pm 90$ per cent confidence level) $\times 10^3$					
	Born in Nebraska, lived in Rochester, ages 1-68		Born in Connecticut, lived in Rochester, ages 14-43		Born in Florida, lived in Rochester, ages 49-52	
	Ra^{226}	Pb^{210}	Ra^{226}	Pb^{210}	Ra^{226}	Pb^{210}
Skull.....	70 \pm 4	201 \pm 15	51 \pm 2	131 \pm 9	32 \pm 3	366 \pm 19
	70 \pm 4	419 \pm 14	100 \pm 7		27 \pm 3	1,330 \pm 21
Tibia.....	12 \pm 3	296 \pm 13	25 \pm 2	90 \pm 9	26 \pm 2	78 \pm 6
Joint.....	16 \pm 1	152 \pm 7	25 \pm 2	83 \pm 8	27 \pm 3	71 \pm 7
Jaw.....	12 \pm 1	93 \pm 5	28 \pm 2	49 \pm 4	30 \pm 3	77 \pm 6
Teeth.....	19 \pm 3	18 \pm 4				

TABLE XVIII. Ra^{226} CONTENT OF BONE AND MUSCLE

Tissue	Number of samples	Ra^{226} content/g ash ($\times 10^{-3} \mu\text{C}$)	Ra^{226} content/g wet tissue ($\times 10^{-3} \mu\text{C}$)
Vertebrae ¹²⁴	10	10.7	3.4
Clavicle ¹²⁴	10	9.2	1.1
Skeletal muscle ¹²⁴	10	5	0.05
Tibia shaft ⁶²	56	12	5.4
Femur ⁶²	37	11	4.8
Muscles ⁶²	12	245	2.5
Bone ⁶⁴	3	14.6	—
Muscle ⁶⁴	3	12.2	—

TABLE XIX. MEAN DOSE-RATES (mrem/y, RBE=10) TO VARIOUS TISSUES OF NORMAL HUMANS¹⁸⁰

<i>Body tissues</i>	<i>Skeletal Ra²²⁶ and daughters (60 μuc) (35% equilibrium)</i>	<i>Skeletal Ra²²⁶ and daughters (40 μuc) (equilibrium)</i>	<i>Skeletal Pb²¹⁰ and daughters (200 μuc) (50% equilibrium)</i>
Osteocytes (5 μ diameter)	10	16	6.6
Haversian canal (10 μ lining, 50 μ diameter) . . .	5.4	8.6	3.6
Trabecular marrow	0.6	1.0	0.4

TABLE XX. SPECIAL AREAS OF HIGH EXTERNAL RADIATION TO RADIO-ACTIVITY FROM SOIL OR ROCK

<i>Area</i>	<i>Approximate population</i>	<i>External dose-rate in air (Cosmic plus terrestrial)</i>	<i>Measuring instruments</i>
Monazite area in States of Rio de Janeiro and Espirito Santo, Brazil—sequence of coastal strips, each several km long and several hundred metres wide	30,000	Average 500 mrad/y, peak 1,000 mrad/y ¹⁸²	Ionization chamber scintillation counter
Mineralized volcanic intrusives in States of Minas Gerais and Goias, Brazil—6 km ² in a dozen scattered places	1 village with 350 inhabitants, pasture land and scattered farms	Average 1,600 mrad/y, peak 12,000 mrad/y ¹⁸³	Ionization chamber scintillation counter
Primitive granitic, schistous and sandstone areas of France—area includes about one-sixth of French population	7,000,000	180–350 mrad/y ¹⁸⁸	Geiger counter and scintillation counter (Na. I and plastic phosphor)
Monazite area in Kerala and Madras States, India—approximately 200 km long and several hundred metres wide	100,000	Population weighted mean 1,300 mrad/y plus about 200 mrad/y beta rays ¹⁴⁶	Ionization chamber
Niue Island, Pacific—volcanic soil and unusually high radio-active content of plants	4,500	Maximum external radiation 1,000 mrad/y. High total α-radio-activity content 50–360 μuc/g in the main foodstuff—taro ¹²³	—
Monazite areas of Northern Nile Delta region, UAR	"Highly populated"	300 and 400 mrad/y in 2 villages; 4 other villages in same area 110 to 150 mrad/y ¹⁸⁸	Scintillation counter

TABLE XXI. COSMIC RAY DOSE-RATES IN HIGH ALTITUDE AREAS AND CORRESPONDING POPULATIONS¹⁴⁵

<i>Area</i>	<i>Altitude (metres)</i>	<i>Latitude</i>	<i>Cosmic ray contribution to tissue dose- rate (based on table I) mrem/y</i>	<i>Population</i>
La Paz, Bolivia	3,630	16°S	270	319,600
Quito, Ecuador	2,850	0°	160	212,873
Bogota, Colombia	2,640	4°N	150	325,658
Cerro de Pasco, Peru	4,259	10°S	330	19,187
Lhasa, Himalayan Area	3,684	30°N	310	~20,000

TABLE XXII. BODY TISSUE DOSE-RATES DUE TO EXTERNAL AND INTERNAL IRRADIATION FROM NATURAL SOURCES OF RADIATION IN "NORMAL" REGIONS

Source of irradiation	Dose rate in mrem/y (see paragraphs 2-3 for RBE values)			Reference in text
	Gonad	Haversian canal	Bone marrow	
<i>External irradiation:</i>				
Cosmic rays (including neutrons)...	50	50	50	Paragraph 8, Table I
Terrestrial radiation (including air).	50	50	50	Paragraph 31
<i>Internal irradiation:</i>				
K ⁴⁰	20	15	15	Paragraphs 80-81
Ra ²²⁶ and decay products (35 per cent equilibrium).....	0.5	5.4	0.6	Paragraph 78
Ra ²²⁸ and decay products (equilib- rium).....	0.8	8.6	1.0	Paragraph 78
Pb ²¹⁰ and decay products* (50 per cent equilibrium).....	0.3	3.6	0.4	Paragraph 78
C ¹⁴	0.7	1.6	1.6	Paragraph 82
Rn ²²² (absorbed into bloodstream)..	3	3	3	Paragraph 41
TOTAL.....	125	137	122	

* Pb²¹⁰ in excess of that expected from Ra²²⁶ and decay products in 35 per cent equilibrium.

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ANNEX F
ENVIRONMENTAL CONTAMINATION
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ANNEX F

ENVIRONMENTAL CONTAMINATION

Introduction

and

PART I

Production and transport of nuclear weapon debris

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Introduction

1. The explosion of nuclear weapons results in the release of radio-active debris. In the case of a nuclear explosion in the atmosphere much of this debris will for

some time be found as airborne activity usually aggregated into small particles although some gaseous activity is also present. The airborne activity is gradually de-

posited on the surface of the earth and this deposit is usually referred to as fall-out. Fall-out constitutes the most important source of environmental contamination from nuclear weapons tests. Other sources, e.g. the pollution of the atmosphere by airborne activity and the oceans by water soluble debris will also be discussed in this annex.

2. The first nuclear explosion occurred in 1945. The rate of testing was especially high over the years 1954 to 1958; from November 1958 to August 1961, on the other hand, the rate was extremely low. The environmental contamination arising from this testing is the main subject of study in this annex. Data relating to the large-scale testing after 1 September 1961 are still too incomplete to permit a detailed evaluation of the consequent contamination.

3. The contamination of the environment subjects man to radiation from sources which may be categorized conveniently as follows:

(a) External sources consisting of the accumulated deposit of fall-out on the earth's surface;

(b) Internal sources arising from: (1) the ingestion of certain radio-nuclides which enter readily into food chains and are absorbed by man to a relatively great extent; and (2) the inhalation of airborne particulate material which is deposited in the lungs.

4. The discharge of radio-activity from atomic energy installations, hospitals and other premises, may also cause external and internal irradiation of certain populations. These populations are small and localized compared with those exposed to contamination from nuclear weapons.

5. This annex presents the available data and estimates the present and future levels of the environmental contamination and the doses received. The estimates are subject to considerable uncertainty because of the in-

herent complexity of the subject and the incompleteness of our knowledge of the mechanisms involved and the exact conditions of testing. However, since the previous report of the Committee, much information has been obtained relating to the dissemination and passage of debris from nuclear weapon tests through the biosphere.

6. This annex has been arranged as follows:

I. PRODUCTION AND TRANSPORT OF NUCLEAR WEAPON DEBRIS

This section deals with the production and dissemination of radio-active debris from nuclear weapons, with such measured rates of deposition and total amounts of debris accumulated in the atmosphere and on the earth as are necessary to evaluate the irradiation from external sources and from inhalation, and with estimates of rates and amounts to be expected in the future under specified conditions.

II. TRANSFER OF RADIO-ACTIVE MATERIAL THROUGH FOOD CHAINS INTO THE HUMAN BODY

This section summarizes measured levels of radio-nuclides in food and the human body as well as the present knowledge regarding the mechanisms through which these radio-nuclides are transferred from fall-out deposits to the human body and their possible future concentrations in the body.

III. EXPOSURE DATA

This section evaluates the irradiation of human populations as calculated from the data in the previous sections.

IV. DISPOSAL OF RADIO-ACTIVE WASTES AND ACCIDENTAL RELEASES OF RADIO-ACTIVITY

Both routine and accidental releases are described, including type and amount of wastes, and the ensuing doses to human populations are estimated.

PART I

Production and transport of nuclear weapon debris

I. Production of radio-active debris in nuclear explosions

7. The radio-active components of nuclear weapon debris are mainly produced through the process of fission. Certain heavy nuclei, like those of U^{235} and Pu^{239} , disintegrate (fission) into two lighter nuclei under the influence of neutrons. These fission products are mostly unstable and undergo radio-active decay. During the process of fusion (i.e., the collision and fusing of light nuclei giving a release of energy) used in large-size nuclear weapons, essentially only one radio-active product is released, namely tritium.

8. The fissionable materials themselves are radio-active, as also is tritium, sometimes used in explosives based on nuclear fusion. Not all of these materials are used up in an explosion and they thus will be found in the radio-active debris.

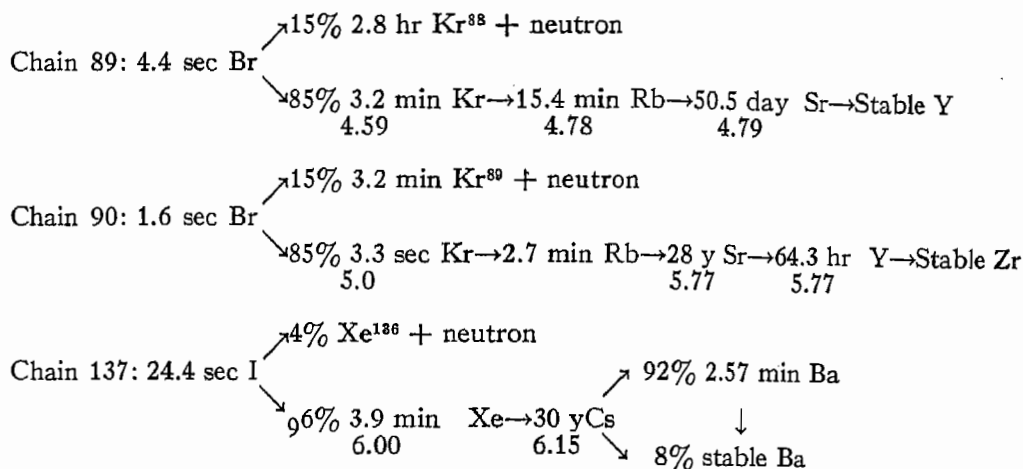
9. An excess of free neutrons is produced in connexion with both fission and fusion reactions. Within a fraction of a second these neutrons are captured either in materials inside the weapon or in the environment of the explosion. In this way a variety of induced radio-active materials are formed.

10. The main contamination of the environment is caused by the radio-active fall-out deposited on the ground. An important characteristic of most fall-out is its particulate nature. These particles are formed when the fire-ball created by a nuclear explosion cools off and the processes and materials involved determine to a large extent the physical and chemical properties of the fall-out.

FISSION PRODUCTS

Production

11. When a heavy nucleus undergoes fission, two new nuclei are usually formed, which in the majority of cases are of unequal mass. This splitting of a heavy nucleus may occur in a number of ways and as a result the fission products formed range in mass from about 70 to 170 atomic mass units. The primary products formed are as a rule unstable and decay to form new nuclides which in turn may be unstable. The fission reaction thus results in the formation of a large number of decay chains,¹ three examples of which are given below for future reference (para. 28):



The half-life of each nuclide is given immediately preceding its symbol. The figure below some of the symbols refers to the fission yield (i.e., the per cent probability per fission of forming the nuclide) in thermal neutron fission of U²³⁵.

12. In most cases the last two or three members of a decay chain are formed mainly from the decay of precursors, i.e., these products have only small independent yields (they are not readily formed as primary fission products). As a consequence the total yield of these late members is close to the chain yield except in those cases where branching occurs, as in chain 137.

13. The yield of any given fission fragment varies considerably according to the nature of the fissionable nucleus and the energy of the neutrons causing the fission.¹⁻⁹ Table I gives numerical values for the fission yields of certain radio-nuclides resulting from the fission of nuclei of various heavy atoms. The table shows, for example, that the fission yield of Sr⁹⁰ varies from 2.2 per cent for Pu²³⁹ to 6.8 for Th²³². Since a combination of different fissionable materials may be used in experimental atomic devices, the actual fission yields are likely to be somewhat different when such devices are exploded. The last two columns in table I give data from measurements on particular examples of weapon debris.⁷⁻⁹ From data like these the production of Sr⁹⁰ and Cs¹³⁷ in past weapon tests has been calculated. Figures of 1.00 Mc Sr⁹⁰ and 1.70 Mc Cs¹³⁷ per 10 megaton of fission energy are usually assumed. Later measurements⁹ indicate values of 1.09 and 1.73 Mc respectively. Individual tests may show fairly large deviations from these values.

Decay characteristics

14. As has been mentioned, the explosion of nuclear devices based on fission of heavy nuclei produces a mixture of nuclides with a wide range of mass numbers. In all, more than 200 nuclides are formed,¹⁰⁻¹⁴ most of them radio-active, having half-lives ranging from less than a second up to many years (in a few cases millions of years, i.e., essentially non-radio-active nuclides). This fission product mixture decays under the emission of beta and gamma rays, the gross activity thus decreasing with time. Since the decay constants of the various nuclides differ widely (figure 1), it is obvious that the variation with time of the mixture's activity cannot be expressed by a simple exponential law. It has been found that the gross decay varies inversely with a power of the time elapsed from the moment of explosion (fission), i.e., according to the empirical law of Way and Wigner¹⁶:

$$A_t = A_1 \cdot t^{-n} \quad (1)$$

where

A_t = activity of the fission-fragment mixture t units of time after the explosion;

A_1 = activity of the same mixture when $t = 1$ unit of time;

n = a parameter which depends on the age of the fission products.

Formula (1) is approximately valid for a mixture of fission products formed in a single explosion. For simultaneous thermal neutron fissions of U²³⁵, for example, the law describes the gross beta decay to within 15 per cent over the time period from one hour to two hundred days if a value $n = 1.15$ is chosen.¹⁴ For the fission products in weapon debris however, much larger deviations are observed, especially for the gross γ -decay.¹⁶⁻²⁰

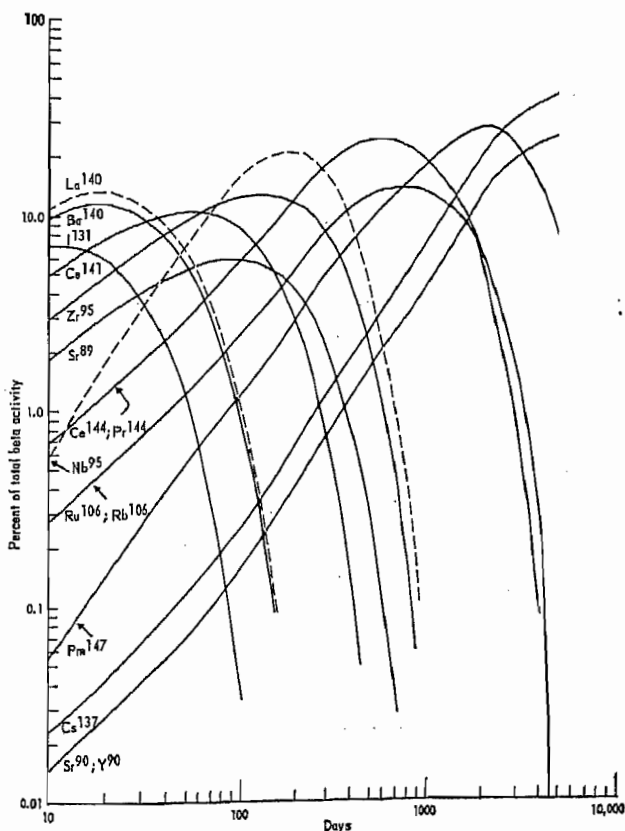


Figure 1. Decay of a fission product mixture

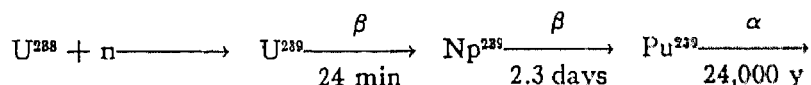
The Way-Wigner law is still useful though, as a simple method of distinguishing nuclear weapon debris from natural radio-activity and as a rough means of estimating the age of fresh debris.

15. The radiation from fission product mixtures has been studied in some detail theoretically^{4, 13, 20-28} and experimentally.²⁹⁻³² It has been found that the γ -spectrum gives a reasonably accurate identification of a fission product mixture, its age and in some cases its mode of origin. The average γ -energy is usually within 0.64 ± 0.10 MeV but the intensity of individual γ -energies may vary to a large extent, for example three years after fission, the total number of gamma quanta per minute from 14 MeV neutron fission of U^{238} is 80 per cent higher than the value from thermal neutron fission of U^{235} . The theoretical ratio of beta to gamma decays is found to be close to 1 for fission products less than one month old, but rises to a maximum of between 3 and 7 three years after fission.⁴

FISSIONABLE MATERIALS AND INDUCED ACTIVITY

General

16. In a nuclear explosion a large number of neutrons



The induced activity of Np^{239} is often found to be of the same order as the gross beta activity of the fission product mixture in fresh weapons debris.^{18, 20, 33} For the same time period, i.e., ten to twenty days after an explosion, it has also been demonstrated³⁴ that another induced activity is present in some debris, namely U^{237} formed through a $(n, 2n)$ reaction in U^{238} in certain weapons. The presence of this nuclide may be taken as an indication of the explosion of a thermo-nuclear weapon.³⁵ Finally, multiple neutron capture may occur in the fissionable materials, giving rise to small amounts of transuranium elements of atomic number as high as 100.^{35, 36}

Tritium

18. Tritium may either be present as such in a weapon or be produced in the explosion by one of the thermo-nuclear reactions involved.^{37, 38} Although the maximum energy of the tritium β -decay is only 18 KeV, the long half-life of 12.5 years and the biological significance of hydrogen makes some consideration of its importance desirable.

Induction in the bomb casing

19. Neutrons captured in the bomb casing and other non-fissile materials in a nuclear weapon induce a number of other activities. Radio-active iron and zinc nuclides have been found in weapon debris³⁹ as have amounts of Mn^{54} , Co^{57} , Co^{58} and Co^{60} .⁴⁰⁻⁴² These substances are of little biological importance in comparison with the fission products. In some weapon tests, sufficient characteristic activities of Rh^{102} and W^{185} have been produced to serve as tracers for the movement of airborne debris.

Induction in the environment

20. The nature of the activity induced in the environment of a nuclear explosion depends on the nature of the environment. In a ground surface explosion, or an explosion at such a low height that the fireball touches the

are released. All of these neutrons are very short-lived, being captured immediately by surrounding nuclei. This property of the neutrons, apart from being essential for the creation of the chain reaction that produces the energy in the explosion, gives rise to various types of induced radio-activity—in the fissionable materials, in the bomb case and in the environment of the explosion. Most of the induced activities are of little biological significance, either because of short half-life or low yield. Those of importance will be treated in detail in the following paragraphs.

Fissionable materials

17. Weapons based on nuclear fission contain materials which are alpha-emitters, e.g. U^{235} , Pu^{239} and U^{238} . Plutonium is the most important among these from the point of view of its possible biological effects. In a weapon in which the fissile material is plutonium, much of this remains unchanged after an explosion. Plutonium may also be produced in a nuclear explosion by the reaction:³³

earth's surface, about 50 per cent of the neutrons may, reach the earth's surface and react with the nuclei of elements in the soil. As a result radio-nuclides of many elements are formed.^{23, 43, 44} They include Si^{31} , Al^{28} and Na^{24} which have short half-lives and also the comparatively long-lived Zn^{65} , Fe^{55} , Fe^{59} and Mn^{54} etc. This neutron capture in mineral substances is predominant in an underground explosion. In the case of an underwater explosion, most of the neutrons will be absorbed by the water and by substances dissolved in it. The major product is inactive H^2 but radio-active isotopes of Na, K, P, Cl, Mg, S and Cd are also formed as well as Zn^{65} etc. mentioned above.^{43, 45} When the explosion occurs high in the atmosphere, practically all the neutrons are absorbed by the nuclei of nitrogen with the formation of the long-lived radio-nuclide C^{14} .

Carbon-14

21. The quantity of C^{14} formed in a nuclear explosion is determined by the number of surplus neutrons entering the atmosphere. The production of C^{14} will depend therefore on the type of nuclear device exploded and also on whether the explosion took place on the surface of the earth or high in the atmosphere. A "surface" test will produce approximately 50 per cent of the C^{14} that would be produced by the same device in the "air" test, because about one half of the escaping neutrons will be captured in the soil or water rather than in the atmosphere. Practically all the neutrons escaping from the exploding nuclear device will produce C^{14} when they are absorbed by the atmosphere.⁴⁶

22. Estimates of the neutron yield per megaton of fission in fission devices have ranged from about 1.5 to 3×10^{26} for various fissionable materials. A value of 2×10^{26} neutrons per megaton has been adopted in this annex. An even wider range of values has been estimated for fusion devices depending on their design. Leipunsky^{37, 47} has found a range of 1.5 to 22 neutrons for an energy release of 180 MeV for different fusion reactions. This may be estimated as $2.2 - 32 \times 10^{26}$ neutrons per

megaton. Libby^{48, 49} suggests a value of 3.2×10^{26} neutrons per megaton of fission and fusion, weighted according to nuclear testing prior to 1958. Machta⁵⁰ gives a figure, based on United States test experience, of 2×10^{26} neutrons per megaton of total (fission and fusion) yield for an air burst and 1×10^{26} neutrons per megaton for a ground burst. These latter values are based on the assumption that equal yields of fission and fusion were employed and are estimated by Machta to have an uncertainty of a factor of 2. For explosions prior to 1959, an assumption that 2×10^{26} atoms of C^{14} are formed per megaton of total yield agrees closely with experimental data on the increase of atmospheric C^{14} .

PHYSICAL PROPERTIES OF SUBSTANCES PRESENT IN THE RADIO-ACTIVE DEBRIS

Atmospheric explosions

23. When a nuclear weapon is exploded, an aerosol of radio-active particles is usually formed. Two processes are involved in this particle formation:⁵¹ the heating of materials brought into the fireball and the condensation of vaporized materials. The relative importance of these two processes varies with the weapon yield and the environment of the explosion. In an atmospheric explosion, i.e., an explosion in the atmosphere at such an altitude that the fireball does not touch the ground, the condensation process is all-important. The contents of the fireball will consist of the vapours of the fissionable elements and their products and of other materials used in building the atomic device. As the fireball cools down, these vapours oxidize and then condense to form tiny, solid aerosol particles.^{52, 53} A prominent constituent of the fireball is often iron vapour, and then many of the particles formed are small, black spheres of magnetite (Fe_3O_4) that are homogeneously radio-active as a result of the incorporation of mainly fission products. The size distribution ranges from 10μ down to 0.01μ , the most probable size perhaps being 0.2μ ⁵⁴ for a kiloton explosion. The specific activity is high, in one case a 4μ particle has been found having an activity of 5×10^{-9} curie 40 days after its formation.⁵⁵

Near surface explosions

24. The situation becomes more complicated in the case of a near surface explosion, i.e., when the fireball intersects the ground or water surface to a small extent (e.g. a tower shot), because large amounts of soil, water or iron are included in the fireball.⁵¹ The same kind of particles present in an air explosion are found, but they are often attached to the surfaces of much larger irregular particles of unaltered soil material, or in the case of a water explosion they have been captured by water to form slurry drops ranging in diameter from about 50 to 250μ . Often, these larger particles have been heated to the melting point and the originally surface-bound radio-activity then distributes more or less homogeneously through the volume of the particle, which is spherical in shape with a diameter of about $\frac{1}{4}$ to 1 mm. The colour of these particles varies from black (iron) to transparent (silicate) with intermediary examples of red or brownish colours (indicating a mixed composition).⁵¹ The specific activity is again high and may range up to the values found in air explosions.^{17, 56-59}

Surface or shallow underground explosions

25. In the case of a surface or shallow underground explosion, i.e., when appreciable crater formation takes

place, huge amounts of soil or water are mixed into the fireball. The particles formed are usually large (up to 2 mm) with an irregular distribution of the radio-activity, sometimes on the surface and sometimes throughout the volume of the particle. The specific activity is lower than in the previous cases.⁶⁰ However, some small (0.1μ) high specific activity particles are also to be found.⁵¹

Other explosion types

26. An underwater explosion in deep water initially creates the same type of particles as those found after an atmospheric explosion. Many of the particles are however soon captured by water to form slurry drops (para. 24). In an underground explosion where the fireball is contained and does not break through to the surface to form a crater, it has hitherto been found that the fireball vapour condenses and mixes with melted ground material which subsequently solidifies. The result for 1-20 kiloton weapons is that 200-500 tons of rock fuse with every kiloton yield of fission products.⁶¹ Some of the gaseous debris does not take part in this process and has occasionally been found to vent to the surface and enter the atmosphere. In a very high altitude explosion it is to be expected that the fireball vapour leaves the point of the explosion too rapidly for appreciable nucleation or particle formation to occur. The weapon debris will therefore be either gaseous or made up of extremely small particles, e.g. clusters of some hundreds of atoms.⁶²

CHEMICAL PROPERTIES OF WEAPON DEBRIS AND FRACTIONATION

Debris solubility

27. The solubility of the debris is very sensitive to the composition of the explosion environment, including the structural materials of the device. Regardless of the weapon yields,⁶³ air explosions produce small particles with high solubility. Solubilities in water of up to 30 per cent and in 0.1 N HCL of close to 100 per cent have been found.¹⁹ Ground surface explosions produce a large fraction which is highly insoluble but also a smaller amount of particles similar to those from an air explosion.¹⁹ Explosions in deep water give particles which are highly soluble (i.e., more than 90 per cent) whether the debris is associated with large amounts of water and falls close in or is more widely dispersed.⁶¹ Shallow water explosions finally give particle solubilities intermediately to these extremes. In general, stratospheric debris is completely soluble and has been shown to be completely available to animals.⁶⁴⁻⁶⁶

Fractionation

28. The process of particle formation takes place in only one or a few seconds after the explosion of a kiloton weapon, and even in a megaton explosion the delay is less than a minute. As has been pointed out earlier (para. 11) some of the fission chains start out with a gaseous or volatile precursor (e.g. isotopes of Kr, I or Xe). Table II shows the percentage of some mass chains that may be in gaseous form during the early period after an explosion.^{47, 68} Substantial fractions of some mass chains are gaseous and this has an important effect⁶⁹ on the distribution of individual nuclides among the aerosol particles that grow out of the supersaturated vapours of the rising cloud. Such distribution differences are referred to as fractionation. This phenomenon is

very complex and not completely understood, although it has been studied both theoretically⁷⁰ and experimentally.^{17, 19, 32, 51, 53, 68, 67-69, 71-73} It is to be expected in general that fractionation would increase with a decrease in either the explosion yield or the height of burst.⁶⁸ Exceptions to this rule have, however, been found.

29. Considering specific radio-nuclides it has been observed⁵³ that the ratio of Sr^{90} to total fission product activity increases with decreasing particle size, and that Sr^{90} associated with large particles is concentrated in a thin surface layer. As a result, all of the Sr^{90} may be water soluble even when appreciable fractions of other radio-nuclides are not. Sr^{90} , I^{131} and Cs^{137} are likely to fractionate even more strongly than Sr^{90} (table II) and this has also been found to be the case.⁶⁸ Correspondingly, nuclides such as Zr^{95} + Nb^{95} concentrate preferentially in large particles of refractory material, e.g. iron oxide or silica.

30. In table II the percentage of some induced radio-nuclides that is in gaseous form is also shown together with the fission products. From the data it is to be expected that U^{235} and Np^{239} will not fractionate, whereas tritium and C^{14} will. This is especially true for C^{14} as it is formed outside the fireball to a large extent. It is also likely that this C^{14} is rapidly converted to CO and CO_2 which will then move upwards with the hot gases from the explosion.

II. Injection and transport of radio-active debris

INTRODUCTION

The atmosphere

31. The structure and characteristics of the earth's atmosphere strongly influence the transport and deposition of injected radio-active debris. Figure 2 gives a very schematic picture of the structure of the atmosphere. In

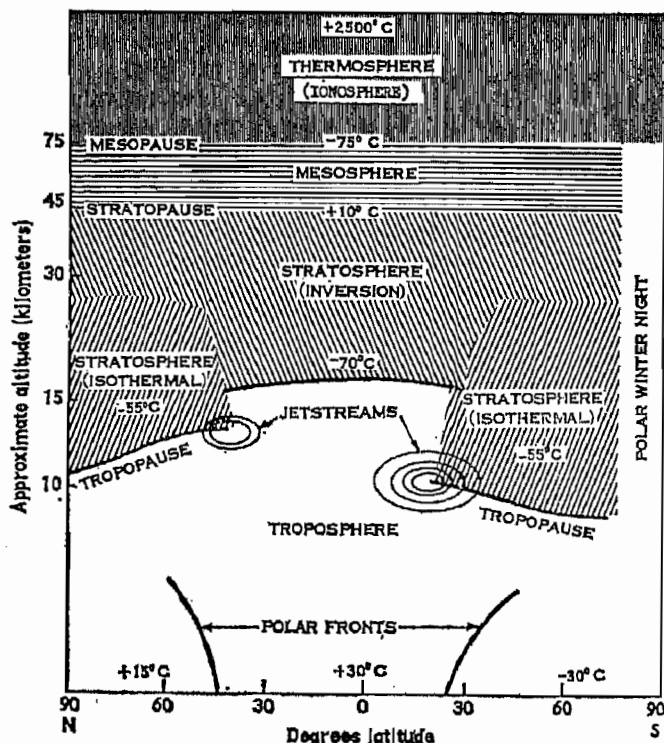


Figure 2. Structure of atmosphere in July

the troposphere, cloud formation, precipitation and turbulent mixing are important phenomena. The stratosphere has a more stable structure because of the temperature distribution. The boundary between troposphere and stratosphere is known as the tropopause and lies at an altitude of about 16 km in equatorial zones and 11 km in temperate and polar regions. There are always two main breaks in the tropopause of each hemisphere (only one break is shown in figure 2), the first one between the polar and middle latitude tropopause and the second between the middle and tropical tropopause. In association with each gap there is a jet stream, a zonal wind of high velocity.

Types of fall-out

32. Particulate radio-active debris injected into the atmosphere is to a large extent deposited on the earth's surface as fall-out. Gaseous debris, e.g. I^{131} , Kr^{85} and C^{14}O_2 may also reach the surface of the earth. Conventionally, three different types of radio-active fall-out are recognized—local (or close-in), tropospheric, and stratospheric:

(a) Local fall-out takes place near the point of explosion and within about one day. It is significant especially in connexion with surface or near-surface bursts;

(b) Radio-active debris that is injected into the troposphere and carried around the world is deposited on the earth's surface as tropospheric fall-out. As long as this activity is airborne (about one month) it is referred to as tropospheric debris;

(c) When debris injected above the tropopause is finally deposited on the ground (which may take one or several years) it is referred to as stratospheric fall-out. Stratospheric debris will naturally be observed in the troposphere some time before it deposits.

33. Gaseous debris usually resides in the atmosphere for a longer time than does particulate debris injected at the same time and place. The atmospheric processes of removal are complex and variable; for instance, I^{131} may reach the ground absorbed on particles, dissolved in precipitation, through gaseous impaction or direct absorption in the pulmonary tract from inhalation of air.

INJECTION OF RADIO-ACTIVE DEBRIS INTO THE ATMOSPHERE

Partitioning

34. The partitioning of the radio-active debris between local, tropospheric and stratospheric fall-out depends upon three factors governing the injection: weapon yield, height of burst, and the meteorological conditions. Figure 3 gives some dimensions of the radio-active cloud as seen about ten minutes after a surface explosion.^{74, 75} The figure shows that the radio-active aerosols from surface explosions with yields greater than 100 kilotons of TNT may rise considerably higher than the tropopause. This becomes true for even smaller weapon yields when the explosion takes place high up in the air, and for an atmospheric explosion above the tropopause of course all the activity is stratospheric.

35. Direct measurements of the partitioning of debris between local, tropospheric and stratospheric fall-out are very few and uncertain. Some values have however been postulated^{40, 40, 70-73} and a summary of these is given in table III.⁷⁰ The data are very approximate in nature. They apply only to the gross activity and not to individual radio-nuclides like Sr^{90} and Cs^{137} which may partition

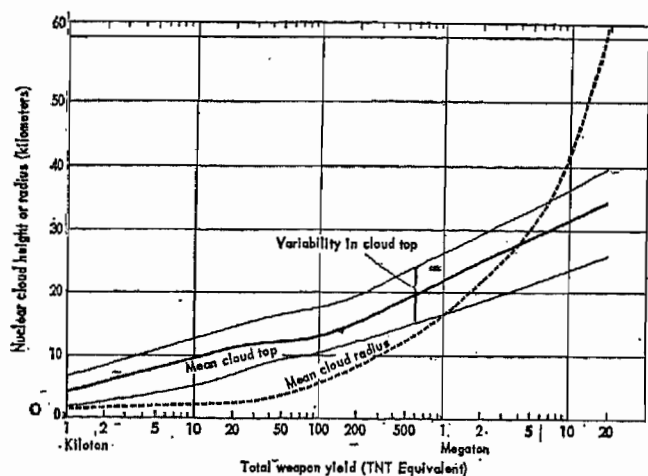


Figure 3. Approximate nuclear cloud dimensions⁷⁵

differently because of fractionation phenomena, giving smaller contributions to the local fall-out in relation to the gross activity. For induced activities, even more extreme conditions may apply. Tritium and C^{14} , for example, contribute a different proportion to the close-in contamination than does activity induced in the soil.

Injection

36. For theoretical predictions of fall-out from nuclear explosions, it is necessary to know the quantity of radio-active products injected into the atmosphere. This quantity is determined not only by the energy yield of an explosion, but also by two quantities dependent on the construction of the nuclear weapon concerned: the fission-fusion ratio which gives the amount of fission products, and the neutron yield per unit of thermonuclear energy which gives the C^{14} production. Such values of these coefficients which have been published are not supported by published experimental and theoretical evidence. Therefore, at present, the Committee's calculations of past injections are based on the measurement of deposition of debris and of inventories of the atmosphere during sufficient periods of time after the explosion. With respect to the explosions produced before 1961, an estimate has been published^{46, 80, 81} of the fission and neutron yields of all the explosions based on postulated values of fission-fusion ratio and neutron yield. This estimate is given in table IV. With the help of coefficients from table III, the stratospheric injection of explosions prior to 1961 is estimated as 68 megaton of fission energy yield, i.e., 6.8 Mc Sr^{90} and the quantity of C^{14} atoms as 24×10^{27} . The amounts of Sr^{90} and C^{14} agree reasonably well with the measured Sr^{90} deposit (table XIV) and in the atmosphere (table XVI) as well as with the amount of C^{14} appearing in the atmosphere (table XVII). This shows that the over-all values of coefficients and energy yield accepted in references^{46, 80, 81} are not in contradiction with experimental figures for Sr^{90} and C^{14} although other combinations are possible. There are estimates of the yield from the 1961 explosions (total energy yield—120 megaton, fission energy yield—25 megaton).^{82, 83} The correctness of this estimate of the stratospheric injection from the 1961 explosions is as yet unknown, as sufficient time has not elapsed to allow measurement and evaluation of the inventory. The principal considerations given at the beginning of this paragraph are applicable to this estimate.

37. At present there are not sufficient data on fall-out from the 1961 tests to make an accurate estimate of the

injection. Based on the limited data available, one approach is to compare the activity levels from the injections of the autumn of 1958 with those of 1961. However, the first months of deposition are not typical of the annual pattern of fall-out because it is expected that the characteristic peak of debris will appear only in the spring of 1962. Only after the measurement of this spring peak at many places of the globe and the evaluations of these results can the 1961 injections be reliably estimated. Data available (as of March 1962) include measurements of deposition of Sr^{90} for three months of 1961 (October, November, December) in Tokyo⁸⁴ and for one month (October) in Abingdon (United Kingdom)⁸⁵ and in four towns of the United States.⁸⁶ Most of these measurements showed that the rate of Sr^{90} deposition in 1961 is less than in the same months of 1958. There are data about the Cs^{137} deposition only in Tokyo in the same months. The rate of Cs^{137} deposition for two months was higher and for one month less than in 1958. Measurements of short-lived activity in air, e.g. in the United Kingdom⁸⁶ and Japan,⁸⁷ showed that levels rose sharply in September 1961 to levels of the same order as in corresponding months in 1958. Notwithstanding the obvious scarcity of data as a basis for long-term extrapolations, the similarity of the character of fall-out levels from the tests in 1958 and 1961 permit an estimate of the 1961 injection as near to the 1958 autumn injection. During 1959, a global integral from monthly collecting sites gave 0.86 Mc Sr^{90} from the autumn tests.⁸⁸ This, combined with an estimate of the corresponding portion of the stratospheric reservoir, gave a total of about 1 Mc Sr^{90} (10 MT fission); a figure in reasonable agreement with injection estimates of 0.6 Mc⁸⁹ and 1.2 Mc.⁴⁶ One might assume that this figure of 1 Mc is an under estimate of the 1961 injection, bearing in mind that fall-out could be distributed over a longer time than was the case after the 1958 injection.

MOVEMENT OF DEBRIS IN THE STRATOSPHERE

General

38. Different theories have been put forward in recent years regarding the mechanisms responsible for the transport of radio-active debris within the stratosphere. It is generally agreed, however, that the factors that are most important comprise advection, diffusion (usually turbulent) and gravitational settling of particles. The first of these processes, the mass movement of air, is the most rapid with wind speeds of even more than 100 km/hr⁹⁰ in the east-west directions. These zonal winds distribute radio-active debris in a latitudinal band of the stratosphere circling the earth within a few days to six weeks after the injection. Vertical movement is not nearly as rapid because of the thermal stability of the stratosphere, and horizontal movement of stratospheric air streams from north to south (and the reverse) is also insignificant in comparison. This will be discussed further in paragraph 42.

Gravitational settling

39. Gravitational settling of debris particles may be important during the first one to two months after an injection but there are indications that it plays a role even for older debris.^{91, 92} One estimate⁹³ shows that at heights of about 20-30 km the fission product activity may be associated with very small aerosol particles of from 0.055-0.095 microns. According to another estimate,⁹⁴ the particle dimensions at these altitudes vary

between 0.02-0.2 microns. Direct measurements⁹⁵ have shown most particles to be less than 0.2 microns and it is thus in general to be expected that the size range should be 0.01-1.0 microns some months after injection.^{96, 97} Below 30 km such small particles settle extremely slowly by the action of gravitational forces and it may therefore be inferred that the particles move mainly with the air masses in which they are suspended.⁷⁶ Above 30 km, on the other hand, settling may occur more rapidly owing, among other things, to the low air density.⁶²

Diffusion

40. With regard to the importance of diffusion as a transfer mechanism of nuclear weapon debris, there seems to be rather firm evidence that the rate of diffusive mixing is smaller in the stratosphere than in the troposphere.^{76, 98}

The stratospheric reservoir

41. Apart from the early time period, when gravitational settling may remove some of the activity, the different processes of removal thus all appear to be rather slow in comparison with the zonal advection. It is therefore generally agreed that radio-active debris injected into the stratosphere may remain there for some time, constituting a reservoir that is only gradually depleted when activity moves down into the troposphere and from there to the surface of the earth. If rapid mixing and constant fractional removal per year is assumed, the rate of depletion may be expressed by giving a half-removal time of the stratosphere, $T_{0.5}$ (the mean residence time T_m is often used alternatively, the relation being $T_m \times \ln 2 = T_{0.5}$). Only data of a very approximate nature^{99, 99} were available for the 1958 report, and it was stated that "the mechanism of transfer from the stratosphere to the troposphere is not completely understood".¹⁰⁰ As no direct measurements of the stratospheric reservoir were available, its size was estimated from the measured rate of fall-out and an assumption of 10 years was made for the mean residence time. This value was recognized as an upper limit (5 years being more probable) and was adopted mainly because it gave a conservative estimate of the size of the reservoir. The situation has improved in subsequent years to a large extent through studies of the atmospheric transport of weapon debris. These studies will be described in the following paragraphs.

The Brewer-Dobson model

42. The first efforts to explain the mechanism of stratospheric transport of radio-active debris were made by Machta¹⁰¹ and Stewart.¹⁰² Their proposal is based on a model originally proposed by Brewer¹⁰³ and Dobson¹⁰⁴ to explain the stratospheric distribution of water vapour and ozone. This model assumes that besides the rapid zonal air movement there is a slower meridional circulation of tropospheric air. This air is heated in the tropical regions and carried up into the stratosphere where at altitudes around 30 km¹⁰⁵ it moves polewards, sinks and re-enters the troposphere in late winter and spring. This model is consistent with such experimental findings about the ground deposition of fall-out as: (a) a seasonal variation of fall-out rate; (b) a maximum fall-out deposition in middle latitudes; (c) a greater deposition in the tropics.^{31, 33, 88, 105, 114-161} Using the nuclear weapon debris injected into the lower polar as compared to the lower tropical stratosphere. Supporting evidence has also been found in measurements of the deposition of naturally produced Be⁷.¹⁰⁶⁻¹⁰⁸

43. Several modifications of the Brewer-Dobson model have been proposed.^{76, 107-113} Clearly the only way of resolving the question of stratospheric transport is through actual measurements in the stratosphere. Many results of such measurements have now been reported.^{31, 33, 88, 105, 114-161} Using the nuclear weapon debris as a tracer it has been possible to map the meridional movement up to altitudes of about 30 km. This information is gathered both through measurements of actual concentrations of such fission products as Sr⁹⁰, Sr⁸⁹, Ce¹⁴⁴ and of induced activities such as C¹⁴, W¹⁸⁵ and Rh¹⁰². Studies of the change with time of the ratio of these activities have also proved useful in evaluating the transport mechanisms. The ratio Sr⁸⁹/Sr⁹⁰ for instance decreases in a known way with time after fission and its measured value is therefore a better indication of the debris age than are data on nuclide concentrations only. In figures 4 and 5 the stratospheric distribution of Sr⁹⁰ and W¹⁸⁵ in the period May-June 1959 and 1960 are shown.¹⁵² It is apparent that the maximum Sr⁹⁰ concentration in 1959 over the equatorial tropopause had vanished in 1960 and there were instead less intense maxima in the polar regions. Although this is consistent with one version¹⁰⁵ of the Brewer-Dobson model, the data on W¹⁸⁵ (figure 5) are not. This nuclide was injected in the tropical stratosphere in 1958 and since then (as of the most recent measurements in June 1960) the maximum concentration has remained stationary over the equatorial region. In addition measurements on Rh¹⁰² show¹⁶² that the polar maxima of Sr⁹⁰ in 1960 were to some extent due to debris injected in 1958 with one explosion at 30 km (this injection was about 3.0 Mc of Rh¹⁰² and the nuclear cloud rose much above 30 km and probably into the mesosphere). This debris has gradually moved downward and poleward. The modified Brewer-Dobson model¹⁰⁵ has therefore met some additional objections

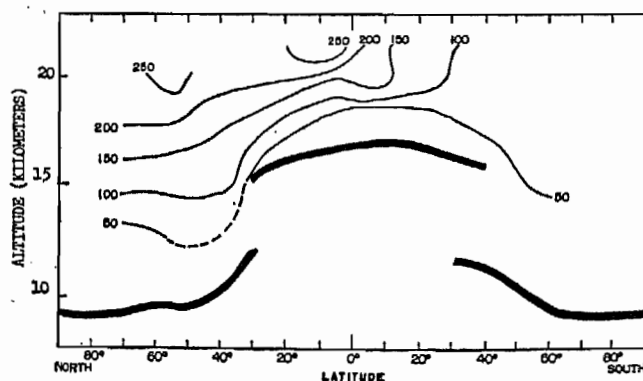


Figure 4a. Stratospheric distribution of Sr⁹⁰ in dpm/10⁸ SCF (= 0.016 $\mu\text{C}/\text{m}^3$) during May-June 1959¹⁵²

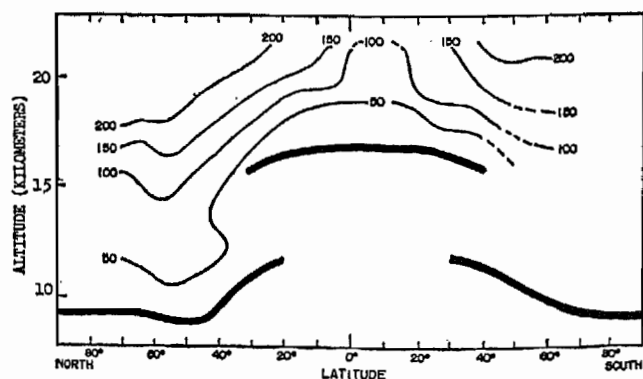


Figure 4b. Stratospheric distribution of Sr⁹⁰ in dpm/10⁸ SCF (= 0.016 $\mu\text{C}/\text{m}^3$) during May-June 1960¹⁵²

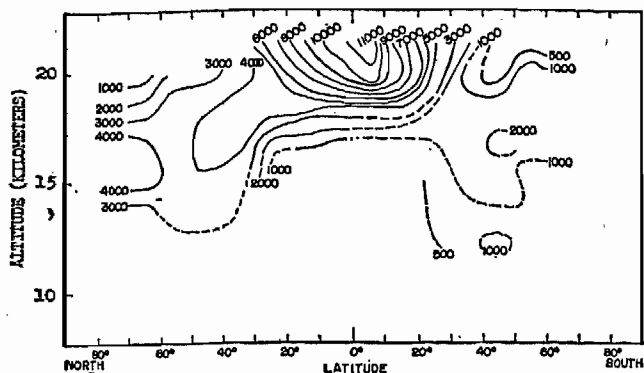


Figure 5a. Stratospheric distribution of W^{185} in $\text{dpm}/10^3 \text{ SCF}$ ($= 0.016 \mu\mu\text{C}/\text{m}^3$) corrected to 15 August 1958, during May-June 1959¹⁵²

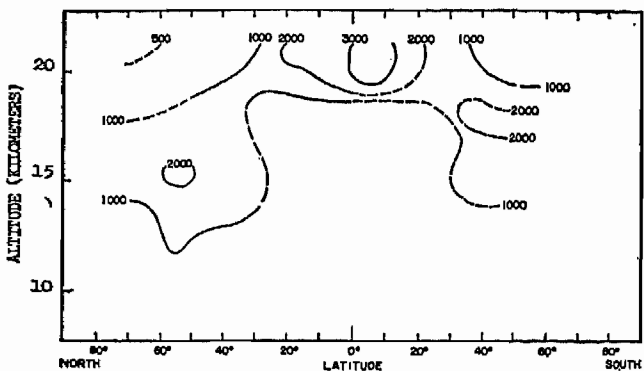


Figure 5b. Stratospheric distribution of W^{185} in $\text{dpm}/10^3 \text{ SCF}$ ($= 0.016 \mu\mu\text{C}/\text{m}^3$) corrected to 15 August 1958, during May-June 1960¹⁵²

as a result of the high altitude samplings. Possibly these and other objections may be overcome through the further modifications suggested by Goldsmith and Brown.¹¹⁸ A basic uncertainty in dealing with this problem is the lack of data from above 30 km altitude.

The Spar-Feely model

44. One difficulty with the unidirectional poleward flow postulated in the Brewer-Dobson model is the finding that although an injection of debris into the tropical stratosphere is noticed after some months in temperate and higher latitudes, there is also a southward movement from polar injections.¹⁵² Evidence of this¹⁵¹ was the collection at 20 km at 30° N on 4 October 1961 of debris from an explosion injected in the polar region some time between 10 and 15 September 1961. The total beta activity was about 40,000 dpm/m^3 and later samples showed even higher concentrations. In order to explain this and other results discussed previously, Spar and Feely^{141, 144, 145} have proposed the existence of a bidirectional, diffusive exchange rather than a unidirectional, mass flow in the stratosphere. Actually two phenomena may be involved in this model, only one of which is diffusion, the second being that the zonal winds are not strictly zonal but show a meandering pattern, the effect being larger in temperate and especially polar latitudes than close to the equator.

Half-removal times

45. Present meteorological evidence is evidently insufficient to permit a definite choice as to what model best represents the characteristics of the stratosphere. However, the measurements referred to have given a better

basis for describing the removal of weapon debris from the stratosphere. There are three parameters that govern the removal of injected debris: altitude, latitude and time of explosion. If the measurements are interpreted in terms of half-removal times these are found to vary also with time after injection, becoming increasingly longer. This is indeed to be expected as the stratosphere is not uniformly mixed and as the rate of removal is seasonal and localized rather than uniform in time and space. The concepts of half-removal time and mean residence time thus have very limited usefulness. A number of estimates of half-removal times have been given in the literature.^{128, 158-165} Some estimates (pertaining to removal of the first half of the injection) have been proposed based on stratospheric measurements.^{146, 152}

	Months
Lower polar stratosphere (autumn injections)	5
Higher polar stratosphere.....	12
Tropical stratosphere up to 20 km.....	10
Tropical stratosphere 20-30 km.....	20
Tropical stratosphere 30-45 km.....	30
Mesosphere above 45 km.....	60

The uncertainty of these figures is great, at least 50 per cent and sometimes maybe 100 per cent. Until there is a more complete understanding of the meteorological factors that influence stratospheric transport of debris the values cited above should be considered tentative and used with caution. It has, for example, been pointed out¹⁵³ that debris injected into the lower, temperate stratosphere may be removed within a matter of hours under exceptional circumstances. The figures for altitudes above 30 km are based only on extrapolations of measured data. Despite these uncertainties it has been said that the upper limit is probably ten years for debris injected anywhere in (or falling on top of) the atmosphere.¹⁵² Similar values are not available for the southern hemisphere, since the northern hemisphere stratosphere acts as a continuing source of debris passing into the southern hemisphere. Two seasonal trends may also be emphasized: the more rapid transport of debris from the tropics into the winter hemisphere than the summer hemisphere and a downward transport of high altitude debris to the vicinity of the polar tropopause in late winter. That much is still unknown about the transport mechanisms at high altitudes can be inferred from the fact that there is only one observation published on the rise of a cloud from a high altitude explosion.¹⁵⁹

46. Although the half-removal time is based on a simplified concept of the mechanism of atmospheric decontamination, some estimate is useful in determining which short-lived fission products may reach the earth's surface before they have fully disintegrated in the stratosphere. The percentage of relatively short-lived radioisotopes (Sr^{89} , Y^{91} , Zr^{95} , Ru^{106} , I^{131} , Ba^{140} , Ce^{141} , Ce^{144}) falling out from the stratosphere onto the earth's surface increases as the stratospheric half-removal time diminishes.

Stratospheric aerosols

47. In connexion with the measurements on stratospheric debris it has been found¹⁵⁷⁻¹⁶⁰ that there exists a natural aerosol layer extending from the tropopause up to about 25 km with a maximum concentration around 20 km of about 1 particle/ cm^3 . The particles are mostly composed of ammonium sulfate or persulfate and have radii in the range from less than 0.1 to 1.5 microns. It has been estimated¹⁶¹ that weapon debris has a coagu-

lation half-life with this natural aerosol at 20 km of 20, 80 and 280 days for particle sizes of 0.005, 0.01 and 0.02 microns. It may thus be that small radio-active particles are incorporated into the natural dust background before they are removed from the stratosphere. This may have some effect on the rate of removal, especially of debris from high-altitude explosions that is of very small particle size. It has also been suggested that the influence of solar radiation on particle transport may be decisive, especially in the early expansion stages of the radio-active cloud.¹⁶² The significance of these two processes can at present not be evaluated from experimental data, however.

TRANSPORT FROM STRATOSPHERE INTO TROPOSPHERE

Transport through the tropopause

48. The characteristics of the tropopause probably play a crucial role in the stratosphere to troposphere transfer of radio-active debris. Danielsen¹⁶³ has made an extensive study of the tropopause concept and demonstrated that it is not that of a "membrane" preventing mass flow of air. Rather, the tropopause should be defined as a surface lying between one high-stability region (the stratosphere where the temperature increases with altitude) and a region with low stability (the troposphere where the temperature decreases with altitude). If isentropic surfaces are calculated from measured data on temperature and pressure, it is found that these surfaces may intersect the tropopause.¹⁶³ This means that mass movement of air is possible across the tropopause, although this may not occur to the extent necessary to explain quantitatively the transport of debris from the stratosphere to the troposphere. However, isentropic air transfer in combination with rapid vertical diffusion may explain the steep gradient of airborne activity concentration immediately above the tropopause (figure 6).¹⁶⁸

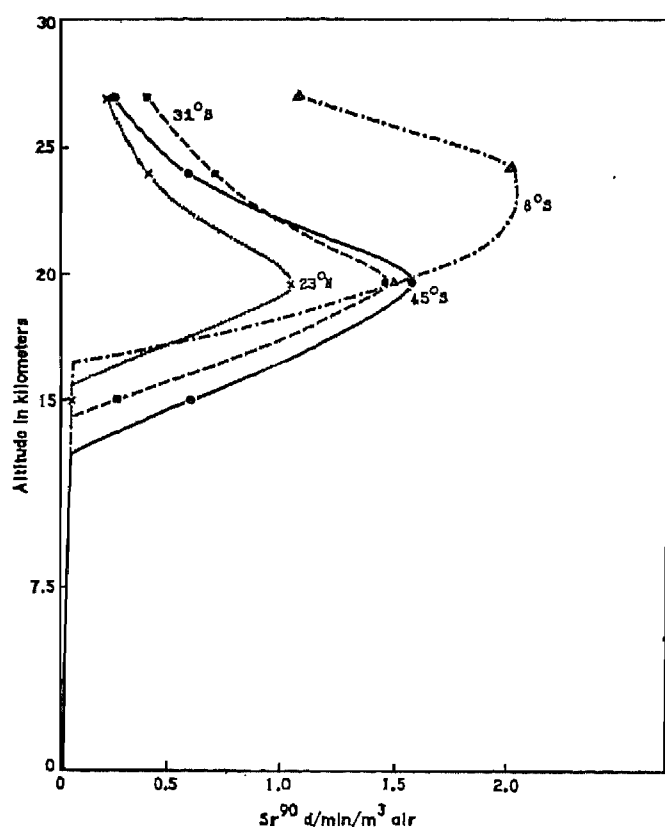


Figure 6. Vertical distribution of Sr^{90} at various latitudes, July 1957-June 1958¹⁶⁸

49. Diffusion across the tropopause may occur but is probably of little importance.¹⁴³ It has been shown¹⁷ that for fresh debris, gravitational settling of 5 micron size particles is faster than diffusion into the troposphere. As the debris gets older, gravitation plays less of a role, although the existence of the natural aerosol layer (para. 47) may still promote some settling of debris.

Tropopause movements

50. There is a seasonal movement of the tropopause (figure 2) that could account for much of the transfer of debris to the troposphere. This movement is noticeable in the temperate latitudes and of particular importance in the polar regions where the tropopause vanishes during arctic and antarctic winters.¹⁶⁴ It is then sometimes noted that the temperature continues to decrease with altitude even above 10 km and turbulent mixing may therefore take place to very high altitudes. In the polar and temperate regions large volumes of the lower stratosphere may thus be incorporated each spring within the troposphere. This trend is reversed in the autumn.

Disturbances of the tropopause

51. Staley¹⁶⁵ has pointed out that in connexion with large-scale atmospheric disturbances in temperate and polar latitudes, vertical air transport may occur from the lower stratosphere and down to an altitude of 1-2 km, i.e., the lower troposphere. Although this observation is based on only one example of an extratropical storm that was considered typical, there is some evidence in support of Staley's finding. Miyake *et al.*¹⁶⁵⁻¹⁶⁸ have found a good correlation both between the incidence of an extratropical disturbance and high radio-activity in air and rain and between the frequency of such disturbances (as measured at the 500 mb level) and the global Sr^{90} deposit (figure 7). For the second correlation to be meaningful the stratospheric concentration of debris close to the tropopause should be fairly constant with latitude. This assumption seems reasonable from figures 4 and 5. Additional support may be found in the fact that a study of the stratosphere between 30°-90° N in the spring of 1959⁸⁸ showed the net zonal removal to be approximately proportional to the area of the zone, i.e., a curve of a shape similar to figure 7 (except between 30°-40° N).

Transport through the tropopause gaps

52. The possibility of mass transfer of air and debris through the tropopause discontinuities or "gaps" (figure 2) has been extensively referred to in the literature. According to Staley,¹⁶⁵ however, "there is no meteorological evidence that jet streams must flow downward". Direct sampling in the gap region¹¹⁶ shows some mixing of stratospheric and tropospheric air but the magnitude of the phenomenon is not impressive as judged from these data.

THE TROPOSPHERE

Horizontal movements

53. The transport of radio-active aerosol clouds within the troposphere has been extensively studied.¹⁶⁹ It has been found that the radio-active clouds from explosions of comparatively low power, reaching altitudes of between 7 and 11 kilometres, enter the zone of persistent horizontal winds. Horizontal air stream speeds in this zone are usually so high that radio-active clouds can circle the earth within two or three weeks, or even less. Direct observation from aircraft of the movements of a com-

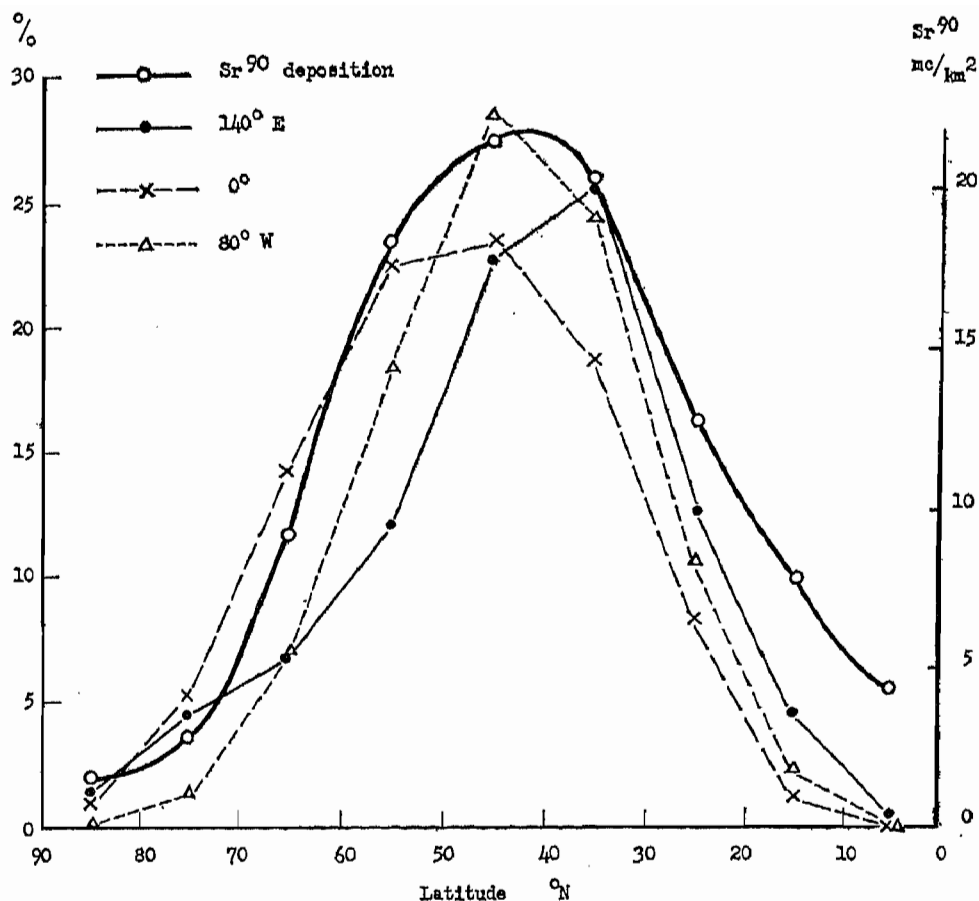


Figure 7. Frequency distribution of trough at 500 mb and fall-out¹⁸⁸

pact radio-active cloud^{170,171} has shown that the cloud lengthens in the direction of movement and in some cases may divide into independent sections where there is a steep wind speed gradient with altitude (figure 8).¹⁷² The assertion is sometimes made that tropospheric debris distributes in the general latitude in which the explosion occurred.^{48, 49, 173, 174} As is evident from figure 8, this is a great oversimplification. Recent measurements have shown that a tropospheric injection at latitude 27° N on 13 February 1960 was found in the ground level air in Ghana (5° N) on 14 February,¹⁷⁵ in Cairo (30° N) the next day,^{176,177} in Bombay (20° N),¹⁷⁸ and Crimea (45° N)¹⁷⁹ on 16 February, in Japan (35° N)¹⁸⁰ and Israel (32° N)¹⁸¹ on 17 February, in Romania

(45° N),¹⁸² in Panama (10° N),¹⁸³ and in England (52° N)¹⁸⁴ on 23, 24 and 28 February respectively, and finally in Sweden (60° N)¹⁸⁵ and Czechoslovakia (50° N)¹⁸⁶ on 1 March 1960. In another case it has been suggested that tropospheric debris from injections at about 70° N appeared in about a month in Australia (15° S).¹⁸⁷ It is perhaps possible to generalize about the average distribution from repeated tests at the same site and say that tropospheric debris tends to produce a maximum air concentration displaced towards temperate latitudes irrespective of the test site location.^{70,188} But it should in any case be realized that only evaluations of the synoptic situation can give a detailed explanation of results such as those shown in figure 9.¹⁸⁹

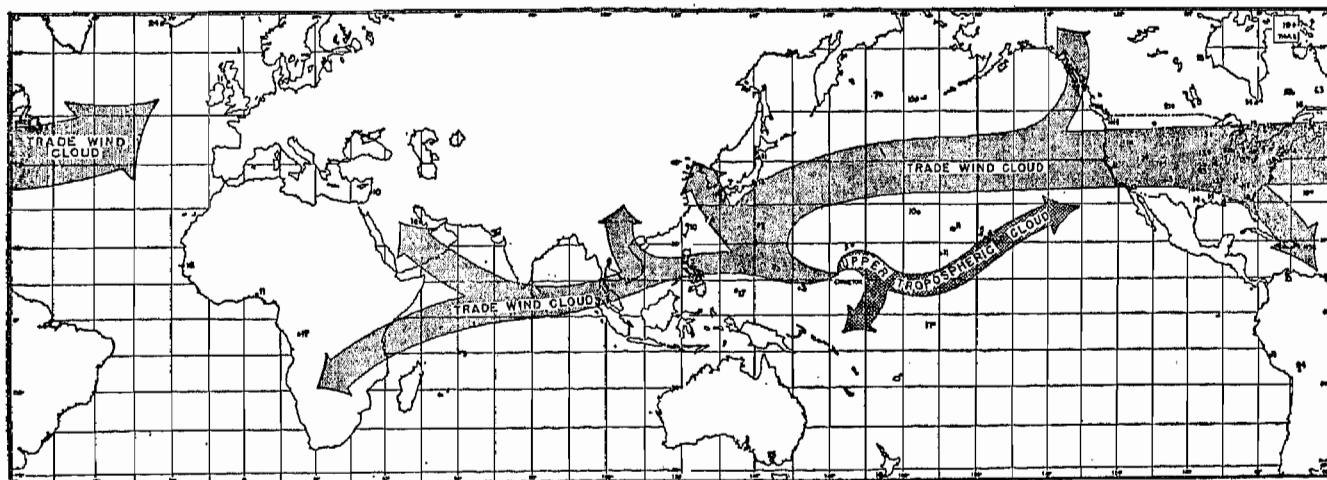


Figure 8. Early history of the Mike cloud¹⁷²

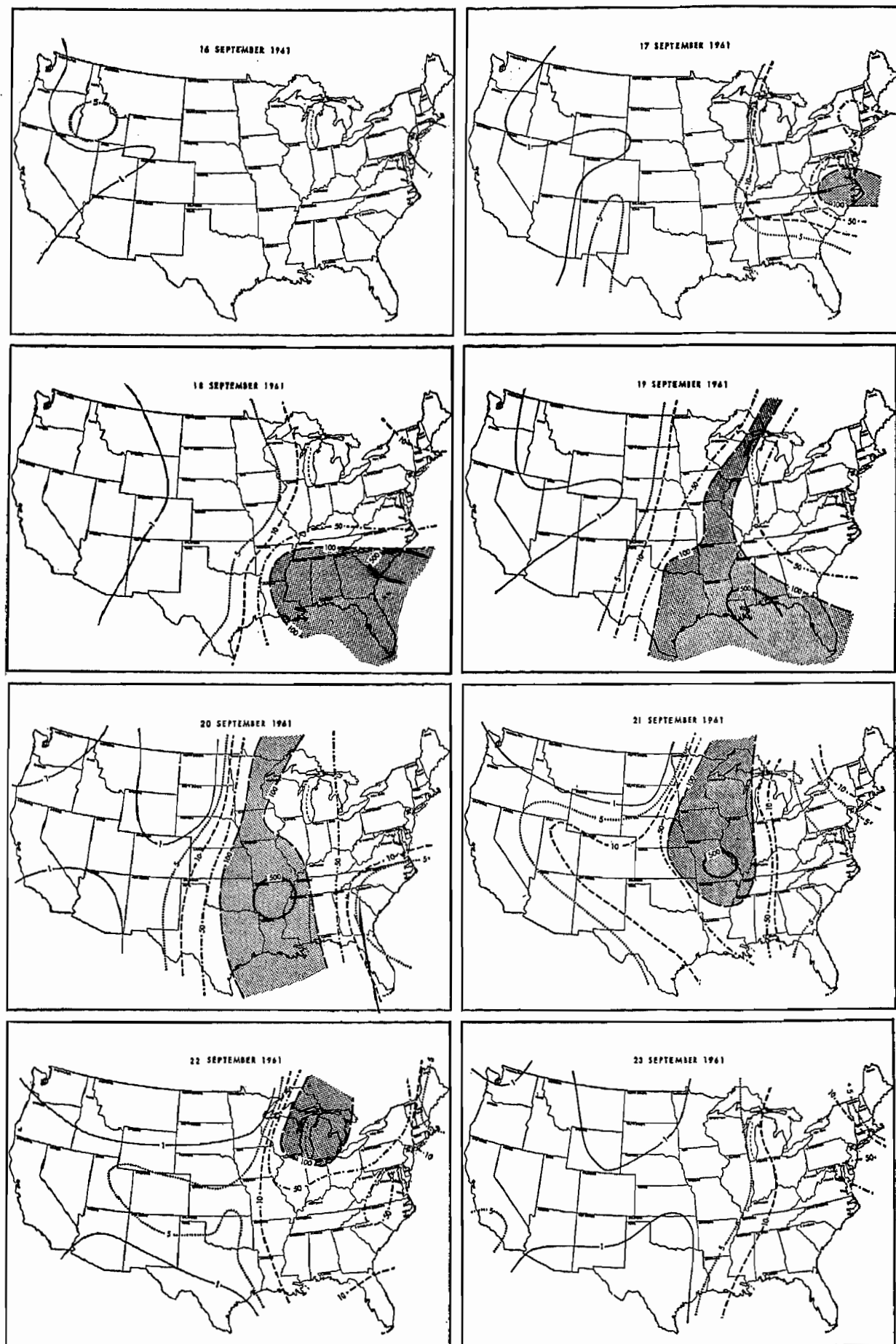


Figure 9. Total beta activity in surface air ($\mu\text{C}/\text{m}^3$)¹⁸⁹

54. A large number of measurements of weapon debris in tropospheric air are now available.^{33, 69, 88, 114-121, 135-140, 154, 175-275} Most of these data relate to measurements of the total beta-activity of fission products. The principal shortcoming of these latter studies is that the age of the investigated activity, with rare exceptions, remains unknown; the energy spectrum of the radiation and the nuclide composition of the activity is then also unknown. It is therefore impossible to utilize these data either for an accurate evaluation of health hazards (F III) or for an explanation of tropospheric transport of debris. In view of the large amount of work that has been done the world over in measuring total β -activity of air (and rain, para. 74) one might express the hope that the general uselessness of total β -measurements might be more widely realized and modifications introduced in future measurement programmes so as to yield meaningful results. In consequence, the data on airborne activity reviewed here will pertain only to measurements giving some indication of the age or composition of the fission product mixture.

55. There are at present relatively few data on activity concentrations in tropospheric air above ground level.^{33, 115, 116, 195, 207, 258, 277, 278} Table V^{195, 207} gives some data on the average concentration of Sr^{90} and Cs^{137} in the atmosphere over the USSR in 1955 and 1956. Figure 10 shows the variation of Cs^{137} with altitude and time, giving some stratospheric and ground level measurements for comparison.^{115, 277, 278} A seasonal variation of airborne debris is clearly demonstrated as well as an increase in concentration with altitude.

56. Measurements of air concentrations at ground level are much more numerous than those at higher altitudes. Existing determinations of Sr^{90} show the same seasonal variations as observed for Cs^{137} (figure 10) although the effect is much less marked for the southern hemisphere.^{69, 121, 154, 192, 205, 215, 216, 220-227, 229, 231, 233, 234} It is also evident that the northern hemisphere has a considerably higher amount of airborne activity than the southern part of the globe, but this difference decreased

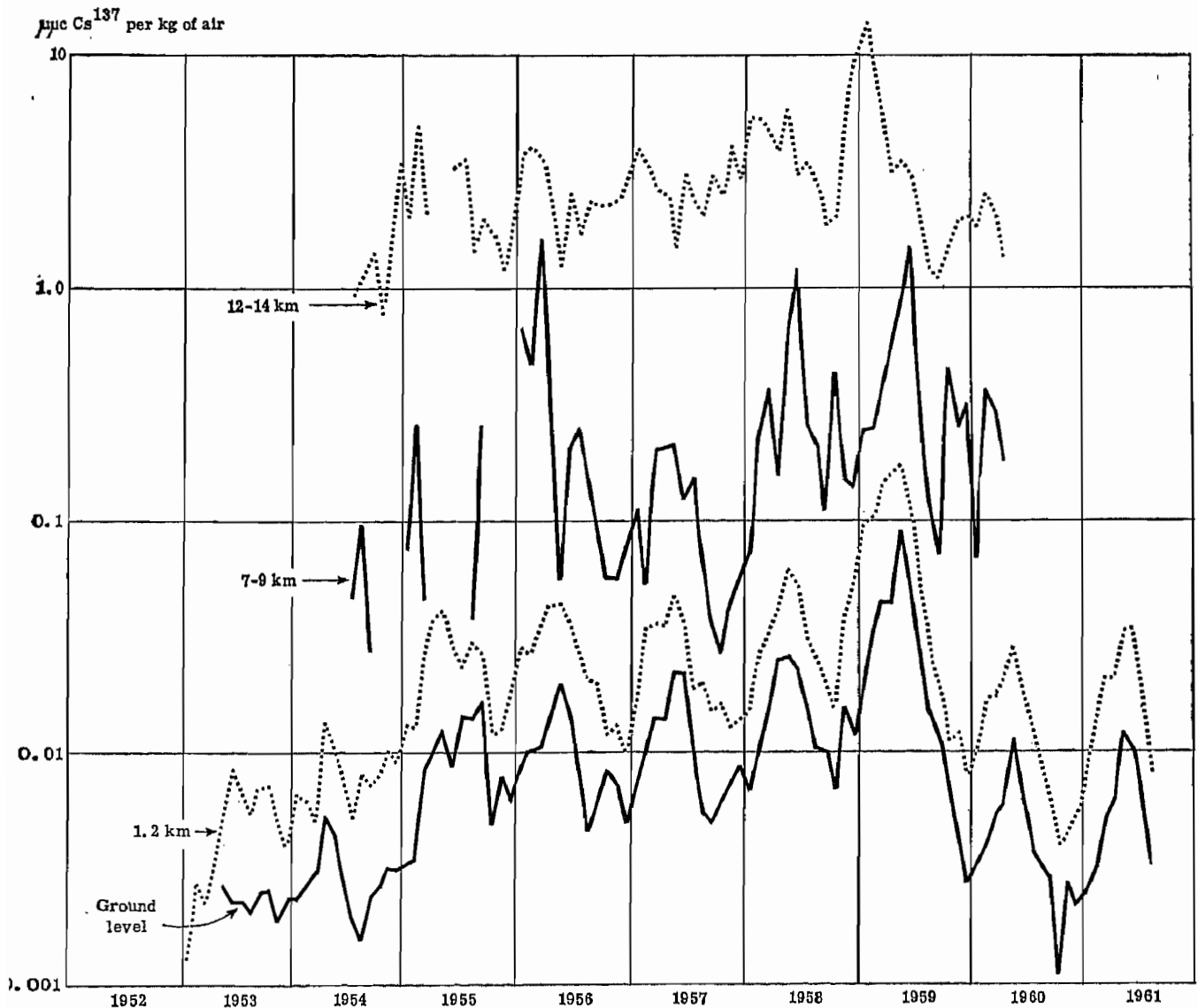


Figure 10. Cs^{137} in air over the United Kingdom^{115, 277, 278}

from 1959 to 1960, presumably because of the rapid fall-out of the debris injected in the polar stratosphere in 1958. As the number and distribution of the sampling stations does not represent a truly world-wide network a detailed evaluation of the global situation is difficult. The latitudinal distribution of different nuclides has been studied in some detail and results of the measurements are given in figure 11^{212, 220, 250, 472} which shows a minimum close to the equator and higher concentrations in temperate latitudes. The time variation of Cs^{137} was exemplified in figure 10 and a large number of studies are now available both on this nuclide^{114, 115, 185, 205, 217-228, 280} and on others.^{120, 185, 205, 210-227, 233, 279} W^{181} and W^{185} produced in the summer 1958 equatorial tests and Rh^{102} produced in the 1958 high-altitude equatorial tests provided unique tracers and made possible the subsequent identification of debris from these tests. Using this technique, it has sometimes been possible to partition the airborne activity between different stratospheric injections. Figure 12 shows such data²⁸¹ for Cs^{137} in air in the vicinity of Chicago. It is of interest to note that debris from injections into the very high equatorial stratosphere was not observed in appreciable quantities at ground level until more than a year^{281, 282} after injection.

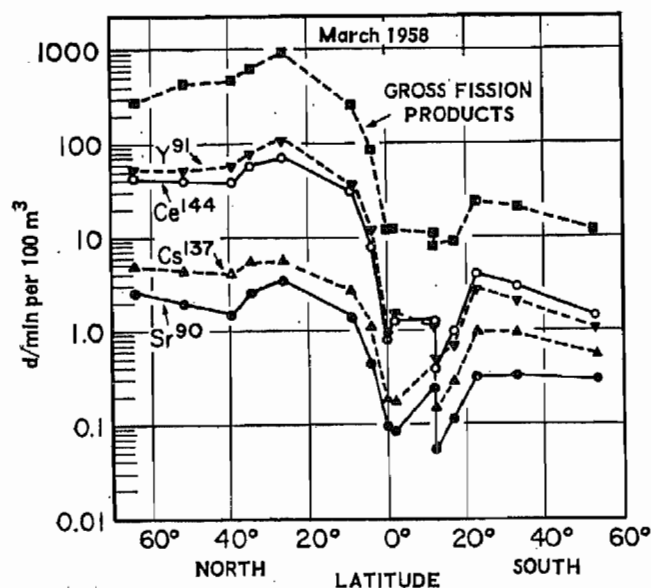


Figure 11. Latitudinal distribution of some fission products in ground level air^{212, 220, 250, 472}

Capture of debris in precipitation

57. A relationship has been established between meteorological factors and the concentration of debris in tropospheric air and rain.^{153, 165-108, 233-288} It has been shown for instance that increased concentrations of fission product ratio-activity in ground level air has accompanied the passage of anti-cyclones, i.e., higher pressures and descending air currents. The formation of "stagnant zones" at the confluence of cyclonic and anti-cyclonic currents is also conducive to more intense deposition of aerosols on the earth's surface. It is apparent from this and other work^{33, 76} that removal of aerosol particles occurs much more rapidly than in the stratosphere. The main reason for this is the scavenging effect of tropospheric precipitation. Although the effect is not understood in detail, several mechanisms have been recognized as possible explanations of the scavenging process.^{76, 287-289}

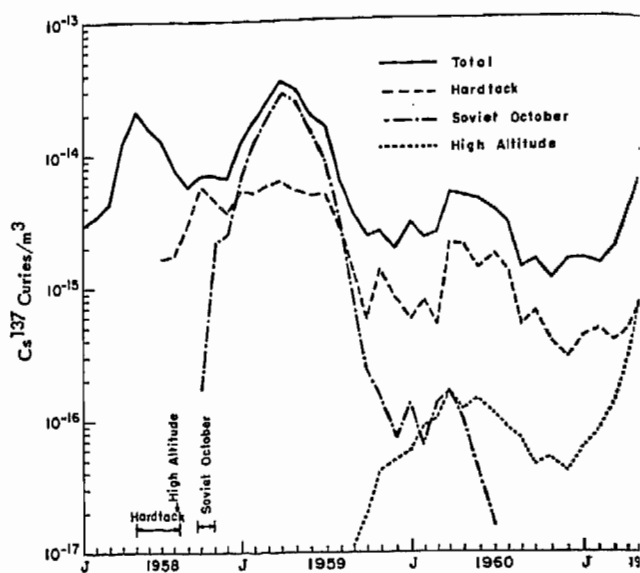


Figure 12. Partition of Cs^{137} in surface air near Chicago, USA²⁸¹

(a) Aerosol particles may act as condensation nuclei for water vapour.^{290, 291} This effect has been shown to be small at least for debris consisting mainly of silicates or iron oxide.²⁹²

(b) The vapour pressure gradient around a growing raindrop or snow crystal may induce capture of aerosol particles. Facy²⁹³⁻²⁹⁵ has shown that this phenomenon may be important for particles smaller than 0.1 micron.

(c) Inertial capture of particles through impact with falling raindrops and snowflakes.²⁹⁶⁻²⁹⁸ This effect has been shown to be of importance only for particle size greater than 5 microns.^{299, 300}

(d) Capture by Brownian motion has been demonstrated to be very effective for particles less than 0.1 micron but becomes unimportant for sizes over 0.1 micron.²⁸⁷

(e) Other alternatives have also been discussed⁷⁶ but seem to be of negligible interest.

Evidently aerosol particles in the range of 0.1-5 microns may not be removed by scavenging as efficiently as are other sizes. Independent evidence of this is furnished by measurements on tropospheric aerosols.³⁰¹⁻³⁰⁴

58. Attempts to establish a correlation between the concentrations of debris in ground level air and in rain have met with varying success. There is usually little or no reduction in the ground level air concentration during rain,^{213, 301, 305, 306} but prolonged, heavy precipitation can lower the air concentration appreciably.^{307, 308} Furthermore, the activity of raindrops from a natural rain cloud has been found to be the same at an altitude of about 2 km as at ground level.³⁰⁹ This means that the mechanism whereby fine aerosol particles are captured by falling raindrops is not very efficient. The scavenging effect of falling snow may, however, be greater. Effective scavenging by aerosol capture apparently occurs during the formation and subsequent growth of the raindrop. Other data in figures 13³¹⁰ and 14¹⁰⁸ show that there is a general tendency for the activity concentration to decrease as the amount of precipitation in a sample increases.¹⁰² This can be explained either by assuming nucleation to be of primary importance and the large drop size of a heavy rain giving more diluted concentrations than in a slight rain, or it may be postulated that drop growth is more important, a greater rate of

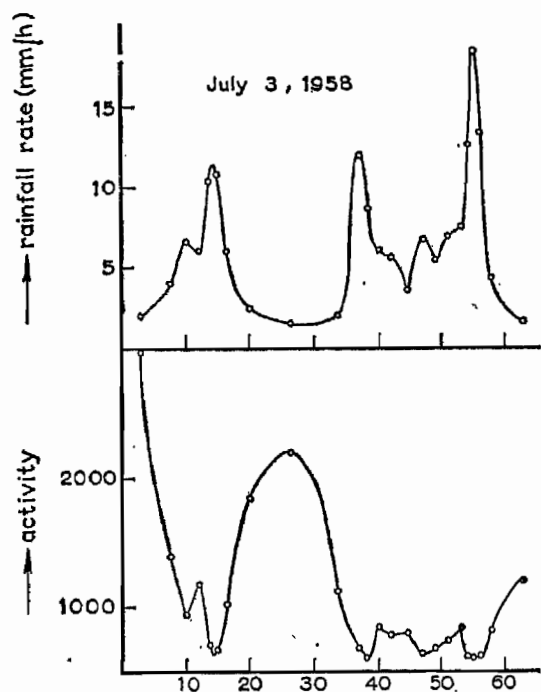


Figure 13. Fluctuations in rainfall rate (mm/h, upper curve) and fluctuations in specific activity (arbitrary units, lower curve) versus time in the Netherlands⁸¹⁰

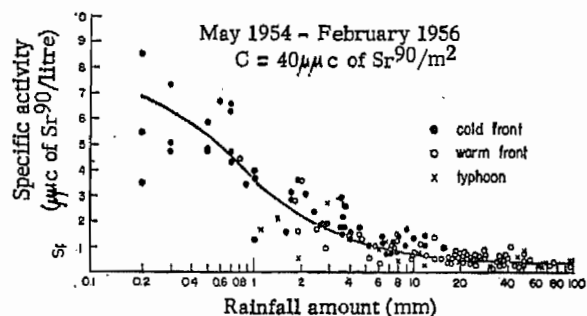


Figure 14. Variation in specific activity of rainwater with amount of precipitation in Japan¹⁶⁸

rainfall depleting the airborne activity inside the rain cloud. A third possibility is that the evaporation of falling raindrops is greater in a heavy than in a light rain. Whatever the detailed explanation, it is found that on the average over a long time there is a good correlation between ground level air and rain concentrations (figures 15 and 16).^{268, 278} This is a reflection of the fact (figures 10 and 16) that the concentration of debris in the air at ground level closely follows the activity fluctuations in higher tropospheric air most of the time.

Dry removal of debris

59. The scavenging action of precipitation is not the only process that removes radio-active debris from the troposphere. Gravitational settling may occur, especially for freshly injected debris. It may also be of some importance even for older debris, however, since there is indication that the presence of natural or industrial aerosols in the ground level air increases the concentration of airborne activity^{97, 311, 312} presumably through coagulation which, as discussed previously (para. 47), may be quite rapid for submicron particles. This conclusion is only tentative, as other explanations are possible³¹³ and the effect sometimes is absent.¹³⁵ Impaction, vertical mass movement and eddy diffusion of air are other

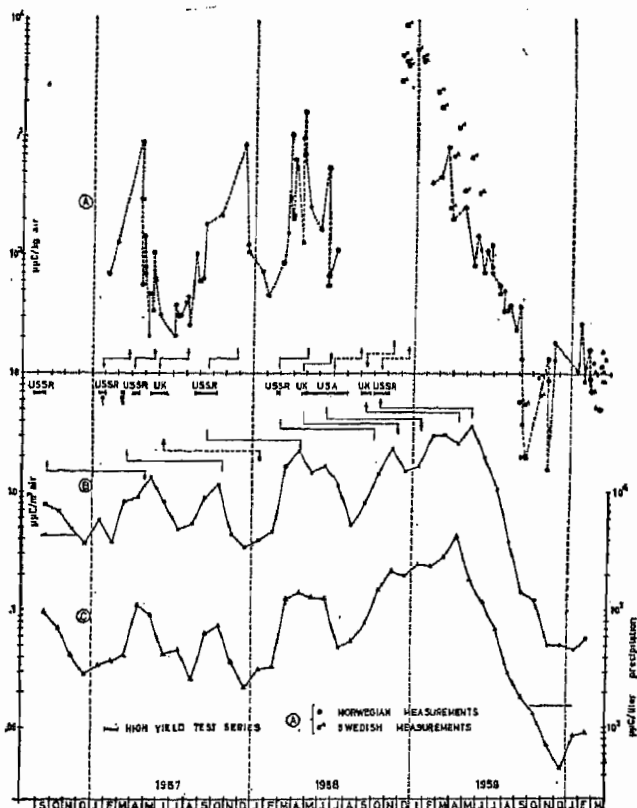


Figure 15. Results of measurements of fall-out materials during the period September 1956-January 1960²⁶⁸

Curve A: Concentration of fall-out materials in the lower stratosphere over SE Norway. Each point represents the result of one measurement.
Curve B: Monthly average concentrations of fall-out materials in air near ground level. Each point represents an average value of measurements from 9 stations.
Curve C: Monthly average concentrations of fall-out materials in precipitation. Each point represents an average value of measurements from 12 stations.

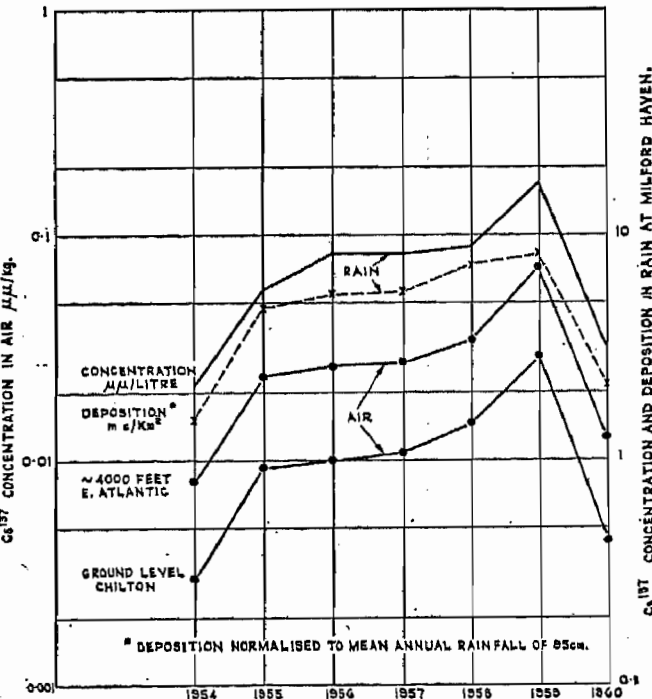


Figure 16. Annual variation of Cs¹³⁷ in air and rain²⁷⁸

factors contributing to the removal of debris from the troposphere. All these factors are, however, best discussed in connexion with measurements of fall-out deposition on the ground (para. 78).

Half-removal time

60. The rate at which tropospheric air is cleared of aerosols is conveniently expressed in terms of a half-removal time. Because of the greater rate of mixing in the troposphere, this concept is more applicable here than in the case of the stratosphere. A summary of available evidence⁷⁰ indicates a value of about twenty to forty days as a realistic half-removal time for debris injected in the troposphere above the rain-bearing layers, i.e., about 4 km.

CARBON-14*

C^{14} in the stratosphere

61. An extensive series of stratospheric CO_2 samples have been collected by the United States Atomic Energy Commission¹⁵⁰ in conjunction with the ASHCAN project. The stratospheric contents of C^{14} at various periods of time have been computed from these data and are given in table VI. The estimated accuracy is ± 30 per cent.

* For discussion of C^{14} see also annex E.

C^{14} in the troposphere

62. The first experimental verification of increased C^{14} levels due to nuclear tests was reported in 1957,³¹⁴ the delay between substantial production in 1954 and experimental verification of an increase in specific activity of the troposphere being due to the hold-up in the stratosphere. Subsequently, this increase has been followed by various workers³¹⁵⁻³²⁹ who have shown that by mid-1959 the increase in the northern hemisphere troposphere was about 27 per cent and in the southern hemisphere troposphere 18 per cent. The rate of increase with time in the troposphere of the two hemispheres is shown in figure 17 and is consistent with that expected from mixing into the troposphere from a stratospheric reservoir of C^{14} , the content of which has been increasing with time. In 1960 a decrease in C^{14} levels was reported,^{330, 332} The C^{14} produced from high yield explosions is virtually all transferred to the stratosphere as shown by the measurements of C^{14} activity of ground level air in the Philippines before and after the United States Castle test series in early 1954.³³³

63. The measurements of C^{14} activity of tropospheric air have been made either by direct separation and collection of CO_2 from the air or by using contemporary plant material. It has been generally assumed that the C^{14} activity of contemporary plant material reflects directly the activity in the troposphere but this may not

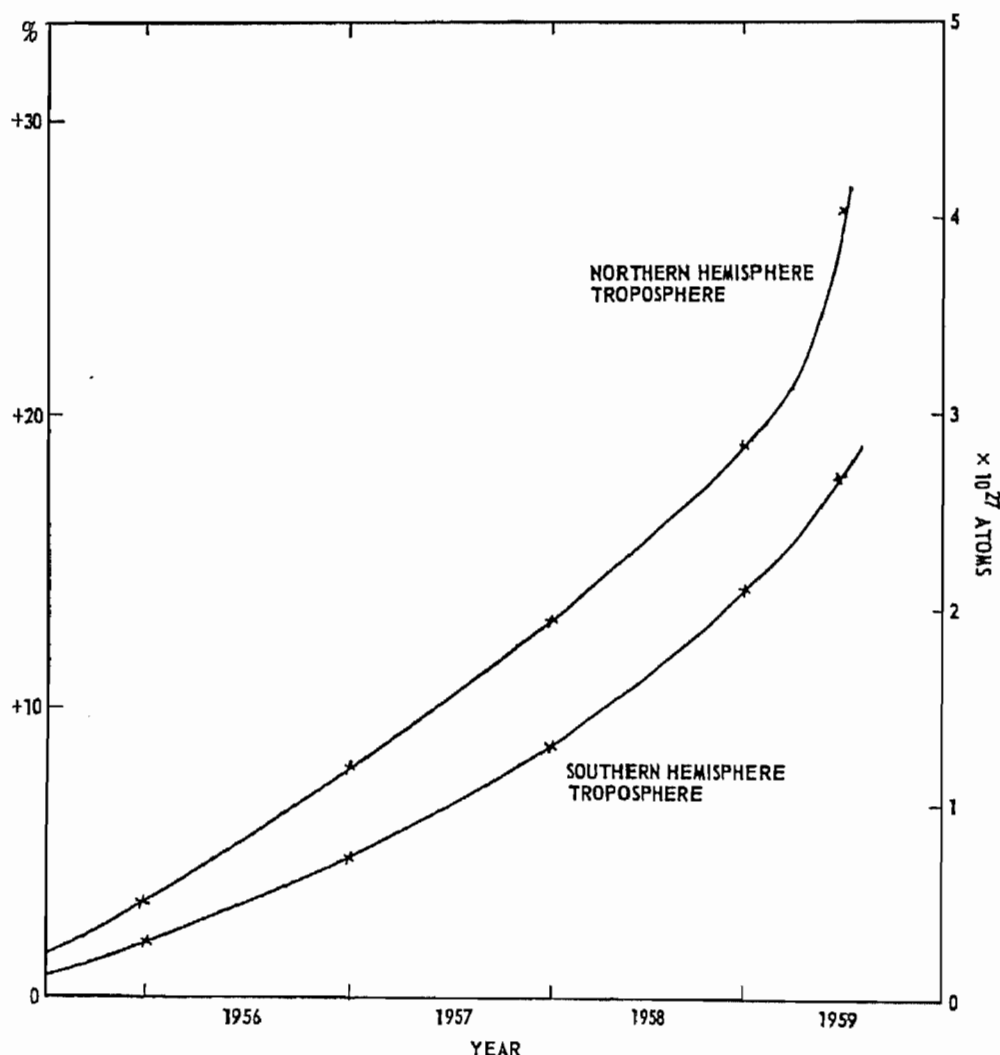


Figure 17. Tropospheric inventory of artificial C^{14}

necessarily be so for trees, since it is possible that significant fractions of the carbon in the young leaves has been derived from sources which have been stored for significant periods in the trunks or roots.³²⁷ Although little information is available, it may perhaps be concluded that analyses of annual plants provides more information on the current C^{14} activity in the troposphere. Thus, while C^{14} activity measurements of contemporary biospheric materials usually give the same value as obtained for ground level air, care is needed in the interpretation of this type of measurement.

64. The greater increase observed in the troposphere of the northern hemisphere compared to the southern hemisphere is as expected, because all large-scale injections of artificial C^{14} have been into the northern hemisphere stratosphere. However, the present difference between the tropospheric C^{14} levels in the two hemispheres would level out in the absence of testing in a few more years owing to the inter-hemispheric exchange of air masses.^{310, 334} Evidence also exists for a small but positive latitudinal effect in C^{14} levels of the northern hemisphere troposphere during the period 1956-1959³³⁵.

Carbon cycle in nature

65. Considerable study of the carbon cycle in nature and the distribution of C^{14} ^{334, 336-363} has been undertaken in the last decade. As a result of biological processes and of circulation in the oceans, the carbon which is contained in the atmosphere, in living matter and in the oceans is cycled at a rate that is very rapid on a geologic time scale (time scale of the order of a few hundred to a few thousand years). The main reservoirs of carbon that are generally considered in order to determine the present and the future distribution of C^{14} , and the relative sizes of these reservoirs, are given in table VII.

66. The amount of carbon in the atmosphere and the total amount of carbon in the carbon cycle are known with reasonable accuracy (within 10 per cent); however, the figures given in table VII for the amounts of carbon involved in the biosphere, humus and surface waters of the ocean could be subject to considerable error (up to 50 per cent).

67. The rate of carbon exchange between the reservoirs of the exchangeable system varies from three to seven years for the mean life of a carbon dioxide molecule in the atmosphere^{316, 318, 334, 350, 351, 361} to approximately 1,000 years for the mean life of a carbon dioxide molecule in average deep ocean water before its transfer back to the atmosphere^{317, 350} (para. 71). In the case of the sedimentary system, exchange of the carbon with that of the atmosphere takes place only very slowly—time scale of the order of millions of years^{334, 343}—and hence the C^{14} content of the sedimentary system is negligible.

Movement of carbon in the carbon cycle

68. Prior to 1900, the C^{14} distribution within the carbon cycle was in a "steady state", for although the carbon in the various reservoirs did not have the same C^{14} specific activity, the C^{14} specific activity in any given reservoir was constant with time. Since 1900, however, mankind has upset this steady state situation in two ways. First, the combustion of coal and oil has added to the atmosphere an enormous amount of " C^{14} -free" CO_2 which has reduced the C^{14} specific activity of the atmosphere and those reservoirs in rapid exchange with it (Suess Effect).^{330, 364} Secondly, in recent years the testing of atomic weapons has added noticeable amounts of

$C^{14}O_2$ to the atmosphere, thereby increasing the C^{14} specific activity of the atmosphere and those reservoirs in rapid exchange with it.

69. There are, therefore, three time periods over which measurements of C^{14} specific activity may be used to assist in the determination of the dynamics of carbon cycle. These time periods are:

- (a) Prior to 1900, steady state distribution of C^{14} ;
- (b) 1900 to 1952, Suess Effect decrease of C^{14} specific activity;
- (c) 1952 to the present, C^{14} incorporated from nuclear weapons and a smaller fraction incorporated from the operation of reactors.

70. A convenient method of investigating the dynamics of the carbon cycle^{334, 350-352, 363, 365-367} is by mathematical analysis of a model consisting of various reservoirs in the exchangeable system between which transfer of carbon is assumed to be determined by first order rate constant and within which mixing rates are assumed to be rapid compared to the transfer rates. The values of the various exchange constants are not known accurately, so there is corresponding uncertainty in predicted levels.

71. The exchange of carbon between the atmosphere and the surface ocean is the main process which determines the distribution of added C^{14} in the carbon cycle. Considerations of the three separate time periods^{316, 350, 352, 368} referred to in paragraph 69 lead to estimates of the mean life of a CO_2 molecule in the atmosphere, before transfer to the ocean, ranging from three to seven years. A less important role is played by the transfer of carbon from the atmosphere to the land biosphere. Investigations of the process of photosynthesis in the biosphere³⁴³⁻³⁴⁵ suggest that the mean life of a CO_2 molecule in the atmosphere before its entry into the biosphere is of the order of thirty years. The average age of deep ocean water relative to surface ocean water is of the order of 1,000 years.^{316, 317, 369-371}

III. Deposition of radio-active fall-out

72. Data on air concentrations were given in the previous section and here experimental values of fall-out deposited in soil and water will be reviewed. These concentrations vary with time and from region to region. Whenever possible, therefore, data on the concentration of radio-isotopes include reference to the geographical co-ordinates and the time of collection. The curves and graphs attached may be used for rough quantitative assessments.

73. The process of fall-out deposition is in general terms the result of the action of atmospheric phenomena (precipitation and wind) at the ground surface. It is customary to distinguish between wet and dry deposition, the first process comprising the impaction of debris contained in rain, snow, etc., on the surface of the earth, the second being the impaction of the debris particles themselves. The wet deposition is usually the more important process except in arid regions where the dry deposit may predominate.

RATE OF FALL-OUT DEPOSITION

Methods of measurement

74. Fall-out rates have been studied in many parts of the world for many years using a variety of methods. Sampling techniques have included funnel and pot col-

lectors, often in combination with an ion exchanger, sticky paper and gauze trays, to mention the more important methods used for the collection of wet and dry depositions. Sampling techniques were discussed in the previous report of the Committee and the differences in collection efficiency described. Subsequent measurements on these samples have employed both advanced techniques of radio-chemistry and gamma-spectrometry as well as simpler measurements of total β -activity. As in connexion with airborne activity (para. 54) it may again be stated that measurements that give only the total β -activity with no indication of the age or composition of the fall-out are of little value for the interpretation of the resulting health hazards.⁸⁷² Again, therefore, greater emphasis will be placed upon data specifying fall-out composition.

Relation to airborne activity

75. The deposition of fall-out has been shown very clearly to result mainly through precipitation falling on to the earth's surface.^{88, 120, 144, 373} As most precipitation originates in the lower troposphere, the rate of fall-out in any particular region should as a rule be determined by the tropospheric airborne activity. It is important in this connexion to distinguish between short- and long-term conditions. Short-term (daily) variations in deposition do not correspond too closely to the short-term variations of the same nuclides in the air. In certain cases, a decline in the fall-out rate of Ce^{144} , Cs^{137} and Sr^{90} coincided with an increase of their concentration in air.²²⁸ If, on the other hand, long-term conditions are considered, one would expect an averaging out of most chance fluctuations in the concentration of airborne activity and of most differences in the properties and origin of the clouds bringing rain to the area concerned.

Relation to debris concentration in rain

76. As was shown earlier (para. 58) the specific concentration of activity in rain varies with the amount of precipitation in the individual rainfall (figures 13 and 14). Yet, taking monthly averages, this effect was found to be less important, the rain concentrations showing a

fairly good correlation with airborne activity (fig 15 and 16). This fact and the assumption made in previous paragraph of a relation between air activity and fall-out rate suggest that only a poor relation should exist between fall-out rate (approximately equal to amount of rain \times concentration in rain) and the total amount of precipitation. This is in fact found to be the case when data are studied as a function of time at one place.^{202, 305} Figure 18 shows monthly from the United States³⁷⁴ and figure 19 gives yearly averages from the United Kingdom³⁷⁵ both based on measurements of Sr^{90} in rain. In addition tables I and IX give values for Sr^{90} and some other nuclides, of special interest to compare figure 19 with the data on airborne activity from the same place (Milford Haven) shown in figure 10. The approximately uniform increase in Sr^{90} accumulation over the period 1956-1958 corresponded to a uniform air concentration over these years. In 1959 there was a threefold increase in the concentration corresponding to a sharp rise in Sr^{90} deposition rate in spite of the fact that the yearly precipitation was almost constant. The low air values in late 1958 and 1960 finally gave rise to an abrupt decrease in fall-out rate.

Relation to total precipitation

77. If there is thus a poor correlation between rainfall and fall-out rate at one place as a function of time, there exists a good correlation between the two quantities for different places over the same period.^{120, 376, 377} This is true at least for limited areas under homogeneous climatic conditions, but the conclusion also holds when points at great distances are compared. Miyake *et al.*^{107, 108} have shown that it may be possible to describe global deposition of Sr^{90} with an empirical formula:

$$F_d = C(1 - e^{-2P} + 0.06P)$$

where F_d is the deposition, C is the amount of airborne radio-activity in the rain-bearing air column above surface area and P the rainfall amount. If C is taken as 0.054 mc Sr^{90} /km² in the northern temperate zone and

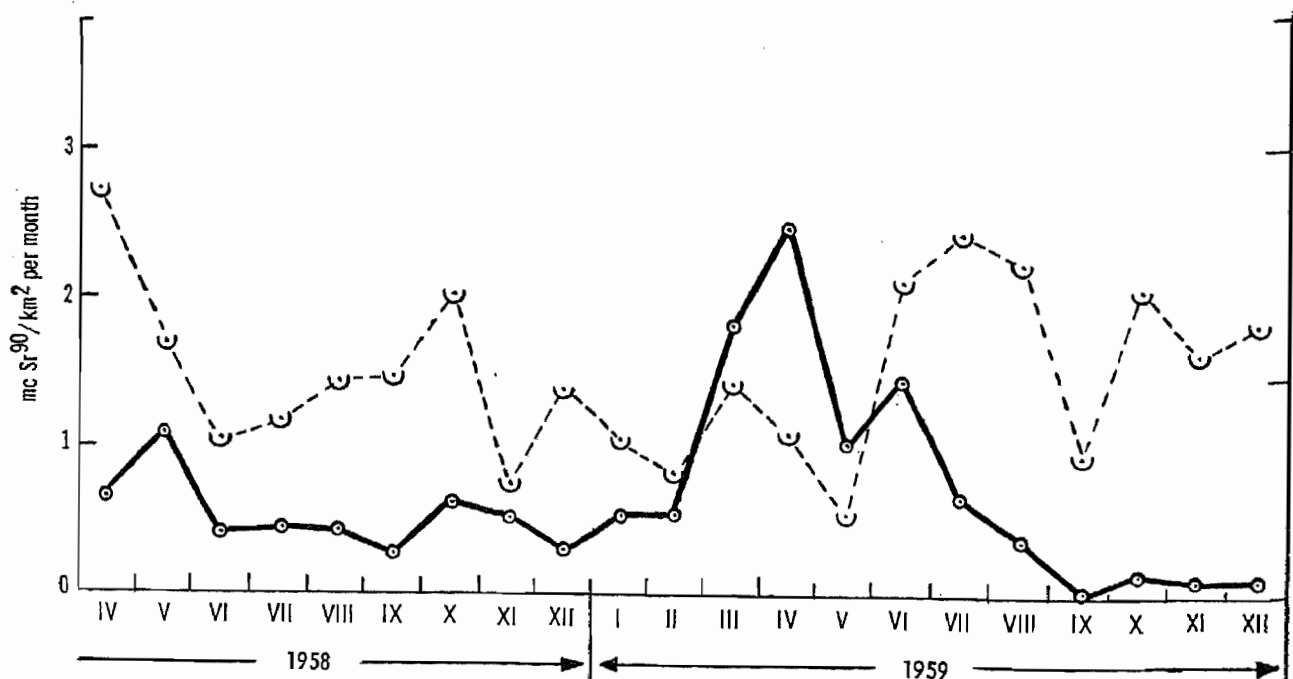


Figure 18. Rainfall (dashed line) and rate of fall-out in Westwood, New Jersey, USA³⁷⁴

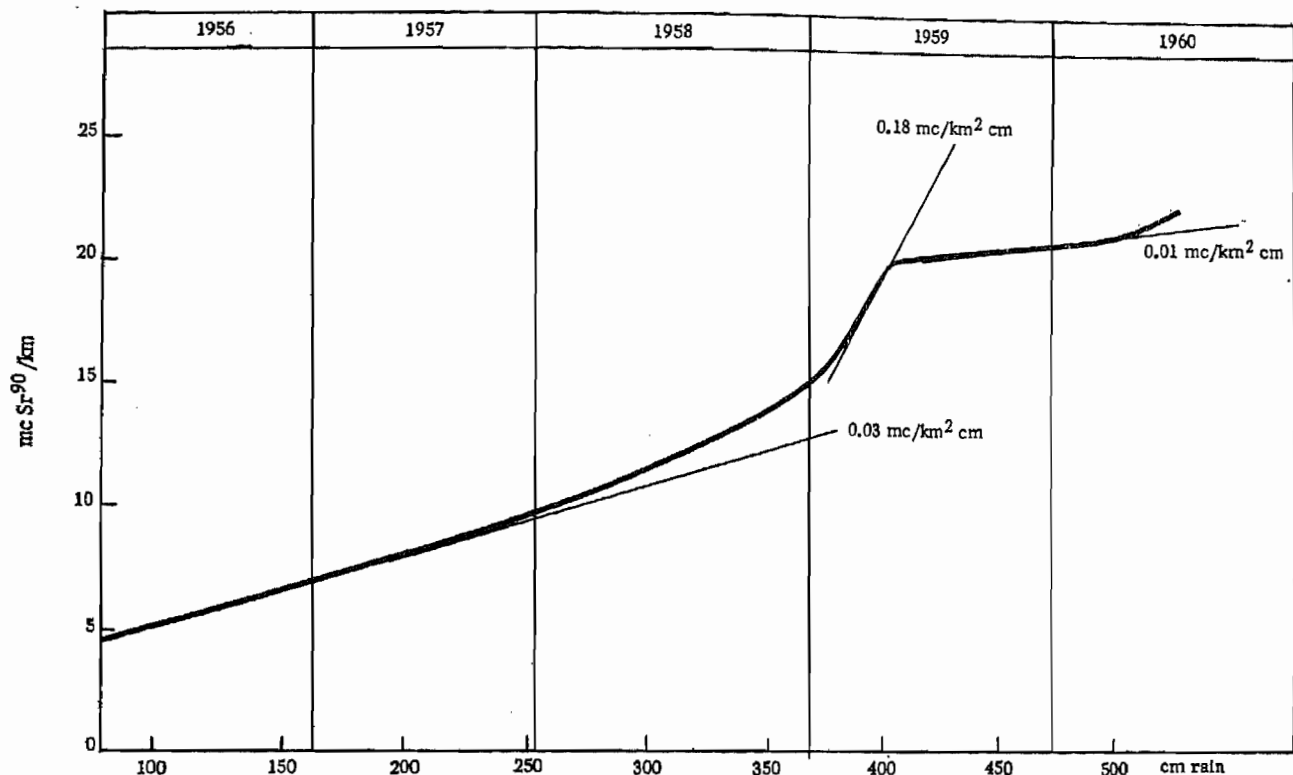


Figure 19. Cumulative Sr^{90} as a function of cumulative rainfall (Milford Haven, United Kingdom)⁸⁷⁸

0.007 mc $\text{Sr}^{90}/\text{km}^2$ in the tropical region between 15°N and 20°S then the fit between theory and data is as shown in figure 20. Examples of limited areas^{876, 877} are shown

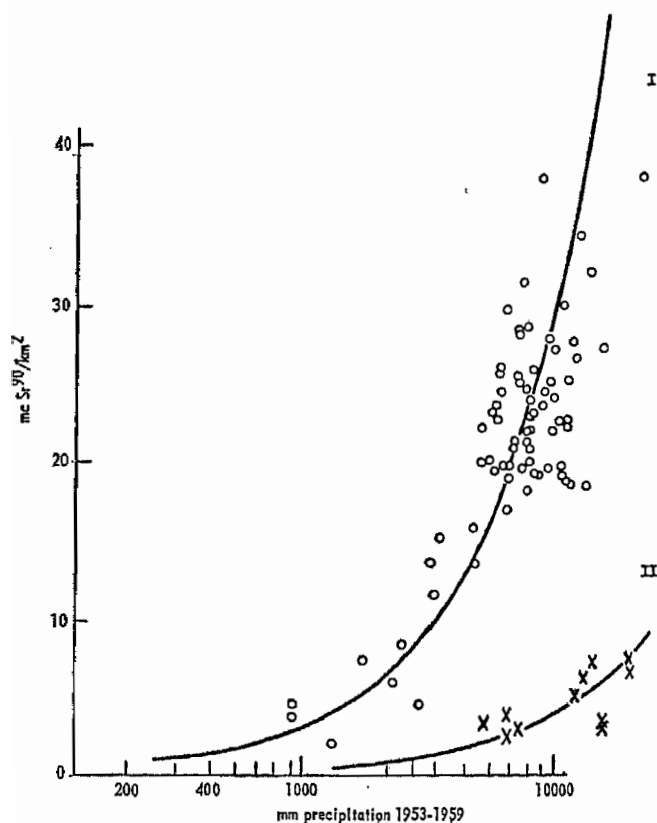


Figure 20. World-wide Sr^{90} fall-out and amount of precipitation^{187, 188}

I: $C = 0.054 \text{ mc } \text{Sr}^{90}/\text{km}^2$ in temperate zone
II: $C = 0.007 \text{ mc } \text{Sr}^{90}/\text{km}^2$ in tropical zone

in figures 21 and 22 based on quarterly data of Sr^{90} and in figure 23 relating the fall-out of Cs^{137} over several years with the precipitation in that same period.¹²⁰ The points in figure 23 correspond to different places in Norway and Sweden. Even within limited areas exceptions to this rule have however been found, giving for example⁸⁷⁸ in 1958 monthly averages of 54 and 69 mc/ km^2 of beta activity in two places where the average monthly rainfall was 306 and 47 mm respectively. This particular finding, however, is not conclusive, as it is based only on a total beta measurement.

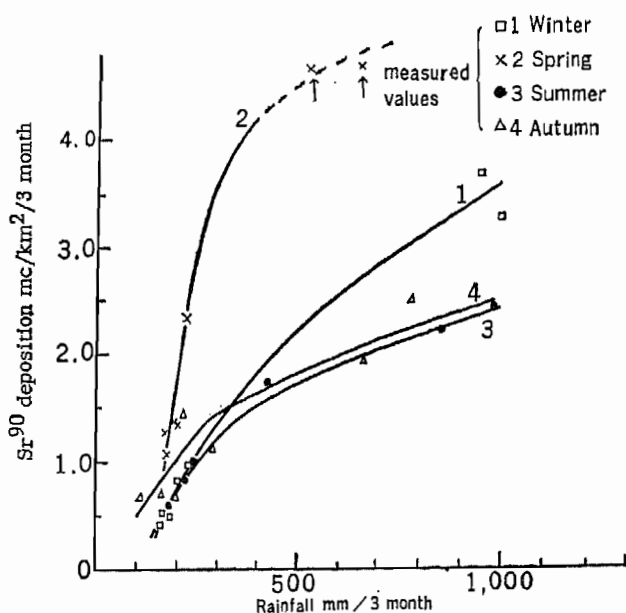


Figure 21. The relation between the quantity of Sr^{90} and the quantity of rain deposited per unit area of ground during three months (United Kingdom, 1958)⁸⁷⁹

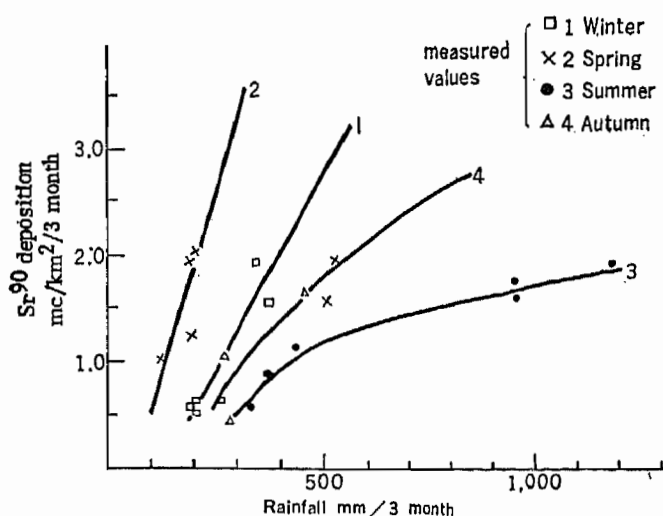


Figure 22. The relation between the quantity of Sr^{90} and the quantity of rain deposited per unit area of ground during three months (Japan, 1958)⁸⁷⁷

Dry deposition

78. Dry deposition of fall-out may occur in at least three different ways. Gravitational deposition may be important for fresh fall-out. Observations in Cairo^{176, 177} two days after a tropospheric injection and in Bombay¹⁷⁸ one day later showed intense fall-out (100 and 170 mc/km^2 of total beta activity respectively) despite the complete absence of rain. The calculated amount of long-lived activity was very small, however, for example less than $0.01 \text{ mc}/\text{km}^2$ of Cs^{137} . Another dry process is the inertial deposition of aerosol particles associated with the flow of air over objects on the ground^{379, 381} mainly grass and leaves of trees. A third mechanism, finally has been described by Facy^{291, 293, 295} proposing that deposition may take place by the nocturnal diffusion of water

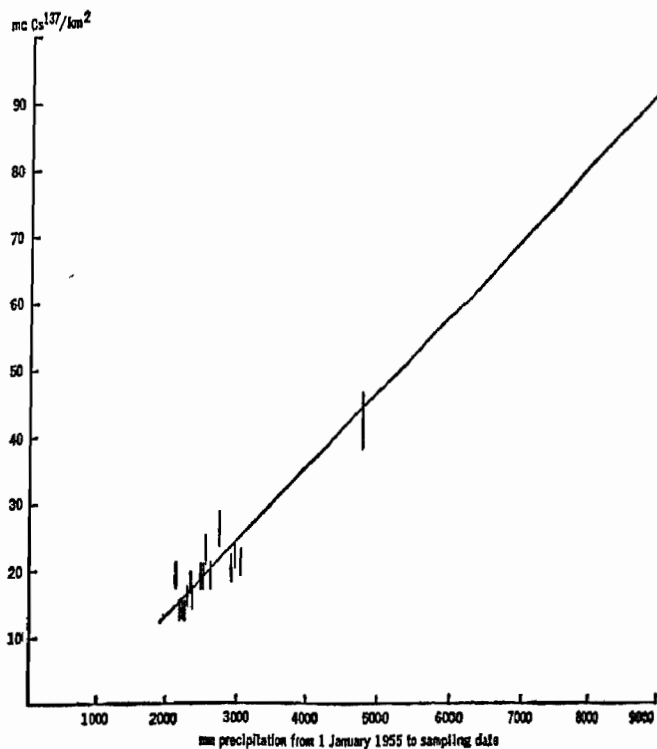


Figure 23. Correlation between Cs^{137} soil activity and rainfall in Sweden¹²⁰

vapour from the atmosphere into the soil^{382, 383} or on to herbage.

79. The quantitative relationship between "dry" and "wet" fall-out of radio-active aerosols on different parts of the earth's surface depends on climatic conditions. For example, in an area with comparatively heavy precipitation, such as Norway, the average monthly proportion

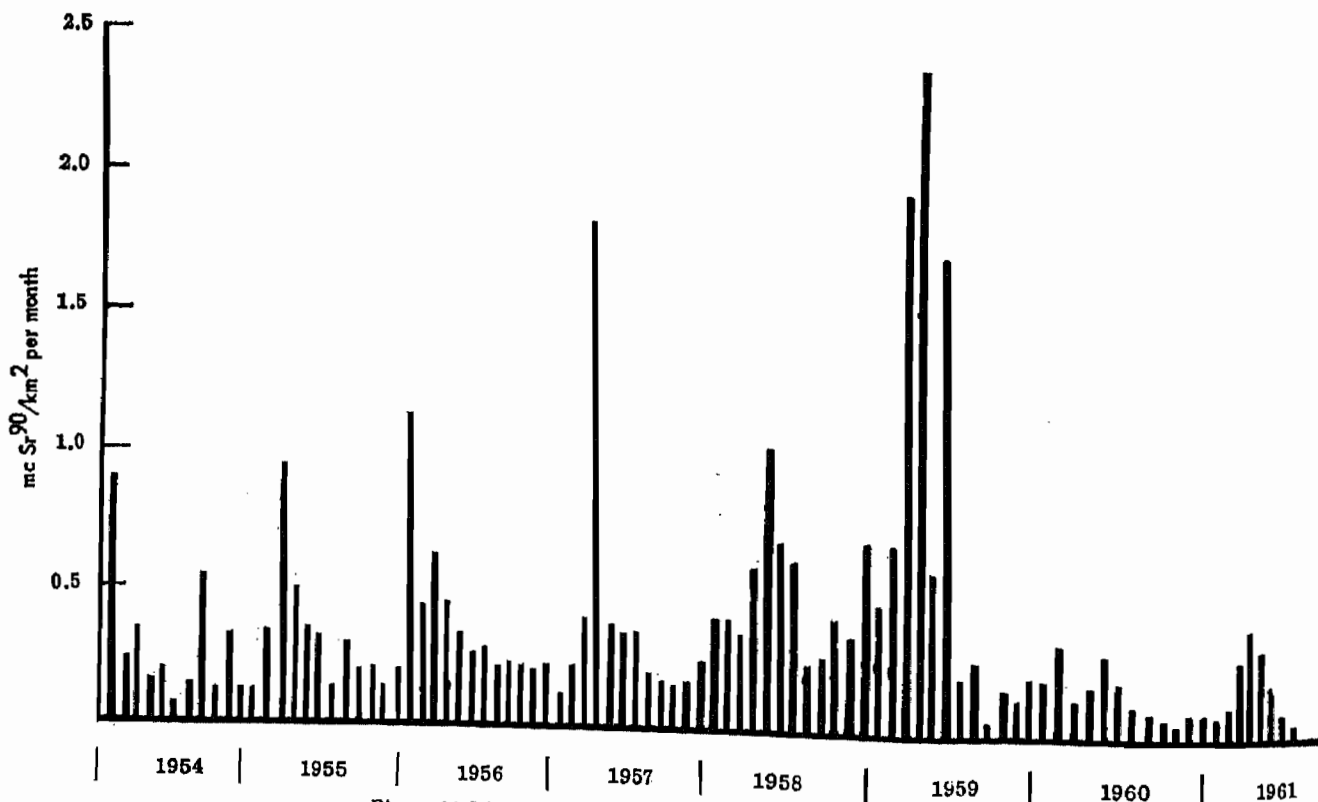


Figure 24. Monthly fall-out rate of Sr^{90} in New York City⁹

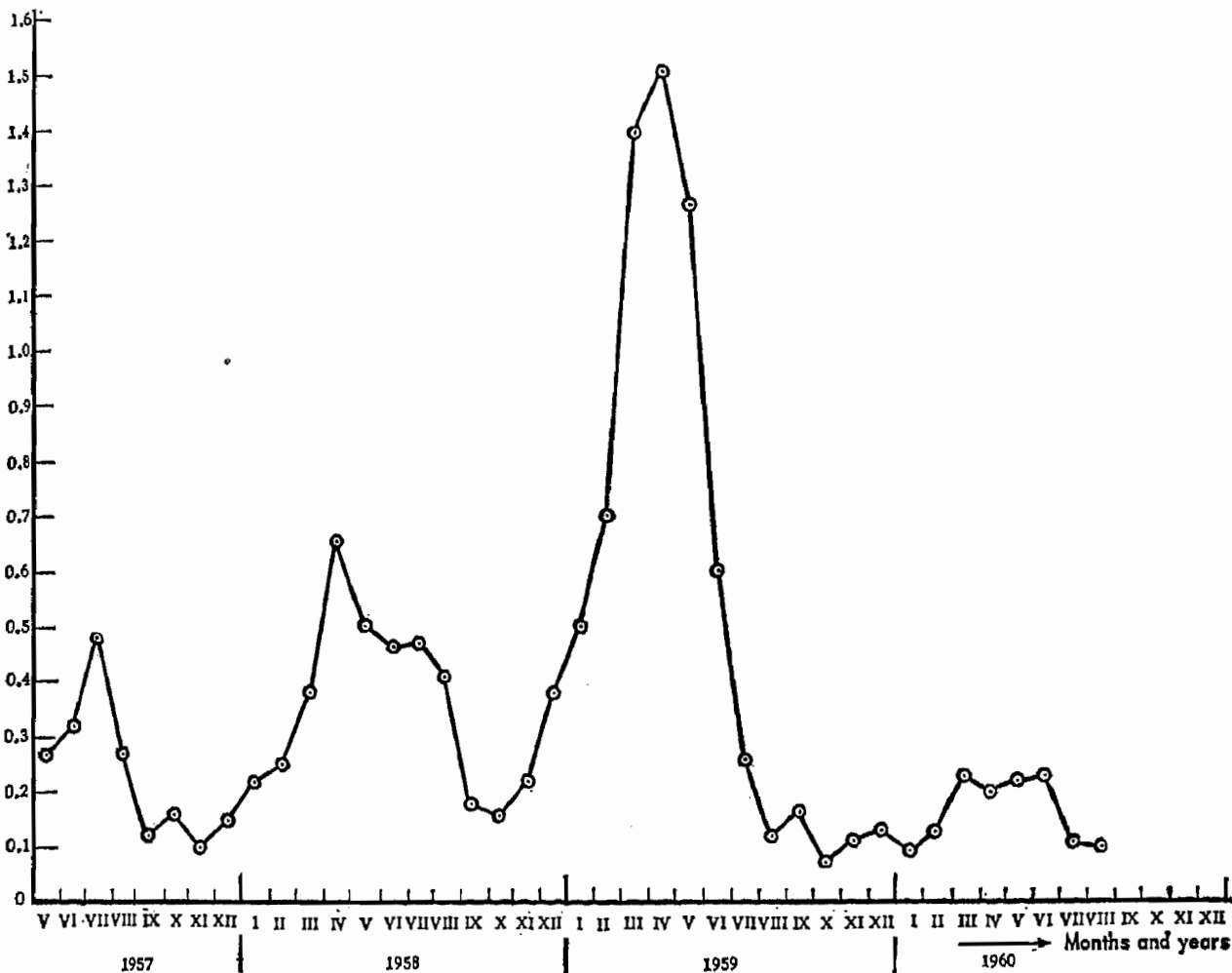


Figure 25. Average monthly fall-out rate of Sr^{90} in USA¹¹⁷

dry" fall-out between November 1958 and September 1959 ranged from about 10 to 72 per cent. This is to have included some gravitational settling of the particles present shortly after a test. The average portion of "dry" fall-out during that period was about 17 per cent.¹²⁰

Measurements of Sr^{90} and Cs^{137}

The Committee has received a large number of test giving data on the fall-out rate. The following tables give measurements of Sr^{90} , 81, 80, 102, 115-119, 166, 192, 196, 200, 205, 207, 208, 216, 224, 226-241, 275-278, 285-413. Some data will be found in figures 24 and 25 and tables X and XI. For Cs^{137} the following references may be 50, 102, 119, 224, 226, 227, 232, 234, 235, 275, 276, 284-294 and for nuclides, like Sr^{90} , Ce^{144} , Zr^{95} etc.: 50, 102, 115, 119, 205, 227, 230, 232-235. Tables XII and XIII contain some of these data. A survey^{88, 110, 138, 276} of the average global distribution of Sr^{90} is given in figures 26 and 27. The latitudinal variation of the fall-out rate changes with time that are consistent with a short residence time of polar injections. Spring maxima are seen in both hemispheres, occurring in March to May in the northern and in September to November in the southern hemisphere. As the number of sampling stations within each latitude band does not constitute a representative selection with regard to geographic differences in annual rainfall, two curves are shown for each period, one giving the arithmetic mean of observed values, the other a mean weighted for annual rainfall.

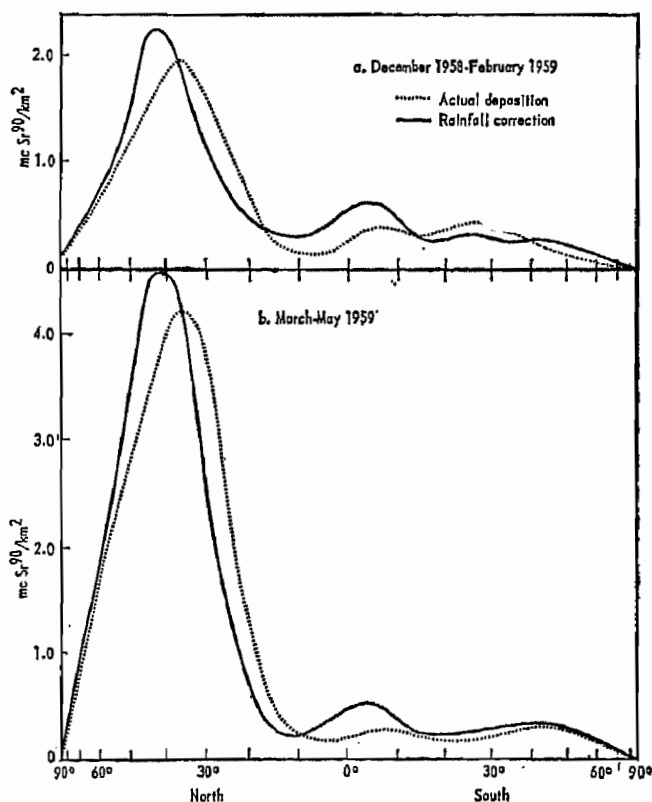


Figure 26a,b. Global distribution of Sr^{90} 88, 116, 138, 276

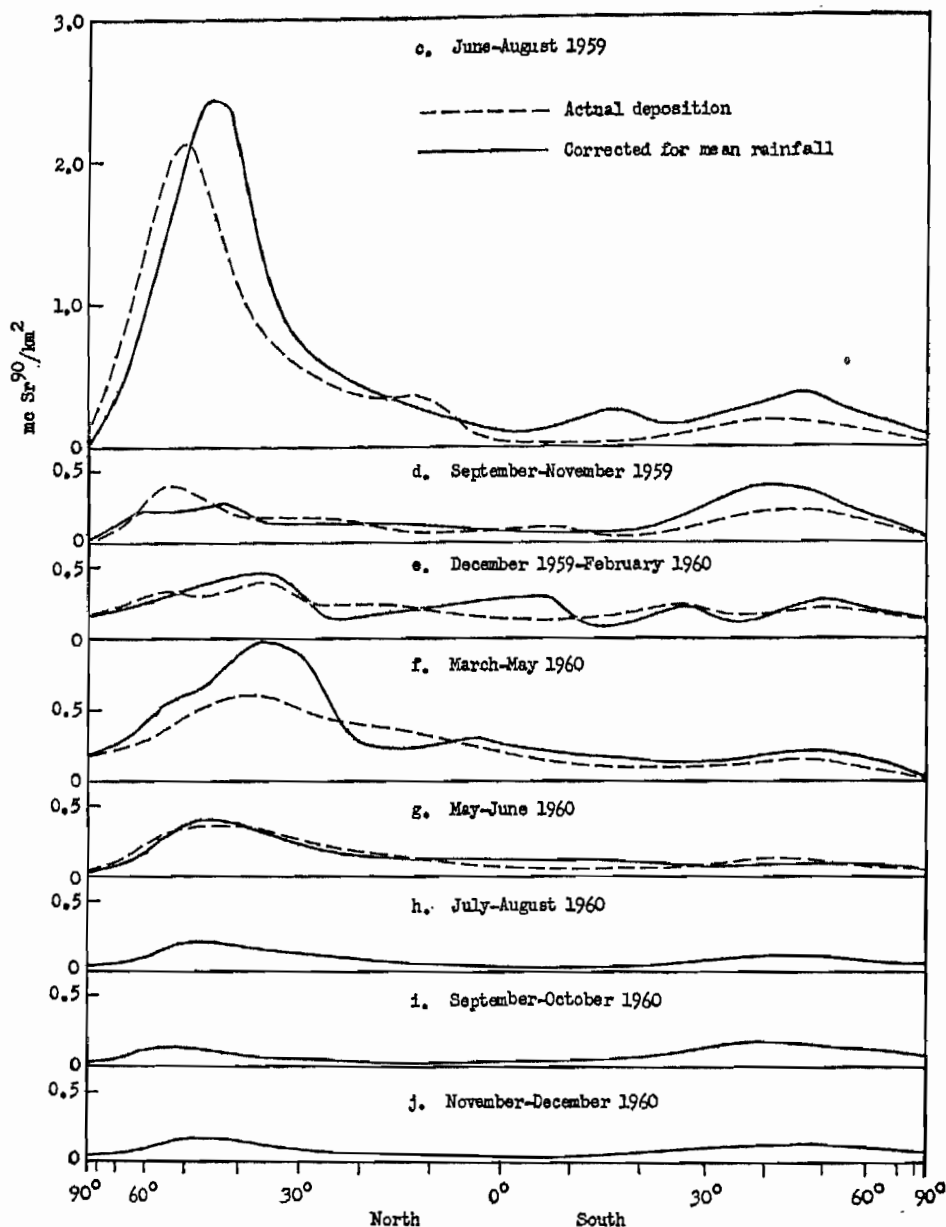


Figure 26c-j. Global distribution of Sr^{90} 88, 116, 188, 276

From figure 27 a fairly good correlation between airborne activity and fall-out rate can be inferred, as was suggested in the previous discussion (paras. 75 and 76).

81. Measurements of Sr^{90} and Cs^{137} could be complementary if the ratio $\text{Cs}^{137}/\text{Sr}^{90}$ were known. This ratio usually lies between 1.5 and 2.0 although occasional values lying outside these limits have been observed. The determination of Sr^{90} involves a complicated chemical analysis and Cs^{137} samples have been found to require considerable care in the collection technique if errors larger than 50 per cent are to be avoided.¹¹⁵ It is therefore not surprising that the $\text{Cs}^{137}/\text{Sr}^{90}$ ratio, which according to some measurements has an average value of 1.7,^{233, 275, 414, 415} in other cases has been reported to be 2.8 with single values up around 8.⁸⁸⁵ All of these deviations need not be analytical errors, as it is evident from table I that the $\text{Cs}^{137}/\text{Sr}^{90}$ ratio may vary between 0.93 and 3.05 for different modes of fission. In addition it has been shown that fractionation¹⁸⁵ and differing transport properties of different size particles may play an important role.^{164, 256, 257}

Measurements of short-lived nuclides

82. The seasonal variations observed in the Sr^{90} and Cs^{137} fall-out rate are not necessarily found with respect to more short-lived nuclides like Zr^{95} , Sr^{89} or Ba^{1} . Here the time of injection becomes more important since the deposition is largely tropospheric. In the case of I^{131} no deposition may be observed later than about two months after injection. Figure 28^{100, 418} shows the variation of Sr^{89} fall-out from 1956 to 1959.

Tritium

83. A number of studies have been made on the atmospheric transport and deposition of tritium.⁴¹⁷⁻ It has been found that tritium is deposited mainly through the action of precipitation, rain and snow containing tritiated water. In figure 29^{417, 418} the fall-out rate of tritium from 1951 to 1960 in the vicinity of Ottawa, Canada, is shown. The values for 1951-1953 correspond to the natural background (E 56) whereas in 1954 the maximum found in individual rains is more than 10

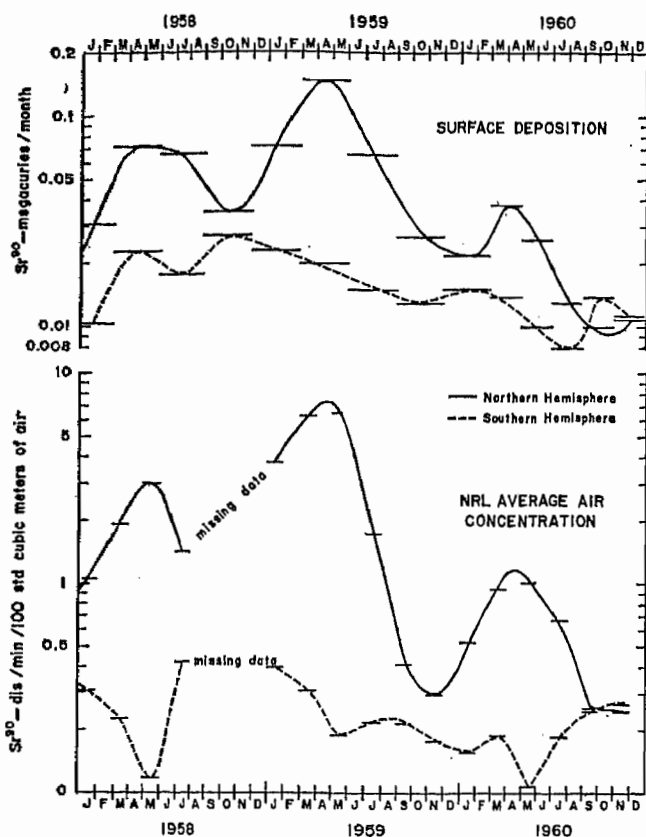
Deposition of Sr^{90} 

Figure 27. Global fall-out rate and surface air concentration²⁷⁶

times higher. From data like these it has been concluded^{418, 424, 428} that the atmospheric half-removal time is no greater than thirty-five or forty days for tritium. Essentially this conclusion holds only for tritium contained in water molecules, but the existence of a large stratospheric reservoir of tritium in the form of hydrogen molecules is not likely as judged from measurements on stratospheric hydrogen.⁴²⁹

84. The cumulative deposit of different nuclides is customarily measured in either of two ways, through extended measurements of fall-out rate or through radio-chemical separation of the activity in soil samples. The first method is preferred for short-lived nuclides like I^{131} and Ba^{140} ; the second method is considered to be more precise for Sr^{90} and Cs^{137} , but most often both sources of information are used for the latter nuclides. Extended measurements of fall-out rate have been presented in previous paragraphs. Integrating the rate gives the deposit and the results of such a procedure are shown in figures 30-32.^{188, 226, 276, 375, 376, 430, 431} There is a large amount of data currently available (December 1961) on radio-chemical analyses of soils for Sr^{90} content.^{69, 102, 118, 117, 174, 192, 196, 207, 224-227, 234-239, 242-244, 384, 387, 393, 398, 402, 409-411, 413, 432-443} The error of most of these data is considered not to exceed ± 10 per cent as a result of the radio-chemical separation. On the basis of 1960-61 data an effort has been made to draw a map of the world-wide distribution (figure 33). Only in North America are the data numerous enough to allow the drawing of isolines.

85. If the soil data are extrapolated through the use of rainfall values and the correlation between rainfall and fall-out rate (para. 77) it is possible to construct more detailed maps,³⁹⁸ but the accuracy of this procedure is perhaps not too great. For North America it has been possible in this way to show⁴⁴⁴ higher Sr^{90} levels due to tropospheric fall-out from the Nevada Test Site injections. Figure 34 shows the Sr^{90} excess above the world average from this cause. The figures have been arrived at through subtracting from the total Sr^{90} deposit a constant value corresponding to the stratospheric fall-out. Recent observations⁴⁴⁵ indicate that this procedure may lead to an overestimate of the tropospheric fall-out.

86. The Sr^{90} data may be combined in 10° latitudinal bands to show the average world-wide distribution (table XIV). The data of table XIV is shown in figure 35. This obviously gives a less detailed picture than

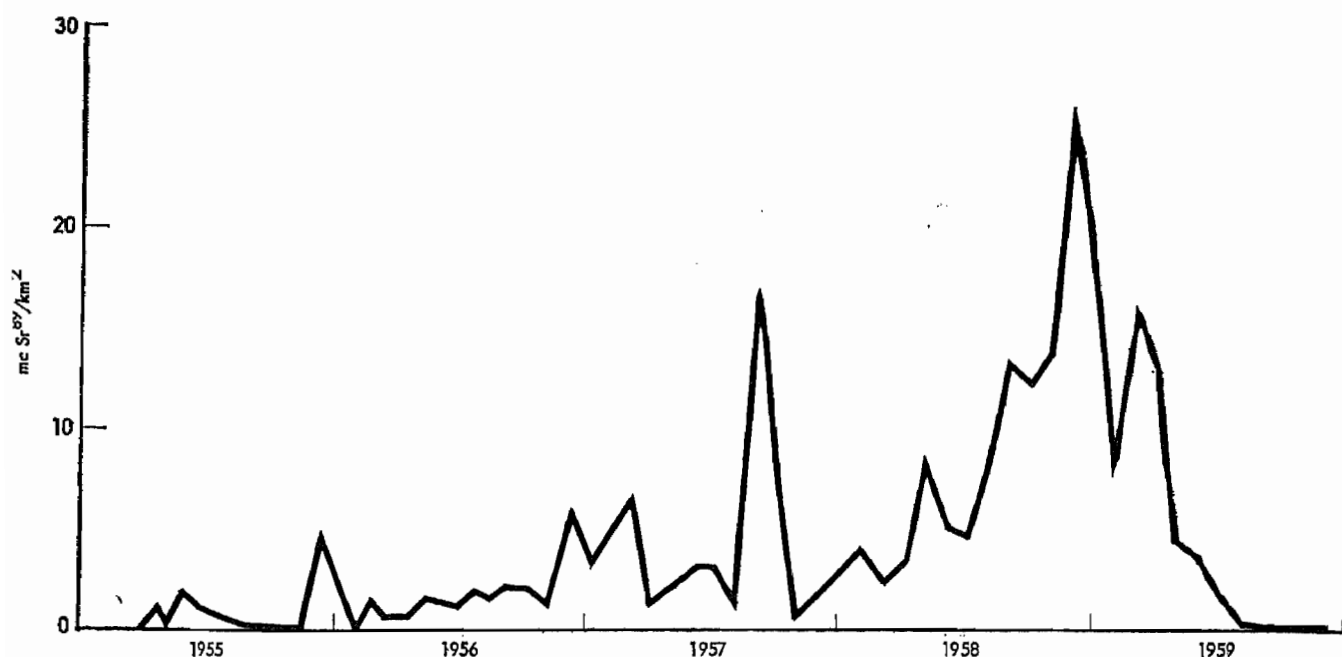


Figure 28. Rate of fall-out of Sr^{90} in Milford Haven, United Kingdom^{102, 375, 376, 394}

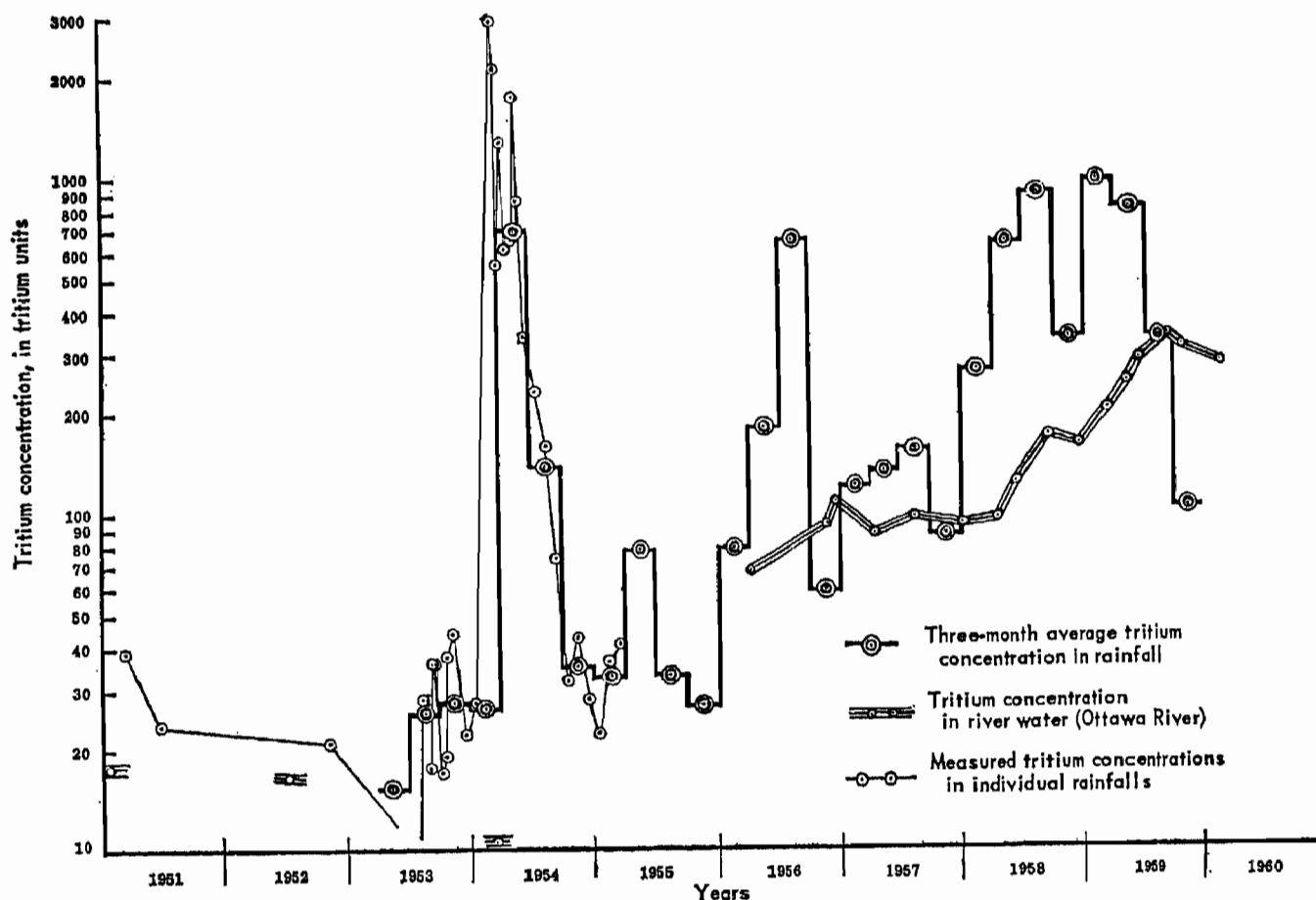


Figure 29. Tritium in rain and river waters in Canada^{417, 418}

a map, the high values, for example, on the west coasts of Norway and the state of Washington, United States, raising the latitudinal mean only slightly. In addition, the values in some latitude bands are based on highly limited numbers of measurements and consequently the error in the average may considerably exceed the 10 per cent⁴⁹⁸ error in measurement.

87. It is finally possible to integrate the latitude distributions of Sr^{90} for different years and to arrive at values for the total deposition as a function of time. This yields for 1956 a figure of $1.4 \pm 0.4 \text{ Mc Sr}^{90}$, while for 1958 the value is 3.1 ± 1.0 , for 1959 5.4 ± 1.6 and 5.4 ± 1.6 for 1960. The uncertainty is obviously great and a much closer network of sampling stations (outside North America) is needed if better data are wanted. It has been found that a correction factor of 1.18 applies to such determinations of Sr^{90} as only 85 per cent of the strontium present is extracted on the average. This factor applies to broad average values but should not be used to correct individual values. Here, therefore, it has been used in giving the average figures above but all other Sr^{90} data given are uncorrected.

Other nuclides

88. Soil data on nuclides other than Sr^{90} may be found in the literature^{431, 446-449} and some are given in table XV. These values are based on gamma spectrometrical methods.

Local factors influencing deposition

89. It should finally be pointed out that local differences of fall-out deposition may be found. Soil samples

taken, for example, at twelve different points of the relatively small island of Hokkaido differed in Sr^{90} content by a factor of more than ten.⁴⁸⁰ Such variations could arise in two ways. Topographic factors may cause marked differences in the deposition of rain and hence of fall-out over small areas; furthermore, after it has been deposited, activity may be displaced by the movement of surface water and wind.

DEPOSITION AND TRANSPORT IN WATER

The oceans

90. The fall-out activity in the oceans arises mainly from three sources: deposition of tropospheric and stratospheric fall-out, close-in fall-out from land and water surface explosions, and rainwater run-off carried by rivers into the oceans. The two first effects presumably dominate the deposition of fall-out over the sea, the first perhaps being 1.5-2 times greater per surface area than over land, as judged from measurements in the Black Sea region.³¹¹ Activity deposited on the water surface rapidly mixes down to about 100 m depth.⁴⁵⁰ From there downwards the rate of exchange is much slower.⁴⁶¹ For this reason and because of the surface movement of ocean water, the variation of water concentrations of fall-out with time, place and depth is extremely complex.

91. Measurements of total β -activity as well as Sr^{90} and other nuclides have been reported.^{224, 227, 294, 295, 395, 461-465} Values^{457, 461} of around $4 \mu\text{C Sr}^{90}/100 \text{ l}$ in the northern Atlantic and a corresponding value of 2 in the southern Atlantic have been reported. The concentration at 50-1,000 m was about half the surface values but

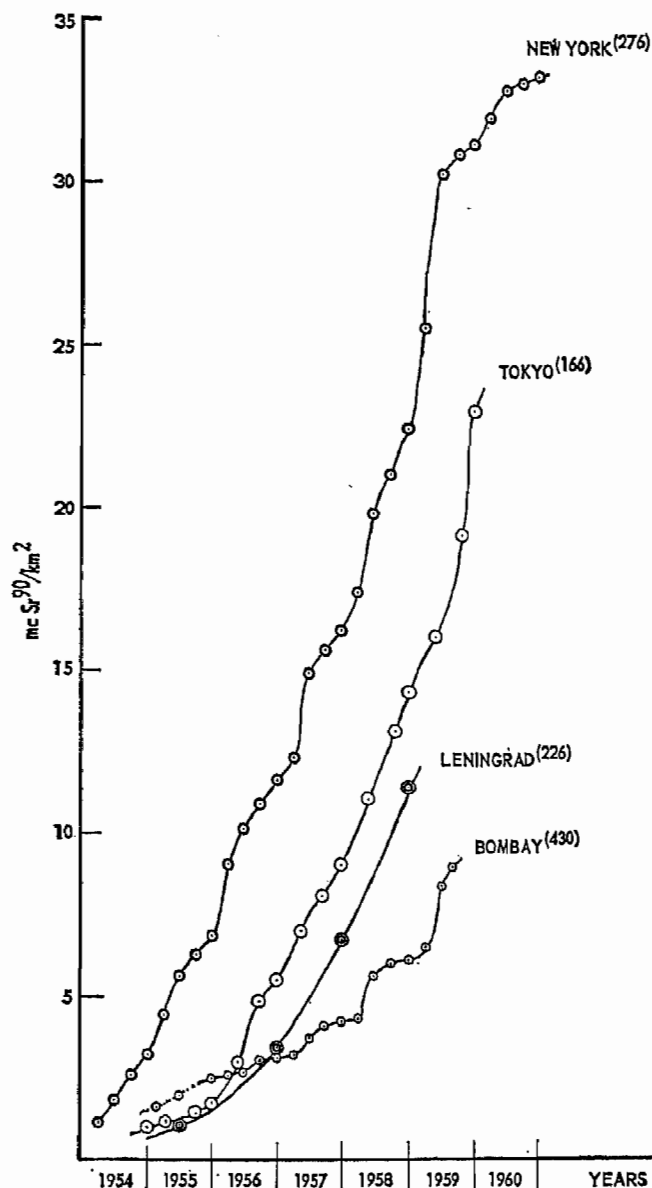


Figure 30. Variation with time in the cumulative Sr^{90} fall-out

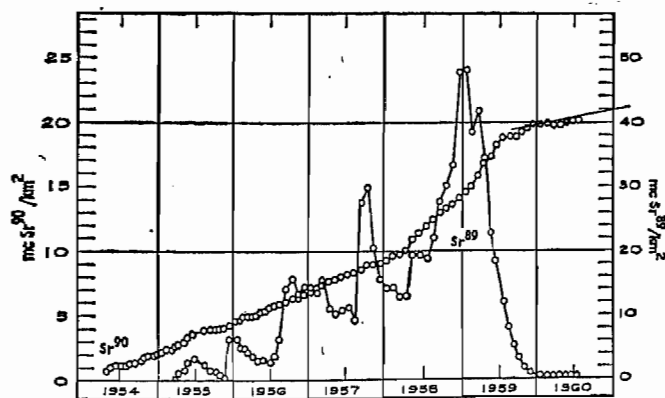


Figure 31. Cumulative deposition at Milford Haven, United Kingdom^{375, 376}

further down at 2,000-3,000 m no strontium was discovered. Higher values have been found in the western Pacific⁴⁵³ varying between 80-310 $\mu\mu\text{C}/100\text{ l}$ of surface water in 1957-59. At 5,000 m⁴⁶³ the values were about one-tenth those at the surface while at 6,000 and 8,000 m no Sr^{90} was found.^{462, 463} Lower values were found in

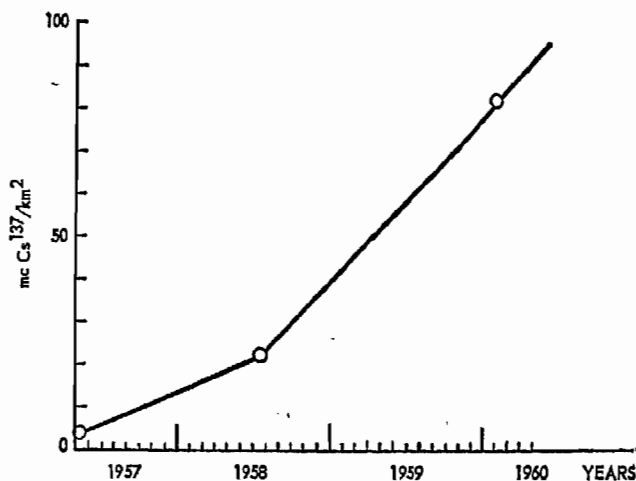


Figure 32. Accumulation of Cs^{137} in soil of Japan⁴⁸¹

1959 in the eastern Pacific. Similar results have been found for Cs^{137} .^{482, 483}

92. Variations in tritium concentration were also observed in seawater.⁴¹⁸ In samples collected from the surface of the sea at a number of widely-spaced points ranging from Arctic latitudes (74° N , 91° W) to 47° N , 47° W , the tritium concentration in the second half of 1954 and the beginning of 1955 fluctuated between 4.2 and about 3 tritium units.* The data are too limited to allow any conclusions to be drawn about the world-wide conditions.

Lakes and rivers

93. Data also exist for lake and river waters the world over.^{211, 225, 280-289, 242-244, 263-270, 405-468} In general values around 0.1-1 $\mu\mu\text{C Sr}^{90}$ and 0.05-0.2 $\mu\mu\text{C Cs}^{137}$ per litre water are found,^{287, 468} but both higher and lower values are occasionally observed. There is a trend in concentration similar to that of the fall-out rate, but the variations with time in any one lake or river are smaller, as could be expected. It has been estimated^{488, 489} that the run-off of Sr^{90} by rivers to the sea is about 1-10 per cent and that of Cs^{137} 2-6 per cent of the yearly deposition but this value is likely to vary between different water sheds. The amount of Sr^{90} in ground water, finally, is usually too small to be detectable.⁴⁶⁸ Measurements of tritium concentrations in ground water samples collected from bores at a depth of 40-50 m⁴¹⁷ showed that, between February 1954 and July 1959, the tritium concentration fluctuated between about 1.4 and 0.4 tritium units, i.e., was appreciably lower than in sea water and very much lower than in rain water.

IV. Predictions of future levels

94. It is obvious from the discussion in the three previous sections that the process of fall-out deposition on the earth's surface is extremely complex. It therefore follows that the task of forecasting the deposition is very difficult. This has indeed been found to be the case already in connexion with predictions of local fall-out although this phenomenon is of short range and duration in comparison with the world-wide fall-out. There are two separate problems to consider in this connexion: (a) prediction of future fall-out from past testing; (b) prediction of future fall-out from hypothetical future testing.

* 1 tritium unit = 10^{-18} H^3 atoms/hydrogen atom.

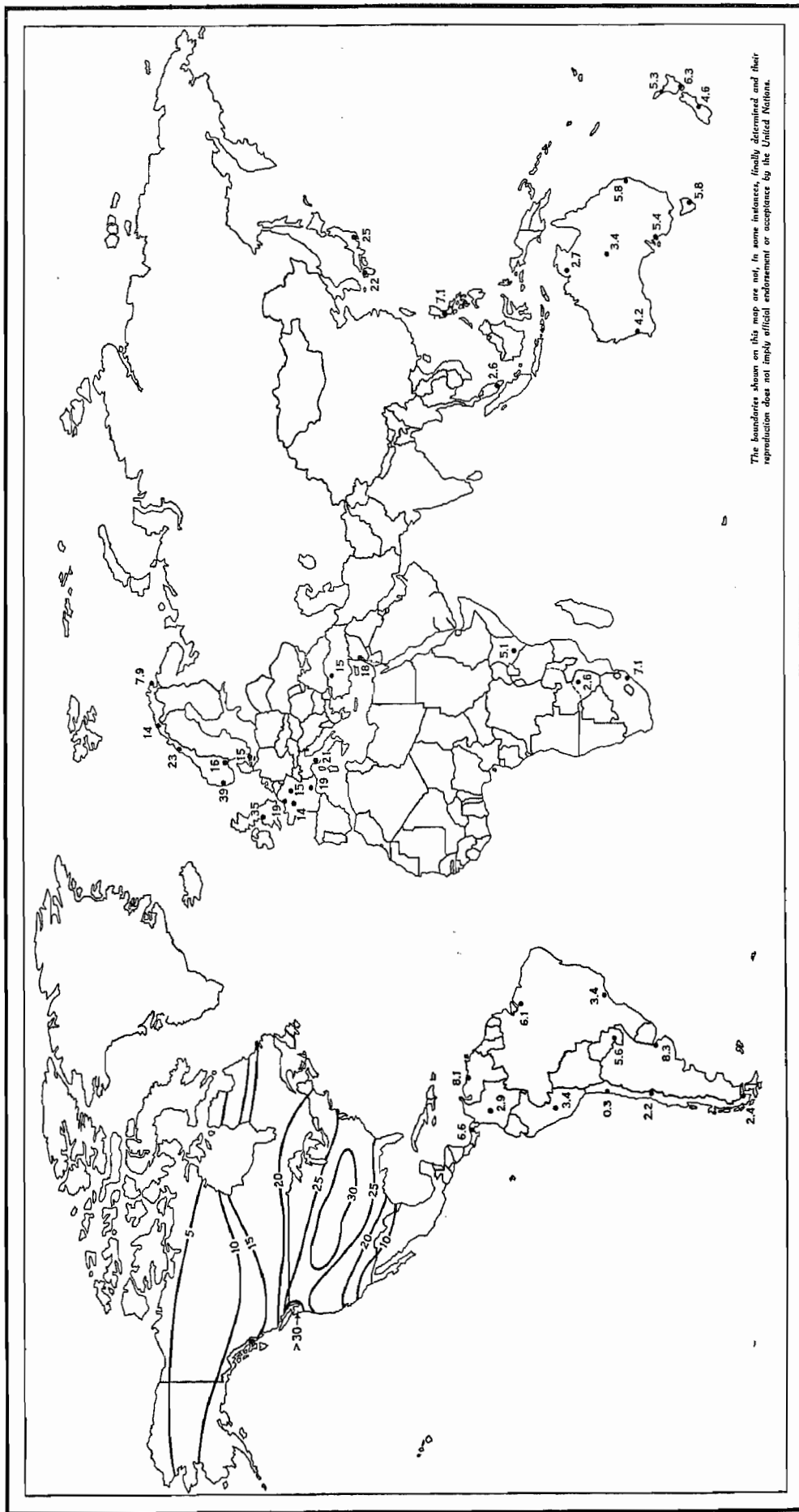


Figure 33. Sr⁹⁰ mc/km² in 1960-1961

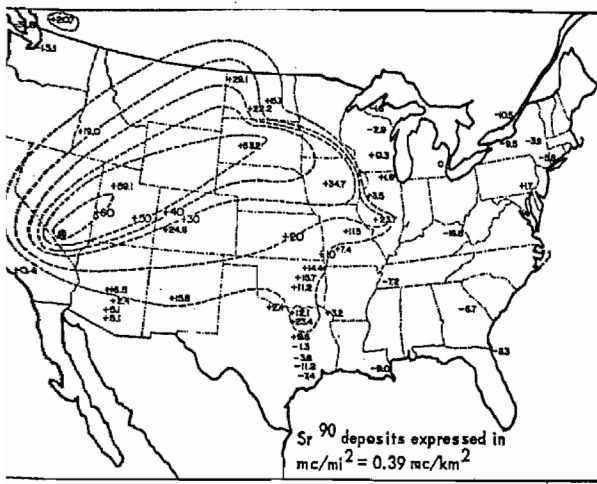


Figure 34. Sr^{90} in USA soils from tropospheric fall-out⁴⁴⁴

The first problem can be given an approximate solution on the basis of experimental measurements. Inventory of present activity levels in the atmosphere, on the ground and in the oceans can be established to within about a factor of 2. The future changes in these activity levels may then be forecast to give a picture of the future world-wide deposition of fall-out in years to come. Also the latitudinal and to a certain extent the geographical distribution may be described in an approximate manner.

The second problem cannot be solved in this way; solution has to be based on assumptions. And a large number of assumptions are necessary to give an answer. Mention the more important ones:

-) Total amount of testing;
-) Types of weapons;
-) Weapon yields;
-) Heights of burst;
-) Season when bursts take place;
-) Test site latitudes;
-) Meteorological conditions.

Inventory of Sr^{90}

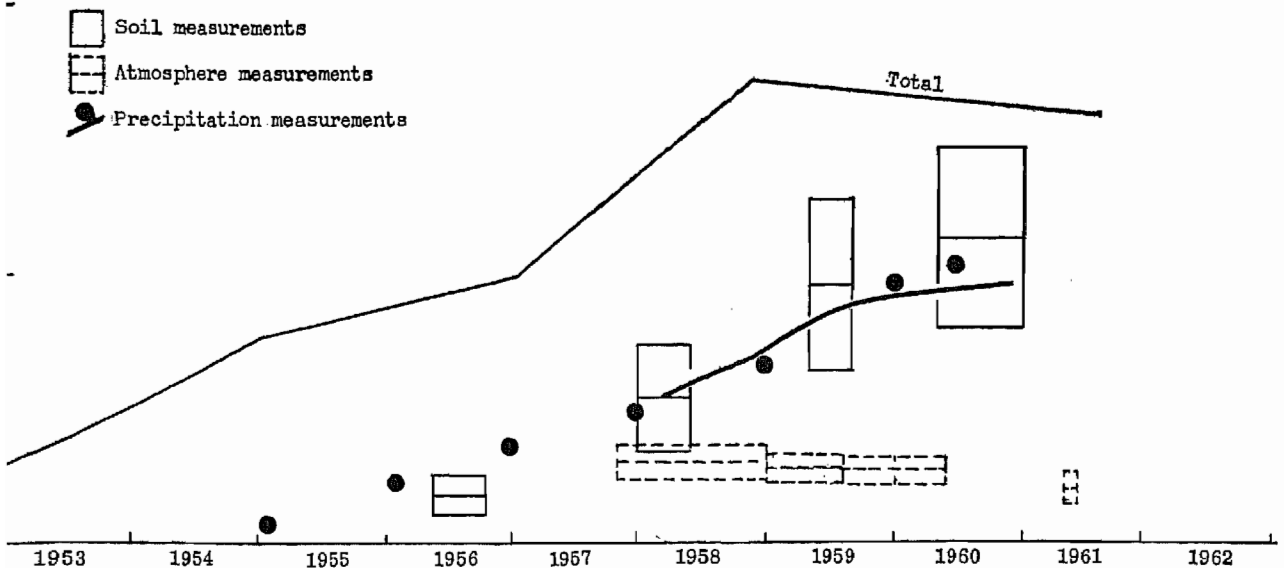


Figure 36. Inventory of Sr^{90}

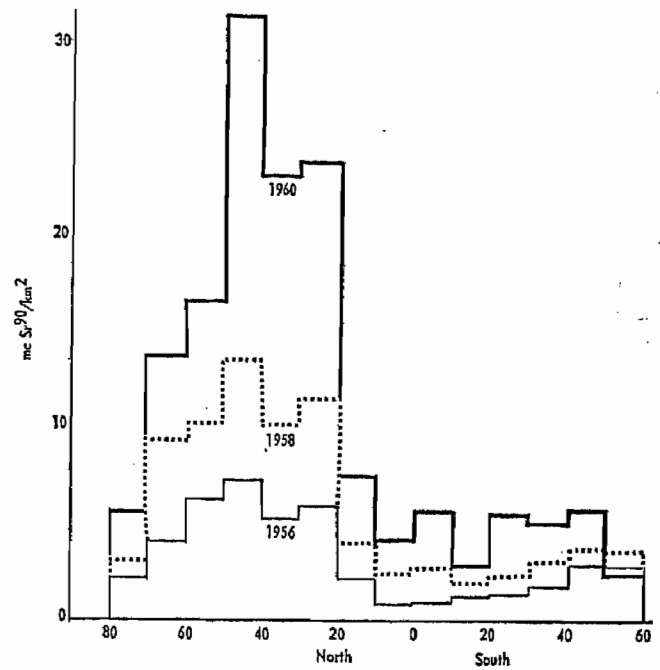


Figure 35. Mean concentration of Sr^{90} in soil at different terrestrial latitudes

Because so many assumptions must be made, no precise calculation is possible, especially as any nuclear devices tested in the future and the conditions of these tests may differ substantially from the past atomic tests with which we are familiar. These considerations must be clearly realized before any conclusions can be drawn from the future predictions that are presented in the following paragraphs.

INVENTORY OF Sr^{90}

97. Measurements of the atmospheric concentrations from close to the ground up to 30 km have been evaluated to give the inventories shown in table XVI.^{152, 470} Data on deposition may be taken from soil measurements (para. 84) and integrations of the fall-out rate.^{88, 110, 188, 152, 276} All these data are summarized in figure 36. Owing

to radio-active decay the total amount of Sr^{90} continuously decreases with time at a rate of 2.5 per cent per year.

98. A closer analysis of the data in figure 36 reveals that from the end of 1958 to mid-1961 the stratospheric reservoir diminished from 1.5 to 1.0 Mc of Sr^{90} , i.e., a difference of 0.5 Mc. Over the same period of time a world-wide deposition of about 1.5 Mc can be inferred from soil and rain measurements. As there were no appreciable injections of Sr^{90} during this time, the data are inconsistent. If, as has been suggested, there is a higher deposition over the oceans than over dry land, this discrepancy would be even greater.

99. The discrepancy in the inventory data is most likely explained by inadequacies in the sampling system:

(a) No samples taken above 30 km in the stratosphere;

(b) Too few samples in the northern polar stratosphere in 1958 and 1959;

(c) No deposition samples reported for large areas of the world, especially the oceans (figure 33).

Thus it is possible only to speculate about the actual situation. One possibility is that the stratosphere above 30 km contains older debris than hitherto assumed. This assumption is supported by the observation^{277, 281} that about 50 per cent of the Cs^{137} in ground level air in late 1960 could be from injections earlier than 1958. On the other hand, stratospheric measurements¹⁵² of the ratio $\text{Ce}^{144}/\text{Sr}^{90}$ (which varies with the age of the debris) do not show any appreciable influx of older debris from above 30 km.

OTHER INVENTORIES

100. The measurements reported on Cs^{137} are too few and limited in scope to allow the establishment of an inventory similar to the one for Sr^{90} . The same can also be said for a number of other nuclides, like Sr^{90} , Zr^{95} and Ce^{144} , that are of some importance as possible health hazards. In the case of Cs^{137} the production in relation to Sr^{90} can be estimated within fairly narrow limits and as this ratio stays almost constant with time, an inventory of Cs^{137} may be arrived at in an indirect way. This procedure is however open to question both because of varying production ratios (table I) and because of the possible importance of fractionation phenomena. Yet this approach is the only possible one at present. For $\text{Cs}^{137}/\text{Sr}^{90}$ a value of 1.7 is usually assumed and this value is also adopted here. A simple multiplication of all Sr^{90} data by 1.7 will therefore describe the Cs^{137} inventory according to paragraphs 97-99.

C^{14} INVENTORY

101. From the measurements of C^{14} levels in the troposphere and the stratosphere the artificial C^{14} inventory may be computed and compared to that calculated from data on the total energy yield of nuclear weapons, as given in paragraphs 36 and 37.

102. The data shown in figure 17 for the increase of the C^{14} activity in the troposphere were obtained by measurement of the increase of C^{14} activity relative to natural C^{14} activity. No measurements above 30 km are available however. Conversion to atoms of C^{14} was done on the following basis: the troposphere contains five-sixths of the mass of the atmosphere, the CO_2 content of the atmosphere is 310 ppm by volume, and the specific activity of natural carbon is 14 ± 1 dpm/g. The troposphere of each hemisphere thus contains 15×10^{27} atoms of cosmic ray produced C^{14} and each 1 per cent increase corresponds to the addition of 0.15×10^{27} atoms of C^{14} to the troposphere.

103. The amount of artificial C^{14} in the biosphere and surface ocean cannot be accurately determined by direct measurements at the present time and hence must be calculated using exchange constants and reservoir size data as deduced from the studies of the carbon cycle. Computed values for the C^{14} content of the biosphere and ocean, along with the stratospheric and tropospheric contents as indicated by experimental data, are given in table XVII for 1 July 1957, 1958, 1959, and May-June 1961.

104. The value of 14×10^{27} atoms for the total artificial C^{14} inventory for 1 July 1958 appears reasonably well established.^{316, 471} An estimate of the C^{14} production from that date up to 31 October 1958 may be obtained from the data given in the hearings of the United States Joint Committee on Atomic Energy.⁸⁰ This leads to an expected production of an additional 5.8×10^{27} C^{14} atoms in that period, i.e., a total inventory of 19 to 22×10^{27} C^{14} atoms as of October 1958. Using the experimentally determined value of 9×10^{27} C^{14} atoms as of 1 January 1957, Hagemann *et al.*⁴⁷¹ estimate a total inventory of 25×10^{27} C^{14} atoms for 31 October 1958.

PREDICTION OF FUTURE FALL-OUT

General

105. The first requisite of an accurate prediction is an accurate inventory. A second necessary condition is a realistic model that describes the complex transport situation. As is apparent from the foregoing discussions, there is appreciable uncertainty on both of these points. Any future prediction will of course inevitably be affected by this. One conclusion may therefore at the present time be that there is no need for adopting a complicated, mathematical treatment of the prediction problem. A simple approach, although more approximate, will be in better line with the uncertainties in the data.

106. In the 1958 report of the Committee the prediction of future fall-out was based on the simple exponential model, i.e., assuming a constant fractional removal of debris from the atmosphere. The deposition $F_d(t)$ and the rate of fall-out $F_r(t)$ were determined by the equations:

$$F_d(t) = e^{-\lambda t} \left[F_d(0) + Q(0) \cdot (1 - e^{-\frac{t}{T_m}}) \right] + \frac{n}{\lambda} \left[\frac{1}{1 + \lambda T_m} + \frac{T_m \lambda}{1 + \lambda T_m} \cdot e^{-\frac{1 + \lambda T_m}{T_m} \cdot t} - e^{-\lambda t} \right]$$

$$F_r(t) = F_r(0) \cdot e^{-\lambda t} \cdot e^{-\frac{t}{T_m}} + \frac{n}{1 + \lambda T_m} \left[1 - e^{-\lambda t} \cdot e^{-\frac{t}{T_m}} \right]$$

where $F_d(0)$, $F_r(0)$ and $Q(0)$ give the deposit, fall-out rate and atmospheric inventory at the start of the prediction period ($t = 0$). T_m is the atmospheric mean residence time, λ the radio-active decay constant and n the rate of injection of debris.

Sr^{90} and Cs^{137}

107. For nuclides like Sr^{90} and Cs^{137} which have half-lives much longer than the mean residence time in the stratosphere, the ultimate deposition on the ground is relatively independent of the value assumed for the residence time. Effects that depend only on the magnitude of the total deposit (e.g. uptake by plant roots) thus vary only little with the assumed residence time.

108. Rate-dependent processes (e.g. uptake by plant leaves and plant base absorption) are directly affected by the residence time. Assuming a short residence time, there will practically be only one year that is characterized by a marked effect. For a longer residence time, several years would show a less marked effect. The overall dose delivered over several years will not vary appreciably with different residence times.

Deposition of Sr^{90} and Cs^{137} from tests up to the end of 1960

109. The deposition of Sr^{90} from these tests was largely completed by mid-1960 and was about 5.4 Mc Sr^{90} (para. 87) and the atmospheric reservoir was about 1.2 Mc (table XVI). The injections of 1959 and 1960 were small enough not noticeably to influence the global distribution of Cs^{137} and Sr^{90} . The Sr^{90} deposit from weapon tests carried out up to 1960 is predicted to reach a maximum value of 5.8 Mc Sr^{90} in 1964 and then to decay with a 28-year half-life (figures 37 and 38).

A model illustrating deposition of Sr^{90} and Cs^{137} from a pattern of tests subsequent to 1960

110. As was pointed out in paragraph 36, for theoretical predictions of fall-out from nuclear explosions it is necessary to know the quantity of radio-active products injected into the atmosphere. At present there are not sufficient data on fall-out from the 1961 tests (para. 37) to make an accurate estimate of the injection from those tests. In addition, there is no way in which the Committee can predict the pattern of future testing and therefore no way of predicting the actual fall-out levels from any such tests. Accordingly, as an illustration, the Committee has chosen a model for the estimation of

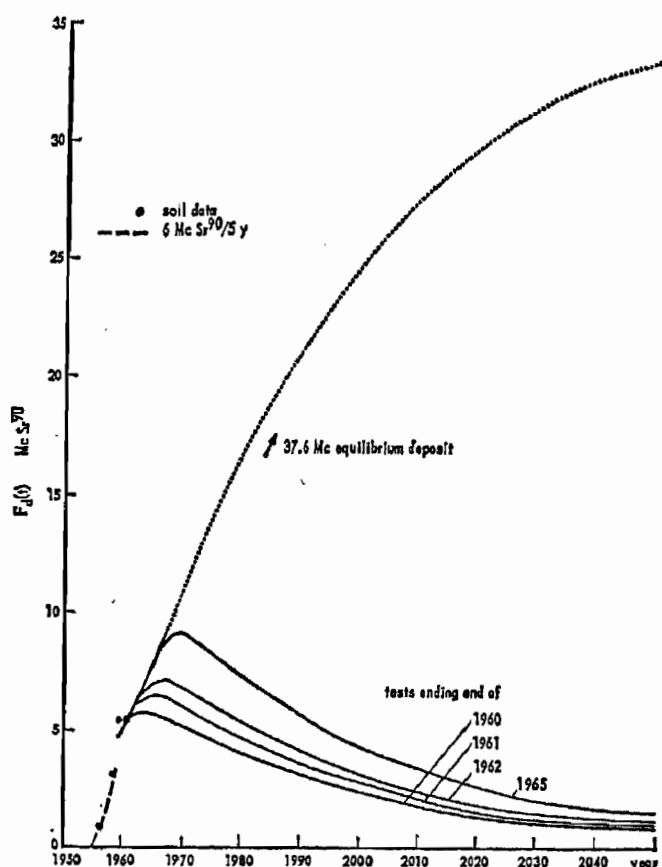


Figure 37. Future deposition of Sr^{90}

fall-out from tests conducted after the end of 1960, in which large-scale testing is resumed in the year 1961 with an injection of 1 Mc Sr^{90} and 10^{28} atoms of C^{14} and continues for specified periods with the same annual injections of Sr^{90} and C^{14} . Within this context, four cases are considered:

- Tests are discontinued at the end of 1961;
- Tests are discontinued at the end of 1962;
- Tests are discontinued at the end of 1965;
- Tests are continued indefinitely.

111. It is assumed that the stratosphere is cleared according to an exponential law with a half-removal time equal to $2\frac{1}{2}$ years. The results of calculations for Sr^{90} are given in figures 37 and 38. Cs^{137} activity is calculated assuming it to be 1.7 times the Sr^{90} activity.

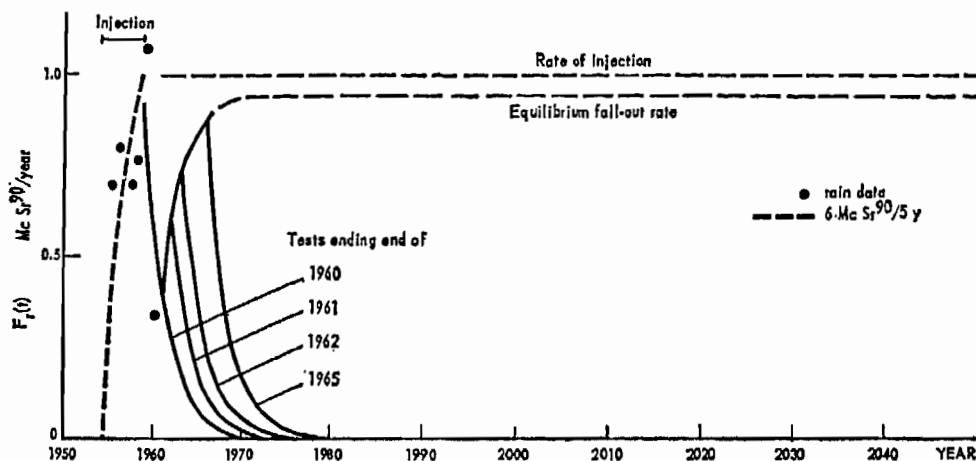


Figure 38. Future fall-out rate of Sr^{90}

112. The latitudinal distribution of future fall-out would be expected to follow the general pattern of figure 35. A larger fraction of debris from polar and temperate latitude injections is deposited in the northern hemisphere. In the past this has amounted to about 15 per cent more for polar injections than for equatorial injections.

113. On these assumptions the maximum deposit from tests completed by the end of 1961 should occur in 1966 and be about 6.5 Mc. The rate of fall-out could in 1962, however, be higher than 0.7 Mc (figure 38) but would then be correspondingly less in subsequent years. In figures 37 and 38 curves have been drawn corresponding to tests being discontinued at the end of 1961, 1962 and 1965. These curves give no indication whatsoever of the actual extent of future weapon testing.

114. For short-lived nuclides, a long delay between injection and deposition will give time for considerable radio-active decay. Early deposition will however bring down measurable amounts of short-lived nuclides. This early deposition has taken place largely in the hemisphere of injection. Probably the residence times for polar and temperate injections are shorter than for equatorial injections, and the doses from short-lived isotopes will be greater for polar and temperate injections than for equatorial injection. Radiation doses from the fall-out of these isotopes have been calculated in annex F, part III.

C¹⁴ from tests up to the end of 1960

115. The present distribution of the inventory of artificial C¹⁴ from tests of nuclear devices to date is known with an accuracy of probably ± 20 per cent. Before the dose received by biospheric material from this added C¹⁴ can be calculated, future biospheric levels of artificial C¹⁴ must be deduced. This can be done mathematically, but the accuracy is limited by the uncertainty in the knowledge of the exchange rates between reservoirs and the total C¹⁴ content of these reservoirs.

116. A limited amount of data on C¹⁴ tropospheric levels for 1960¹⁷⁸ has come to the attention of the Committee. From the available information, it now appears that the tropospheric levels resulting from the injection of C¹⁴ by nuclear testing up to the end of October 1958 may be described as follows:

(a) A peak C¹⁴ increase of about 30 per cent above normal was reached in the northern hemisphere troposphere in late 1959, and levels are now decreasing, being about 25 per cent above normal in the troposphere of both hemispheres in late 1960;

(b) There will be a fall with a half-period of several years to between 10 and 20 per cent above normal—owing to equilibration with the biosphere and surface ocean;

$$N_I = Q \left[\frac{K_I}{K_I + K_{II}} \cdot e^{-(K_I + K_{II} + \lambda)t} + \frac{K_{II}}{K_I + K_{II}} \cdot e^{-\lambda t} \right] = Q \cdot f(t)$$

If all quantities of C¹⁴ are to be expressed as fractions of the natural C¹⁴ level, we shall, dividing by N_{I0} , obtain the following results:

$$\frac{N_I}{N_{I0}} = \frac{Q}{N_{I0}} \cdot f(t)$$

where

N_I , N_{II} are the total number of atoms of C¹⁴ in reservoirs I and II

(c) There will be a further fall with a half-period of about 1,000 years—owing to equilibration with the deep ocean. When equilibration is complete, the C¹⁴ level in the troposphere will be approximately 1 per cent above normal;

(d) This 1 per cent increase above normal will then decay with the mean life of C¹⁴—8,000 years.

117. Figure 39 shows the biospheric level of artificial C¹⁴ expected on the basis of both a 5 and a 2 reservoir model for the following conditions: addition of 22×10^{27} atoms of C¹⁴; average residence time of C¹⁴ in the stratosphere before transfer to the troposphere—five years; average residence time of C¹⁴ in the troposphere before entrance into the biosphere—thirty years; average residence time in the troposphere before transfer to the surface ocean—five years; average residence time in the surface ocean before transfer to the deep ocean—1,000 years. The value of 22×10^{27} atoms of C¹⁴ represents a probable value for what has been injected as of the end of 1960 (para. 104).

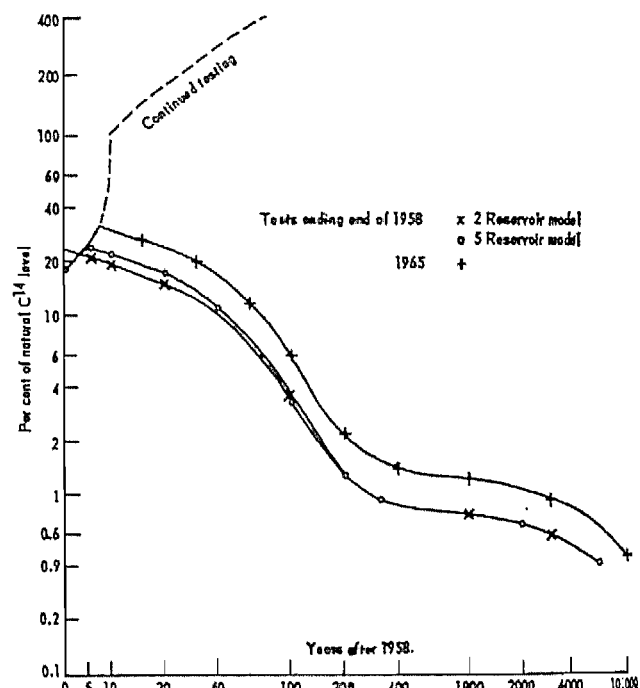


Figure 39. Future levels of C¹⁴ from nuclear tests

118. In the simpler 2 reservoir model, the exchange of carbon between stratosphere, troposphere and surface ocean is assumed to be rapid and they are considered as a single reservoir which is in exchange with the deep ocean. The resulting mathematical expression, according to this mode, for the future atmospheric and biospheric levels will be:

K_I , K_{II} are the exchange rates of reservoirs I and II. Index 0 stands for natural C¹⁴

Q = number of atoms formed

or in numerical form, the addition of 22×10^{27} C¹⁴ atoms to the atmosphere can be expressed as

$$N = 25 (0.96 e^{-0.02031t} + 0.04 e^{-0.000125t})$$

where N is expressed as a percentage of the natural C¹⁴ level.

C¹⁴ from continued testing

119. The rate of testing and/or the rate of injection of C¹⁴ atoms into the atmosphere varied considerably in the period before cessation of nuclear testing. In paragraph 103 and table XVII we see that the total C¹⁴ inventory as of 1 July 1957, 1 July 1958 and 1 July 1959 was 10.5, 13.8 and 21×10^{27} atoms respectively. We shall now consider a hypothetical case of continued testing which results in an average annual production of 10^{28} C¹⁴ atoms per year.

$$N_I(t) = B \int_0^t f(t) dt = B \left[\frac{K_I}{(K_I + K_{II}) (K_I + K_{II} + \lambda)} \left(1 - e^{-(K_I + K_{II} + \lambda)t} \right) + \frac{K_{II}}{K_I + K_{II}} (1 - e^{-\lambda t}) \right]$$

If the quantity of C¹⁴ is expressed as a fraction of the natural C¹⁴ level we shall, dividing by N_{I0}, get a formula, as follows:

$$\frac{N_I(t)}{N_{I0}} = \frac{B}{N_{I0}} \int_0^t f(t) dt$$

where $\frac{B}{N_{I0}}$ = annual injection of C¹⁴, or in numerical form with an annual rate of production of 10^{28} atoms C¹⁴

120. The future distribution of this additional C¹⁴ could be found by estimating the content of each reservoir at some future time on the assumption that it contains the C¹⁴ from each of the previous years as estimated by either the 5 reservoir or 2 reservoir model analysis (paras. 117 and 118). On the basis of the two reservoir model and continued injection of C¹⁴, the future atmospheric and biospheric levels at any time (t) will be:

$$N = 525 (1 - e^{-0.0209t}) + 3,650 (1 - e^{-0.000125t})$$

where N is expressed as a percentage of the natural C¹⁴ level. This means that under these conditions, the biospheric level would be expected to increase over the next one or two hundred years to a value of about four times its natural C¹⁴ content, and then increase much more slowly over tens of thousands of years to a value of the order of thirty times the natural C¹⁴ level (figure 39).

TABLE I. FISSION YIELD OF CERTAIN RADIO-NUCLIDES RESULTING FROM THE FISSION OF HEAVY NUCLEI BY THERMAL AND FAST NEUTRONS¹⁻⁹

Fission product	Half-life	Fission yield (%) from fission by thermal neutrons, fission spectrum neutrons (fast) and neutrons with energy of 14.6 MeV								
		^U ²³⁵ (thermal)	^U ²³⁵ (fast)	^{Pu} ²³⁹ (fast)	^U ²³⁸ (fast)	Th ²³² (fast)	^U ²³⁵ (14 MeV)	^U ²³⁸ (14 MeV)	TID 5555	HASL (117)
Kr ⁸⁵	10.6 years	0.30	0.25	0.07	0.14	—	0.42	0.25	—	—
Br ⁸⁰	50.5 days	4.79	4.15	1.44	2.81	6.7	4.2	3.2	2.93	2.56
Br ⁹⁰	28 years	5.77	4.38	2.23	3.2	6.8	4.5	3.1	3.5	3.50
Y ⁹¹	58 days	5.4	5.21	2.69	3.68	7.2	4.64	3.78	3.65	3.76
Zr ⁹⁵	65 days	6.2	6.72	5.12	5.7	—	4.69	5.40	5.17	5.07
Ru ¹⁰³	7 days	3.0	3.97	6.25	6.6	0.16	3.5	4.89	—	5.20
Ru ¹⁰⁵	1.01 years	0.38	0.47	6.17	2.7	0.042	1.58	3.11	—	2.44
Sb ¹²⁵	2.0 years	0.011	0.059	0.123	0.024	—	0.48	0.65	—	0.29
I ¹³¹	8.05 days	3.1	3.11	4.85	3.33	1.2	4.02	5.29	—	2.89
Te ¹³²	77 hours	4.7	4.44	6.32	4.7	2.4	4.2	4.7	—	4.24
I ¹³³	20.8 days	6.9	6.02	6.19	5.72	—	5.4	—	—	—
Ce ¹³⁷	30 years	6.15	6.18	6.8	6.2	6.3	5.10	5.71	5.76	5.57
Ba ¹⁴⁰	12.8 days	6.35	5.79	5.0	5.7	6.2	4.16	4.65	4.88	5.18
Ce ¹⁴¹	33 days	6.0	5.29	4.65	5.62	9.0	4.47	4.45	—	4.58
Ce ¹⁴⁴	288 days	6.0	4.76	3.66	4.5	7.1	3.3	3.3	4.42	4.69

TABLE II. PERCENTAGE FRACTION OF MASS CHAIN IN GASEOUS OR VOLATILE FORM^{10, 68}

Mass chain	Time after fission		
	1 sec.	17 sec.	35 sec.
89.....	100	100	100
90.....	100	99	94
95.....	20	0	0
103.....	—	65	—
131.....	100	100	100
132.....	—	—	60
137.....	100	100	100
140.....	96	90	75
141.....	—	30	15
144.....	10	0	0
Other nuclides			
H ³	100	100	100
C ¹⁴	100	100	100
U ²³⁷	0	0	0
Np ²³⁹	0	0	0

TABLE III. ESTIMATED PARTITION PERCENTAGE OF DEBRIS (FISSION PRODUCTS) BECOMING LOCAL, TROPOSPHERIC AND STRATOSPHERIC FALL-OUT BY TYPE OF SHOT⁷⁹

Type of shot	Shot size equal to or over 1 MT			Shot size under 1 MT	
	Local	Tropo-spheric	Strato-spheric	Local	Tropo-spheric
Air.....	0	1	99	0	100
Land surface.....	79	1	20	80	20
Water surface.....	20	1	79	20	80
Deep underwater.....	100	0	0	100	0
Contained underground.....	—	—	—	100	0
Low tower.....	—	—	—	80	20
High tower.....	—	—	—	80	20
Balloon.....	—	—	—	0	100

TABLE IV. FISSION AND FUSION ENERGY YIELDS OF NUCLEAR DEVICES^{46, 81}

Period	Fission yield (megatons)		Fusion yield (megatons)	
	Air tests	Surface tests	Air tests	Surface tests
1945-1951.....	0.19	0.57	—	—
1952-1954.....	1	37	—	22
1955-1956.....	5.6	7.5	5.4	9.5
1957-1958.....	31	9	26	19
1959-1960.....	—	0.07	—	—
TOTAL	37.79	54.14	31.4	50.5

TABLE V. MEAN CONCENTRATIONS OF Cs¹³⁷ AND Sr⁹⁰ IN THE ATMOSPHERE OVER THE USSR^{196, 207}

Date of sampling	Altitude of activity sample (in metres)	Concen- tration of caesium-137	Concen- tration of strontium-90	Ratio of number of atoms	
		$\mu\mu$ curies/m ³ of air	$\mu\mu$ curies/m ³ of air	Cs ¹³⁷	Cs ¹³⁷
				Sr ⁹⁰	Sr ⁹⁰
Over European USSR					
May 1955.....	From 3,000 to 7,000	0.026	(0.005)*	5	—
Over Far Eastern USSR					
July-August 1956.....	From 3,000 to 7,000	0.020	(0.006)*	3.5	—
Average over USSR					
March-April 1954.....	From 3,000 to 7,000	—	0.0014	—	0.34
March-May 1955.....	From 3,000 to 7,000	—	0.014	—	0.44
December 1955.....	7,000	—	0.013	—	0.25
April-July 1956.....	7,000	—	0.018	—	0.35-0.74
August-December 1956.....	5,000	—	0.011	—	0.4

* Values in parentheses are calculated.

TABLE VI. STRATOSPHERIC CONTENT OF ARTIFICIAL RADIO-CARBON¹⁵⁰

Date	Radio-carbon content (10 ²¹ C ¹⁴ atoms)	Date	Radio-carbon content (10 ²¹ C ¹⁴ atoms)
1 July 1955.....	8.6	1 July 1957.....	7.4
1 January 1956.....	8.0	1 January 1958.....	6.1
1 July 1956.....	5.6	1 July 1958.....	8.4
1 January 1957.....	6.6	May-June 1961 (preliminary data).....	8.0

TABLE VII. DISTRIBUTION OF CARBON ON THE EARTH AND C^{14} CONTENT OF RESERVOIRS IN THE EXCHANGEABLE CARBON CYCLE

Carbon reservoir	Reservoir	Mass of carbon— (g/cm ² of earth's surface)	Normal inventory of C^{14} atoms
Atmosphere.....	I	0.125	36×10^{27}
Biosphere (terrestrial).....	—	0.06	18×10^{27}
Humus.....	—	0.20	50×10^{27}
Surface waters of ocean (above thermocline)....	I	0.18	50×10^{27}
Remainder of ocean (deep ocean water).....	II	7.50	$1,950 \times 10^{27}$
TOTAL, in "exchangeable" system		8.1	$\sim 2,100 \times 10^{27}$
Sedimentary carbon.....		3,500	
Organic carbon in sediments.....		1,300	
Coal, oil, etc.....		1.4	
TOTAL, carbon in ("sedimentary" systems)		4,800	

TABLE VIII. DATA ON THE SPECIFIC CONCENTRATION OF Sr^{90} AND THE RELATIVE CONCENTRATION OF CAESIUM-137, STRONTIUM-89 AND CERIUM-144 IN RAINFALL IN THE UNITED KINGDOM^{278, 275, 294}

Milford Haven area

Time	Rainfall cm	Specific concentration of strontium-90 in rainwater micromicrocuries litre	Amount of strontium-90 fall-out on earth's surface mc/km ²	Proportion Cs^{137}/Sr^{90}	Proportion Sr^{89}/Sr^{90}	Proportion Ce^{144}/Sr^{90}
Up to the end of						
1954.....			1.97			
1955.....	82.51		2.42			
1956.....	78.77		2.47			
1957.....	90.21		2.60			
1958.....	115.37		5.04			
1959						
I.....	8.00	6.1	0.49	1.8	35	—
II.....	1.30	25	0.33	1.3	23	—
III.....	8.18	12.2	1.00	1.7	16	—
IV.....	5.84	16.8	0.98	1.7	13	19
V.....	1.83	29.3	0.54	1.4	8.1	24
VI.....	3.02	25.8	0.78	1.3	4.6	17
VII.....	6.12	10.2	0.62	1.6	2.9	20
VIII.....	3.07	5.9	0.18	2.0	1.6	25
IX.....	0.71	8.0	0.056	1.0	0.7	43
X.....	21.91	1.21	0.27	1.9	0.5	11
XI.....	29.03	1.01	0.29	1.9	0.4	11
XII.....	16.23	1.18	0.19	2.1	—	12
TOTAL, in 1959	105.24		5.73			
1960						
I.....	13.58	1.22	0.166	1.7	—	7
II.....	8.94	1.62	0.15	1.9	0.5	8
III.....	4.52	2.34	0.11	1.4	2.0	7.5
IV.....	7.54	2.78	0.21	1.7	0.4	4.0
V.....	3.84	5.54	0.21	1.7	—	5.3
VI.....	2.64	3.71	0.098	1.5	—	6.3
VII.....	10.30	2.0	0.20	1.5	—	4.9
VIII.....	8.48	1.65	0.14	1.1	—	2.3
IX.....	20.42	1.00	0.20	1.6	—	3.3
X.....	14.42	0.54	0.078	1.7	—	5.1
XI.....	20.37	0.59	0.12	1.6	—	3.4
XII.....	13.45	0.60	0.080	1.8	—	3.6
TOTAL, in 1960	128.50		1.77			
1961						
I.....	11.55	0.95	0.110	1.8	—	3.0
II.....	6.93	1.88	0.130	1.4	—	2.7
III.....	3.99	2.2	0.088	1.8	—	3.0
IV.....	11.94	2.3	0.27	1.6	—	2.0
V.....	4.56	3.4	0.153	1.7	—	~ 3.6
VI.....	4.95	1.66	0.083	1.9	—	3.4
VII.....	4.44	1.80	0.08	1.6	—	3.0
VIII.....	10.46	1.10	0.115	1.7	—	2.9

TABLE IX. AVERAGE CONCENTRATION OF STRONTIUM-90 IN RAINFALL PER QUARTER*278, 375

No.	Sample collection station	Latitude	Longitude	Average annual precipitation cm	1959 $\mu\text{mc Sr}^{90}/\text{litre}$				1960 $\mu\text{mc Sr}^{90}/\text{litre}$				1961 $\mu\text{mc Sr}^{90}/\text{litre}$	
					I	II	III	IV	I	II	III	IV	I	II
1	Tromsø	69°42'N	19°01'E	70	24.5	21.8	4.4	1.4	2.89	4.5	2.12	1.41	1.0	—
2	Bodo	67°17'N	14°22'E	90	20.8	52.9	5.8	2.6	4.42	5.4	3.4	1.0	1.38	3.8
3	Reykjavik	64°10'N	22°00'W	80	13.5	15.6	3.4	1.2	3.0	3.6	1.20	—	—	—
4	Kinloss	57°39'N	03°34'W	70	9.5	17.8	8.9	1.16	1.79	5.1	1.62	0.61	1.10	2.4
5	Sylt	54°54'N	08°17'E	50	—	24.6	7.7	—	—	—	—	—	—	—
6	Liverpool	53°04'N	04°01'W	85	11.4	18.9	8.3	1.36	1.51	4.0	1.63	0.52	0.80	—
7	Snowdon L.	53°04'N	04°01'W	350	14.6	20.7	8.3	1.44	1.60	2.60	1.61	0.74	—	2.7
8	Abingdon	51°41'N	01°18'W	65	11.2	18.6	7.4	1.69	1.71	3.50	1.52	0.60	1.14	1.35
9	Millford Haven	51°41'N	05°09'W	95	13.4	20.3	7.7	1.62	2.02	3.6	1.55	0.97	1.12	2.5
10	Felixstowe	51°58'N	01°02'E	55	14.9	22.2	6.3	—	—	5.1	1.80	0.58	1.31	1.95
11	Esquimalt	48°30'N	123°00'W	80	8.8	28.8	5.6	1.22	1.22	6.2	2.6	1.17	1.09	—
12	Linz	48°20'N	14°30'E	80	12.8	—	5.4	1.90	1.75	4.0	2.1	0.97	1.86	—
13	Gosausee	47°40'N	13°30'E	250	11.7	9.8	5.7	2.00	1.72	3.9	2.3	0.82	1.91	—
14	Ottawa	45°20'N	75°41'W	100	13.8	28.1	2.9	3.20	5.8	4.4	2.6	1.3	—	—
15	Gibraltar	36°10'N	05°21'W	90	17.8	32.8	9.4	2.0	2.2	5.2	15.8	0.68	3.4	—
16	Akrotiri (Cyprus)	35°00'N	33°23'E	40	—	90.0	No rain	2.2	1.99	2.9	No rain	1.64	2.7	—
17	Caenwood	18°13'N	76°35'W	280	8.3	9.0	1.4	1.14	—	1.23	0.68	0.37	—	—
18	Palisadoes	17°56'N	76°47'W	80	13.5	7.2	8.0	0.6	0.62	0.58	0.32	0.11	<1	—
19	Lagos (Nigeria)	06°30'N	03°40'E	250	3.6	2.0	0.83	0.47	1.06	0.36	0.59	0.25	0.6	—
20	Singapore	01°19'N	103°49'E	240	1.1	0.45	0.35	0.06	0.10	0.09	0.15	0.10	0.16	—
21	Suva (Fiji)	18°05'S	178°28'E	290	<0.3	<0.3	0.25	0.37	0.19	<0.2	0.56	0.4	—	—
22	Melbourne	37°45'S	144°50'E	65	1.6	5.0	1.0	1.7	1.2	0.43	0.91	2.3	2.2	—
23	Ohakea	40°12'S	175°23'E	100	1.1	1.0	1.2	1.1	0.72	0.63	0.79	1.31	1.4	—
24	Port Stanley	51°42'S	57°52'W	65	1.1	1.3	1.4	0.64	0.76	0.60	0.89	1.02	1.0	—

TABLE X. RATE OF Sr^{90} FALL-OUT mc/km^2 AND MONTH 207, 226, 231, 239, 278, 375, 385, 394, 396

	Richmond USA	Milford Haven UK	Ispra Italy	Leningrad USSR	Buenos Aires Argentina	Japan		Richmond USA	Milford Haven UK	Ispra Italy	Leningrad USSR	Buenos Aires Argentina	Japan
1957							1959						
I.....	—	0.23	—	0.25	—	—	I.....	0.57	0.49	0.63	0.45	—	0.33
II.....	—	0.22	—	0.21	—	—	II.....	0.52	0.33	1.66	0.28	—	0.12
III.....	—	0.45	—	—	—	—	III.....	0.23	1.00	3.90	0.15	—	1.02
IV.....	—	0.6	—	0.33	—	—	IV.....	0.13	0.98	6.20	—	—	1.12
V.....	—	0.16	—	—	—	—	V.....	0.06	0.54	3.10	—	—	1.86
VI.....	—	0.28	—	0.10	—	—	VI.....	0.01	0.78	0.80	—	—	0.78
VII.....	—	0.24	—	0.11	—	0.03	VII.....	0.02	0.62	0.15	—	—	0.14
VIII.....	—	0.12	—	—	—	—	VIII.....	0.00	0.18	0.20	—	—	0.17
IX.....	—	0.36	—	0.09	—	0.21	IX.....	0.02	0.06	0.08	—	—	—
X.....	—	0.30	—	0.13	—	0.14	X.....	0.01	0.27	0.05	—	—	—
XI.....	—	0.03	—	0.22	—	0.07	XI.....	0.00	0.29	0.08	—	—	—
XII.....	—	0.15	—	0.53	—	0.11	XII.....	0.03	0.19	0.10	—	—	—
1958							1960						
I.....	—	0.21	—	—	—	0.15	I.....	0.10	0.17	—	—	0.05	—
II.....	—	0.34	0.55	0.48	—	0.13	II.....	0.11	0.15	—	—	0.05	—
III.....	—	0.15	0.60	—	—	0.13	III.....	0.12	0.11	—	—	0.09	—
IV.....	—	0.28	0.50	0.16	—	0.22	IV.....	0.02	0.21	—	—	0.04	—
V.....	—	0.94	1.60	0.72	—	0.65	V.....	0.02	0.21	—	—	0.02	—
VI.....	—	0.52	1.45	1.16	—	0.33	VI.....	0.00	0.10	—	—	0.03	—
VII.....	—	0.62	1.25	0.78	—	0.46	VII.....	0.01	0.20	—	—	0.04	—
VIII.....	—	0.51	1.10	0.25	—	0.34	VIII.....	0.01	0.14	—	—	0.04	—
IX.....	—	0.58	0.25	0.23	—	0.14	IX.....	0.00	0.20	—	—	0.11	—
X.....	—	0.35	1.05	0.30	—	0.44	X.....	0.01	0.08	—	—	0.18	—
XI.....	—	0.29	0.46	0.44	—	0.32	XI.....	0.03	0.12	—	—	0.07	—
XII.....	—	0.61	0.40	0.20	—	0.49	XII.....	—	0.08	—	—	0.07	—

TABLE XI. AVERAGE QUARTERLY FALL-OUT OF STRONTIUM-90 ON THE EARTH'S SURFACE²⁷⁶

No.	Sampling station	Latitude	Longitude	Average annual precipitation cm	Average strontium-90 fall-out per quarter mc/km ²				Strontium-90 fall-out in 1959 mc/km ²				Average caesium-137/strontium-90 ratio per quarter			
					1959				1960				1959			
					I	II	III	IV	I	II	III	IV	I	II	III	IV
1	Tromsø	69°42'N	19°01'E	70	10.6	4.6	1.78	0.25	0.86	—	—	—	1.7	1.4	1.9	1.8
2	Bodo	67°17'N	14°22'E	90	4.57	10.7	2.7	0.48	1.03	—	—	—	1.5	1.4	1.6	2.7
3	Reykjavik	64°10'N	22°00'W	80	—	2.59	1.29	0.52	0.37	0.98	—	—	—	1.3	2.0	1.9
4	Kinloss	57°39'N	03°34'W	70	1.13	2.14	0.76	0.19	0.27	0.74	—	—	1.4	1.6	1.7	2.4
5	Sylt	54°54'N	08°17'E	50	—	1.61	0.68	—	—	—	—	—	—	1.6	1.6	—
6	Liverpool	53°21'N	02°58'W	85	1.28	3.55	1.02	0.38	0.31	0.40	—	—	1.6	1.6	1.6	1.7
7	Snowdon L.	53°04'N	04°01'W	350	9.91	9.40	2.46	2.18	1.70	1.35	—	—	1.5	1.4	1.4	1.8
8	Snowdon U.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
9	Abingdon	51°41'N	01°18'W	65	6.62	9.46	1.97	3.32	1.73	1.41	—	—	1.7	1.6	1.2	1.5
10	Milford Haven	51°41'N	05°09'W	95	1.73	1.75	0.74	0.34	0.26	0.54	—	—	1.4	1.8	1.3	1.3
11	Felixstowe	51°58'N	01°02'E	55	2.34	2.21	0.76	1.09	0.55	0.50	—	—	1.7	1.6	1.7	1.5
12	Esquimalt	48°30'N	123°00'W	80	0.97	1.28	0.51	—	—	0.28	—	—	1.9	1.5	1.9	—
13	Linz	48°20'N	14°30'E	80	4.54	1.4	0.39	0.47	0.35	0.40	—	—	1.5	1.7	2.3	2.4
14	Gosause	47°40'N	13°30'E	250	—	—	—	—	—	—	—	—	—	—	—	—
15	Ottawa	45°20'N	75°41'W	100	6.3	3.6	3.3	0.53	0.65	0.97	—	—	1.5	1.7	2.0	1.7
16	Gilbraltar	36°10'N	05°21'W	90	2.26	4.69	0.77	0.69	1.4	0.70	—	—	1.8	1.4	2.9	1.9
17	Akrotiri	35° N	33°23'E	40	8.39	2.89	0.47	0.49	1.18	0.28	—	—	1.7	1.6	2.0	4.0
18	Caenwood	17°13'N	76°35'W	280	—	0.27	—	0.37	—	—	—	—	—	1.0	—	1.6
19	Palisades	17°56'N	76°47'W	80	3.25	10.8	0.12	—	—	—	—	—	1.6	1.6	1.9	—
20	Lagos	06°30'N	03°40'E	250	0.32	1.06	0.2	0.16	0.085	—	—	—	1.9	1.4	0.9	1.7
21	Singapore	01°19'N	103°49'E	240	0.70	1.85	0.51	0.11	0.19	—	—	—	2.0	1.3	1.5	2.4
22	Suva	18°05'S	178°28'E	290	0.95	0.28	0.17	0.046	0.05	—	—	—	1.85	1.5	1.4	1.4
23	Melbourne	37°45'S	144°50'E	65	0.4	0.25	0.22	0.20	0.21	—	—	—	—	—	2.2	1.7
24	Ohakea	40°12'S	175°23'E	100	0.24	0.54	0.17	0.29	0.12	—	—	—	1.9	1.6	1.8	1.9
25	Port Stanley	51°42'S	57°52'W	65	0.33	0.23	0.17	0.17	0.15	—	—	—	1.8	1.4	1.4	1.5
					0.28	0.18	0.14	0.09	0.11	—	—	—	1.6	1.9	1.7	1.9

TABLE XII A. EXPERIMENTAL DATA ON FALL-OUT OF CERTAIN RADIO-ISOTOPES IN 1957 ON THE EARTH'S SURFACE IN THE LENINGRAD AREA²⁰⁷

Fall-out sampling period	Total beta-activity mc/km ²	Cerium-141		Yttrium-91		Strontium-89		Cerium-144	
		mc/km ²	% of total	mc/km ²	%	mc/km ²	%	mc/km ²	%
1957									
I.....	21.4	2.49	11.06	0.8	3.7	2.4	11.2	7.58	—
II.....	23.7	—	—	—	—	1.6	6.9	1.87	7.9
III.....	20.4	—	—	0.12	5.9	1.1	5.6	—	—
IV.....	118.4	9.73	8.2	1.1	9.5	3.8	3.2	5.91	5.0
V.....	70.0	—	—	1.0	1.43	12.6	18.0	9.40	13.4
VI.....	34.5	—	—	1.5	4.3	0.64	1.86	3.03	8.8
VII.....	19.5	—	—	3.9	20.2	3.1	15.9	—	—
VIII.....	39.3	—	—	6.0	15.4	3.77	9.6	3.22	8.2
IX.....	119.5	22.5	18.9	14.4	12.2	27.3	22.8	6.10	5.1
X.....	92.8	9.63	10.4	6.6	7.2	4.47	4.8	4.08	5.2
XI.....	18.9	1.86	9.9	7.4	3.9	—	—	1.37	7.3
XII.....	27.9	—	—	2.7	9.9	3.96	14.2	4.8	17.2
Total for year with extrapolation for missing months.....		75.0		49.7		70.7		57.7	
Average fall-out per month, 1958.....		50.5	6.25	4.14		5.89		4.81	

TABLE XII B. EXPERIMENTAL DATA ON FALL-OUT OF CERTAIN RADIO-ISOTOPES ON THE EARTH'S SURFACE IN THE LENINGRAD AREA IN 1958²⁰⁷

Fall-out sampling period	Total beta-activity mc/km ²	Cerium-141		Ruthenium-103		Zirconium		Cerium-144		Caesium-137		
		mc/km ²	%	mc/km ²	%	mc/km ²	%	mc/km ²	%	mc/km ²	%	
1958												
I.....	31.0	3.47	11.2	3.43	11.1	3.02	9.7	4.94	5.0	{	—	—
II.....	25.7	4.04	15.7	3.57	13.9	4.03	15.7				—	—
III.....	42.3	3.34	7.9	2.14	5.1	3.36	7.9				—	—
IV.....	56.87	8.14	14.3	3.76	6.6	7.00	12.3	5.21	9.2	—	—	
V.....	134.2	12.50	9.3	7.77	5.8	12.71	9.5	14.90	11.1	1.33	0.99	
VI.....	194.2	29.60	15.2	13.80	7.1	21.47	11.1	10.58	5.5	2.03	1.05	
VII.....	93.5	9.86	10.5	5.87	6.3	7.58	8.1	4.82	5.2	1.19	1.30	
VIII.....	55.5	5.67	10.2	3.71	6.7	4.20	7.6	3.20	5.8	0.90	1.60	
IX.....	29.64	2.31	7.8	1.45	4.9	2.31	7.8	2.04	6.9	1.53	5.20	
X.....	216.2	13.30	6.2	6.66	3.1	10.42	4.8	5.21	2.4	0.94	0.40	
XI.....	233.3	18.76	8.0	12.85	5.5	16.67	7.2	8.59	3.7	0.46	0.20	
XII.....	124.0	2.68	2.2	3.42	2.8	5.81	4.7	3.01	2.4	—	—	
Total for year with extrapolation for missing months.....		113.7		68.4		98.6		62.5		14.4		
Average fall-out per month, 1958.....		103.00	9.47	5.70		8.21		5.21		1.20		

TABLE XII C. EXPERIMENTAL DATA ON FALL-OUT OF CERTAIN RADIO-ISOTOPES ON THE EARTH'S SURFACE IN THE LENINGRAD AREA IN 1959²⁰⁷

Fall-out sampling period	Total beta- activity mc/km ²	Cerium-141		Ruthenium-103		Zirconium-95		Cerium-144		Caesium-137		Proportion Cs ¹³⁷ /Sr ⁹⁰
		mc/km ²	%	mc/km ²	%	mc/km ²	%	mc/km ²	%	mc/km ²	%	
1959												
I.....	155.9	19.20	12.3	22.97	14.7	22.89	14.7	10.95	7.0	1.54	0.99	3.4
II.....	89.3	6.60	7.4	6.67	7.5	10.66	11.9	8.31	9.3	1.07	1.20	3.8
III.....	42.4	1.23	2.9	2.63	6.2	4.36	10.3	4.05	9.6	0.57	1.34	3.8
Total for first quarter 1959....		270.03		322.7		379.1		23.31		3.18		
Average fall-out per month in first quarter 1959....		~ 0.95	0.90	~ 1.07		~ 1.26		~ 0.77		1.05		

TABLE XIII. MEAN MONTHLY FALL-OUT OF SOME RADIO-ISOTOPES IN THE VICINITY OF RICHMOND (USA)⁸⁹⁸

Date of sample	mc/km ³				
	Sr ⁹⁰	Pu ²³⁹	Ce ¹⁴⁴	W ¹⁸⁵	Sr ⁹⁰ /Sr ⁹⁰
1959					
I.....	14.7	—	—	3.8	30
II.....	17.2	—	—	2.3	31
III.....	2.6	—	—	0.85	13
IV.....	1.2	—	—	0.39	10
V.....	0.37	—	—	0.31	6.9
VI.....	0.029	—	—	0.12	6.0
VII.....	0.058	—	—	0.050	—
VIII.....	0.009	—	—	0.015	2.6
IX.....	0.024	—	—	0.018	1.5
X.....	0.004	—	—	0.014	0.96
XI.....	0.003	—	—	0.012	3.0
XII.....	0.021	—	—	0.016	0.74
1960					
I.....	0.080	0.0029	0.84	0.043	0.90
II.....	0.075	0.0015	0.74	0.021	0.81
III.....	0.56	0.0017	0.83	0.017	0.10
IV.....	0.012	0.0005	0.15	0.005	0.58
V.....	0.005	0.0005	0.12	0.005	0.33
VI.....	0.001	0.0009	0.029	—	—
VII.....	—	0.0006	0.038	—	1.00
VIII.....	—	0.0012	0.054	—	—
IX.....	—	0.0002	0.018	—	—
X.....	—	0.0003	0.098	—	—
XI.....	—	0.0017	0.13	—	—

TABLE XIV. VARIATIONS IN THE MEAN STRONTIUM-90 CONCENTRATION IN THE SOIL AT DIFFERENT LATITUDES

No.	Latitude	Increase in quantity of strontium-90 during period from 1956 to 1958		Quantity of strontium-90 at the first half of 1958		Quantity of strontium-90 at the middle of 1959		Quantity of strontium-90 at the middle of 1960		Area of belt of earth's surface 10 ⁴ km ²
		Mega c	mc/km ²	Mega c	mc/km ²	Mega c	mc/km ²	Mega c	mc/km ²	
1	80°-70°N.....	0.03	2.2	0.03	3.1					11.1
2	70°-60°N.....	0.08	4.1	0.17	9.5	0.22	11.6	0.25	13.2	18.9
3	60°-50°N.....	0.16	6.4	0.26	10.3	0.30	11.8	0.43	16.9	25.4
4	50°-40°N.....	0.23	7.4	0.43	13.6	0.76	24.1	0.76	24.1	31.6
5	40°-30°N.....	0.19	5.3	0.36	10.1	0.81	22.3	0.87	24.0	36.3
6	30°-20°N.....	0.24	6.0	0.47	11.6	1.04	25.9	0.93	23.2	40.1
7	20°-10°N.....	0.09	2.2	0.17	4.1	0.40	9.4	0.33	7.7	42.7
8	10°- 0°N.....	0.03	0.8	0.10	2.3	0.22	5.0	0.17	3.8	44.3
9	0°-10°S.....	0.04	1.0	0.12	2.7	0.27	6.1	0.24	5.4	44.3
10	10°-20°S.....	0.06	1.3	0.08	1.8	0.12	2.8	0.13	3.0	42.7
11	20°-30°S.....	0.06	1.4	0.10	2.4	0.14	3.5	0.17	4.2	40.1
12	30°-40°S.....	0.07	1.8	0.11	3.1	0.15	4.1	0.18	5.0	36.3
13	40°-50°S.....	0.09	2.9	0.12	3.8	0.15	4.7	0.15	4.7	31.6
14	50°-60°S.....	0.07	2.9	0.09	3.6					25.4
	TOTAL Megacuries	1.43		2.60		4.58		4.61		

TABLE XV. CONCENTRATIONS (mc/km²) OF GAMMA-RADIATING FISSION FRAGMENTS IN SOIL SAMPLES COLLECTED IN THE VICINITY OF CHICAGO, USA⁴⁴⁶

Radio-nuclide	Zr ⁹⁵ - Nb ⁹⁵ 65-35 days	Cs ¹³⁷ 30 years	Ru ¹⁰⁶ 1 year	Ru ¹⁰⁸ 40 days	Ce ¹⁴¹ 32 days	Ce ¹⁴⁴ 290 days
1957						
V.....	69	13.5	67	67	42	92
VII.....	75	13.0	69	77	46	100
X.....	89	14	69	92	54	106
1958						
III.....	80	17	65	50	23	96
VI.....	36	25	58	13	6	83
IX.....	120	38	81	31	15	104
1959						
III.....	280	49	240	127	223	435
IV.....	380	52	310	89	156	560
V.....	400	54	340	71	103	590
VI.....	360	57	450	46	70	655
VII.....	290	58	463	35	43	700
VIII.....	230	61	340	20	29	655
IX.....	170	66	385	11	19	680
X.....	140	74	370	—	—	740
XI.....	100	72	380	—	—	710
XII.....	77	72	390	—	—	660
1960						
II.....	58	76	380	—	—	615
III.....	43	75	365	—	—	620
IV.....	35	76	350	—	—	635

TABLE XVI. APPROXIMATE Sr⁹⁰ ATMOSPHERE INVENTORIES (IN MEGACURIES)^{162,470}

Height	Nov. 57-Dec. 58	Jan. 59-Aug. 59	Sept. 59-Dec. 59	Jan. 60-May 60	May 60	Nov. 60	May 61
<i>Northern hemisphere</i>							
Above 30 km.....	0.20 ± 0.04	0.20 ± 0.04	0.17 ± 0.04	0.13 ± 0.04	0.14	0.13	0.12
20-30 km.....	0.15 ± 0.05	0.27 ± 0.08	0.30 ± 0.08	0.25 ± 0.10	0.23	0.20	0.14
Tropopause—20 km.....	0.61 ± 0.09	0.38 ± 0.06	0.33 ± 0.05	0.37 ± 0.06	0.25	0.24	0.19
TOTAL	0.96 ± 0.20	0.85 ± 0.16	0.80 ± 0.15	0.75 ± 0.15	0.62	0.57	0.45
<i>Southern hemisphere</i>							
Above 30 km.....	0.20 ± 0.04	0.19 ± 0.04	0.16 ± 0.04	0.12 ± 0.04	0.14	0.13	0.12
20-30 km.....	0.11 ± 0.03	0.15 ± 0.05	0.17 ± 0.06	0.13 ± 0.05	0.23	0.20	0.14
Tropopause—20 km.....	0.22 ± 0.03	0.13 ± 0.02	0.16 ± 0.08	0.27 ± 0.08	0.19	0.24	0.26
TOTAL	0.53 ± 0.13	0.47 ± 0.10	0.49 ± 0.13	0.52 ± 0.13	0.56	0.57	0.52
<i>Global troposphere</i>							
	0.03	0.03	0.03	0.03	0.03	0.02	0.03
<i>World total</i>							
	1.52 ± 0.33	1.35 ± 0.26	1.32 ± 0.28	1.30 ± 0.28	1.21	1.16	1.00

TABLE XVII. DISTRIBUTION OF C¹⁴ BETWEEN RESERVOIRS AND TOTAL INVENTORY AS OF JULY 1957, 1958, 1959, AND MAY-JUNE, 1961

Reservoir	C ¹⁴ content in units of 10 ²⁷ atoms*			
	1 July 1957	1 July 1958	1 July 1959	May-June 1961**
Stratosphere.....	7.4	8.4	(10-13)	8.0
Troposphere.....	2.5	4.0	6.7	13.0
Ocean.....	(0.5)	(1.2)	(2.2)	(6.2)
Biosphere.....	(0.1)	(0.2)	(0.4)	
TOTAL	10.5	13.8	(19-22)	(27)

* Computed values in brackets, other experimental data.
** Preliminary data.

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ANNEX F

ENVIRONMENTAL CONTAMINATION (continued)

PART II

Transfer of radio-active material through food chains into the human body

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I. Introduction

1. Since the Committee's 1958 report, much information has been obtained on the levels of radio-nuclides in man and in foodstuffs and on the mechanisms by which they are transmitted through food chains. Many countries publish information on the former regularly, and detailed reviews of some aspects of the passage of fission products through food chains are available.^{10,11} This part of the annex summarizes the present state of knowledge in this field, emphasizing those factors which are relevant to the assessment of the exposure of human populations. While the measured levels of radio-nuclides described in this section apply only to fall-out from nuclear explosions, it will be appreciated that the general description of food chain behaviour is applicable also to other releases of the radio-nuclides treated. These releases are described in part IV of the present annex and the behaviour of C^{14} is discussed in parts I and III.

RADIO-NUCLIDES OF IMPORTANCE

2. Many radio-nuclides are produced by the explosion of nuclear weapons (F I, 11-13) and a limited number of them are important as sources of internal radiation in the human body. The potential importance of radio-nuclides in this respect is determined by:

(a) *Their production yield and half-life.* Radio-nuclides with relatively high yields and moderate to long half-lives include those of the rare earths, zirconium-niobium, ruthenium-rhodium, iodine, caesium and the alkaline earths, especially strontium and barium;

(b) *The rate at which they enter into food chains after being deposited on the earth's surface.* All radio-nuclides may be ingested by man or by domestic animals after direct deposition onto the aerial parts of plants but the isotopes of strontium are more readily absorbed from soils by plants than are other fission products. This has been shown by experiments with separated radio-

isotopes and with debris from nuclear weapons;^{133, 144, 165-167}

(c) *The extent to which they enter into foods of animal origin.* Strontium, caesium and iodine are relatively readily transferred into milk and caesium into meat. This also has been demonstrated by experiments with separated isotopes^{182, 187, 220, 223, 287} and with debris from nuclear weapons.²¹⁹ The importance of these radio-nuclides is also emphasized by experience with fall-out distributed worldwide as a result of the testing of nuclear weapons;¹⁹

(d) *The extent to which they are absorbed from the gastro-intestinal tract of man.* Strontium, iodine and caesium are well absorbed but radio-isotopes of the rare earths, the actinides and noble metals are absorbed to a very small degree.¹⁹ All radio-nuclides in the diet, whether or not they are absorbed, will contribute to the irradiation of the gastro-intestinal tract;

(e) *The fraction deposited in the critical organ in man and the time for which it is retained.* Radio-strontium is deposited in bones and some part is retained there for a period of years. Sr^{90} is the strontium nuclide of major biological significance because of its long half-life, but it may be necessary to give some consideration to Sr^{89} in periods when the major part of the fall-out is of relatively recent origin. Caesium-137 is generally distributed throughout the body and the major portion is retained with a half-life of some months. Iodine isotopes are concentrated in the thyroid gland but, owing to their short half-lives, are of importance only in periods of fresh fall-out. Major attention is devoted to Sr^{90} and Cs^{137} when long-term effects are being considered.

3. Pu^{239} is not considered in detail because it is absorbed to a negligible extent from soil by plants²⁸⁵ and is very poorly absorbed from the gastro-intestinal tract of animals and man.²⁸⁶ Estimates made in the United Kingdom in 1959 at the period of highest air contamination suggested that the ingestion of Pu^{239} in food was negligible, while the Pu^{239} inhaled amounted to $10^{-2} \mu\text{C}$ per day per person.⁹⁸ Similarly it was calculated that in the United States over the period 1954-1958, the amount of Pu^{239} entering the diet was only 1/3,000 of that inhaled.¹²⁰

METHODS OF INVESTIGATION

4. In order to calculate the radiation dose to man, it is necessary to estimate the content of radio-nuclides in the body. This can be done directly by the analysis of post-mortem samples or for gamma-emitting radio-nuclides by whole body counting, or it can be ascertained indirectly by the analysis of the diet or excreta.

5. Direct measurement can provide more certain information for the calculation of dose and the values obtained for Sr^{90} and Cs^{137} in man in many areas are adequate for the necessary dose computation. There are some practical difficulties in sampling the population in a fully representative manner. For Sr^{90} , samples of human bone must be obtained. In interpreting the results it should be remembered that samples may not have been obtained from the whole area of interest, and that, while samples obtained as a result of accidental death may be assumed to be representative of the population with respect to diet, those from individuals dying from other causes may not be representative either in diet or in calcium metabolism. The total content of Cs^{137}

in the body can be measured by *in vivo* counting but the limited number of whole body counters and the fact that they are usually immobile have hitherto made it difficult to obtain representative information for large populations; the introduction of mobile counters may reduce this limitation. The measurement of Cs^{137} in post-mortem samples may enable the radiation dose to individual tissues to be more precisely determined.

6. The measurement of the levels in diet provides corroborative evidence of the levels in the body. When the relationship between the level of the radio-nuclide in diet and in the body has been well established for a few areas, body levels for other areas where direct measurements are inadequate or unavailable can be estimated from analyses of the diet. It has recently been suggested that the monitoring of urine can serve as an alternative method for estimating the current intake of Sr^{90} ; Cs^{137} , but the practical value of this procedure has yet been established.^{218, 219, 280}

7. The sampling of food also offers a method of indirectly detecting changes in the levels of intake and determining the chief contributors of radio-activity to the diet. The levels of radio-nuclides in fall-out foodstuffs can be correlated and the results related to particular local agricultural and climatic conditions, relating levels in the body and in diet to the pattern of fall-out. Some estimate can be made of possible future levels.

8. In order that these relationships should not be purely empirical, knowledge is required of the manner in which the radio-nuclides of interest behave in biological systems and pass through food chains into man. In the following sections, therefore, a summary of the present knowledge of these subjects is described before the present and predicted future levels are given.

II. Strontium-90

Sr^{90} IN FOOD CHAINS

Relationships between strontium and calcium

9. Sr^{90} (and Sr^{89}) behave in the same manner as stable strontium normally present in biological systems and in a manner generally similar to that of calcium with which it is related chemically. Stable strontium is present in nature in very small and variable amounts relative to calcium, and the transfer of Sr^{90} through food chains is largely determined by the amount of calcium which is present. For this reason the concentration of Sr^{90} in biological materials is frequently reported as a ratio of strontium to calcium (expressed as micromicrocuries Sr^{90} per gram of calcium). This mode of expression is convenient, as the calcium content of bone and of many other important tissues are relatively constant and tissue doses can therefore be inferred from the calcium content. Furthermore, because the ratio in bone is largely determined by the ratio in diet, the content of Sr^{90} in the total diet, or in its major constituents, is appropriately expressed in these terms. In other circumstances, however, the expression of results in terms of unit weight or volume is to be preferred.

10. While the behaviour of Sr^{90} is similar to that of calcium, it is not identical with it and this has led to the need to express quantitatively in a clearly defined manner, the relative rates of transfer or utilization of strontium and calcium in biological systems. In the

ent report the over-all discrimination is expressed by the "observed ratio" or OR (sample/precursor):*

$$OR = \frac{\text{Sr/Ca ratio in sample}}{\text{Sr/Ca ratio in precursor}}$$

The term "discrimination factor" (DF) is used to express the contribution of individual physiological processes to the over-all discrimination.^{124, 288} The OR may be a result of any number of discriminatory stages. Thus,

$$OR = (DF_1) (DF_2) (DF_3) \dots (DF_n)$$

The DF values are given appropriate specific names. When a single stage process is being studied the OR and DF are, of course, identical, but the OR (milk/diet), for example, expresses the result of discriminatory processes in gut, udder and kidney.^{187, 224}

11. The true OR can be measured only in systems in steady state or where the strontium and calcium being introduced cannot be confused with that already present in the system. It is especially important also to ensure that the strontium to calcium ratios as measured in the precursors truly represent the ratios available to the organism. While the OR obtained in practice may depend to some extent on the method used, it appears that generally comparable results are obtained by the various possible methods. Three principal methods have been used:¹²⁴

(a) *The measurement of the ratio of stable strontium to calcium in the precursor and sample.* This has found particular application in determining the OR (bone/diet) in humans where Sr^{90} has been present in the diet for only a short period of time, and where tracer experiments can only be performed with difficulty. The value obtained reflects any changes in the ratio of stable strontium to calcium in the precursor or in the OR which may have occurred in the life history; it represents a lifetime integrated value. The difficulty of making precise measurements of stable strontium in the presence of large amounts of calcium and of using this procedure experimentally has limited its application;

(b) *The measurement of the ratios of radio-strontium and stable calcium.* If this method is to be used experimentally it is necessary to supply the radio-strontium and calcium over the entire life history in order to prevent interpretation from being complicated by the presence of calcium absorbed before the radio-strontium was applied. Studies with fall-out Sr^{90} belong in this category; the difficulties in the derivation of OR (bone/diet) values from measurements of fall-out Sr^{90} are discussed in a subsequent section (para. 90). This method has been used successfully for the determination of the OR (milk/diet) on the assumption that the Sr^{90} and calcium in milk come largely from that ingested in the previous few days;

(c) Alternatively, radio-isotopes of both strontium and calcium may be used. The radio-isotopes can be distinguished from the stable nuclides which have previously entered the system being studied. Hence the result is unaffected by the previous nutritional history of the subject and the necessary feeding time is short. However, the value represents the behaviour only during the

* The following nomenclature was adopted in the 1958 report:⁹¹

$$DF \text{ (precursor/sample)} = \frac{\text{Sr/Ca ratio in sample}}{\text{Sr/Ca ratio in precursor}}$$

The over-all discrimination factor was considered to be the result of several individual factors corresponding to separate stages. However, the alternative nomenclature is widely used and possesses some advantages.

experimental period. This technique has many advantages in case of measurement by radio-chemistry.

12. Some criticism has been made of the use of observed ratios on the grounds that they may vary when experimental conditions are changed.^{193, 194} However, the practical use of the OR concept is considered justified^{178, 201} since in many processes (for example, absorption by plants, secretion into milk, absorption into the body and deposition in bone) the OR may be very nearly constant and predictable. On the other hand, the quantities of Sr^{90} per unit weight or volume of tissue may be much more variable. In particular, the OR (bone/diet) reflects the contamination in local areas of bone which are active at the time and is comparable at all ages, except perhaps in the very young. In contrast, the actual retention of radio-strontium varies markedly with age and diet and with the degree of attainment of steady state conditions.

Soils and plants

13. Sr^{90} may enter plants either through their roots from the soil or by the direct contamination of their above-ground tissues. It is important to distinguish between these two modes of entry because the amount absorbed from the soil is determined by the cumulative total deposition, while the extent of direct contamination depends on the magnitude of the recent deposit.

Absorption of Sr^{90} from the soil

14. Field experiments in the United Kingdom and Sweden indicate that, depending on soil type, the ratio of strontium to calcium in plants is likely to be in the range of 1-10 $\mu\text{g Sr}^{90}/\text{g Ca}$ if 1 mc Sr^{90} per km^2 is present in the soil.^{135-137, 204, 283} The quantity entering crops each year is usually in the range 0.2 to 3 per cent of that in the soil,^{19, 135-137, 142, 147, 283} depending on the factors discussed in the following paragraphs.

15. *The effect of calcium.* The quantity of labile* calcium in soil is the most important of the factors determining the extent to which Sr^{90} is absorbed by plants. Experiments in Sweden,¹³⁵⁻¹³⁸ the United States,^{139, 140, 143, 145, 151} the United Kingdom^{142, 147} and the Union of Soviet Socialist Republics¹⁴⁴ show that the uptake of Sr^{90} is greatest in soils of low calcium content. The uptake of Sr^{90} from these soils is reduced by the addition of lime, but usually not by a factor exceeding 3.^{10, 129} When soils contain adequate calcium for the growth of crops and the cation exchange capacity is largely saturated with calcium, the addition of lime has little or no effect. Although wide differences exist in the ability of various species to absorb Sr^{90} , it is well established that this character is correlated with the ability to absorb calcium.

16. The results of experiments in water culture show that the OR (plant shoot/solution) is close to 1 (table 1). This is also generally true of plants growing in soil when the strontium is uniformly distributed or when differences in the rooting depth of plants are taken into account.^{124, 128} Some apparent differences between the ratio of strontium to calcium in different species growing under the same conditions have been reported¹⁴³ but these are not accepted as typical.¹³⁶ Variations in ratios of strontium to calcium, however, occur between different tissues of the plant. Somewhat higher ratios are usually found in roots and stems than in the leaf tissue in which the major part of both strontium and calcium

* Labile calcium consists of calcium present in the soil solution together with readily exchangeable calcium with which the solution can be replenished.

is normally contained.^{125, 126} Those for fruits are lower; the ratios of strontium to calcium in wheat grain and edible legumes are about 0.5 of that in leaf tissue.^{130, 283} the ratio in wheat flour is about 0.7 of that in the whole grain.²⁸²

17. Varying values for the OR (plant shoot/soil) have been reported^{133, 135} but it is now clear that the variation was mainly due to the difficulties of estimating the relative availability to plants of strontium and calcium in the soil. The conventional extraction procedures with ammonium acetate may give inaccurate information especially in soils which contain large quantities of slightly soluble calcium; in other conditions, however, useful comparative data can be obtained.¹²⁸ The ratios in which the two ions are available can be estimated more precisely by analysing solutions with which the soil is in equilibrium or by equilibrating the soil with dilute solutions of calcium chloride.^{86, 131, 132, 227, 283} Under field conditions, however, the non-uniform distribution of the two ions in the soil will normally prevent proper evaluation.

18. *The influence of soil factors other than calcium.* The extent to which both strontium and calcium are absorbed from the soil varies depending on the clay and humus content, the pH, the concentration of electrolytes other than calcium, and the moisture content.^{19, 134, 144, 145} Soil conditions which encourage shallow root development usually cause the absorption of Sr⁹⁰ to be increased. The addition of organic matter in large quantities^{144, 146} and of fertilizers may have varying and complex effects^{129, 187, 144, 145, 154, 285} which are, however, usually not large when these materials are applied at normal agricultural levels.

19. *Movement of Sr⁹⁰ in soil.* When soil is not disturbed the downward penetration of Sr⁹⁰ is slow, and even after several years most of it remains in the upper few centimetres.^{19, 140} The rate of downward movement varies with soil type; a low content of clay and humus, a high content of electrolytes and a rapid movement of water increase penetration^{19, 108} The mechanism of movement is uncertain but both mass flow in water and self diffusion may be involved.¹⁴⁰ A horizontal movement of Sr⁹⁰ due to transmission through the roots of plants is reported.¹⁶⁷ The repeated cultivation of soils causes the distribution of Sr⁹⁰ to become progressively more uniform throughout the plough layer;¹⁴⁸ the depth to which it is incorporated in this way may have a marked effect on the ratio of Sr⁹⁰ to calcium in plants. Ploughing to the depth of 20 to 30 cm has been found to reduce the ratio by a factor of up to 3 compared with placement on the surface, when shallow rooted crops such as rye grass or kale were grown.^{142, 147, 283} With more deeply rooted crops, the effect was smaller. Marked reductions in uptake by several crops with increased depth of placement have also been noted on a podsol¹⁴⁴ and with soybeans in a loamy soil.¹⁴⁵ In laboratory experiments, lowland rice, which is normally grown in flooded fields with a strong development of surface roots, absorbed more Sr⁹⁰ when the activity was placed on the surface than when it was mixed in the upper soil layer. The reverse was found with upland rice, which is grown in conditions similar to those in which wheat is grown.^{127, 106}

20. *Changes with time in the availability of Sr⁹⁰ for absorption.* Considerable attention has been given to the possibility that with the passage of time Sr⁹⁰ may be slowly converted into sparingly soluble forms which cause it to be more slowly absorbed relative to calcium. Some investigators have found no evidence of this

effect.¹⁵¹ However, in other soils it has been shown that a small per cent of Sr⁹⁰ may cease to be labile during three or more years^{152, 153} and it is possible that this effect is considerably greater in certain soils.¹⁵⁵ The present evidence suggests that the fixation of Sr⁹⁰ is of little practical significance from the viewpoint of the contamination of human diet but results over considerably longer periods are necessary for a final evaluation.

Direct contamination of plants

21. Three routes of direct contamination have been distinguished: Sr⁹⁰ may be retained on the leaves or on inflorescences of plants (termed foliar or floral contamination respectively), or it may be trapped by the basal parts of plants from which it is absorbed without being incorporated in the soil (plant base absorption).^{19, 201} These three mechanisms of direct contamination lead to contrasting distributions of Sr⁹⁰ in different types of edible tissue. Sr⁹⁰ which enters by plant base absorption moves upwards through the stem to all aerial tissues like material absorbed through the roots, but little of that which enters leaves or inflorescences is redistributed to other tissues.

22. *Foliar contamination.* The extent to which Sr⁹⁰ is retained on vegetation depends on both the extent and duration of rainfall and the extent and form of the exposed leaf tissue.^{121, 122, 123} Experimental studies using spraying equipment suggest that when Sr⁹⁰ descends in rain about one-quarter of the deposit may initially lodge on the leaf tissue of permanent pastures which cattle consume.²²⁷ Absorption into the leaves is relatively slow and the superficial material can readily be lost, especially in rain.¹²² In the United Kingdom this may cause only about one-tenth of the initial deposit to remain after two months.²²⁷

23. *Floral contamination.* Attention was first directed to this process by the fact that the ratio of Sr⁹⁰ to calcium in grain and flour usually exceeded that in vegetables by a considerable factor (tables XI-XVII). Comparisons of the ratio of Sr⁹⁰ to stable strontium in different tissues of wheat grain provided evidence on the mechanism of entry.^{84, 201, 210, 235} Since the soil is the sole source of stable strontium this ratio would be constant throughout tissues formed at the same time if Sr⁹⁰ entered only from the soil. It was found, however, that this ratio was considerably greater in bran than in flour, and this was ascribed to direct contamination of the outer layers of the wheat grain. It was calculated that in the United Kingdom in 1957, an average of 66 per cent had entered by direct absorption,^{84, 201} while in the United States values of 20 and 90 per cent were obtained in 1959.^{210, 285} An investigation in Japan, where the levels of Sr⁹⁰ in wheat flour in two years were compared with the fall-out rate and deposit, suggested that, while in 1959 50 per cent or more of the Sr⁹⁰ in wheat flour was attributable to the recent deposit, the corresponding figure for 1960 may have been less than 15 per cent.³²⁷ These results are consistent with those of experimental studies that show that higher concentrations of radio-strontium are found in the grain of wheat plants sprayed with solutions of Sr⁹⁰ after the ears have emerged than in those sprayed earlier; this could be prevented if the ears were protected from the spray by small caps.¹⁵⁰ The much higher values which were recorded up to 1960 for the ratio of Sr⁹⁰ to calcium in husked (brown) rice than in milled (white) rice have also been attributed to direct uptake, since tracer experiments and the measurement of stable strontium indicate that such a difference could not occur if only soil uptake were involved.^{127, 195}

24. *Plant-base absorption.* Some of the material not directly retained on leaves, or leached downwards from them, may be washed into the axils of leaves or into the crown of plants, or the root mat. It may also be trapped on decaying vegetation where it is available for absorption by the surface roots. Retention in this way is particularly likely to occur in permanent pastures. The Sr^{90} so trapped is relatively undiluted with the calcium in the soil and in a particularly favourable position for absorption.^{19, 201}

Relative importance of different routes of contamination

25. The rapidity with which Sr^{90} is transferred from rain into food chains provides evidence on the magnitude of direct contamination, because entry by these routes is dependent on the recent deposit, while absorption from soil is determined by the cumulative total deposit, though not necessarily in a simple manner. The extent to which short-lived nuclides (I^{131} , Sr^{90} , Ba^{140}) were transferred to milk when relatively fresh fission products were present in fall-out underlined the importance of direct contamination.^{201, 251} However, quantitative assessment of the relative importance of the recent deposit and of the cumulative total deposit is rendered difficult by fluctuations in the rate of deposition of Sr^{90} , differing soil characteristics, the changing availability of Sr^{90} as it penetrates the soil, seasonal and annual variations in agricultural practices, delays between the production and consumption of food, climatic differences among various areas, and variable weather at individual locations. These problems have been discussed elsewhere.¹⁹ The calculations and the validity of quantitative estimates derived from available survey data are discussed in subsequent sections (paras. 103-119).

Aquatic food chains

26. Aquatic food chains have attracted comparatively little study in relation to worldwide fall-out since aquatic products provide little Sr^{90} to most diets, even when the calcium intake from fish is appreciable (see tables V and XIX).^{19, 33, 267-269} However, information is available from Japan^{23, 265, 266} and extensive studies have been carried out in relation to discharges from nuclear facilities²⁶⁸ and to the sites of nuclear weapons tests.²⁶⁹ These have shown that Sr^{90} is accumulated by the calcareous parts of marine organisms—bones, scales, shells—up to a concentration many times that of the environment, but no concentration of Sr^{90} occurs in the flesh of marine organisms even under conditions of chronic exposure.^{267, 269} The equilibrium concentration in flesh is usually less than one-tenth of that in the surrounding water.^{19, 267} A value for the OR (flesh or bone/water) of 0.4 was observed experimentally in fresh water fish and an OR (whole body/water) of 0.2-0.3 for marine fish can be estimated by comparing the ratio of stable strontium to calcium in fish bone and water.⁹⁰ The level of Sr^{90} in fresh water organisms is generally higher than that in marine organisms from corresponding areas (table XIX). A detailed bibliography on this subject is available.²⁸¹

Milk and animal products

27. The chief practical interest in the metabolism of Sr^{90} in animals is in the extent to which it may be transferred into milk, and the possible concentrations that may be found in meat. Experimental studies with animals can, however, contribute to the understanding of its metabolism in man.

28. *Quantity transferred into milk.* The total quantity of ingested Sr^{90} secreted into the milk of cows is variable;

like the quantity of calcium it is related to the milk yield.^{220, 224, 289} Values ranging from 0.5 to 2 per cent of a single administration are found.^{187, 220, 223, 224} In comparison with continuous ingestion under normal conditions of feeding, several independent investigations have shown that about 0.08 per cent of the amount given daily is secreted per litre of milk.^{188, 224, 225} The amount of ingested calcium and strontium appearing in the milk is inversely related to the dietary calcium level²²⁴ since the concentration of calcium in milk varies little, regardless of the dietary intake. It may be noted that the percentage of ingested radio-strontium secreted per litre of goat's milk is more than ten times the amount in cow's milk owing to the greater proportion of the dietary calcium secreted into the former.²²⁴ In man, it was shown in one investigation with five women that an average of 0.27 per cent of the dietary Sr^{90} was secreted per kilogram of milk.¹⁶⁸

29. *Observed ratio (milk/diet).* Knowledge of the OR (milk/diet) is more useful for many purposes than that of absolute quantities. The available data for this ratio are summarized in table II. Values range from 0.08 to 0.16 but the majority of more recent experimental measurements fall close to 0.1 and this value may be adopted for practical purposes. The values are similar in cows and goats and also in man. The OR (milk/diet) in cows and goats does not vary significantly with calcium levels in the diet from one-half to three times the normal level, nor with increased levels of stable strontium.²²⁴ The ratio in milk appears to be about half that in plasma.^{124, 178, 186, 187, 224} Hence, it may be assumed for practical purposes that the ratio of Sr^{90} to calcium in meat is twice that of milk, if dairy and beef animals have feed with a similar ratio of Sr^{90} to calcium.

30. *Observed ratios in poultry.* OR (sample/diet) values of 0.5-0.6 were found for bone, egg shell and egg yolk of laying hens; plasma and egg white, however, had OR values of about 1.5.²⁹³

Metabolic behaviour in man

31. *Absorption and retention of Sr^{90} .* Ingested radio-strontium is absorbed from the gastro-intestinal tract into the bloodstream, where some of it forms a loose complex with proteins. It enters bone by exchange and accretion; some is excreted in urine and some is excreted in faeces after secretion from the bloodstream into the gastro-intestinal tract. For practical purposes it is important to distinguish between the assimilation of Sr^{90} over short periods of time, when retention in the body will be governed to some extent by exchange reactions in the skeleton, and over longer periods in which the bones will approach a state of complete labelling and exchange reactions will cause no net retention. In an adult exposed to dietary Sr^{90} , about 20 per cent of ingested radio-strontium may be retained initially but the net retention decreases to zero as the skeleton becomes labelled under constant intake. The amount retained therefore depends on the previous history of the subject in relation to dietary intake of radio-strontium.

32. Experimental studies with Sr^{85} in man have shown that a mean of 20 per cent of orally administered strontium is absorbed from the gastro-intestinal tract; this compares with 40-50 per cent of Ca^{45} . However, much variation occurred between individuals.²²⁴ The kinetics of removal of injected radio-strontium in normal man has been studied by means of a whole body counter; the excretion was characterized at least by three different rate processes:²¹⁴

(a) A rapid excretion within twenty to thirty days accounting for some 70 per cent of the dose;

(b) One of intermediate rate, with a half period of about fifty days accounting for 15 per cent;

(c) A stage of chronic retention in which excretion was low. The findings are consistent with the general concepts of the manner in which calcium and strontium are deposited in or removed from the skeleton. The over-all data could also be fitted by a power function and are very similar to those previously described for sheep.²²³ This type of information is especially important in understanding situations involving accidental short-term exposures. It also forms a basis for interpreting relationships between the intake of Sr^{90} and the resultant irradiation of body tissues.

33. *Observed ratio (body/diet).** When it is necessary to consider chronic ingestion the evaluation of the OR (body/diet) appears to be more useful than estimating actual retention. This ratio has been studied for man with a variety of techniques based on different assumptions:

(a) Direct experimental observations on the retention of Sr^{90} and Ca^{45} have been made. Recent results with sixteen patients suggest an OR (body/diet) of 0.29;²¹⁸ earlier measurements based on measurements of blood plasma gave values of 0.44 and 0.54 for groups of patients on two different types of diet;¹⁸⁹

(b) The measurement of stable strontium to calcium ratios in representative samples of bone and diet in several countries gave values for the OR (bone/diet) ranging from 0.16 to 0.25 (table III);

(c) The ratios of Sr^{90} from fall-out to stable calcium in body tissues or fluids and in diet have also been examined. The use of the measured values in bone is discussed in a later section when a detailed presentation of the bone and diet data has been made. An indirect estimate can be made from the OR (milk/diet) of 0.11 measured in women.¹⁸⁸ If the OR (milk/plasma) has a value of about 0.5 in man as in animals (para. 29), an OR (body/diet) of about 0.25 is suggested. The measurement of the Sr^{90} to calcium ratio in large samples of human plasma, though subject to considerable uncertainty, gave a result consistent with an OR (body/diet) of 0.25.¹⁹²

34. While the OR (body/diet) is reasonably constant with ordinary diets it may change with unusual dietary modifications or age.^{19, 178} In rats, the presence of large quantities of milk, lactose or lysine or nutritionally abnormal ratios of calcium to phosphorus have been shown to alter the OR.^{10, 178, 288, 291, 292} However, double tracer experiments in man do not suggest that the OR is affected by the presence or absence of milk.^{189, 218} Consistent differences in OR, as measured by stable strontium and calcium, between countries with very different diets cannot be established on the limited data available (table III). In very young rats¹²⁴ and calves²²³ a higher OR is observed than in later life. The observed ratios of strontium to calcium in the bones of very young children suggests that the OR may be higher in infants than in adults.²⁶⁶ However, their juvenile state, which is asso-

*The term OR (body/diet) is more appropriate when the amount of strontium and calcium retained in the body are estimated from measurements of strontium and calcium in diet and in excretions, the term OR (bone/diet) being reserved for those estimates based on direct measurement of the concentrations in bone. Since by far the greater part of the strontium and calcium in the body are in bone, the values of the OR (bone/diet) and of the OR (body/diet) will be closely similar under steady state conditions.

ciated with considerable reformation of bone, is of short duration. Thus, over a period of several years it is probable that an OR (bone/diet) of about 0.25 would be obtained. This conclusion is supported by the results of surveys of Sr^{90} in diet and bone reviewed later in this annex (table XXIV and para. 100); the average ratio of Sr^{90} to calcium in the bone of children has been close to, and often slightly less than, one-quarter of that in their diet. Accordingly a value of the OR (bone/diet) of 0.25 is used for prediction of levels in bone.

35. *Processes of discrimination from diet to body.* It is of interest to estimate the magnitude of the principal processes of discrimination which bring about the OR (body/diet). The measured excretion in faeces of Sr^{90} and Ca^{45} orally administered,²¹⁸ or studies of stable strontium and calcium balances⁸¹¹ suggest an approximately twofold discrimination in absorption by the gastro-intestinal tract. There is evidence however that this may not occur in infants.²⁰⁸ From measurements following intravenous injection, the DF urinary can be estimated as 0.70. Thus the OR (body/diet) of about 0.25 is mainly brought about by a twofold discrimination in the gastro-intestinal tract and one of somewhat less than twofold in the kidney. The OR (bone/plasma) is close to unity.^{124, 189}

36. *Observed ratio (foetus/mother).* A further important discriminatory process is in placental transport from mother to foetus. Direct experimental evidence of discrimination across the placenta is not available for man but values of OR (foetus/mother) for rats and rabbits of about 0.5 are reported.²⁵⁷ Calculation from extensive measurements of stable strontium in the bones of newborn in the United Kingdom gave a value of about 0.6.²⁶⁰

MEASURED LEVELS OF Sr^{90} IN DIET

General considerations

37. Two considerations are of primary importance. First, while the experience of the past years has shown that the concentration of Sr^{90} in foodstuffs may fluctuate over short periods of time owing to the varying rates of fall-out, it is more important to consider mean levels of intake over extended periods. For this reason data in the following tables are summarized where possible over calendar years. Second, in order to estimate the ratio of Sr^{90} to calcium in new bone, the total intake of Sr^{90} and calcium in the complete diet or at least in the most important components must be known. It is therefore necessary to examine the composition of diet and, for comparing the intake of Sr^{90} in different parts of the world, it is convenient to identify broad dietary classes.

38. Diets might be classified in any of the following manners:

(a) *On the basis of the most important contributors of Sr^{90} .* However, the relative contribution of different foods is dependent on the relative quantities of current and accumulated fall-out and consequently may vary considerably;

(b) *On the basis of quantities consumed by weight.* Frequently, however, certain foods consumed in quite large quantities may contribute little Sr^{90} or calcium to the diet;

(c) *On the basis of the amount of calcium contributed by different foods to the diet.* The quantity of Sr^{90} in different articles of diet cannot be inferred directly from their content of calcium both because of the variable

extent to which plants may be subject to direct contamination (para. 25) and because of discrimination between strontium and calcium in their passage to animal products. Nevertheless, the classification of diets in terms of the principal sources of calcium has been found the most convenient way of examining the effects of dietary composition on the intake of Sr^{90} and of predicting future concentrations in diet and hence in bone (paras. 103-121). Hence this method of classification is adopted in the present report.

39. Information on the calcium content of diets is available.^{19, 172} For the present purpose, it is more important to consider the relative quantities of calcium provided by different foods than the absolute amount ingested per day. Wide variations exist between different countries, but three broad dietary classes can be identified, namely:

Class I diets. Dairy produce is the predominant source of calcium; this applies to the greater part of North America, Europe and Oceania. Calcium intakes in these areas are generally from 800 to more than 1,000 mg per day. In Southern Europe and Latin America, calcium intakes may be only of the order of 600-700 mg;

Class II diets. Milk provides less than half total dietary calcium and vegetables approach it in importance, for example, India, Turkey and Egypt. The total calcium intake may be only 300-450 mg per day;

Class III diets. Dairy produce is a minor source of calcium, for example, in Japan and other countries of the Far East. The calcium is derived mainly from vegetables, with cereals and fish making significant contributions. The calcium intake may vary from 200-400 mg per day.

Approximate model diets for these three classes have been calculated from the food survey data from the principal countries where they are consumed (table XXIII) and are used for subsequent calculations. With only a few exceptions the composition of the diet of other countries lies between the limits set by these three classes.

40. The data from which these groupings were derived are in most cases derived from gross figures for production and consumption of individual foods, combined with average values for the calcium content of these foods. However, in some cases, the actual calcium content of the diet may greatly exceed that expected on this basis.^{19, 172} This may be caused by the use of unusual sources of calcium, for example, the use of crude sea salt containing calcium for cooking in Ceylon and South India or the enrichment of bread with mineral calcium (United Kingdom), with groundnut meal and fish flour (Union of South Africa), and with non-fat milk solids (United States).¹⁹ Calcium propionate may also be added to bread as a mould inhibitor.¹⁹⁹ Corn (maize) grain is very low in calcium but when used for tortilla-making in Central America, is boiled with lime water in the initial stages of preparation. This process greatly enriches the diet in calcium: in some areas 75 per cent of the total calcium in the diet may be obtained in this way.¹⁹ The chewing of betel leaves may also contribute substantial amounts of calcium to the diet. When cereals such as ragi or quinoa, which are rich in calcium, are used, the contribution of calcium to the diet is much greater than with other cereals.

Estimates of the ratio of Sr^{90} to calcium in the total diet

41. Since the previous report, many values for the Sr^{90} and calcium content in diet have been published.

The period of time and geographical area covered, the frequency of sampling, the number of foods sampled and the method used have varied very considerably and thus the precision also varies. In tabulating the results a primary distinction has been drawn between those analyses based on continuing sampling and those based on a single limited sampling over a short period of time.

42. To provide further information on the nature of the samples and to assist in the evaluation of the results, the methods used have been distinguished as follows,¹⁷² and also indicated in table IV:

(a) The use of values, often countrywide averages, obtained from separate surveys of the Sr^{90} content of the most important dietary constituents, together with estimates of the quantities of these foods consumed, to calculate the Sr^{90} content of the complete diet;

(b) The calculation of the content in the total diet on the basis of data obtained from the analysis of foods purchased locally in stores. This method may often be used in relatively small areas and therefore some caution must be exercised in applying the results to larger areas;

(c) The analysis of composite samples of complete diet often based on local purchases. The composition of the diet may be based on dietary surveys or local estimates of "typical" consumption;¹⁷

(d) The analysis of samples of the complete diet actually consumed by certain individuals or groups—military forces, hospital patients, or volunteers in metabolic studies. These diets may or may not resemble the average diet of the community.

43. In the first two methods the major sources of error, when accurate knowledge of the average quantities consumed is available, may be inadequacies in the representativeness of the sampling of the foodstuff for Sr^{90} . In the last two methods an additional bias may be introduced when estimates of "typical" diets or duplicate samples of the actual diets of individuals or groups are used, its magnitude depending on the extent to which the composition of the diet analysed is representative of that of the population as a whole. However, the values from the United States suggest that comparable results may be obtained by the various methods.^{74, 171}

44. *North America and Europe.* Amongst countries in which milk is the major calcium source in the diet, the most complete series of estimates of the Sr^{90} to calcium ratio in the diet is available from the United Kingdom and the United States. Variation by a factor of three in the values from different areas of the United States in 1959 was observed, particularly low values being observed on the West Coast. The values from Europe in 1959 and 1960 fell within the same limits. In the United Kingdom and the United States a rise was shown from 1957 to 1959 followed by a marked drop in 1960 and early 1961. This fall was also shown in Denmark. Values for 1959 and 1960 in Canada were comparable with the higher values from the United States.

45. *Asia and the Far East.* An extended series of estimates is available for Japan. Although the diet of Japan is not typical of that of the Far East, the results for that country are of particular interest because it is the only area in which regular surveys have been carried out where the diet is not of class I. The mean value for the ratio of Sr^{90} to calcium in diet rose from 1957 to 1960. No decrease occurred in 1960, probably owing to

the storage time of the large cereal component. The values for Japan were lower than those in Europe and North America in 1957 but in 1960 were rather greater. Samples of composite diets, collected over a short period of time were taken in Viet-Nam in 1959, and Thailand and Taiwan in 1960. Though wide variation was observed the mean values are comparable with or lower than those in Europe in the same period and lower than those in Japan. In 1961 the average Sr^{90} to calcium ratios of vegetarian meals in India was comparable with the average value for total diet in the United States.

46. *Africa.* In Africa a series of samples, consisting principally of cereals, legumes and milk, was taken in 1958 in a number of cities. From these the ratio of Sr^{90} to calcium in the total diet has been estimated, including and excluding milk.³⁸ It is suggested that the latter will approximate the diet of those groups of the African population who consume little milk.³⁸ The limited area and time covered by the survey indicate the need for caution in using the values. They appear, however, to be lower than those in Europe and in the United States. A limited sampling of the diet of the African population of Southern Rhodesia was made in 1959-1960. The values were comparable to those found in North America and Europe in the same period. The mean value for the composite diets in the Delta region of the United Arab Republic in late 1961 was comparable with that found in the United States earlier in the year.

47. *Central America.* A series of estimates was also made for Central America in 1958. The values found were very low, of the order $< 1.2 \mu\text{C } \text{Sr}^{90} \text{ per g Ca}$. The calculations for the total diet were based only on the analyses of corn, beans and milk. No analyses of leafy vegetables or fruit were made, so that the diet cannot be regarded as completely examined, but the values indicate the general level of Sr^{90} in the area. The values of the ratio of Sr^{90} to calcium calculated for the total diet for Guatemala and Honduras were particularly low owing to the practice already mentioned of preparing maize for tortilla-making by boiling in lime water.^{19, 29, 55, 56} This is particularly common in rural communities. In urban communities the values are likely to be higher since more wheat and rice, or maize boiled with wood ash, may be used, and therefore the extra calcium contribution is not obtained.

48. *South America.* Results from surveys of brief duration in several countries of South America in 1957 and 1958 are available, as well as analyses of composite military rations, based on local foods, in two countries in 1959. Composite diet samples were obtained from local communities in Colombia and Chile in 1960. The wide variation in the Sr^{90} to calcium ratios of different samples is attributed to differences in climate.³¹⁹ This is particularly well shown in Chile where the average for the dry northern districts (2.4) is only one quarter of that from the wetter southern districts (9.6).³¹⁹ In general values for the Sr^{90} to calcium ratio of total diet in South America are lower than in Europe and North America.

49. *Oceania.* The Sr^{90} to calcium ratio in the total diet in Australia has been estimated from analyses of milk, cabbages and wheat.³²⁰ Little change occurred in the level between 1957 and 1960. Values were always below the average for North America and Europe which are regions of similar diet. No marked rise in the level in 1959 comparable with that which occurred in the Northern Hemisphere was detected.

Contributions of Sr^{90} by individual components to the total intake

50. The relative contributions from different components of the diet in 1959 and 1960 in the few countries from which a detailed breakdown is available is shown in table V. In all the countries listed, except for Japan, the diet is of class I and about three quarters of the calcium (excluding mineral calcium) is supplied from milk. In contrast, milk usually supplied only from a quarter to a half of the Sr^{90} , owing to the discrimination against Sr^{90} in passage into milk (para. 29). The value was higher in Canada. Cereals, which are particularly subject to direct contamination by fall-out (para. 23), also supplied a major fraction, especially in Denmark and Austria. In these class I diets, leaf and root vegetables together contributed from 6 to about 30 per cent of the Sr^{90} , and meat, fish, eggs and drinking water very small proportions. In Japan, where the diet is of class III, milk supplies only a small proportion of the calcium in the diet, and even less of the Sr^{90} . In 1960 cereals supplied one quarter of the Sr^{90} in the Japanese diet and some 65 per cent was attributed to vegetables and fruit.

Factors causing intake to vary from the average

51. The foregoing estimates are for the average intake of the population as a whole. However, there is interest in the intake of special groups or of individuals, depending on their dietary habits. Unfortunately, very little information is available on the variation of dietary habits among special groups on which estimates might be based.¹⁹

52. *Age.* The diet of very young children is of particular interest and in some countries analyses of prepared baby foods have been made. The results are shown in table VI. The values are comparable with those of normal samples of similar foods. The intake in the diet of infants has been calculated in Germany,²⁴ the United Kingdom,^{65, 227} and the United States,^{71, 198} and composite diets have been analysed in the United States.³¹² The results indicate that the Sr^{90} to calcium ratio in the diet of young children, when they are fed on prepared baby foods or cow's milk, differs relatively little from that in the diet of adults (table IV). The same applies also to older children.^{24, 312} The Sr^{90} to calcium ratio in the diet of breast-fed infants will however be considerably lower than that of other groups,²⁴ since this ratio in human milk is approximately one-tenth of that in the mother's diet.¹⁰⁸ There may also be metabolic differences between breast-fed infants and those fed on cow's milk.²¹¹

53. *Quantity of food consumed.* Differences in the intake of Sr^{90} of adults may arise through normal variations in the amount of different foods consumed. Dietary estimates in the United States suggest that high consumption of the major components of the diet may be taken as approximately twice the average amounts.¹¹² When the ratio of Sr^{90} to calcium in an individual food differs little from that in the total diet, alteration in the amount consumed has little effect on the ratio in the total diet. This is generally the case with milk in countries where substantial quantities of milk are consumed.

54. The effect of increasing the quantity consumed of components in which the Sr^{90} to calcium ratio exceeds that in the total diet is roughly in proportion to the Sr^{90} contribution; this is small in diets containing reasonable quantities of milk. In the United Kingdom it was esti-

mated that doubling the intake of root or leaf vegetables or fruit would have increased the Sr^{90} to calcium ratio of the total diet in 1959 by only a few per cent.⁸⁵ Inspection of the detailed analyses of diet in the United States¹⁰⁸ shows that the highest contribution of Sr^{90} from any of these three items is only 15 per cent; doubling the quantity of the food consumed would therefore increase the ratio of Sr^{90} to calcium in the diet by only a small amount. Where milk consumption is normally small, increasing the quantity of milk consumed may reduce the average ratio of Sr^{90} to calcium in the diet since the ratio in the milk is generally less than that in other components.

55. *Special dietary habits.* Certain groups may have special dietary habits which affect Sr^{90} intake. One such is the consumption of unmilled cereals. Attention has been paid to this particular habit since the ratio of Sr^{90} to calcium is often much higher in unmilled than in milled grain (see tables XI-XIV).

56. Because the ratio of Sr^{90} to calcium is higher in wholemeal bread or flour than in white bread or flour^{78, 85, 227} the replacement of white bread by wholemeal bread in the diet causes the dietary intake of Sr^{90} to be increased. The effect, however, appears to be relatively small^{108, 171} except in countries, such as the United Kingdom, where mineral calcium is added to all white flour,^{84, 85, 227} but not necessarily to wholemeal flour. It may be noted that cereals supply a relatively high proportion of the dietary Sr^{90} in Denmark and Austria, where the proportion of wholemeal flour consumed is greater than in the United Kingdom or the United States (table V).

57. The milling of rice also has a considerable effect on the Sr^{90} to calcium ratio of the diet in those countries where rice is an important food. A total diet sample in Viet-Nam containing "unpolished" (presumably unmilled) rice was three times as high in Sr^{90} per g of calcium as was a diet sample containing milled rice.¹¹⁰

58. *Geographical location.* Differences in the total dietary content of Sr^{90} , owing to variation in the degree of contamination of foodstuffs produced in different areas are difficult to assess since it is unlikely that any individual would receive all his intake from the most highly contaminated sources. In many countries the variation is likely to be largely controlled by the levels in milk, since it contributes a large proportion of the Sr^{90} . Further, variations due to geographical position will be more readily reflected in milk which is consumed relatively locally, especially in rural areas, while other foodstuffs, such as cereals, are often distributed over very large areas.

59. Inspection of the range of values for milk within countries (table VII) suggests that a variation between sites by a factor of 4 is common in moderate-sized areas, with narrower ranges in smaller areas. In larger countries, such as the USSR or the United States, variation by a factor of up to 10 may occur. The ratio in the total diet may be expected to show a less extreme range because of more uniform contributions from other sources. A study of twenty-five cities in the United States in 1959 showed that the Sr^{90} to calcium ratio in the diet ranged from 4.9 to 16.7 with a mean of 11.8.²⁷ Calculation in the United Kingdom in 1959 and 1960 based on the most pessimistic assumption that all items in an individual's diet were obtained from the areas where highest contamination was found suggested that the average level would not be exceeded by a factor as much as 10.^{85, 227}

60. *The source of drinking water.* The concentration of Sr^{90} in drinking water may vary according to its source. The radio-nuclide concentration in rain is reduced by contact with absorptive surfaces and purification in rivers and lakes occurs by sedimentation or percolation. Conventional processes of water purification do not remove radio-nuclides to any great extent.¹⁷⁴ A survey in the United Kingdom showed that well water (0.02 $\mu\text{mc}/\text{l}$) was very low in Sr^{90} compared with surface waters (0.3-0.9 $\mu\text{mc}/\text{l}$).^{109, 170, 803} Concentrations similar to the latter were measured in surface water in the United States^{66, 73, 173} and Japan.⁸⁰⁴ Higher concentrations were shown in 1959 following heavy fall-out than at other times^{173, 803, 804} but the intake of Sr^{90} in drinking water is unlikely to have exceeded 1 μmc per day for most of the period and variations in this quantity due to the nature of the water supply are unlikely to have caused large differences in the total dietary intake.

61. People drinking water which has not had contact with the ground surface may have higher intakes of Sr^{90} . Mean values for Sr^{90} in cistern water for periods of some months ranging from 2-6 $\mu\text{mc}/\text{l}$ have been reported from the Federal Republic of Germany (1959-1960), Japan (1954-1957) and the United States (1958-1959).^{22, 83, 78, 175} If it is assumed that no decontamination of the rainwater occurs in the collecting system, the concentrations reported for rainwater (F I, table IX) can also be considered. Comparison of these data with an estimated daily intake of Sr^{90} in 1959-1960 of the order of 10 μmc (tables IV and XXIV) suggests that the drinking of rainwater would have appreciably increased the daily intake of Sr^{90} for short periods in 1959 when the rate of fall-out was high. However, expressed as an annual average, the increase would have been smaller in 1959, and in 1960 smaller still.

Sr^{90} in individual foods

62. The limited number of areas from which estimates of the Sr^{90} content in total diet are available makes it necessary to find some basis for extrapolation if levels in other areas are to be inferred. Measurements of individual foods, when considered in relation to the diet type and general distribution of fall-out provide the best opportunity.

Milk

63. Since milk is a major calcium source in many areas of the world and is easy to sample, it has received more attention than any other component of the diet. In some areas regular surveys are in progress or widespread surveys have been made. Results of these are given in table VII and descriptions of the surveys in table VIII. From many other areas only isolated samples are available, sufficient to give some indication of the relative levels. These data are summarized in table IX. Values are available from areas accounting for more than 90 per cent of the world production.

64. Data from some regular surveys are plotted in figure 1. In the Northern Hemisphere, a more or less steady rise from 1954 to 1957 was followed by sharper rises in 1958 and especially in 1959. It is interesting to note that the increment was roughly similar in most of the countries although the 1958 level differed by a factor as much as 5. Subsequently in 1960 the levels fell off, often by an amount comparable to the rise in 1959. In 1961, levels continued to fall by a variable amount. These observations show the partial dependence of the Sr^{90} in milk on the rate of fall-out and are consistent

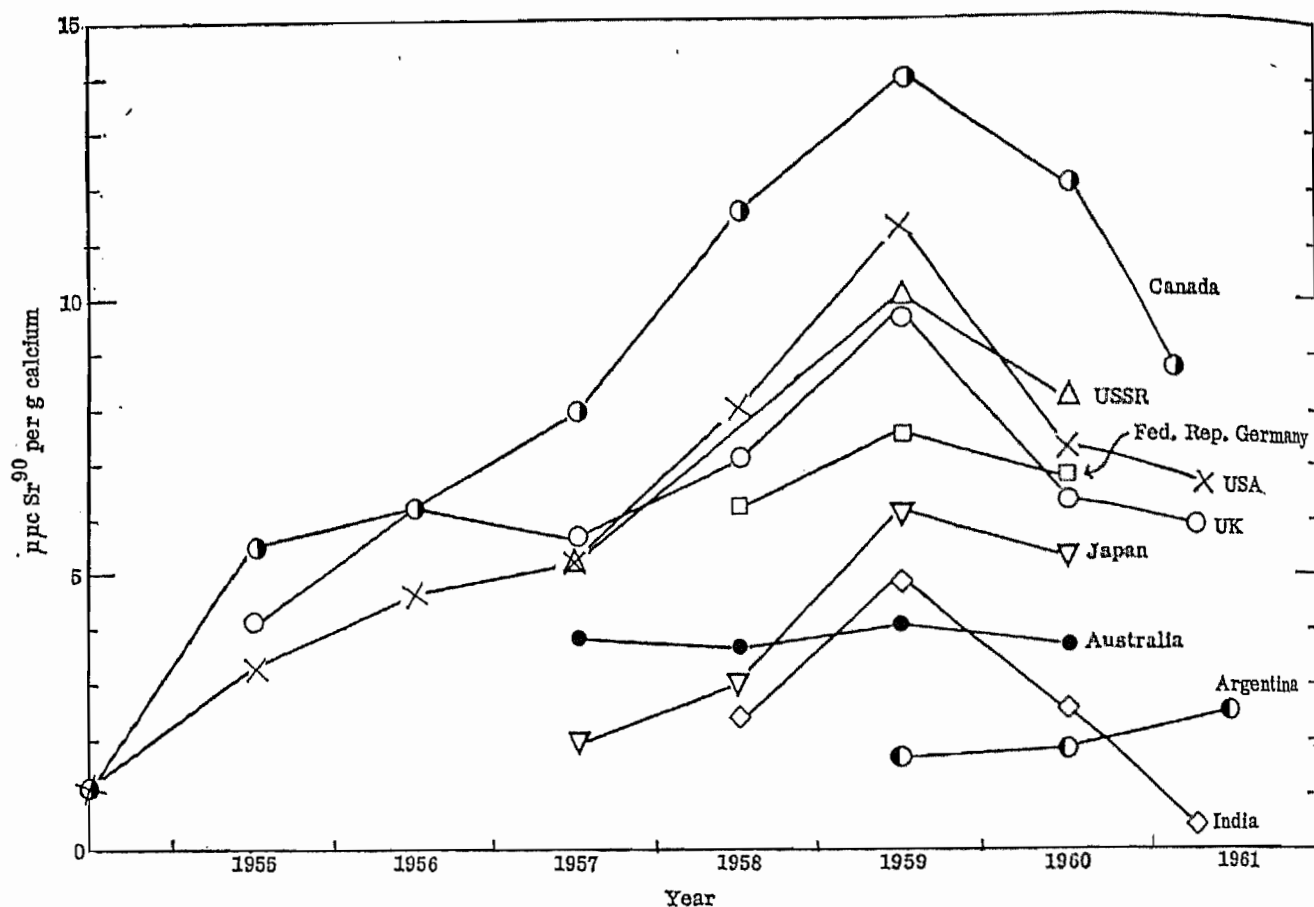


Figure 1. Yearly mean concentrations of Sr^{90} per g of calcium in milk from 9 countries (from table VII). For details of the surveys see table VIII

with the heavy deposition in the Northern Hemisphere in late 1958 and early 1959. In contrast with these changes, the levels in Australia and Argentina changed only slightly. The Southern Hemisphere was not subjected to the heavy increase in the rate of fall-out in 1958-1959.

65. Detailed comparisons of the data in table VII may be misleading because, even within regular programmes, the data from year to year are rarely strictly comparable, since the areas covered and techniques of sampling have changed as the programmes developed. The values of spot samples may be greatly affected by the season at which they are taken and all values will be affected by local agricultural and climatic factors. Consequently, in order to summarize the data so as to show the broad trends, mean values for large geographical areas have been calculated for the years up to 1960 (table X). Means for each country have been weighted for production in calculating the area-wide average in order to represent more closely the true average in the milk over the wider area. Sufficient data are not yet available for 1961 to calculate comparable mean values.

66. Tables VII, IX and X show that a correlation exists between geographical latitude and the level of Sr^{90} in milk. Between 1955 and 1960 the mean values for the ratio of Sr^{90} to calcium in milk in each year were of very much the same order in most of North America and Europe, including the USSR. The scattered values from the Mediterranean area, and data from India and Japan were lower than those of North America and Europe. Very low values were recorded in Central America, especially in its southernmost region. Unfortunately, no data from comparable latitudes are avail-

able from Africa or Asia. Low average values were found in South America, but in the Republic of South Africa, Australia and New Zealand, the levels were somewhat higher. On the average, therefore, the highest values were recorded from the mid-northern latitudes, and the lowest in the equatorial region, with intermediate values further south. This general correlation with latitude is consistent with the known variation with latitude of the intensity of deposition of Sr^{90} .

Cereals

67. The comparison of cereal data is complicated by the number of species, differing in structure, growing season and dietary importance. The range of values is generally very wide. General points that may be noted are that milled cereals normally contain less Sr^{90} per unit weight or per g of calcium than unmilled, and that the Sr^{90} to calcium ratio of both is considerably higher than that of milk from the same area.

68. *Wheat.* The major wheat-producing areas of the world are North America, Europe, the USSR and the Far East.²⁰ Sufficient data are available to provide a reasonable estimate of the levels of Sr^{90} in wheat and wheat products from all these regions except the Far East (table XI). In the latter the only detailed data are from Japan which is responsible for only a very small proportion of the total production. The most widespread sampling was carried out in 1959. Values were comparable in the USSR and in Western Europe but were higher by a factor of 2 or more in North America and in Japan. In the Southern Hemisphere, values were half or less than those in Europe. Trends from year to year are difficult to interpret; in the USSR and Canada

values changed only slightly from 1956-1959, but in the United Kingdom they were markedly higher in 1958 than in 1957 or 1959. The reverse was true in Japan, but a lower value in 1959 than 1958 was recorded also in the United States and Australia. These inconsistencies are probably related to the high degree of dependence of the level of contamination on current fall-out, during the time the grain is developing.¹²² Little data for 1960 is yet available but markedly lower values than in 1959 were recorded in the United States and Canada. No significant fall was noted in Denmark and the Federal Republic of Germany.

69. *Wheat flour*. The ratio of Sr^{90} to calcium is less in wheat flour than in the whole wheat grain. This is illustrated in table XIII where the Sr^{90} content of milling products from Canada, the United Kingdom and the United States are tabulated. The Sr^{90} calcium ratio in flour was approximately one-third to one-half of that in whole grain and one-quarter of that in bran. All the available values for flour are tabulated in table XII. Differences are shown between areas comparable to those found in the whole grain.

70. *Rye, barley and oats*. Rye is an important cereal in Northern and Eastern Europe. Data on the Sr^{90} content are available for Germany, Denmark and the USSR which are responsible for a major share of the world's production⁹⁰ (table XIV). Mean values were very similar to those for wheat and this encourages the view that this may also be true in North America for which values are not available. World production of barley is spread over a large part of the Northern Hemisphere, with some production in Oceania and Africa. Only scattered analyses are available, probably because in many areas barley is not used directly for human food. Mean values for barley in Denmark in 1959 were similar to those for wheat; this was also approximately true in the Federal Republic of Germany in 1956-1958. Values for barley from South America and Africa are very considerably lower than in the Northern Hemisphere. Few analyses of oats are available, again probably because of the much lower importance of this cereal in the diet.

71. *Maize*. Maize is grown in many areas but is of minor importance in the average diet of North American and European countries and extensive sampling has not been carried out (table XIV). Analyses in the United States in 1958-1959 indicate values per kg very much lower than those in wheat. However, since the calcium content of maize is very low, the calculated ratio of Sr^{90} to calcium is lower than that in wheat by a factor of only 2-3. Comparable values were recorded in Rhodesia in 1959 and it was calculated that maize may have supplied about half the Sr^{90} in the total diet of the African population.²²⁷ In Central America, where maize is also important in the diet, the ratio of Sr^{90} to calcium was very low in 1958.

72. *Rice*. Rice is a staple cereal in the diet of many populations but has been sampled systematically only in Japan (table XIV). The ratio of Sr^{90} to calcium in brown rice (unmilled or under-milled rice) is roughly comparable to that of wheat from the same area. Milling markedly reduced the ratio of Sr^{90} to calcium in rice grain in 1956-1957, but in 1960 the Sr^{90} to calcium ratio in milled and unmilled rice was similar. In 1960 the Sr^{90} content of brown rice had decreased to about one-quarter of that in the immediately preceding years because the amount of direct contamination was greatly reduced. The few values which are given in table XIV for rice from other areas in Asia are consistent with lower fall-out rates in tropical latitudes.

73. *Other cereals*. Millet, quinoa and native grains from a few areas where these are used commonly in the diet have been analysed but no wide-spread sampling has been carried out. None of the samples is particularly high in Sr^{90} (table XIV).

Vegetables

74. *Green vegetables*. Recent and extensive measurements of green vegetables are available only for North America, Europe and Australia (table XV). In 1959 and 1960 the mean values in the Northern Hemisphere were generally comparable. They were significantly lower in Australia. The ratio of Sr^{90} to calcium is normally somewhat higher than that of milk from the same area.

75. *Legumes*. In many countries where leguminous vegetables are eaten fresh and are not major items in the diet, there is no real necessity to consider them separately from other green vegetables. The available results from the Federal Republic of Germany and the United States show that mean ratios of Sr^{90} to calcium in pea and bean crops are similar to those in leafy vegetables. In many other areas, however, dried legumes contribute a substantial fraction of the total calories and this justifies separate treatment (table XVI). Surveys conducted in Africa and South and Central America in 1957-1958 show that in these areas the ratio of Sr^{90} to calcium in beans and other legumes did not exceed 4 and was often below $2 \mu\text{Ci Sr}^{90}$ per g calcium.

76. *Potatoes and starchy roots*. The available values for potatoes are given in table XVII. Like green vegetables they normally show ratios of Sr^{90} greater than those of milk from the same area. In 1957-1960, mean levels of Sr^{90} in potatoes in the United States, the United Kingdom, the USSR and the Federal Republic of Germany were of the same order. Comparison of the Sr^{90} content per kg and per g of calcium indicates that the mean calcium content is very variable. There is wide variation in the Sr^{90} content according to region in individual countries; this shows some correlation with rainfall.⁸⁴ The data from other areas are too few to permit any comparisons to be made. Analyses of types of starchy roots which are important in the diet in South America have been made (table XVII). A wide-spread survey in Venezuela in 1958 indicated a mean value for yucca (cassava, manioc) of $22 \mu\text{Ci Sr}^{90}$ per g of calcium with a very wide range. The wide range may have resulted from a deliberate attempt to discover extreme values; the median value of these figures was only 12. Samples of potato and sweet potato from the same area gave lower mean values.

Fruit

77. The few available data for fruit are summarized in table XVIII. They are derived from analyses made in only a few countries and include home grown and imported fruits. The nature of the fruits is so varied that summarization and comparison is difficult. In the Federal Republic of Germany, Denmark and Australia, mean values of the ratio of Sr^{90} to calcium for locally grown fruits appear to be rather higher than for vegetables. Imported fruits, coming from tropical or sub-tropical areas were often lower in Sr^{90} than those from north temperate latitudes.

Meat, eggs and fish

78. Meat, eggs and fish have not been extensively examined because they generally contribute only a little Sr^{90} to the diet. Some data are presented in table XIX. They indicate values of the ratio of Sr^{90} to calcium in

meat and eggs generally comparable to or lower than in milk. The value in marine fish is particularly low; in river fish it is higher.

Tea

79. A beverage which might appear to contribute much Sr^{90} to the diet is tea, since some high values for the Sr^{90} to calcium ratio in tea have been reported.^{33, 76, 85} However, laboratory experiments suggest that only a small percentage of the Sr^{90} is released into the infusion.^{85, 227} The estimated contribution to the diet is small, and comparable to that from drinking water (table V).

MEASURED LEVELS OF Sr^{90} IN HUMAN BONE

80. The Sr^{90} content of a sample of human bone depends on:

(a) The rate of deposition of Sr^{90} in the bone, which has been determined hitherto primarily by the age of the individuals. However, when fall-out has continued for a longer period, this factor will be less important;

(b) The dietary intake of Sr^{90} which in turn depends on the composition of the diet and on the variation in time, and between geographical areas, of the Sr^{90} in fall-out. It is thus related to the year of death and the geographical location.

81. Values for the concentration of Sr^{90} in bone from any given area show a wide range (table XX). This arises from the natural biological variation, which also occurs with stable strontium and the error associated with the measurement of the small quantities of Sr^{90} in the bone. In the accompanying comprehensive table (table XX), the range of values is shown in those cases where detailed information is available. Because the number of samples is rarely as many as 100, only general comparisons can be made between different areas, and the significance of differences based on small numbers of samples is doubtful.

Effect of age

82. Sr^{90} has been present in the environment for a relatively short period so that a large amount of pre-formed bone existed in adults and, to a lesser extent, in older children. In addition to true growth which occurs only in children, in both children and adults existing bone is, to a variable extent, replaced by new bone; the proportion of bone undergoing such changes is likely to be very much smaller in adults than in children. A recent estimate²⁵⁶ based on the comparison of Sr^{90} to stable strontium and Sr^{90} to calcium ratios in different age groups suggests that the annual skeletal turnover is nearly 100 per cent in the first year of life and very high in the second. It falls to about 10 per cent in the third to eighth year, and to very low values during the second burst of growth around puberty. In adults, rate of turnover in ivory bones such as the femur shaft is only about 1 per cent but may be as high as 8 per cent in vertebrae.*

* The difference in turnover rates means that the particular bone chosen for analysis is not important in the case of young children since the ratio of Sr^{90} to calcium differs little between different bones but this is not so in adults.^{35, 88} Analyses of a number of whole adult skeletons have shown that the relative concentrations of Sr^{90} are as follows: vertebra/skeleton 2.1; rib/skeleton 1.4; femur/skeleton 0.45.³⁰ These values were obtained from whole skeletons in New York in the years 1958-1959. Similar values have been obtained in the United Kingdom.²⁵⁶ It has been considered legitimate to use these factors for other areas in order to facilitate comparison where different bones have been used for analysis. In table XX, adult bones have been normalized by the use of these factors, where identification was possible.

83. The ratio of Sr^{90} to calcium in newly formed bone of all age groups should be similar, except possibly in very young infants (para. 34) provided that the ratio of Sr^{90} to calcium in their diet is the same. However, the ratio in the whole skeleton of adults is considerably lower than that for children because of the absence of growth and differences in turnover rates. Analyses of the bones of children may be used to give a direct measure of the concentration in newly formed bone. The bones of the newborn have special value since they reflect the average ratio of Sr^{90} to calcium in the mother's diet during the later months of pregnancy. While the diet of pregnant women may differ from that of the average adult, this difference may be less than between adult and very young children. The variation with age in the average ratio of Sr^{90} to calcium in bones is shown in figure 2 which utilizes the very extensive data obtained in the United Kingdom in 1959. The concentration in the newborn was a little over $1 \mu\text{mc}$ Sr^{90} per g of calcium. The highest mean values, in the bones of children 1 to 2 years old, were about four times higher than in the newborn. The concentration was less in older children and at the age of 8 years was about the same as in the newborn. In adults the value was very low, about one-quarter of that in the newborn if the normalization factor of 0.45 from femur, the bone analysed, to whole skeleton is adopted.

84. Less detailed data are available from most other areas so that wider age groups have been used in showing similar data for eight countries in figure 3. It can be seen that the highest values always obtain in the 0-4 year age group and the lowest in adults but the relative difference between the 0-4 year age group and adolescents in different countries is variable. Figure 3 also shows that, between Japan, the United Kingdom and the USSR, the values for the newborn are more nearly comparable than are those for the 0-4 year age group. These apparent differences between countries in the relative concentrations in bones from different age groups may be due to unavoidable sampling errors but may also represent real differences in Sr^{90} and calcium intake caused by differences in dietary habits in the young. In particular, the extent of breast feeding will have a great influence on the Sr^{90} to calcium ratio of the diet owing to the discrimination in passage from mother's diet to milk (para. 28).

Geographical location

85. The geographical origin of a bone sample may affect its Sr^{90} concentration because of variation in the fall-out deposit in different areas or because there are regional differences in dietary habit. In table XXI the detailed data for 1959-1960 have been summarized for broad geographical areas, the mean values from individual countries being weighted for total population. The mean values in table XXI suggest that the Sr^{90} to calcium ratio in the bones of adults, adolescents and newborn is similar in areas above the latitude of 30°N ; that is, in North America, Europe and Japan. The value for the 0-4 year old group in Japan, however, appears to be rather lower than that of other areas above this latitude. This may be due to differences in the extent of breast feeding, but it may be noted that the levels of Sr^{90} in milk from Japan also appeared to be lower than in North America and Europe (table VII).

86. For Central America, data are available from only two countries and a marked difference is shown between them. Values for Puerto Rico are comparable with those

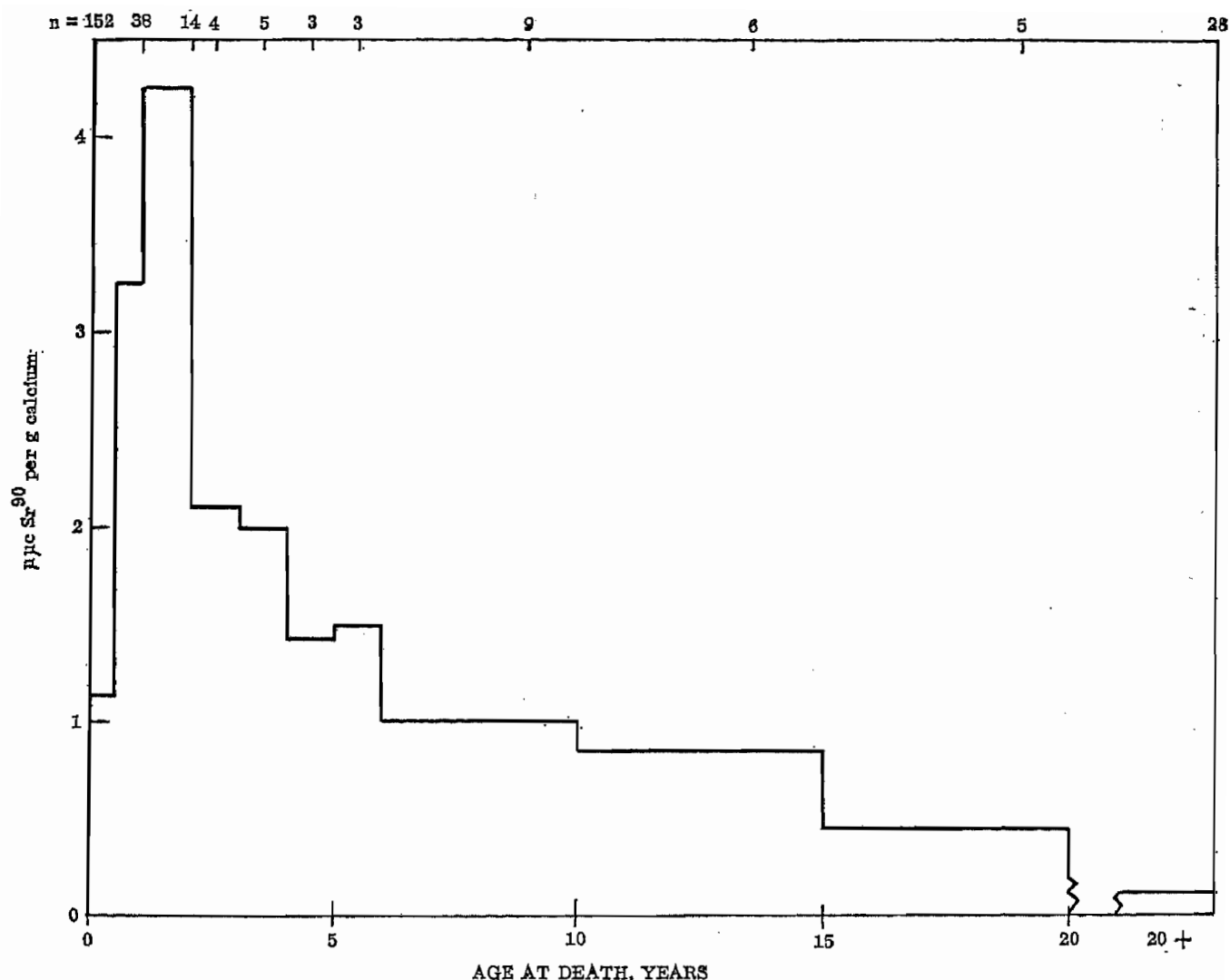


Figure 2. The concentration of Sr^{90} in human bone in the United Kingdom in 1959 in relation to age at death. The number of samples (n) is shown above each age group²⁵⁶

in the United States, but those for Guatemala are distinctly lower. The latter corresponds with the low intake of Sr^{90} calculated from dietary information (table IV). From Africa in the latitude band $0-30^\circ \text{N}$ no information is available, but a few values from the Near East (Israel) suggest levels rather below those in Europe. From South-East Asia data are few but again suggest levels lower than or comparable with those from countries further north. Mean values from the Southern Hemisphere (South America, Australia, Republic of South Africa) are generally lower by a factor of two or more than those in North America and Europe.

87. Such differences between areas in the Sr^{90} content of bone correspond roughly with what is to be expected from latitudinal differences in the deposition of fall-out. It has been noted, however, that the difference in bone levels are rather less than those in deposition.³¹⁹ A major contributory reason is likely to be differences in diet, but this cannot be invoked in a comparison of, for example, Australia and North America where the diets are similar. The transport of food from one region to another may also be important in producing more uniform bone levels.

Trends with time

88. In figure 4 values for the Sr^{90} content of the bone of 0-4 year old children are shown for some countries

in which regular sampling has been carried out. Similar rises were shown from 1956-1958 in four countries of North America and Europe. Thereafter the time courses were divergent, with a marked rise in 1959 being shown only in the United Kingdom. The value for Canada in 1960 (no data are available for 1959) was distinctly lower than that in the United States, both values being based on a large number of samples. This order is the reverse of that shown by the milk levels in the preceding years. Only a slight rise was shown in Japan. No consistent change was observed in Australia or Chile. The general differences in trend between northern and southern hemispheres are consistent with the differences in deposition of Sr^{90} . The more detailed differences may depend in part on lack of representativeness in sampling but may well arise from genuine differences in dietary habit in the young.

89. Detailed information from the United Kingdom (figure 5) shows a marked increase with time in the values for children but no significant change with adults.⁹⁸ The data in table XX suggest that this was generally true in other areas.

Observed ratio (bone/diet) from measurements of Sr^{90} in bone

90. It is not possible to calculate the OR (bone/diet) for adults from fall-out data because of the short time

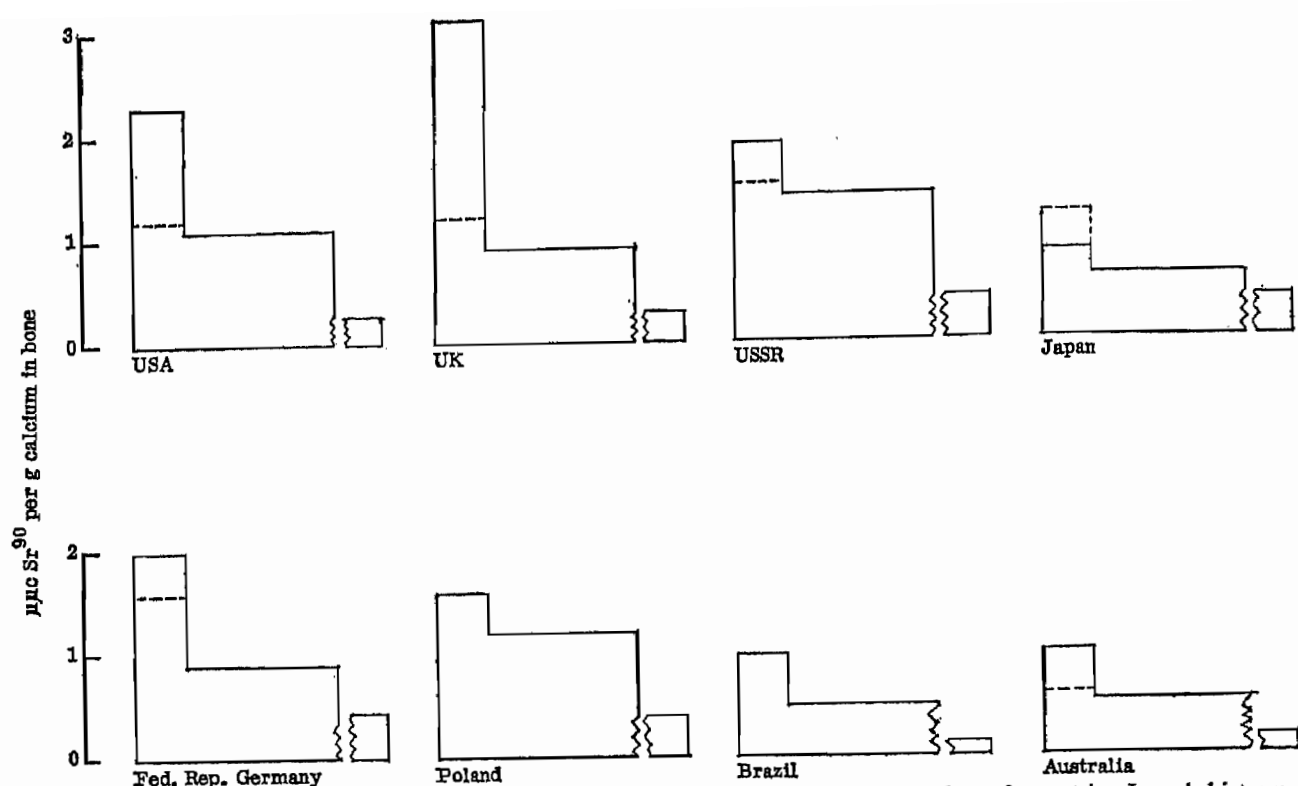


Figure 3. Concentrations of Sr^{90} per g of calcium in bones from different age groups in 1959, from 8 countries. In each histogram from left to right 0-4, 5-19 and >19 years. Dotted line in 0-4 group shows the level in the new-born (data from table XX)

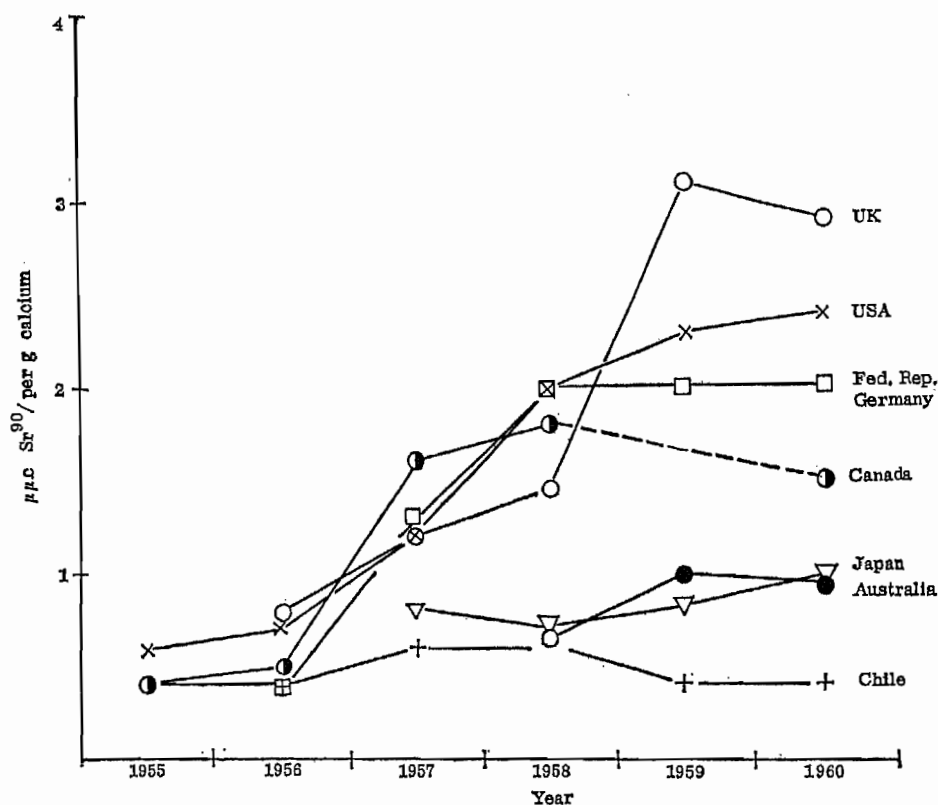


Figure 4. Sr^{90} in the bones of young children 0-4 years old 1955-1960 (data from table XX)

which it has been present in the environment, relative to the period during which the bones of adults have been formed. This difficulty does not arise with respect to young children, but the composition of their diet is very varied and is often not well known, so that no detailed evaluation of the OR from survey data is justified at the present time.

91. The bones of the newborn, or still births, however, provide an opportunity for estimating the OR (foetus/mother's diet) since relatively large numbers of bones of the newborn have been analysed and much information is available on the adult diet. For different countries in Europe and North America (table XXV) the values range from about 0.1 to 0.13. This result is

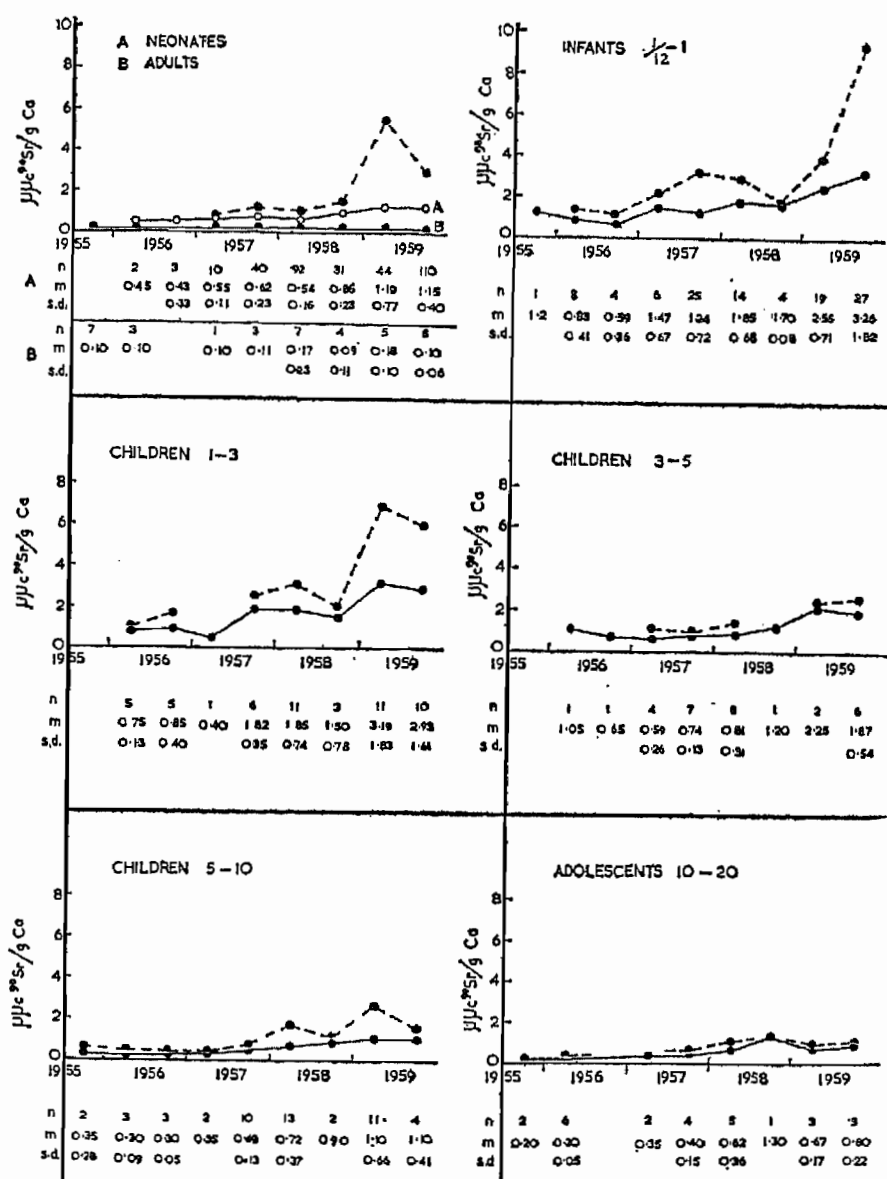


Figure 5. The concentration ($\mu\mu\text{c}$ per g of calcium) of Sr^{90} in human bone, 1955-1959, in the United Kingdom

Notes:

- In each group the mean values are linked by a continuous line and the maximum values by an interrupted line. In the first category the lower continuous line (B) relates to the bones of adults and no maxima are drawn as they differ so little from the mean; the upper continuous line (A) relates to the mean values and the interrupted line to the maximum values for still-born infants whose bones are formed indirectly from the maternal plasmas.
- The subscript tables for each category give: (n) the number of individuals; (m) the mean value in $\mu\mu\text{c}$ per g calcium; (s.d.) the standard deviation of the values in $\mu\mu\text{c}$ per g calcium⁹⁸

in good agreement with that which can be inferred from experimental studies on animals; the OR (foetus/mother) is about 0.5 and when this is combined with the OR bone/diet of 0.25 a value of 0.125 is obtained. The variable values for Japan shown in this table may have been due either to the small number of samples or differences in the composition of diet.

EVALUATION OF MEAN LEVELS OF Sr^{90} IN DIET AND BONE

92. In the previous sections of the present annex, measurements of Sr^{90} in individual foods, in total diet and in bone have been presented and discussed. Attention has been drawn to the fact that the Sr^{90} to calcium ratios in individual foods, in diets of similar types and

in bone in different areas appear to vary in a generally similar manner to the levels of Sr^{90} deposition, particularly in regard to geographical latitude.

93. An attempt is now made to summarize these data and compare the values found in bone with those predicted from diet. The data are considered as means, weighted appropriately for production or population over broad areas. A comparison is made between the Sr^{90} to calcium ratio in the bones of young children and newborn in 1959-1960 as representing the newly formed bone in the population, and the dietary levels in 1958-1960. It would be preferable to use bone data from 1960 only for comparison but this is not yet available from all areas. Such data as we have suggest that the increase

from 1959 to 1960 was small and that the use of the 1959 values for these areas is a reasonable approximation. Values for diet before 1958 are not used because they are fewer than in later years. It is, in any case, probable that the age distribution of samples of bone in the 0-4 age group is generally biased to younger ages owing to the higher mortality rate in the first years of life; consequently, much of this bone would have been formed in the period 1958-1960.

Evaluation of Sr^{90} to calcium ratio in total diet, 1958-1960

94. Measurements for the total diet are available only from limited areas (table IV). However, by adopting one food as a reference standard and comparing with it the level in total diet or in other foods, extrapolation to wider areas is possible. Milk has been chosen as the reference standard not because it necessarily supplies a large proportion of the dietary Sr^{90} but because it has been most widely sampled.

95. Two approaches have been used:

(a) A comparison of the estimated levels in total diet from table IV with those in milk from the same countries from table VII. The results are given in table XXII. In diets of class I the Sr^{90} to calcium ratio in the total diet ranged from 0.9 to 2.9 times that in the milk. The average of all results (excluding Denmark, the value for which fell outside the usual range) is 1.4. In Japan (class III) the ratio total diet/milk increased from 1.4 in 1957 to 3.6 in 1960, since the level in the total diet increased more than did that in the milk over this period. From the limited surveys in Central and South America values for the ratio of total diet to milk from 0.9-3.3 are suggested. The single value for Africa (10-13, based on limited sampling in Rhodesia in 1959-1960) is comparatively high. The diet in this area, however, shows quite distinct features.²²⁷

(b) A comparison of the Sr^{90} to calcium ratio in milk and in cereals, vegetables and fish, where measurements were available from the same area in 1958-1960 and subsequently to compile ratios for the ratio total diet/milk for a number of different types of diet. This calculation may be justified on the basis that while actual levels of Sr^{90} in foodstuffs in different areas will depend on the extent of deposition, the relative degree of contamination of different types of crops may be expected to bear some roughly constant relationship to one another. Considerable variation may occur because of differences in agricultural conditions and practices, but if comparisons are made over sufficiently large areas, useful relationships may be established.

96. Three types of diet have been used, based on the classification according to calcium contributions previously established (para. 39). Attention should be drawn to the fact that this classification applies only to the diets for which detailed information on the calcium contributions was available and is not necessarily complete. Since the Sr^{90} to calcium ratio in unmilled cereal is much higher than in milled cereal, additional calculations have been made for diets in which 30 per cent or all of the cereal is unmilled. (This would in fact change the calcium contribution from cereals to some extent but this has not been taken into account owing to the approximate nature of the calculation.)

97. Details of the diets and values obtained are set out in table XXIII. Values for the calculated ratio total diet/milk range from 1.5 for diets of class I to 4.2 for

a diet of class II in which a high proportion of the calcium is derived from unmilled cereal. These values are of the same order as those calculated from measured levels in total diet. It must be pointed out, however, that the two methods are not entirely independent since some of the data used have already been used in the calculation of the total diet values. However, this second method does permit the inclusion of many more data.

98. This calculation provides an opportunity of estimating the differences that might have occurred in the Sr^{90} to calcium ratio in different types of diet. It suggests that in areas of similar deposition of Sr^{90} the ratio in diets of classes II and III, which have relatively little milk, may have been only about twice that in diets of class I. In fact, since much of the area of Asia and Africa, where diets low in milk are common, has been one of low deposition of Sr^{90} , the differences are likely to be much smaller. This is borne out by the measured levels in total diets in Viet-Nam and Africa compared with those for Europe and North America (table IV).

99. The substitution of unmilled cereal for milled cereals appears to increase the ratio of Sr^{90} to calcium in the total diet by at most about 50 per cent; this is a rather smaller effect than has been noted for some individual countries (paras. 56 and 57). Mention should be made here of diets not included in the classification above in which up to 80 per cent of the calcium in the diet comes from cereals and the rest from vegetables.¹⁷⁵ Calculation from the values given in table XXIII suggest that even in this case the ratio total diet/milk would not exceed 5-10, the exact value depending on the proportion of the cereal which was milled.

Comparison of calculated and measured Sr^{90} in bone

100. Table XXIV sets out:

(a) Production weighted mean levels in milk for the period 1958-1960, based on tables VII, IX and X;

(b) Mean levels in diet for 1958-1960, based on table IV;

(c) Calculated levels in total diet, using the weighted mean levels in milk and the ratios total diet/milk derived from measured levels in the total diet (table XXII). Since milk values, other than those used in calculating this ratio, are available only in Europe and North America, this method cannot be applied to other areas;

(d) Calculated levels in total diet based on mean worldwide ratios of the Sr^{90} to calcium ratios in individual foods to milk and the approximate diets, assuming that the cereal was all milled (table XXII). This has been applied to all areas except Central America, where the diet has special features (para. 40) and appears not to be classifiable on this basis;

(e) Calculated ratios of Sr^{90} to calcium in new bone on the assumption of an OR (bone/diet) of 0.25. The basis for this value has been previously discussed;

(f) Calculated ratios of Sr^{90} to calcium in new bone using observed values in newborn (table XXI) and assuming that the Sr^{90} to calcium ratio in foetal bone would be one-half that in new bone of the mother owing to placental discrimination (para. 36);

(g) Observed levels of Sr^{90} in the bones of children 0-4 years old in 1959-1960 (table XXI).

101. The approximate nature of these calculations must be stressed. Nevertheless a very reasonable correspondence of calculated and measured bone levels is

found. In general, measured bone levels are somewhat lower than those predicted from the diet. Greatest uncertainty must attach to the calculations for Asia and the Far East where systematic surveys are few and where large populations are unrepresented by data. However, the measured values in bone from these areas are lower than in North America and Europe.

102. The generally good agreement between values in bone predicted from dietary surveys and the observed levels (table XXIV) is of considerable importance from the viewpoint of design of surveys of Sr^{90} in the human diet. The conduct of surveys which conform to strict statistical principles is laborious and expensive even in highly organized countries; and it is likely to be impossible elsewhere. Present results encourage the view that the standard of sampling which has been adopted in many areas is adequate to show the approximate average level of Sr^{90} in the bones of large population groups; furthermore it appears that especially when milk constitutes an appreciable part of the diet, the ratio of Sr^{90} to calcium in bone could have been predicted reasonably from the assay of milk alone. Considerably more elaborate surveys are, however, necessary to elucidate food chain mechanisms.

FUTURE LEVELS OF Sr^{90} IN DIET AND MAN

103. In the detailed description of the routes of entry into food chains described previously (paras. 13-24) attention has been drawn to the importance of alternative routes of entry of Sr^{90} into vegetation in addition to absorption from the soil. This is emphasized by the changing degree of contamination of milk, vegetables and cereals between 1958, 1959 and 1960 (paras. 62-76) which can be seen to have been related to the changing rate of fall-out. Some estimates of the relative magnitude of direct contamination and of absorption from the soil have been made. In the United Kingdom, for example, absorption from the soil was estimated to have contributed only about 40 per cent of the Sr^{90} in milk in 1958 and 1959, but some 75 per cent in 1960 when the rate of fall-out was considerably lower.²⁴⁷ Estimates of the amount of Sr^{90} in wheat due to direct contamination range from 20-90 per cent.^{84, 210, 286} It is clear then that both factors must be taken into account in estimating future levels in diet and bone under specified conditions.

104. The many factors affecting the relative importance of the rate of fall-out and the cumulative deposition in the contamination of food have been stressed previously (para. 25). Because of these factors it appears preferable to attempt evaluation for world-wide predictions on a country-wide basis so that local fluctuations assume less importance.

Method of evaluation

105. In the previous report of the committee and in other publications,^{203, 204, 247} attempts have been made to predict the future levels of Sr^{90} in diet on the basis of an expression of the following general form:

$$C = p_d F_d + p_r F_r$$

where

C is the concentration of Sr^{90} ($\mu\mu\text{c}$) per gram of calcium in a food,

F_d is the cumulative deposition of Sr^{90} (mc/km^2)

F_r is the current rate of deposition of Sr^{90} ($\text{mc}/\text{km}^2/\text{y}$)

and p_d and p_r are proportionality factors.

They can conveniently be termed the "cumulative" and "rate" factor respectively. Neither factor can be regarded as a true constant. The cumulative factor will vary with location depending on soil type, and will vary with time as the distribution of Sr^{90} in soil changes (paras. 14-20). It will decrease as leaching and possibly fixation occurs (paras. 19 and 20). The rate factor is dependent on the many variables affecting foliar retention and contamination, and on the extent of plant base absorption (paras. 23 and 24). The reliability of the estimates of the proportionality factors is discussed in paragraph 118.

106. The factors were evaluated for the previous report by means of regression techniques, using data for milk, and preliminary results of experiments in which Sr^{90} uptake by crops growing in the field was measured. There are now considerably more data available for longer periods of time during which the fall-out rate varied considerably. More experimental evidence is also available.

107. A number of methods can be used to evaluate the two factors using the data set out in tables VII to XVII and the estimates of fall-out rate and deposit (F I, figures 37 and 38). The principal method used is to assume that in late 1960 when the fall-out rate was low, the contribution of the fall-out currently being deposited to Sr^{90} in food was insignificant. Thus the cumulative factor may be determined by dividing the measured ratio of Sr^{90} to calcium in foodstuffs by the accumulated deposit. Since the fall-out rate was not zero, a maximum value is obtained. Where possible, mean values for wide areas have been used. This method enables values to be obtained for a considerable number of areas, especially for milk. The rate factor can then be determined by applying the calculated value of the cumulative factor to the results of previous years when the rate of fall-out was considerably greater relative to the cumulative total in the soil. This method has been preferred as the general basis for evaluation because it makes it possible to use survey results from wide areas. Supplementary information can however be obtained in other ways:

(a) By regression analysis providing adequate data on the rate of fall-out, the cumulative deposit and the level of contamination in the foodstuff are available. Such data are available only for milk and in relatively few areas;

(b) By calculating the cumulative factor from the results of experimental investigations of the absorption of radio-strontium by crops growing under field conditions. This can be the most precise method for evaluating the situation in any one locality. However, since results are available only for Sweden¹⁸⁶ and the United Kingdom,^{142, 247} they do not provide an adequate basis for assessing the world-wide situation;

(c) By assuming that, in the absence of direct contamination, the ratio of Sr^{90} to stable strontium in all parts of the plant should be the same. The existence of a higher ratio in whole grain than in roots,²³⁵ or in bran compared with flour,^{84, 210} indicates direct contamination. This fraction can be evaluated and compared with the annual fall-out deposit to obtain the rate factor. The value of the cumulative factor may be determined from the difference. Since the assumption must also be made that none of the Sr^{90} in flour is due to direct contamination, this method gives maximum values for the cumulative factor and minimum values for the rate factor;

(d) The approximate value of the rate factor is also

indicated by laboratory experiments in which radio-strontium was deposited on crops in various stages of growth and the amount in the edible parts determined at maturity.¹⁵⁰

Estimated values of proportionality factors

108. *Milk.* By assuming that in late 1960 or in early 1961 the contribution of Sr^{90} to milk from current fall-out was insignificant, values of the cumulative factor for several areas have been calculated. Table XXVI shows that they range from 0.2-0.8. Comparison of the values calculated in this manner with the results of regression analysis for areas in the United States and the United Kingdom, and the values calculated from field experiments in the United Kingdom, show that good correspondence between the different methods is obtained. For the purposes of calculation, a world-wide mean value of 0.3 will be assumed. Values close to this are achieved for broad regions by comparing the weighted mean values in milk for 1960 (table X) with the average cumulative depositions in appropriate latitudinal bands (F I, table XIV).

109. The value of the rate factor obtained by comparison with previous years or from regression analyses when the rate of fall-out was comparatively high, ranges from 0.3-1.2. A value of 0.8 will be used for calculation.

110. At present, much of the Sr^{90} in unploughed pasture land remains in the upper centimetres of soil. Field experiments indicate that with deeper penetration of Sr^{90} in the soil, the value of the cumulative factor will be reduced by about one-third.²⁴⁷ Hence, for the long-term situation a value of 0.2 is adopted.

111. It may be noted that these estimates show that the rate factor is considerably greater relative to the cumulative factor than appeared from the very limited data available to the Committee at the time of the previous report, when the rate factor for Perry, New York, was estimated as 0.23 and the cumulative factor as 0.34.

112. *Green vegetables.* Direct estimates of the cumulative factor for vegetables, calculated from the limited data available for late 1960 (table XXVI) and from field experiments,^{130,142} indicate values ranging from 0.5 to a little greater than 1. The value of the rate factor from the comparison of 1960 values with those in previous years ranges from zero to 0.8.

113. *Potatoes and starchy roots.* The values of the cumulative factor calculated from the limited data for 1960 available, range from 1-3 (table XXVI). Field experiments in the United Kingdom and Sweden suggest a range of 0.7-1.4. The value of the rate factor from a comparison of 1960 values with those of earlier years is indicated as close to zero. For calculation, the cumulative factor will be taken as 1, the rate factor as zero. The adoption of somewhat higher values for these factors has little influence on the over-all prediction since the contribution of calcium from this source in all the approximate diets is very small.

114. *Cereals.* The value of the cumulative factor cannot be derived from the 1960 data because of the extent of floral contamination (para. 23) which was significant in 1960 in spite of the low fall-out rate. However, because the rooting depth of cereals and vegetables is often similar, and the soil is prepared in the same way for both crops, the value for cereals has been derived from that for vegetables. Allowance has been made for dis-

crimination against strontium in passage into the cereal grain (para. 16) in adopting a value of 0.5. This is similar to the mean value from field experiments in the United Kingdom and Sweden.^{130,142} Adoption of a value of 1 would not increase the over-all cumulative factor for any of the diet types by more than about 10 per cent.

115. Using this value of the cumulative factor, the rate factor has been calculated from the available data for wheat and rice by the methods described in paragraph 107. Considerable variation between different years and different areas may be expected since the values are based on crude estimates of annual fall-out rates, while the concentration in the grain is dependent on the rate during a short period before harvest. For calculation the rate factor is taken as 20 for whole grain and 7 for milled cereal. These values are assumed to apply for all cereals.

116. *Total diet.* The values of the cumulative and rate factors adopted for individual foods are set out in table XXVII. They have been used to calculate factors for the total diet weighted according to the calcium sources in the diet types previously used for evaluation of present and past levels. It should be noted from this table that the rate and cumulative factors for the various diets differ only by a factor of about 2. For calculating future levels a rate factor assuming 20 per cent of the cereal is unmilled has been adopted as a conservative estimate.

117. Because of the delay in consuming such foods as cereals and potatoes, these weighted factors will be applicable only if the rate of fall-out is reasonably constant from year to year. Owing to such delays and the presence of considerable amounts of imported foods in many diets, direct determination of the proportionality factors from measurements of total diet, though theoretically possible, is unlikely to give reliable results at the present time, since the rate of fall-out has varied very considerably over the few years (1957-1960) for which such measurements are available. Such an evaluation will be more useful when data are available for a period which is long in comparison with the lag in consumption. However, approximate comparisons can be made, realizing their limitations. Total diet measurements in the United States in early 1961 indicated an average level of $6.7 \mu\mu\text{c Sr}^{90}$ per g of calcium in total diet, which on the basis of a deposition of 27 mc/km^2 indicates the cumulative factor for total diet in the United States to be about 0.25 (diet I), compared with the previously calculated value of 0.4. In Japan, the latest values in 1960 show a value of $19.3 \mu\mu\text{c Sr}^{90}/\text{g Ca}$ in total diet and a deposit of 25 mc/km^2 . Hence the cumulative factor for total diet is 0.77 (diet III). These values must however include some component from the fall-out rate; this suggests that the values calculated from the individual foods lead to conservative estimates of the factors for total diet.

118. *Reliability of the values adopted.* Before attempting to calculate future levels of Sr^{90} in the total diet, the accuracy of these forecasts should be considered. Inaccuracies may arise from:

(a) The error associated with the measurement of Sr^{90} in foodstuffs and in fall-out deposits, particularly in regard to the representativeness of the samples;

(b) The lack of coverage for certain large areas of the world which leads to the necessity for extrapolation;

(c) The fact that annual fall-out values are used whereas vegetables and cereals are subject to contamina-

varied considerably throughout the year;

(d) The uncertain pattern of future fall-out particularly in regard to distribution throughout the year.

119. However, the reasonable agreement between estimates made by different methods and for different areas suggests that the values adopted may provide a satisfactory basis for estimating possible future exposures of populations, at least in those regions from which the basic data were obtained. The values should be applied only to large regions. They may be open to considerably greater error if applied to particular localities.

Calculated future levels

120. In calculating the levels of Sr^{90} which may occur in the future, on the basis of proportionality factors (tables XXVI and XXVII) and predicted levels of deposition (F I, figures 37 and 38), account must be taken of the fact that some Sr^{90} will be lost from the soil by run-off, leaching and removal in crops; part of the Sr^{90} which crops absorb may, however, be returned to the land in organic manure. Moreover, slow fixation processes may lead to some reduction in the availability of Sr^{90} . These processes are discussed in paragraphs 14-25. For predicting the world-wide levels of Sr^{90} in diet, it is assumed that the net losses of Sr^{90} will be 2 per cent per annum. This is considered to be an adequately cautious average which will not under-estimate the general level of dietary contamination. Between different regions, wide variation is to be expected; considerably larger losses have been estimated for some areas⁹⁸ but elsewhere it seems possible that losses may be considerably lower.

121. Estimated future levels of Sr^{90} in the three classes of diet adopted are given in figure 6 for two of the cases considered in part I of this annex (F I, 110). These levels are calculated for the mean diet of large populations; smaller groups may have intakes differing from the average as discussed in paragraphs 51-61. The levels are calculated for the average world fall-out (F I, 33). If the present pattern of latitudinal distribution were observed in the future, the mean levels in the temperate zone of the Northern Hemisphere would be about twice those in the figure, whereas the levels in the Southern Hemisphere would be lower than in the figure. A discussion of the factors to be used to calculate values for different latitudes and to calculate a population weighted mean diet value for the world is given in annex F, part III, paragraph 33.

(a) *Tests ended in 1961.* Figure 6 shows that after a slight rise the levels in diet will quickly fall off until values of less than $2 \mu\mu\text{c Sr}^{90}$ per g of calcium are reached by the year 2000. If tests continued until 1965 the levels in the year 2000 would be near to or less than $3 \mu\mu\text{c Sr}^{90}$ per g of calcium. Thereafter radio-active decay and removal would cause the level to drop by about 5 per cent per year;

(b) *Continued testing.* Under continued testing the levels would rise until at equilibrium the levels would be about three times those calculated for 1960.

III. Caesium-137

CAESIUM-137 IN FOOD CHAINS

Relationships between caesium and potassium

122. The chemical similarity of caesium and potassium and the opportunity offered by the gamma spec-

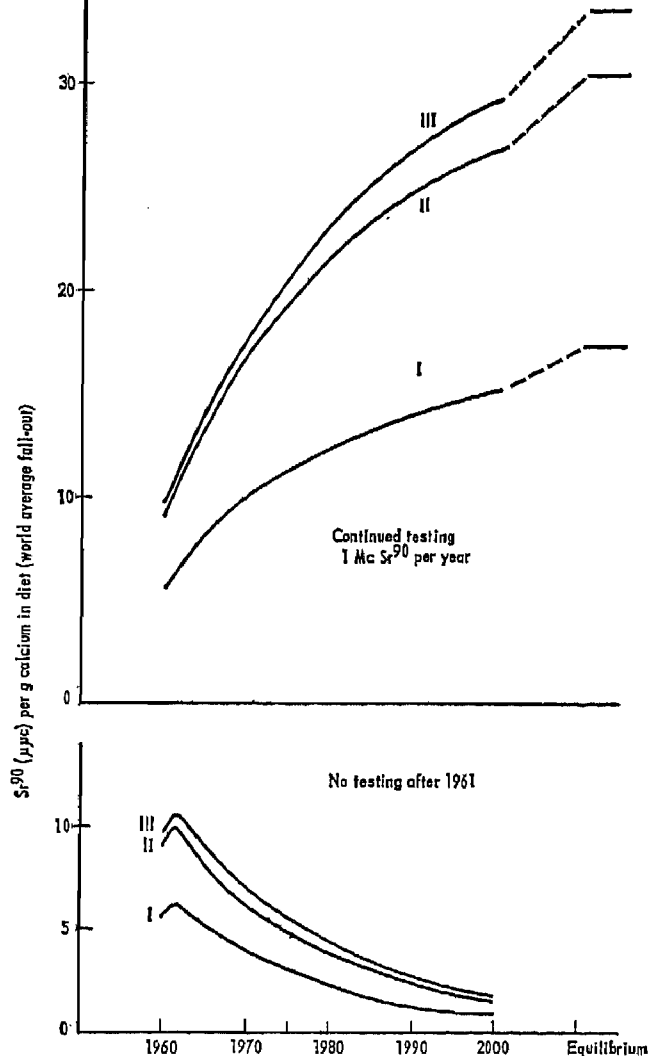


Figure 6. Calculated levels of Sr^{90} in three diet types (para. 39) under two conditions of testing, following the model adopted (F I, 110, 114). The values are calculated for world average fall-out. For values in particular latitudes, see discussion in paragraph 119 and F III, 33.

trometer to make simultaneous measurements of Cs^{137} and the naturally radio-active K^{40} has encouraged the expression of Cs^{137} concentrations in terms of potassium in a manner analogous to that used for strontium and calcium (para. 9). However, while strontium and calcium are interdependent and behave in a relatively similar and regular manner in biological systems, this is apparently not true of caesium and potassium. For example, in absorption by plants, the OR (plant/solution) may increase by a factor of 2-10 as the concentration of potassium in the external solution is increased.^{176, 177} Similarly in rats, it has been found that a ninefold change in the dietary potassium level causes an almost proportional change in the OR (tissues/diet).²⁰⁰ It has also been shown that, in the animal body, Cs^{137} and potassium may be distributed in quite different ratios in different tissues and organs.^{262, 290, 293} Since the observed ratio changes markedly under different conditions, it appears that this concept cannot usefully be applied for this pair of elements. However, as a matter of practical necessity, values for the Cs^{137} content of diet and man in the following tables are expressed in terms of the ratio of caesium to potassium, since this is the method

of presentation in many publications.* The ratio of Cs^{137} to potassium is, in fact, the preferable unit in which to express the content in man, since it correlates better with lean body mass, and hence with organ dose, than does Cs^{137} per kg of body weight. This, however, is quite independent of considerations of the similarity of metabolic behaviour of Cs^{137} and potassium.

Soils and plants

123. Cs^{137} , like Sr^{90} , can enter plants both by direct contamination and from the soil. However, Cs^{137} is absorbed from the soil to a considerably lesser extent than Sr^{90} . Once absorbed, unlike Sr^{90} , it is readily redistributed within plants, its distribution being relatively similar to that of potassium.

124. *Absorption from soil.* Large-scale field experiments, comparable to those with Sr^{90} , have not been carried out for Cs^{137} . However, the relative uptakes of Sr^{90} and Cs^{137} have been compared in many laboratory experiments and these may be used as a basis from which the behaviour of Cs^{137} in the field may be inferred. These experiments show that Cs^{137} is less well absorbed from soil by plants than Sr^{90} ; the relative amounts vary with the soil type. In short-term experiments, with typical soils of temperate regions, Cs^{137} is absorbed to an extent only 1/10 or less of that of Sr^{90} .^{19, 185, 149} With the passage of time the absorption of Cs^{137} relative to Sr^{90} decreases, and after three years the quantity absorbed may be about 1/25, or less, of that of Sr^{90} .^{149, 283} Marked differences, however, occur between soils and in some soils of tropical origin the absorption of Cs^{137} is considerably greater.²⁸⁸ High uptake of Cs^{137} relative to Sr^{90} was also found in lowland rice growing in paddy soil;¹¹⁸ this was ascribed to the presence of nitrogen in the form of ammonium ions.

125. *Reaction of Cs^{137} with soil and downward movement.* The relatively low absorption of Cs^{137} by plants is due to chemical reactions which tend to bind it to soil constituents.^{19, 135, 179} Cs^{137} enters into the crystal structure of micaceous minerals in a manner similar to but not necessarily identical with that of potassium.^{135, 179, 180} Once bound, caesium is replaced from soils to only a small extent by divalent cations, but more readily by caesium, ammonium or potassium ions.¹⁸⁰ The addition of carrier caesium can increase the uptake of Cs^{137} by plants.^{118, 135} The addition of potassium may decrease the absorption of Cs^{137} in soils low in available potassium; it may, however, have no effect when the available potassium is high.^{134, 135} Owing to this strong binding, the downward movement of Cs^{137} in soils is considerably slower than that of Sr^{90} .^{227, 272}

126. *Direct contamination of plants with Cs^{137} .* Cs^{137} , like Sr^{90} , may enter plants by foliar, floral or plant base absorption. Cs^{137} is retained by the plant surfaces on which it lodges directly to about the same extent or perhaps a little better than Sr^{90} .^{122, 158, 159} and the factors affecting retention appear to be generally similar. The relative rates of penetration of Sr^{90} and Cs^{137} into tissues are not known. A very marked difference in behaviour occurs after absorption because of the ready redistribution of caesium throughout the plant.^{122, 196}

127. *Plant base absorption.* Little is known regarding the extent to which Cs^{137} enters plants by plant base absorption. However, it may be noted that although in

many areas the ratio of Cs^{137} to Sr^{90} in milk decreased owing to the low rate of fall-out in 1960,²⁵¹ in others the ratio remained relatively constant from 1959-1960.^{227, 242} This may be interpreted as due to differences in pasture management affecting the degree of retention in the root mat and of incorporation of Cs^{137} in the soil. It suggests that retention of Cs^{137} in the root mat of permanent pastures may cause Cs^{137} to be relatively available to plants for a period of a year or more.

Aquatic food chains

128. Experimental studies have shown that Cs^{137} may be concentrated by the flesh of aquatic organisms to a degree one or more orders of magnitude higher than the surrounding water.²⁰⁷ However, analyses of Cs^{137} in fish do not suggest a very large contribution to the total content of the diet (table XXXI).^{33, 108} Consequently, detailed discussion of this aspect is unwarranted.

Transference into milk

129. The metabolism of Cs^{137} in animals has been less well studied than that of Sr^{90} . However, it has been shown that some 10 per cent of orally ingested Cs^{137} is secreted into the milk of dairy cows; this corresponds to about 1.3 per cent of the amount ingested per litre of milk.^{181, 182, 207, 221} The amount of Cs^{137} transferred into milk is slightly greater than that of potassium.^{207, 204} No information is available on the secretion of Cs^{137} into human milk.

Metabolic behaviour in man and mammals

130. Cs^{137} and potassium are absorbed from the gut virtually completely, and are mainly distributed in the soft tissues in the body. The distribution of Cs^{137} from fall-out in human tissues has been studied in a number of post-mortem samples. The results indicated a concentration of Cs^{137} in rib bones which were free of muscle but not of marrow, comparable with that in soft tissues.^{222, 226} The results were variable and further information is necessary before firm conclusions can be drawn. When Cs^{137} was injected into patients, the bones at autopsy had somewhat lower concentrations of Cs^{137} than the soft tissue.²⁰⁷ Studies with mice have indicated that Cs^{137} concentrates in cartilage.²⁰⁵

131. At least two exponential processes can be recognized in the excretion of Cs^{137} from the body of most species including man,^{40, 298, 314} following the administration of a single dose. In man two components are well established: a small fraction (10 to 15 per cent) is excreted with a short half-life (1.0 to 1.5 days) while the remainder is excreted more slowly. There is considerable variation among individuals, and half-lives as low as 50 to 60 days^{297, 298} and as high as 150 to 160 days^{298, 314} have been reported. The average appears to be in the region of 100 to 120 days.^{217, 298, 314} This contrasts with the more rapid turnover of potassium, the apparent half-life of which depends very largely on the dietary intake.^{40, 108, 264, 298}

132. The rate of turnover in different species is generally related to body size, being particularly rapid in small animals such as the mouse and rat.^{203, 315} Ruminants form an exception to this rule, however, having a relatively rapid biological half-life.^{263, 294} The level of dietary potassium has little effect on the rate of removal of Cs^{137} from the human body;⁴⁰ an increase in daily potassium intake produces only a transitory increase in the urinary excretion of Cs^{137} , and it subsequently returns to its former rate.²⁶⁴

* These may be approximately converted to other units since the potassium content is roughly constant in milk (1.4 g/l) and in the human body (2 g per kg of body weight).

133. The gamma-radiation associated with Cs¹³⁷ can be distinguished from that emitted by the naturally radio-active K⁴⁰ using a scintillation spectrometer. Direct estimates of Cs¹³⁷ and potassium contents of living subjects, of large samples of diet and of samples of human excreta can be obtained. Since the biological half-life of Cs¹³⁷ in the human body is relatively short, there is comparatively little variation in the concentration of Cs¹³⁷ (per kg of body weight or per g of potassium) between different age groups. Thus measurements on adult subjects can be used for estimating the dose to the whole population. It will be recalled that for Sr⁹⁰, measurements on adults were of very limited use, and emphasis was placed on measurements of the concentration in the bones of children and in the total diet. For Cs¹³⁷ much less importance attaches to the analysis of diet or to other indirect methods of estimating body content, and comparatively few values are available.

Cs¹³⁷ in the total diet

134. Few estimates of the concentration of Cs¹³⁷ in the total diet have been made. Estimates available from the United States in 1956-1957 and Canada in 1959,^{40, 108} (table XXVIII) indicated an intake of about 60 μCi per day and a ratio of Cs¹³⁷ to potassium of about 20 $\mu\text{Ci/g}$. In mid-1961, analysis of composite diets in the United States of America indicated an intake of only 33 μCi per day.⁸¹² In these countries some 60 per cent of the Cs¹³⁷ was supplied from milk and 25-35 per cent from meats. In Japan, analyses on composite diets indicate a total daily intake of close to 50 μCi Cs¹³⁷ per day in 1959 and 1960.³³⁰ Approximate calculation from the levels of Cs¹³⁷ in foodstuffs at Gunma (table XXXI) suggests that perhaps half of the Cs¹³⁷ was derived from cereals and that vegetables, milk and meat were other important contributors. In Argentina in 1961 the total daily intake of Cs¹³⁷ was estimated as 40 μCi .⁴⁴

135. An alternative to analysis or estimation of dietary Cs¹³⁷ is analysis of the mean daily excretion of Cs¹³⁷. A few data are available for the United States³¹⁶ and the United Kingdom.²⁰⁸ In 1957 two American subjects excreted 33 and 40 μCi Cs¹³⁷ per day in the urine;⁸¹⁰ the daily total excretion of one subject in the United Kingdom was 81 μCi and 36 μCi in April 1959 and April 1961 respectively. Two other men excreted 42 μCi and 10 μCi in April 1961.²⁰⁸ These values are very similar to those quoted above as estimates or measurements of daily diets.

Cs¹³⁷ in milk

136. Measurement of Cs¹³⁷ in food has with few exceptions been confined to milk, because of its importance as a supplier of Cs¹³⁷ to some diets, and because of the ease with which it can be sampled. Mean values for Cs¹³⁷ in milk are set out in tables XXIX and XXX. Regular surveys of milk have been carried out for some years in North America, and have been started recently in a number of countries in Europe. Surveys are also carried on in India, Japan and Australia. The rest of the world is represented by isolated samples; no recent results are available for large areas of Asia, South America and Africa.

137. The Cs¹³⁷ content of milk may be regarded as largely determined by the current rate of fall-out or the level in the recent past owing to the small quantity of Cs¹³⁷ absorbed from the soil. Large fluctuations are observed

following those in the rate of fall-out. This is illustrated in figure 7 which shows the quarterly mean concentration of Cs¹³⁷ in milk in several areas. Sharp rises in the concentration of Cs¹³⁷ in milk were shown in the United States, Norway and India following heavy fall-out in the spring of 1959. That the peak value was not as high as in 1958 in the United States in spite of heavier fall-out may indicate the importance of the distribution of fall-out in relation to the grazing period in determining levels in milk. Following the drop in fall-out rate a sharp decline occurred in the concentration of Cs¹³⁷ in milk in the United States and India, which reached low levels in late 1960. In Norway the pattern was different. Although a sharp rise in 1959 was shown, the concentration showed no consistent fall until late 1960. This type of difference must be ascribed to differing climatic and agricultural conditions; in particular, it raises the possibility of a lengthy hold-up of Cs¹³⁷ in the root mat of certain types of permanent pasture.

138. The wide variation with time in the concentration of Cs¹³⁷ in milk from a single area, and the scarcity of really representative data which cover a complete year make comparisons between different areas difficult. The limited data in table XXIX indicate that levels in North America and Europe are comparable, with rather low levels being shown in Denmark and very high ones in Norway. Values from Japan are also somewhat higher than in North America; in India and Australia they are distinctly lower.

Cs¹³⁷ in other foods

139. Some data for Cs¹³⁷ in foods other than milk have already been presented in table XXVIII. Other data chiefly from a single location in Japan are presented in table XXXI. It may be noted that wheat from Canada and cereals from Japan have a ratio of Cs¹³⁷ to potassium of the same order of magnitude. The vegetables from Japan, however, have higher ratios of Cs¹³⁷ to potassium than those from North America (table XXVIII). A comparison of values based on such limited sampling is, however, of doubtful significance. Meat from Norway shows high contents of Cs¹³⁷ which are in proportion to those in milk from the same areas.²⁵¹ Not enough is known about the metabolism of Cs¹³⁷ in the cow for the concentration in meat to be deduced from that measured in milk, but there will certainly be a correlation assuming similar feed for dairy and beef animals. The exceptionally high values which are recorded in reindeer meat are attributed to the grazing of lichens.²⁷⁸

Measured levels of Cs¹³⁷ in the human body

140. Few whole body counters have been available in recent years; in consequence, determinations of Cs¹³⁷ in large numbers of individuals have been restricted to North America and Western Europe. Measurements have been made recently also in Japan. While many other countries are represented in table XXXII, the determinations were carried out on relatively few individuals who were visitors to a laboratory where a counter was situated. The extent to which such visitors are representative of their native population depends on the interval between leaving their country and being measured, and also on the extent to which socio-economic differences in diet exist. Neither factor can be evaluated with the available information. Consequently, in table XXXII results for visitors to each laboratory have been grouped together in broad geographical regions. Results for indigenous populations of countries in which the

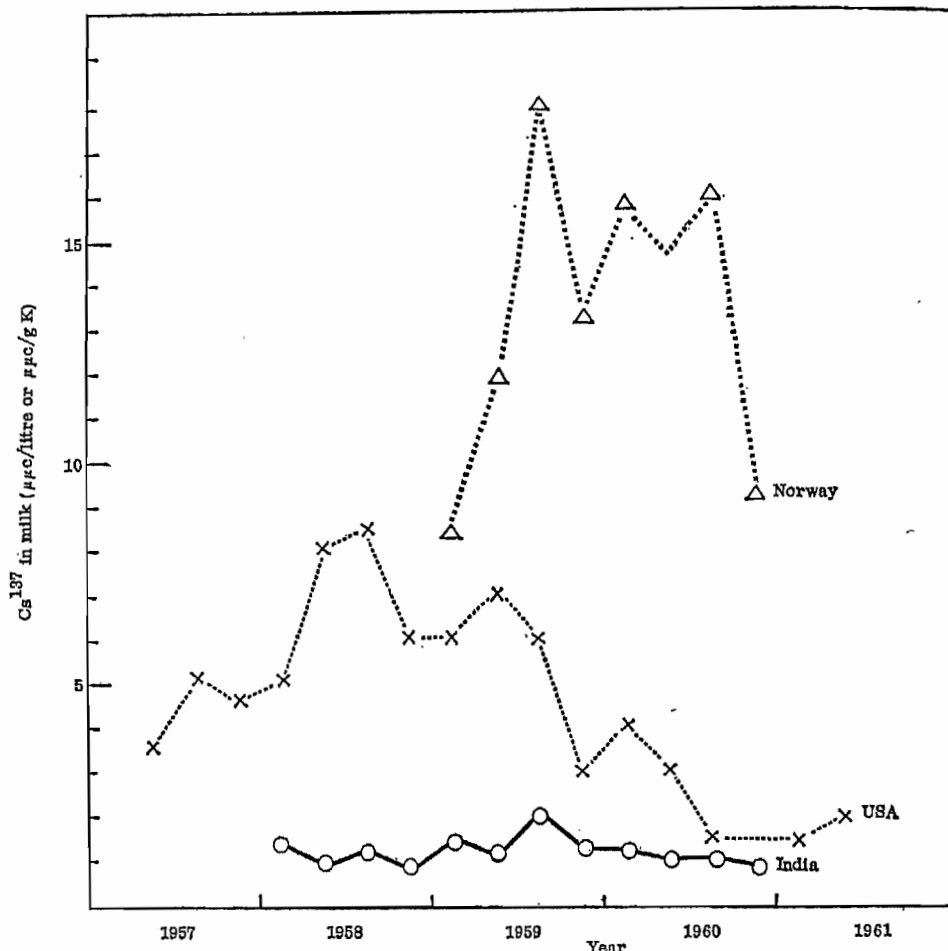


Figure 7. Cs¹³⁷ concentrations in milk in three countries

— India (Bombay)²⁴⁴
 Norway (mean of 3 sites)^{251, 245}
 - - - - - USA (mean of 10-12 sites)²⁵¹

measurements are carried out are presented separately. It may be seen that there is good correspondence between the results of different laboratories where reasonable numbers of samples are available. Consequently, all results have been summarized by broad geographical regions in table XXXIII.

141. *Geographical variation.* The mean values for those areas in the Northern Hemisphere where large numbers of measurements have been made are very similar. Far fewer values are available for persons representative of the Southern Hemisphere, but the mean values (for South America, for example) appear to be somewhat lower than those from the Northern Hemisphere. There is thus some suggestion of a correlation with the latitudinal distribution of fall-out, although this is much less clearly established than for Sr⁹⁰ in bone.

142. Some local groups have been reported with body contents consistently in excess of the averages reported here.²⁷⁵⁻²⁷⁷ Small groups from Oslo and Bergen in Norway were measured in Sweden; their body contents were 184 and 477 μμc/g K respectively in 1960. It may be noted that the Cs¹³⁷ in milk in Norway was also found to be higher than in other areas of Europe (table XXIX). There is also the possibility that high consumption of goat's cheese may have led to higher body contents.²⁷⁷ Considerably higher values have also been found in people living in the north of Sweden.^{275, 276} These higher values can be ascribed to the eating of reindeer meat, which is high in Cs¹³⁷ (table XXXI). It may be

noted that in countries with diets high in milk, a correlation exists between the quantity of milk drunk and the Cs¹³⁷ content of the body.^{108, 194, 274}

143. *Trend with time.* The trend with time in several groups of subjects is shown in figure 8. Repeated measurements on two groups of persons have been carried out in Chicago (United States) and Berkshire (England). They follow an almost identical trend. Mean values for random samplings in New Mexico and Germany are higher but in all cases the pattern is similar, a rise from 1956 to 1959 followed by a distinct fall through 1960 to early 1961. This is consistent with a dependence of the body content on the rate of fall-out since the latter declined sharply in 1960. In contrast, the considerable rise in cumulative fall-out over this period was not accompanied by any comparable rise in body content.

144. The rate of response of the content in the body is slow compared with the rate at which changes in fall-out occur. This is well illustrated in figure 9 which shows the changes in Cs¹³⁷ content of the body and the fall-out rate in Berkshire (England) during 1956-1960. It results from at least two factors. The first is the time necessary for changes in the rate of fall-out to be reflected in the diet. This may be quite short for foods such as milk during the grazing season, but will obviously be much longer when stored foodstuffs, both animal and human, are involved. The second factor is the time necessary for the body to reach equilibrium with the diet. This is determined by the biological half-life, which is of the



Figure 8. Trends with time of Cs^{137} in man

- ×—×: 8 subjects measured repeatedly at Chicago^{279, 283}
- : Subjects measured in Berkshire, England (in later years repeated measurements on the same subjects)^{274, 298}
- Δ—Δ: Subjects living in New Mexico³
- : Subjects from USA; measured at Walter Reed Army Research Center^{118, 280}
- : Subjects living in Germany (Fed. Rep. of)

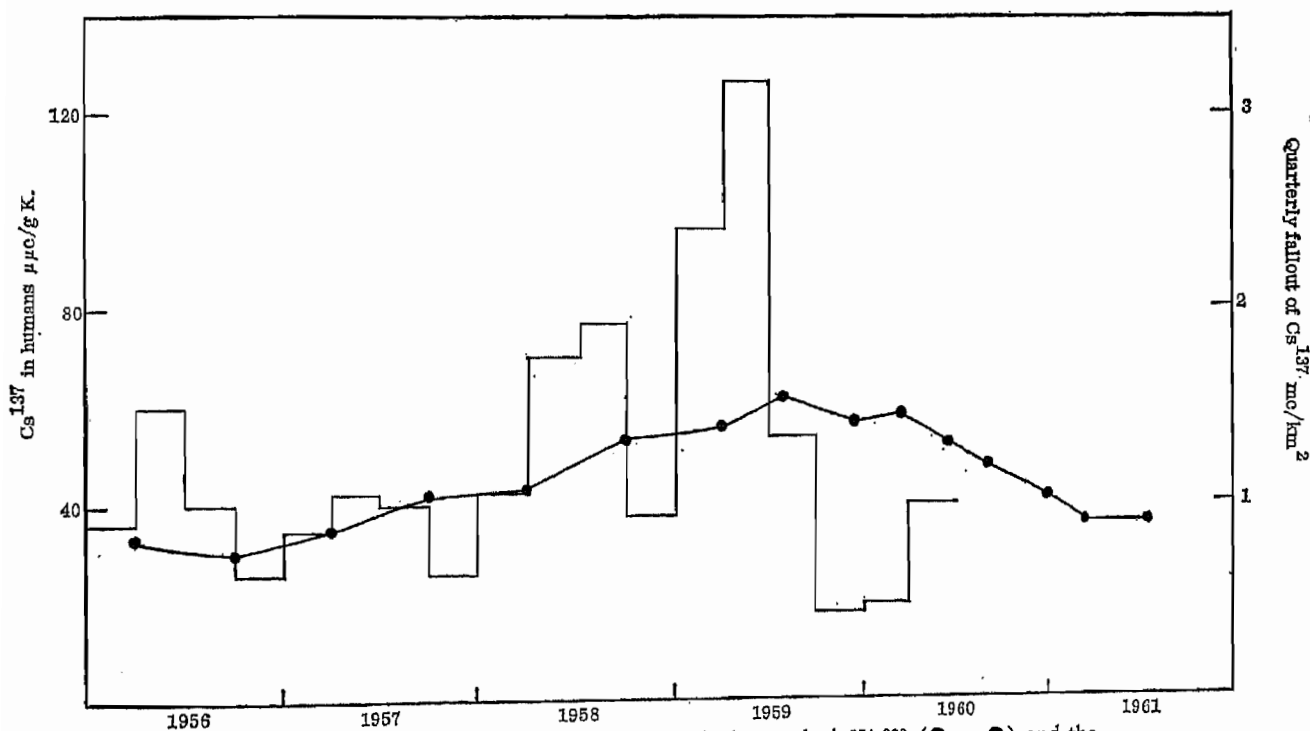


Figure 9. The relationship between Cs^{137} in the human body^{274, 298} (●—●) and the rate of fall-out (—) in Berkshire, England^{205, 208, 800}

order of four months. Marked changes in fall-out rate may occur in shorter periods than this.

Evaluation of mean levels of Cs^{137} in the human body

145. The paucity of data from many areas prevents any detailed comparison of the levels of Cs^{137} in diet and corresponding levels in the human body. The summary table XXXIII, together with the data set out in figure 8,

indicate that over the period 1958-1960 the mean annual level of Cs^{137} in the human body did not change more than ± 25 per cent from the value in 1958. Bearing in mind the limitations of the data for subjects from regions other than North America and Western Europe (para. 140), it seems likely that the average values for the broad geographical regions would also fall within this range. Allowing for the number of observations and the

greater proportion of the world's population in the Northern Hemisphere, it appears reasonable to suggest that the world average in this period was $60 \mu\text{C Cs}^{137}$ per g of potassium (± 25 per cent).

FUTURE LEVELS OF Cs^{137} IN DIET AND MAN

146. The levels of Cs^{137} in diet and in the body were largely determined up to 1960 by the rate of fall-out. The contribution from the accumulated deposit has been small but it will become proportionately larger, either when the rate of fall-out is very low some time after the cessation of weapon testing, or if the accumulated deposit becomes larger in comparison with the rate of fall-out owing to continued testing.

147. Present data are insufficient to justify the prediction of future levels of Cs^{137} in diet by methods similar to those used for Sr^{90} . Considerably less experimental information is available. Moreover, the contribution from the soil cannot be estimated from the results of surveys by assuming an insignificant contribution from the fall-out deposit during 1960, as was done for Sr^{90} , because the rate factor for Cs^{137} is very large relative to the cumulative factor. The delay which can occur between the deposition of Cs^{137} and its incorporation in the soil is a further cause of uncertainty (para. 136).

148. In view of these difficulties, alternative approaches have been examined. The approximate estimates of the future doses from Cs^{137} , which are made in the following paragraphs, are based on the relationship between the internal and external dose rates. They take into account the facts that the accuracy with which it is necessary to estimate the contribution to the internal dose from Cs^{137} absorbed from the soil should be considered in relation to the total dose from this nuclide, and that the external dose depends on the total deposit.

149. On the cessation of the testing of nuclear weapons, the levels of Cs^{137} in diet and in the body would decline in a manner similar to that observed in late 1959 through 1960. Estimates of the amount of Cs^{137} absorbed from soil suggest that the level in the diet and body would within a few years fall to less than 1/10 of the levels observed in the year of maximum fall-out. The external dose-rate would decrease considerably more slowly.

150. If the effect of continued testing on the contamination of diet is to be evaluated, account must be taken of the contribution of the increasing levels of Cs^{137} in the soil. Because of the difficulties referred to in paragraph 147, no precise estimate of the actual dietary levels can be made. However, limits can be set to the magnitude of the resultant internal radiation dose in relation to the external dose from this nuclide. If fall-out were to continue at a steady rate the components of both internal and external dose due to the cumulative deposit must show the same proportional increase. While the cumulative deposit determines the external dose it has hitherto been responsible for only a very small fraction of the internal dose* (para. 146). It follows therefore that, as the cumulative deposit increases, the internal dose from Cs^{137} will tend to become smaller relative to the external dose. Thus an upper limit can be set to the future internal dose by assuming that the relationship between this and the external dose will remain the same

*In some cases, however, absorption from the soil may be considerably greater than the average (para. 124); in these areas the cumulative deposit would make a greater contribution to the internal dose.

as in 1959 when the highest levels of dietary contamination were observed (a calculation on this basis is given in annex F, part III, paragraph 41).

IV. Short-lived radio-nuclides

151. Radio-nuclides of short half-life reach measurable concentrations in food only during or shortly after a series of nuclear weapons tests. The levels reached depend very much on the size and altitude of the explosions. Tropospheric debris, which is deposited relatively quickly, gives rise to proportionately greater levels, particularly of those radio-nuclides with very short half-lives, than debris injected into the stratosphere.

152. The amount actually present in the diet will be greatly affected by the seasonal nature of agricultural production and the delay between consumption and production of many foods. Because of the short half-lives, absorption from the soil is unimportant and entry into food chains occurs mainly through direct contamination. Deposition in winter months, if dairy animals are not grazing and if few crops are exposed, is of less significance than comparable deposition in the summer. Food-stuffs other than those consumed very soon after production contribute a negligible quantity of short-lived radio-nuclides to the diet. Milk is the major source of these radio-nuclides in many areas. In other areas where less milk is consumed, fresh vegetables will be the major source.

RADIO-NUCLIDES OF IMPORTANCE

153. The following radio-nuclides must be considered:

(a) *Strontium-89*. Sr^{89} (half-life 51 days) behaves similarly to Sr^{90} in food chains. It has a special importance in that comparative measurements of Sr^{89} and Sr^{90} lead to valuable information on the rate of passage through food chains;

(b) *Barium-140*. Ba^{140} (12.8 days) is also an alkaline earth element and is deposited in bone in a similar manner to Sr^{90} and calcium. However, it is relatively poorly absorbed from the gastro-intestinal tract. About 0.4 per cent of ingested Ba^{140} is secreted into cow's milk¹⁹ with an OR (milk/diet) of 0.06.¹⁸⁷ The OR (bone/diet) in humans has been estimated as 0.06.²⁸⁴

(c) *Iodine*. Several radio-nuclides of iodine are formed in fission but, owing to the very short half-lives of most of them, only I^{131} (8.1 days) is of importance at times more than a few days after fission. I^{131} is readily absorbed by the gastro-intestinal tract and concentrates in the thyroid gland. About 5-10 per cent of the ingested dose is secreted in cow's milk.^{19, 220, 223}

154. Many other short-lived radio-nuclides pass through terrestrial food chains to only a small extent and are not absorbed by man in appreciable amount. However, some consideration has been given to the possibilities of Ce^{144} , Zn^{65} or Fe^{55} , which may be concentrated in marine products, reaching man through this route.¹⁹ On the most pessimistic assumptions, however, the amount absorbed appears to be only a very small fraction of the total intake of Sr^{90} .

MEASURED LEVELS

155. Measurements of short-lived radio-nuclides in food have been made in comparatively few areas, and

are mainly concerned with milk. Measurements of these nuclides in foods such as cereals or root crops, which are stored for an appreciable period before consumption, is unimportant. The most comprehensive sampling of milk has been carried out in the United States. Annual mean levels from 1957-1960 are shown in table XXXIV. Figure 10 shows the variation of levels with time at three sites in the United States. The generally similar

fluctuations in the levels of the three nuclides measured (Sr^{89} , I^{131} and Ba^{140}) were related to the timing of nuclear explosions and to the fact that in some areas during the winter, the cattle eat mainly stored food in which the short-lived activities have decayed.

(a) *Strontium-89*. The mean levels of Sr^{89} in milk in the latter half of 1957 and in 1958 in the United States are shown in table XXXIV. During this period ratios of Sr^{89} to Sr^{90} in milk, comparable to those in the United States, were recorded in Canada (1957-1958) and in the United Kingdom (1958).²⁰¹ By the latter part of 1959 the Sr^{89} had fallen below detectable levels (fig. 9). Information of Sr^{89} levels in milk following the renewed testing of nuclear weapons in 1961 is not yet available. Some measurements in the United Kingdom in 1958 showed that an appreciable contribution of Sr^{89} could be made to the diet by leafy vegetables;⁸⁴

(b) *Iodine-131*. The levels of I^{131} in milk in the United States which were relatively high in 1957-1958 (table XXXIV) rapidly fell, so that the average for 1959 was below detectable levels. In September 1961, the resumption of nuclear testing resulted in appreciable levels in milk. Measurements made in the United Kingdom and the United States are shown in figure 11. The initial levels were higher in the United States, but over a ten-week period an average value of a little more than 100 $\mu\text{C}/\text{l}$ was recorded for both countries;

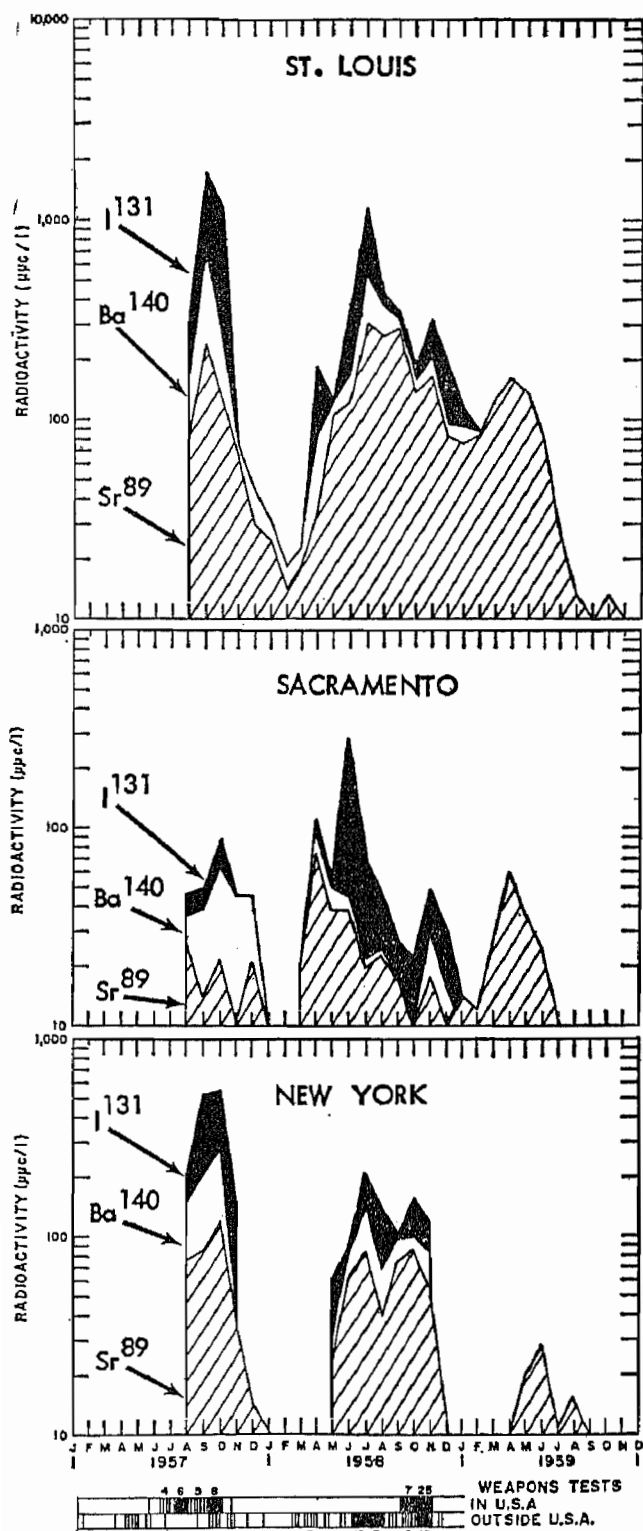


Figure 10. Concentrations of short half-life radio-nuclides in milk from three sites in the USA (1957-1959)⁸²³

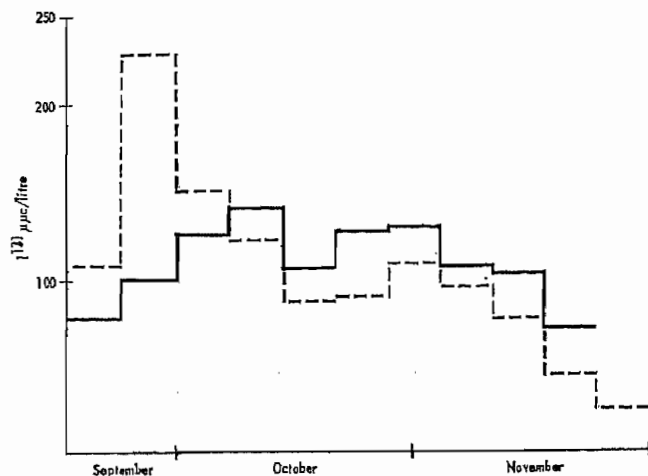


Figure 11. Weekly average concentration of I^{131} in milk in the United Kingdom (—)⁸⁰⁵ and United States (---)⁸²²⁻⁸²⁴ in late 1961

(c) *Barium-140*. The time course of Ba^{140} in milk resembled that of I^{131} in 1957-1959 (fig. 10). The average level in 1959 was below the limits of detection. In late 1961, levels of up to 300 $\mu\text{C}/\text{l}$ of milk were recorded in the United Kingdom⁸⁰⁵

FUTURE LEVELS

156. In the absence of testing these short-lived radio-nuclides quickly decay and become of no significance. Under conditions of continued testing, an equilibrium between deposit and decay would be quickly established. The levels reached in diet would depend on factors relating to the type of explosion and agricultural factors, as discussed in paragraphs 151-152.

TABLE I. STRONTIUM-CALCIUM OBSERVED RATIOS IN ABSORPTION BY PLANTS

<i>Species</i>	<i>Method</i>	<i>OR</i> (<i>plant/solution</i>)	<i>Reference</i>
Barley.....	Sr ⁸⁹ , Ca ⁴⁵	≈1	126
Ten species.....	Sr ⁸⁹ , Ca ⁴⁵	0.7-1.3	124
Tomato.....	Stable Sr, Ca	≈1	125
Five species.....	Sr ⁸⁹ , stable Ca	1.1	202
Wheat.....	Sr ⁸⁹ , stable Ca in sand culture	{1.0} {0.9}	144
Pea.....			

TABLE II. STRONTIUM-CALCIUM OBSERVED RATIOS (MILK/DIET)

<i>Species</i>	<i>Method</i>	<i>Number of subjects</i>	<i>OR</i>	<i>Reference</i>
Cow.....	Sr ⁹⁰ assay	Herd	0.16	184, 185
	Sr ⁹⁰ assay	Herd	0.09	148
	Sr ⁹⁰ assay	Herd	0.08	8
	Stable strontium, calcium	Herd	0.13	209
		Herd	0.11	148
	Radio-strontium, calcium in different experiments	3-5	0.14	223
	Simultaneous dosage Sr ⁸⁹ , Ca ⁴⁵	8	0.11	224
		2	0.11	187
		4	0.15	188
Goat.....	Double tracer daily Sr ⁸⁹ , Ca ⁴⁵	2	0.09	186
		8	0.12	224
Man.....	Sr ⁹⁰ assay	4	0.10	168

TABLE III. STRONTIUM-CALCIUM OBSERVED RATIOS (BONE/DIET) IN MAN

<i>Method</i>	<i>Detail</i>	<i>OR</i>	<i>Reference</i>
Stable strontium and calcium in diet and bone.....	Canada.....	0.24-0.26	284
	USA.....	0.18	209
	United Kingdom.....	0.23-0.25	10, 84, 149
	Japan.....	0.16	101
	16 patients.....	0.29	213
Sr ⁸⁹ , Ca ⁴⁵ , single oral dose.....			

TABLE IV. RATIOS OF Sr^{90} TO CALCIUM IN THE TOTAL DIET
Expressed as $\mu\text{mc } Sr^{90}/g \text{ calcium}$

Area	Latitude	Country	Town	Method ^a	1957	1958	1959	1960	1961	Reference
<i>A. Values based on continued, often widespread, sampling</i>										
N. America.....	> 30°N	Canada USA	— 25 cities	A C	—	—	16.1 11.8 (4.9-16.7)	13.1 —	— 6.7	301 17, 273
			New York Chicago San Francisco	A, B (60-61) B B	6.5 — —	12.6 — —	17.7 — —	11.2 9.2 4.4	10.2 7.4 3.4	35, 74 198 237, 308, 309
Europe.....	> 30°N	UK Fed. Rep. Germany	— —	A A	5.5 —	5.9 —	9.0 13.6 ^c	6.4 —	— —	10, 84, 85, 227 24
		Denmark Austria	— —	A A	— —	— —	11.5 10.6 ^c	11.6 7.0	— —	24, 241 228
			—	A	—	—	—	16.8	—	255
Asia and Far East.....	> 30°N	Japan	3-4 cities	C	2.8	5.2	14.2	19.5	19.6	28, 243
	< 30°N	India	Bombay	D	—	—	—	—	4.9 ^c	302
	< 30°N	Egypt	Delta region	C	—	—	—	—	5.6	329
	> 20°S	Australia	—	A	3.8	4.1	4.8	4.4	—	320
<i>B. Values based on single, often very limited, sampling</i>										
Asia and Far East.....	< 30°N	Viet-Nam, Rep. of	—	D	—	—	9.4	—	—	110
	< 30°N	Thailand	—	D	—	—	—	7.0	—	319
	< 30°N	China (Taiwan)	—	D	—	—	—	5.2	—	—
Central America.....	< 20°N	Costa Rica	—	A	—	2.2	—	—	—	—
		Guatemala	—	A	—	0.2 ^b	—	—	—	—
		Honduras	—	A	—	0.2-0.5	—	—	—	38
		Nicaragua	—	A	—	1.2	—	—	—	—
		Panama	—	A	—	0.8	—	—	—	—
	< 10°N	Columbia	—	D	—	—	—	4.7	—	319
	< 10°N	Venezuela	—	A	—	2.0 ^b	—	—	—	38
	< 5°S	Ecuador	—	A(58) D(59)	—	6	2.3	—	—	38, 110
	< 20°S	Peru	—	A(57) D(59)	1.5	—	2.6	—	—	38, 110
	< 20°S	Bolivia	—	—	—	6.6	—	—	—	38
	> 20°S	Argentina	—	—	—	2.8	—	—	—	38
	> 20°S	Chile	—	D	—	—	—	4.8	—	319
S. America.....	< 30°N	UAR	Cairo	B	—	3.9(4.7) ^d	—	—	—	—
	< 30°N	Sudan	Khartoum	B	—	2.8(4.1) ^d	—	—	—	38
	5°N-5°S	Kenya	Nairobi	B	—	3.0(4.9) ^d	—	—	—	—
	< 20°S	S. Rhodesia	Salisbury	B(58) A(59)	—	5.1(8.5) ^d	10-13 ^e	—	—	38, 227
	> 20°S	S. Africa	Johannesburg	B	—	3.1(7.4) ^d	—	—	—	38

^a Methods. A: Calculated from widespread sampling of major foods. B: Calculated from localized sampling of major foods. C: Composite diet analysed. D: Actual diet of individuals or groups analysed. (For fuller description see text, paragraph 39.)

^b These values have been recalculated after consultation with the original author.

^c Values representative of composite vegetarian meals.

^d The higher figure is calculated for a diet including no milk.

^e The Sr^{90} content of some types of food is estimated by assuming values similar to those in the UK and USA.

^f This was stated to be an upper limit.

TABLE V. THE PERCENTAGE CONTRIBUTION OF INDIVIDUAL FOODSTUFFS TO THE TOTAL YEARLY INTAKE OF Sr^{90} IN SEVERAL COUNTRIES, 1959-1960

Values in parentheses are based on indirect evidence

	USA (71, 237)		UK (85, 227)		Denmark (228)		Fed. Rep. of Germany (24)	Austria (255)	Canada (301)	Japan (320)
	1959	1960	1959	1960	1959	1960	1959	1960	1959	1960
Milk products.....	39	29-51	57	53	38	27	26	51	72	2
Root vegetables and potatoes..	3.1	3-16	5.9	7.1	3.2	4.7	12	2.7	3.8	65
Leaf vegetables.....	29	7-22 ^a	5.5	4.6	(10.6)	11.3	14	3.1	4.6	
Fruit.....	7.7	1-14	(3.5)	(2.9)	(8.1)	3.7	24	1.6	4.0	
Meat.....	—	2-8 ^b	—	(3.5)	(2.8)	1.5	—	—	5.2	(11) ^d
Fish.....	1.8	0.1-0.7	(5.6)	(0.1)	—	—	—	—	0.1	(4)
Eggs.....	—	1-4	—	1.7	(0.8)	1.0	—	—	0.7	—
Cereals.....	17	16-32	13	15.4	35	49	24	42	6.6	25
Tea.....	—	—	4.4	6.5	(0.8)	(1.2)	—	—	0.6	—
Water.....	2.3	—	4.4	5.2	—	—	—	—	1.8	3
TOTAL, Sr^{90} μC	6,534	1,349-4,760	3,568	2,529	6,125	4,040	5,800	4,020	6,170	3,650
TOTAL, Ca g	370	383	396	396	580	580	—	239	383	187
Sr^{90} $\mu\text{C/g Ca}$	17.7	3.1-12.3	9.0	6.4	10.6	7.0	—	16.8	16.1	19.5

^a Including dried beans and canned vegetables.

^b Including poultry.

^c The value for the composite diet and for milk, cereals and water are based on direct measurement; the percentage for the

vegetables and fruit was found by difference. (Recalc. from 330.)

^d Including eggs.

TABLE VI. Sr^{90} IN BABY FOODS AND THE DIET OF INFANTS
 $\mu\text{C Sr}^{90}/\text{g Ca}$

	Fed. Rep. of Germany ^a 1959	UK ^b		USA ^c	
		1959	1960	1959 (Aug.)- 1960 (Jan.)	1960 (Aug.)
Food based on:					
Cereals.....	13	5.4	18	2.8	1.9
Fruits.....	18			26	16
Vegetables.....	19			25	23
Meats.....				1.0	8.1
Milk.....	13	9.8	6.4	25 ^d	12 ^d
Infant diet.....	12	9	8	14 ^e	10 ^e
Adult diet (table IV).....	13.6	9.0	6.4	14	8.8
				11.2	10.2

^a Means of 9-13 samples.⁷¹ Total diet value for infants 0.1 years old.²⁴ Milk value is for manufactured food based on milk.

^b Means of representative samples of five different types of cereal based foods.^{85, 227} The milk value is the countrywide average for fresh milk. The total diet value is an approximate upper limit.

^c Means of number of samples of different brands and types.^{71, 288}

^d Formula milk.

^e Evaporated milk.

Region, country or area	Latitude	1954	1955	1956	1957	1958	1959	1960	1961	Reference
<i>N. America</i>	> 30°N	1.0°	5.5°	6.2°	7.9°	11.6 (13, 5.4-19)	14 (14, 6.1-21)	12 (16, 5-18)	*8.7 (Jan.-Mar.)	26, 13, 14, 258-261
<i>Canada</i>										
USA										
Desert areas....					2.0 (6, 1.1-3.0)	3.2 (5, 1.7-4.7)	4.3 (5, 2.8-4.0)	3.4 (5, 2.7-4.0)	*3.4 (4, 0.8-6.9)	4, 39, 62,
Mid-West.....				8.8 (1)	5.8 (9, 2.2-16)	8.0 (12, 3.0-20)	11.0 (13, 4.1-26)	7.6 (12, 3.0-18)	*6.2 (9, 1.8-12)	65-73,
Central States..				4.0 (4, 2.9-5.5)	5.0 (13, 2.4-8.5)	7.9 (24, 3.0-12)	10.0 (18, 5.3-18)	7.2 (28, 3.8-15)	*6.5 (27, 1.5-14)	75-83,
East.....	1.4 (1)	2.7 (1)	2.7 (1)	3.9 (1)	6.4 (9, 4.5-9.5)	8.7 (12, 6.1-13)	14 (10, 8.4-18)	8.2 (19, 4.1-13)	*7.5 (18, 3.3-19)	198, 237,
N. W. coast....		3.8 (1)	4.8 (1)		9.9 (2, 7.4-12)	13.0 (4, 8.7-15)	22 (4, 8.8-24)	8.8 (2, 8.1-9.4)	*8.5 (3, 4.5-12)	110-112,
Countrywide										248-253,
average.....	1.2	3.4	4.7	5.2	5.2	8.0	11.3	7.3	*6.6 (Jan.-Aug.)	308, 309
<i>Europe</i>	> 30°N									
UK.....										
Ireland.....										
France.....										
Fed. Rep. Germany										
Switzerland.....		1.7 (1)	2.0 (1)	4 (—, 2-5)	8 (—, 3-14)	6.2 (50)	7.6 (150)	6.4 (150)	*5.9 ^a (Jan.-June)	84, 85, 227, 11, 115, 305
Austria.....										227, 240
Italy.....										32
Denmark.....										21-25, 241, 310
Norway.....										246
Sweden.....										255
Finland.....										31, 296
Czechoslovakia....										18, 228
USSR.....										49, 230, 242
(Moscow)										27, 113
<i>Far East</i>	> 30°N									54
Japan.....										233
<i>Pacific</i>	20°N									51
USA (Hawaii)....										37, 50, 234
<i>Asia</i>										
India.....	5-30°N									
(Bombay).....	20°N									
<i>Central America</i>	< 30°N									
Mexico.....										
<i>South America</i>	> 30°S									
Argentina.....										
<i>Africa</i>										
UAR (Delta region)	< 30°N									
S. Rhodesia	~ 20°S									
(Salisbury).....	> 20°S									
<i>Oceania</i>										
Australia.....										
New Zealand.....										

* Not a complete year.

^a Samples from many depots representing 40 per cent of the country's milk supply.^b Assuming 1 litre of milk contains 1.2 g of calcium.

* Adjusted to be comparable with 13 stations sampled later.

^a Results for the first 9 months are from powdered milk, not the regular survey of liquid milk (5).^b Weighted average for Delta region.

TABLE VIII. DESCRIPTIONS OF MAJOR SURVEYS FOR RADIO-ACTIVITY IN MILK

Country or area	Date started or duration	Nuclides measured	Area	Number of sites	Type of sample	Reported by
Canada.....	Late 1955	Sr ⁹⁰	Widespread	6-16	Single monthly sample from dried milk factory	Radiological Protection Division, Dept. National Health and Welfare
USA.....	1954	Sr ⁹⁰	New York City	1	Daily purchases from store composited monthly	US Atomic Energy Commission, Health and Safety Laboratory
	1954	Sr ⁹⁰	Perry, New York	1	Weekly samples of dried milk composited monthly	US Atomic Energy Commission, Health and Safety Laboratory
	1955	Sr ⁹⁰	Mandan, N. Dak.	1	Monthly samples from liquid milk collecting centre	Radiological Health Data, Dept. of Health, Education and Welfare
	1957	Sr ⁹⁰	Widespread	5-12	Distributing centres	Radiological Health Data, Dept. of Health, Education and Welfare
	1960	Cs ¹³⁷	Widespread	60	Weekly samples of powdered milk composited monthly	Annual Reports, Lamont Geological Observation, Columbia University (Sr ⁹⁰), Los Alamos Scientific Laboratory (Cs ¹³⁷)
	1957	Sr ⁹⁰	Widespread	25-54		
UK.....	1955-57	Cs ¹³⁷	Widespread	1-9	Monthly samples of powdered milk	A.E.R.E., Harwell
	1957-58	Sr ⁹⁰	Widespread	9	Monthly samples from factory	Ref. (8)
	1958	Cs ¹³⁷	Countrywide	Many	Liquid milk depots providing 40% of country's milk supply; two weekly samples composited every 6 or 12 weeks	Radiobiological Laboratory, Agricultural Research Council
Ireland.....	1960	Sr ⁹⁰	Dublin, Cork	—	Liquid milk, representative of production; two weekly samples composited every 6 weeks	An Roinn Saínte, Dublin
France.....	1958	Sr ⁹⁰	Widespread	Unknown	Daily samples of powdered milk composited monthly	Ref. (32)
Federal Republic of Germany.....	1957	Sr ⁹⁰	Widespread	Few-150	Samples from dairy composited monthly	Federal Minister of Nuclear Energy and Water Economy
	1960	Cs ¹³⁷	Lindau	1	Two per week	Federal Commission of Radioactivity
Switzerland.....	1954	Sr ⁹⁰	Lowland	1-3	Powder from 1954, then liquid	National Committee for Nuclear Research
Italy.....	1960	Sr ⁹⁰	N. Italy	4	1-2 samples per month, collecting depot	
		Cs ¹³⁷				
Denmark.....	1959	Sr ⁹⁰	Widespread	4	Monthly samples of powdered milk	Danish Atomic Energy Commission
		Cs ¹³⁷				
Norway.....	1957-59	Sr ⁹⁰	S. Norway	1-4	Several samples per month from dairies composited monthly	Norwegian Defence Research Establishment
		Cs ¹³⁷				
	1958-59	Sr ⁹⁰	S. Norway	2	Monthly samples from factory	Ref. (43)
	1960	Cs ¹³⁷	Countrywide	11	Local purchase from shop	Norwegian Defence Research Establishment
Sweden.....	1957-59	Sr ⁹⁰	Mid-Sweden	1	Powdered milk from factory, irregular samples	Research Institute of National Defence
		Cs ¹³⁷				
Czechoslovakia.....	1957	Sr ⁹⁰	—	2	Daily samples from dairy composited monthly	Ref. (51)
	1960	Sr ⁹⁰	Moscow	2	Farms; all year	State Committee of the USSR on the uses of atomic energy
Poland.....	1958	Cs ¹³⁷	Lowland regions	5	Powder and liquid milk samples	Ref. (233)
India (buffalo milk).....	1958	Sr ⁹⁰	Bombay	1	Daily samples from milk depot composited monthly	Indian Atomic Energy Commission
		Cs ¹³⁷				
Hawaii.....	1959	Cs ¹³⁷	Widespread	21	Irregular	—
	1959	Sr ⁹⁰	Honolulu	2	Weekly samples from dairy composited monthly	US Atomic Energy Commission, Health and Safety Laboratory
Mexico.....	1960	Sr ⁹⁰	Mexico	—	—	Ref. (270)
Argentina.....	1959	Sr ⁹⁰	Buenos Aires Province	—	1-2 samples per week composited monthly	Argentine Atomic Energy Commission
Australia.....	1957	Sr ⁹⁰	Capital cities	5	1-2 samples per year representative of bulk supplies	Australian Atomic Weapons Tests Safety Committee

TABLE VIII. DESCRIPTIONS OF MAJOR SURVEYS FOR RADIO-ACTIVITY IN MILK (continued)

Country or area	Date started or duration	Nuclides measured	Area	Number of sites	Type of sample	Reported by
New Zealand.....	1960	Sr ⁹⁰	Widespread	7	Liquid and powder	Dominion X-ray and Radium Laboratory
	1957	Cs ¹³⁷	Sydney	1	Irregular samples from factory	Los Alamos Scientific Laboratory
Rhodesia.....	1959	Sr ⁹⁰	—	—	Bulk supplies	United Kingdom
	1960		—	—	Dried milk	United Kingdom
UAR.....	1961	Sr ⁹⁰	Delta region	—	Liquid milk composite samples	UAR Scientific Committee on the Effects of Atomic Radiation
<i>Widespread surveys for a limited period of the year</i>						
USSR.....	1957-59	Sr ⁹⁰	Widespread	8	Samples of powdered milk	USSR Academy of Sciences
	1960	Sr ⁹⁰ Cs ¹³⁷	Widespread	9	Samples of powdered milk	—
Finland.....	1959	Sr ⁹⁰ Cs ¹³⁷	Widespread	6-9	From dairies and factories	State Institute for Technical Research
Japan.....	1957	Sr ⁹⁰	Widespread	6	Powdered milk from factory	Ref. (57, 243)
India.....	1959	Sr ⁹⁰ Cs ¹³⁷	Widespread	16-21	Liquid milk	Indian Atomic Energy Commission

TABLE IX. Sr^{90} IN MILK AND CHEESE: INFREQUENT OR SPOT SAMPLINGResults presented as $\mu\text{C Sr}^{90}$ per g Ca

Figures in parentheses indicate number of samples; C indicates cheese

Region	Latitude	Country or area	1954	1955	1956	1957	1958	1959	1960	1961	Reference
Europe.....	>30°N	USSR.....	—	—	—	3.2	3.4	11.9	—	—	59
		Norway.....	1.5 (1)	0.7 (2)	—	—	—	—	—	—	65
		Denmark.....	—	—	—	2.8 ^a	4.8 ^a	6.4 ^a	—	—	38, 318
		France.....	—	1.35 (1)	—	7.9 ^a	10 ^a	11.6 ^a	—	—	38, 65, 318
		Switzerland.....	—	—	—	7.7 ^a	9.0 ^a	11.3 ^a	—	—	38, 318
		Italy.....	—	1.09 (1)	—	5.1 (2)	4.4 (2)	7.3 (1)	—	—	67, 71
		Spain.....	—	—	—	—	4.3 (7)	—	—	—	67
Mediterranean—Near East..	>30°N	Turkey.....	3.6 (2)	14.6 (1)	—	—	—	—	—	—	65
		Cyprus.....	—	—	—	C2 (1)	C4 (2)	—	—	—	66
		Lebanon.....	—	—	—	—	C2.3 (2)	—	—	—	66
		Jordan.....	—	—	—	C5 (1)	—	—	—	—	66
		Tunis.....	—	—	—	C5.5 (4)	—	—	—	—	66
		Iran.....	—	—	—	—	C6.5 (2)	—	—	—	71
		Japan.....	0.8 (1)	2.1 (12)	2.9 (6)	2.2 (6)	3.5 (4)	4.5 (1)	5.0 (1)	—	4, 65, 67, 33 38, 318
Asia.....	{ 10°–20°N	Pakistan.....	0.14 (1)	0.4 (1)	—	—	—	—	—	—	65
		India.....	—	—	—	2.7 (2)	C13 (1)	—	—	—	66, 67
		Thailand.....	—	—	—	—	2.5 (1)	—	—	—	71
		Mexico.....	—	—	1.2 (4)	3.0 (6)	2.1 ^a	4.6 ^a	1.2 (5)	—	2, 45, 38, 318
C. America.....	{ 5°–30°N	Guatemala.....	—	—	—	1.7 ^a	1.1	—	—	—	38, 318
		Honduras.....	—	—	—	1.2	—	—	—	—	
		El Salvador.....	—	—	—	1.3	1.4	—	—	—	
		Nicaragua.....	—	—	—	—	—	—	—	—	71
		Costa Rica.....	—	—	—	—	2.3 ^a	—	—	—	
		Cuba.....	—	—	—	—	2.3 (2)	5.7 (2)	—	—	
		Panama.....	—	—	—	—	0.4	—	—	—	38
		Colombia.....	—	—	—	0.6 ^a	0.9 ^a	3.0 ^a	—	—	38, 318
		Venezuela.....	—	—	—	0.6 ^a	0.7 ^a	—	—	—	38, 318
		Peru.....	0.05 (1)	—	—	0.4 (4)	—	—	—	—	65, 67
S. America.....	{ 0–20°S	Ecuador.....	—	—	—	1.1 (7)	—	1.2 (3)	—	—	38, 320
		Brazil.....	—	—	—	2.7 (3)	3.1 ^a	5.3	—	—	53, 38, 318
		Bolivia.....	—	—	—	2.9 ^a	—	—	—	—	38
		Argentina.....	0.2 (2)	—	—	1.7	1.7 (2)	2.0 (2)	—	—	65, 67, 71
		Chile.....	—	—	—	2.4 (3)	1.5 (3)	—	—	—	67
		Australia.....	—	1.7 (3)	—	5.0 ^a	3.4 ^a	4.6 ^a	—	—	38, 318
		New Zealand.....	0.2 (1)	0.7 (2)	—	—	2.6 (6)	3.0 (1)	—	—	71
Oceania.....	{ >20°S	Tanganyika.....	—	—	—	—	3.3 ^a	—	—	—	38
		Union of South Africa.....	—	—	—	—	1.8 (4)	—	—	—	71
Africa.....	{ 0–20°S	—	—	—	—	—	12 (1)	—	—	—	71
		—	—	—	—	—	C3.6 (1)	—	—	—	66
Africa.....	{ >20°S	—	—	—	—	—	—	—	—	—	—
		—	0.4 (2)	—	—	3.5 ^a	2.6 ^a	2.6 ^a	—	—	38, 318

^a Monthly or quarterly samples for all or part of year (38, 318).

TABLE X. REGIONAL AVERAGES FOR THE RATIO OF Sr^{90} TO Ca IN MILK*

Region	Latitudes	1954	1955	1956	1957	1958	1959	1960
N. America.....	> 30°N	1.2	3.7	4.9	5.5	8.5	12.2	7.9
W. Europe.....	> 30°N	—	3	5.0	6.4	7.2	8.6	8.6
E. Europe (USSR).....	> 30°N	—	—	—	5.2	—	10	8.2
Far East (Japan).....	> 30°N	—	—	—	1.9	3.8	6.2	5.4
Asia (India).....	0–30°N	—	—	—	—	2.3	5.9	2.3
Central America.....	10°N–30°N	—	—	1.2	2.8	1.9	—	0.8
S. America.....	10°N–50°S	—	—	—	1.8	1.9	3.3	1.9
Oceania (Australia).....	> 20°S	—	—	—	3.8	3.7	4.1	5.7
Africa.....	> 10°S	—	—	—	2.6 ^b	2.6 ^b	—	1.0 ^c

* Mean values have been calculated utilizing primarily the data from the regular surveys shown in table VII, but using also the data from table IX where necessary. The means have been weighted by the quantity of milk produced in each country. It is

important to note that varying numbers of countries are represented in different years.

^b Union of South Africa.

^c Rhodesia.

TABLE XI. Sr^{90} IN WHOLE WHEAT GRAINResults as μc per g Ca or, italicized, as μc Sr^{90} per kg

Figures in parentheses indicate the number of samples and range

Region	Latitude	Country	Area	1956	1957	1958	1959	1960	Reference
N. America.....	> 30°N	Canada	—	—	103 \pm 10 ^a 37 \pm 4	125 \pm 13 ^a 44 \pm 5	124 \pm 37 39 \pm 10 114 ^b	—	114, 198
		USA	Minnesota	107 (7, 74-169) 45 (17-76)	217 (7, 105-606) 66 (47-112)	156 (8, 111-213) 44 (35-60) 164 ^b (19)	36 —	56 ^b 15	301 67
			Widespread	—	—	62	129 ^b (41-377) 53 (14-198) 67 (12, 9-271) 44 (9-96)	32 (20-72) 21 (4-48)	70, 73, 74 74
		Alaska	—	—	23 (1)	105 (1)	125 (1)	—	38, 58
Mean						160	100-130		
E. Europe.....	> 30°N	USSR	Widespread	70 (10, 28-140) 26 (14-45)	—	71 (11, 40-126) 26 (14-58)	83 (12, 42-220) 39 (18-54) 64 (8, 15-87) 30 (7-47)	—	37, 60, 73 227
		UK	—	—	38 (7, 21-49) 25 (13-46)	131 (7, 109-174) 66 (54-75)	70 (7, 51-90) 34 (19-54) 100 (6, 61-213)	—	84, 85 227
		Denmark	Widespread	—	—	—	39 (19-89) 88 (43, 29-280) 32 (9-97)	89 (8, 48-212) 32 (19-71) 92 (23, 42-146) 40 (18-63)	18, 228 46, 307
		Fed. Rep. of Germany France Greece	Widespread — —	— — —	— — —	— — —	53 (9, 29-85) 20 (12-32) 79 (2, 60-98) 35 (30-40)	— — —	73 73
Mean							65		
Far East.....	> 30°N	Japan	Widespread	145 (1) 36	141 (4, 120-170) 44 (34-48)	89 (4, 43-114)	242 (8, 116-375) 78 (29-133) 155 (1)	—	243 73
		Manchuria	—	—	—	—	64	—	
	5°N-10°S	Congo (Leopoldville)	—	—	*6 (1) 2.5	—	—	—	66
		Bolivia Peru	— —	— —	*16 (2) *4 (2)	— —	— —	— —	38 65
S. America.....	0°-60°S	Argentina	—	—	*8 (4, 0.7-18)	1958-59 —	31 (14, 21-48) 16 (12-33)	—	65, 73 66
		Chile	—	—	—	*4.5 (2, 4.4-4.6) 12.3 (1)	—	—	319
	> 20°S	Australia	—	—	—	25 (5, 15-42) 9.5 (6-13)	19 (6, 14-27) 7.0 (4-8)	—	227, 239, 320

* 1959-60
* 1958-59

* (results were used, not listed for previous time)

TABLE XII. Sr⁹⁰ IN WHEAT FLOUR
Results as $\mu\text{C Sr}^{90}$ per g Ca or, italicized, as $\mu\text{C Sr}^{90}$ per kg
Figures in parentheses indicate the number of samples and range

Region	Latitude	Country or area	1957	1958	1959	1960	Reference
N. America.	> 30°N	Canada.....	31 \pm 3 ^a 4.6	38 \pm 4 ^a 5.4	—	—	114
		USA.....	—	69 (19) ^b 9.5	62 ^b 11	—	70, 73
E. Europe.	> 30°N	USSR.....	—	85 (1) 23	30 (8, 7-43) 7.4 (47-13)	—	85, 227
W. Europe.	> 30°N	UK.....	13 (7, 5-26) 2 (1-4)	48 (6, 28-90) 12 (8-19)	24 (6, 13-48) 5.4 (2.8-8.9)	—	84, 85, 227
		France.....	—	*15 (1) 3	—	—	84 255
		Austria.....	—	—	—	40 (47) 7.3	—
Far East.	> 30°N	Japan.....	53 (1) 9	—	160 (1) 30 (1)	95 (1) 18	33, 30
Africa.	< 30°N	UAR.....	—	*16 7.2	—	—	38
		Sudan.....	—	* 8.4 3.8	—	—	38
	5°N-5°S	Kenya.....	—	* 4.9 2.8	—	—	38
	< 20°S	S. Rhodesia.....	—	* 7.5 3.3	—	—	38
	> 20°S	Union of South Africa.....	—	* 7.4 1.6	—	—	38
		—	—	—	—	—	—
S. America.	> 20°S	Argentina.....	1957-58	1958-59	1959-60	—	84 319
Oceania.	> 20°S	—	—	*19 (2, 7-31) 3 (1-5)	—	—	—
		Australia.....	7 (3, 4-12) 1 (1-2)	10.7 (5, 7-16) 2.0 (1-3)	7.5 (6, 5-10) 1.4 (1-2)	—	84, 85, 227 239

* Year of sampling, not necessarily production.

^b From production weighted composite samples.

^b Weighted mean representing production from main growing areas.

TABLE XIII. DISTRIBUTION OF Sr⁹⁰ IN MILLING PRODUCTS OF WHEATResults presented as $\mu\text{c/g}$ Ca or, italicised, as $\mu\text{c/kg}$

Range shown in parentheses

Country and year of harvest	Grain	Bran	Flour ^a	Ratio flour/grain	Reference
1957					
Canada ^b	103 \pm 10	134 \pm 15	31 \pm 3	0.40	114
	37 \pm 4	118 \pm 15	4.6 \pm 0.5		
UK ^a	38 (21-49)	93 (49-136)	13 (5-26)	0.34	84
	25 (13-46)	87 (42-158)	2 (1-4)		
1958					
Canada ^b	125 \pm 13	163 \pm 20	38 \pm 4	0.30	114
	44 \pm 5	141 \pm 20	5.4 \pm 0.5		
USA ^d	164	201	69	0.42	70, 73
	62	231	15		
UK ^a	131 (109-174)	160 (133-224)	48 (28-90)	0.37	85
	66 (54-75)	262 (162-433)	12 (8-19)		
1959					
USA ^d	129	142	62	0.48	73
	53	163	11		
UK.....	70 (51-90)	93 (68-134)	24 (13-48)	0.34	227
	34 (19-54)	94 (54-171)	5.4 (2.8-8-9)		

^a Of about 70 per cent extraction.^b Calculated from composite whole grain samples and average distribution in milling products.^c Mean of seven samples from various parts of country.^d Weighted means for a number of states.

TABLE XIV. Sr⁹⁰ IN WHOLE CEREAL GRAINS (other than wheat).Upper figure is $\mu\text{Ci Sr}^{90}/\text{g Ca}$; lower figure (*italicized*) is $\mu\text{Ci Sr}^{90}/\text{kg}$

Figures in parentheses indicate the number of samples and range

Grain	Region, country or area	1956	1957	1958	1959	1960	Reference
Rye	Europe						
	USSR	—	67 (5, 57-90) 27 (19-33)	93 (4, 51-121) 33 (22-48)	—	—	37, 60
	Denmark	—	—	—	142 (8, 93-188) 55 (37-74)	88 (7, 64-137) 33 (24-45)	18, 228
	Germany, Fed. Rep. of	87 (1)	128 (1) 45	—	82 (24, 29-236) 36 (12-101)	84 (24, 42-185) 44 (19-63)	34, 66 24, 307
Barley	Far East						
	Japan	—	—	—	180 (1) 63	101 (1) 53	30
	Europe						
	Denmark	—	—	—	80 (9, 44-130) 35 (20-62)	58 (7, 47-94) 25	18, 228
Oats	Germany, Fed. Rep. of	64 (2)	55 (3)	124 (3)	—	—	34, 66
	Africa						
	Syria	—	*10 (1) 5	—	—	—	66
	Sudan	—	—	0.7 ^a 2.1 2.1	—	—	38
Maize	Union of South Africa	—	—	*6.5 ^a 3.8	—	—	38
	S. America						
	Peru	—	2.5 (1)	—	—	—	65
	Bolivia	—	3.4 (2)	—	—	—	38
Oats	Europe						
	Denmark	—	—	—	46 (9, 13-111) 34 (9-65)	42 (8, 25-64) 38 (23-62)	18, 228
	Germany, Fed. Rep. of	—	155 (1) 10	—	—	—	66
	S. America						
	Argentina	—	*8 (1) 4.5	—	—	—	66
Maize	N. America						
	USA	—	—	**69 4.8 (8, 1.0-18)	**47 3.3 (4, 0.2-4.6)	—	63
	C. America						
	Costa Rica	—	1.0 (1)	—	—	—	38, 318
Maize	Guatemala	—	—	*2.4 (1)	—	—	38
	Honduras	—	3.5 (1)	—	—	—	38, 318
	Nicaragua	—	*1.0 (1)	—	—	—	38
Maize	S. America						
	Ecuador	—	4.1 (1)	—	—	—	318
	Venezuela	—	—	*6.1 (7, 1.9-13)	—	—	38
	Peru	—	*3.1 (1)	—	—	—	65
Maize	Bolivia	—	*1.4 (2)	—	—	—	38
	Africa						
	Union of South Africa	—	—	*11.3 ^a	—	—	38
	Rhodesia	—	—	—	< 38 ^a < 3	—	38 227

TABLE XIV. SP⁹⁰ IN WHOLE CEREAL GRAINS (other than wheat) (continued)

Grain	Region, country or area	1956	1957	1958	1959	1960	Reference
Rice	<i>N. America</i>						
	USA.....	—	—	— 37 (1) 8.9	—	—	22
	<i>Europe</i>						
	Italy.....	—	—	— 280 (1) 22	—	—	22
	<i>Africa</i>						
	UAR.....	—	—	*1.8 ^a 0.2	—	—	38
	Sudan.....	—	—	*6.6 ^a 0.8	—	—	38
	<i>Asia and Far East</i>						
	Ceylon (brown).....	—	—	*150 (1) 41	—	—	66
	India						
	(paddy).....	—	—	23 2.1	—	—	302
	(boiled).....	—	—	—	22 1.5	—	—
	(surty).....	—	—	—	15 0.8	—	—
	Burma.....	—	—	—	*19 (2) 1.3	—	22
	Thailand.....	—	—	—	*54 (2) 0.9	18 (3, 6.3-24) 4.3 (1.7-6.4)	22, 319
	China (Taiwan).....	—	—	—	—	16 (1) 8.3	319
	Viet-Nam (Rep. of (unmilled).....	—	—	—	26 (1) 6.6 (1)	—	319, 110
	Japan.....	171 (8, 81-250) 22 (15-43)	242 (5, 103-270) 40 (10-80)	239 (8, 78-425) 32 (10-58)	264 (21, 52-448) 29 (4-54)	62 (12, 28-98) 5.7 (2.6-9.0)	30, 33, 127, 243
	*** (brown) (milled).....	31 (4, 12-62) 2.0 (1.3-2.6)	24 (2, 20-28) 1.6 (1.4-1.7)	—	—	62 (12, 19-99) 3.6 (1.0-5.4)	33, 127, 243, 325
	<i>S. America</i>						
	Venezuela.....	—	—	*2.8 (1)	—	—	38
	Surinam.....	—	—	—	50 (1) 5	—	22
	Colombia.....	—	—	—	—	10.5 (1)	319
	Bolivia.....	—	*14 (5) < 2 (3)	—	—	—	38
	Ecuador.....	—	—	—	—	—	318
	<i>Africa</i>						
	Sudan.....	—	—	*0.2 ^a 2.6	—	—	38
	Kenya.....	—	—	**14 ^a 4	—	—	38
	<i>S. America</i>						
	Peru.....	—	7.7 (1)	—	—	—	65
	<i>S. America</i>						
	Bolivia.....	—	2.7 (2)	—	—	—	38
	<i>Africa</i>						
	Sudan.....	—	—	*19 ^a 3.9	—	—	38
Millet							
Quinoa							
Native grain							

* Indicates year of sample, not necessarily the year of harvest.

*** Brown rice is unmilled rice (with germ removed).

TABLE XV. Sr^{90} IN GREEN LEAFY VEGETABLESResults presented as $\mu\text{c Sr}^{90}$ per gram calcium, or italicized, as $\mu\text{c Sr}^{90}/\text{kg}$ *Figures in parentheses indicate the number of samples and maximum and minimum values*

Region	Country	Description	1956	1957	1958	1959	1960	Reference
N. America..	USA.....	Simple means of samples of cabbages from several states.....	8.1 (9, 1-29)	—	—	17 (12, 1-76) 16 (2-48)	—	74, 35
		Spinach.....	—	7.1 (5, 1.2-14)	—	241 (8, 21-461)	—	35, 76
		From Tricity study.....	—	—	—	—	21 (9, 6-50) 7 (2-18)	198, 237
Europe.....	UK.....	Weighted means of countrywide sampling of brassicas.....	—	—	8.7 (5-47) 7.5 (3-17)	14 (4-42) 10 (2-40)	8.5 (7.3-19) 4.9 (1-12)	84, 85, 227
		Simple mean of miscellaneous samples.....	—	17 (6, 7-30) 9 (1-22)	30 (6, 3-80) 14 (2-49)	13 (22, 6-39) 4.5 (1-12)	14.5 (16, 1.3-30) 8.9 (3.1-19) 11.3 (9-16)	66, 24, 71, 310 228
	Denmark.....	Composite samples of 8 types.....	—	—	—	—	13 (2-34)	255
		Cabbages, composite samples.....	—	—	—	—	9.8 (5) 5.1	232
	France.....	Cabbage, spinach.....	—	—	21 (6, 10-62)	35 (7, 0-82)	—	—
		Spinach, molokhia ^a	—	—	—	—	—	—
Asia.....	Japan..... China (Taiwan) Thailand	Leafy vegetables.....	8 (2)	14 (6, 4-23) 19 (10, 2-60)	—	—	—	33
		Miscellaneous samples.....	—	—	32 (4, 6-58) 10 (1)	—	—	65, 67
		Lettuce.....	—	—	66	—	—	66
S. America..	Venezuela..... Chile.....	Cabbage.....	—	—	3.1 (7, 1.5-7.2) 0.5 (1)	—	—	38
		"Greens".....	—	6.1 (1)	—	—	—	65, 66
Oceania.....	Australia.....	Composite samples of cabbage at 5 sites.....	—	2.6 (2.1-4.0)	5.9 (4.0-9.4)	4.9 (3.9-8.6)	8.5 (10)	12, 239 320

^a Values for 1961 of 3.4-4.2 $\mu\text{c Sr}^{90}/\text{g}$ calcium were obtained for bulked samples representing the Delta region. 125-126

TABLE XVI. Sr^{90} IN LEGUMINOUS VEGETABLES—PEAS AND BEANSResults presented as $\mu\text{c Sr}^{90}$ per gram calcium, or *italicized*, as $\mu\text{c Sr}^{90}/\text{kg}$ *Figures in parentheses indicate the number of samples and the maximum and minimum values*

Region, country or area	1956	1957	1958	1959	1960	Reference
<i>N. America</i>						
USA.....	8.7 (14, 1-21)	8.8 (5, 4.6-14)	—	18 (3.4-88) ^b 49 (9-178)	6.0 (3-12) ^a 4.0 (2-7)	35, 74 198
<i>Europe</i>						
Fed. Rep. of Germany	—	—	22 (8, 12-47) 61 (7-100)	20 (30, 1-100) 7.5 (1-27)	10.5 (6, 9-12) 6.4 (4-8)	69, 71, 70 24, 22, 310
Denmark.....	—	—	—	—	15 (2, 15-16) 6.5 (5-8)	228
<i>Far East</i>						
Japan.....	4.5 (1)	—	—	—	—	33
<i>C. America</i>						
Costa Rica.....	—	2.8 ^a	—	—	—	38
Guatemala.....	—	0.8 ^a	—	1.3 ^a	—	38
Honduras.....	—	0.8 ^a	—	—	—	38
Nicaragua.....	—	0.8 ^a	—	—	—	38
Panama.....	—	0.3 ^a	—	—	—	38
<i>S. America</i>						
Bolivia.....	—	1.2 (1, 0.3-22)	—	—	—	38
Venezuela.....	—	—	3.4 (18, 0.7-18)	—	—	38
Colombia.....	—	—	—	—	3.0 (1)	319
<i>Africa</i>						
UAR.....	—	—	0.8 (4, 0.2-1.4) 1.6 (1.0-2.3) 1.7 (1)	—	—	38
Sudan.....	—	—	6.3	—	—	38
Kenya.....	—	—	1.1 (5, 0.3-2.0) 2.5 (0.9-6.8)	—	—	38
S. Rhodesia.....	—	—	3.7 (3, 2.2-5.2) 4.7 (2.0-7.5)	—	—	38
Union of South Africa	—	—	2.0 (4, 0.3-3.9) 6.1 (1.6-8.6)	—	—	38

^a Samples collected and analysed by Lamont Geological Observatory.^b Composite samples from 10 states.
^a From "Tri-city" study.¹⁹⁸

TABLE XVII. Sr^{90} IN POTATOES AND STARCHY ROOTSResults presented as $\mu\text{c Sr}^{90}$ per g Ca or, *italicized*, as $\mu\text{c Sr}^{90}/\text{kg}$ *The figures in parentheses indicate number of samples and the maximum and minimum values*

Region and country	1957	1958	1959	1960	Reference
POTATOES					
<i>N. America</i>					
USA.....	—	—	25 (12, 1-61) 3.7 (0.8-8.2)	39 (5-130) ^a 4.0 (0.5-10)	74, 198
(Alaska).....	—	—	7.8 (1)	—	39, 58
<i>Europe</i>					
UK.....	—	14 (4-32) ^a 1.6 (0.7-3.6)	23 (4-85) ^a 1.9 (0.5-7.1)	20 (5-62) ^a 1.6 (0.5-4.8)	84, 85 227
Fed. Rep. of Germany.....	11 (10, 2-22) 2.6 (0.7-5)	28 (10, 6-36) 7.6 (2-15)	25(1) 2.5	27 (15, 11-65) 4.1 (1.9-8.2)	69, 71 241, 307
Denmark.....	—	—	33 (9, 12-63) 1.4 (0.6-2.3)	47 (9, 14-83) 1.8 (0.7-3.1)	228
Austria.....	—	—	—	25 (16) 1.5	255
USSR.....	17 (3, 9-33) 0.8 (0.5-1.3)	36 (3, 24-46) 1.7 (0.9-2.4)	42 (3, 34-52) 2.3 (1.5-3.0)	—	59
<i>Africa</i>					
UAR ^d	—	5.4 ^b 1.1	—	—	38
Sudan.....	—	2.1 ^b 0.5	—	—	38
<i>S. America</i>					
Colombia.....	—	—	—	6.1 (1)	319
Venezuela.....	—	4.2 (2)	—	—	38
Chile.....	0.5 (1)	10 (3, 1-24)	—	28 (3, 14-35) 5.4 (2.5-7.8)	65, 66 319
YUCA (CASSAVA, MANIOC)					
<i>S. America</i>					
Venezuela.....	—	22 (21, 0.5-182)	—	—	38
Bolivia.....	—	5.9 (4, 4-9)	—	—	38
Colombia.....	—	—	—	21 (4, 1.5-70)	319

^a Weighted mean from samples representative of countrywide production.^b Composite samples.^c From Tricity study: year consumed.^d Values for potatoes of 17 $\mu\text{c Sr}^{90}/\text{g Ca}$ and for colcasia of 9.4 $\mu\text{c Sr}^{90}/\text{g Ca}$ were found for the Delta region of the UAR in late 1961.²³⁹

TABLE XVIII. Sr⁹⁰ IN FRUIT

Region and country or area of origin	Fruit	Year	Sr ⁹⁰		Total number of samples	Reference
			μc/kg	μc/g Ca		
<i>N. America</i>						
USA.....	Apples	1959	4.3	—	5	
	Peaches: canned	1959	2.2	—	4	
	Peaches: canned	1959	117	—	1	74
	Raisins	1958-59	8	—	2	
	Strawberries	1959	24	—	Composite	
	Apricots: dry	1959	17	—	1	
<i>Europe</i>						
Fed. Rep. of Germany.....	Eight types	1958	9.3 (2-29)	47 (16-96)	13	69, 71
	Eight types	1959	14 (3-35)	42 (18-90)	8	70, 71
	Peaches	1959	12.9	162	1	70
	Berries	1959	4.3 (1.7-8.3)	36 (8.4-81)	7	74
	Strawberries	1959	19 (7.1-37)	69 (25-130)	4	72
	Tree fruits	1959	3.3 (0.4-6.1)	23 (4.3-42)	22	74
	Denmark.....	Apples and pears	1960	2.0 (0.7-5.1)	22 (6.5-67)	10
Denmark.....	Soft fruits	1960	4.1 (1.9-10)	16 (7.7-30)	17	238
	Imported fruit (12 kinds)	1960	0.4-22	5.0-48	Composite	238
	Nuts	1960	7-122	9.0-56	—	238
	Austria.....	Apples	1960	1.8	49	4
Austria.....	Pears	1960	4.1	80	3	231
	Plums	1960	1.9	12	1	231
Spain.....	Oranges	1957	6	10	1	60
Portugal.....	Figs	1958	12	—	3	76
Greece.....	Figs	1958	13	—	1	76
Italy (Sicily).....	Hazelnuts	1957	14	5.3	—	60
<i>Near East</i>						
Iraq.....	Dates	1958	8 (5-11)	—	4	74
Iran.....	Melons	1958	5.4	4.9	—	60
	Apples	1958	2.7	35	—	60
<i>Asia</i>						
Fed. of Malaya.....	Pineapples	1958	143*	97	—	66
	Pineapple juice	1958	6.4	82	—	66
<i>Caribbean</i>						
West Indies.....	Bananas	1957	1.5	4.8	—	66
<i>Africa</i>						
Sudan.....	Peanuts	1958	14.4	6.5	1 Composite	38
	Dates	1958	0.8	1.0	1 Composite	38
Union of South Africa.....	Pecan nuts	1958	3.2	4.7	1 Composite	38
	Mixed nuts	1958	12.8	5.7	1 Composite	38
	Plums	1957	2	4.5	—	60

* Dry weight.

TABLE XIX. Sr⁹⁰ IN MEAT, POULTRY, EGGS, AND FISH—1958-1960

Country	Year	μc/kg	μc/g Ca	Reference
<i>Meat</i>				
USA.....	1960	1.0 (0.5-1.9)	10 (1-14)	Tri-city study* 108
<i>Poultry</i>				
USA.....	1960	1.7 (0.7-2.5)	3.0 (1.6-4.5)	Tri-city study* 108
<i>Eggs</i>				
USA.....	1960	3.8 (1.9-11)	4.6 (3.5-5.9)	Tri-city study* 108
UK.....	1959	5.2	9	Countryside sampling 85
	1960	4.0	6.3	Countryside sampling 227
Australia.....	1959	—	7.3	Eight samples from New South Wales 61
<i>Fish</i>				
<i>Fresh</i>				
USA.....	1960	0.35 (0.1-1.0)	0.3 (0.1-0.6)	Tri-city study* 108
<i>Shell</i>				
USA.....	1960	0.8 (0.5-1.8)	1.0 (0.6-1.5)	Tri-city study* 108
Fed. Rep. of Germany.....	1958	1	0.1	Samples from North Sea 60
Spain.....	1959	8	—	Tuna analysed in USA 70
Japan.....	1958	0.6	—	Tuna analysed in USA 74
	1959	—	0.4	Deep sea, 4 samples 24
	1959	—	3.2	Coastal, 2 samples 24
	1959	—	15	Fresh water, 9 samples 24

* These results arise from an extensive survey of the total diet carried out in three cities in the USA.¹⁰⁸

TABLE XX. Sr^{90} IN HUMAN BONE, 1955-1960Values are given as $\mu\text{C Sr}^{90}/\text{g}$ calcium with the number of samples and the range in parentheses

Region, country or area	Latitude	Newborn										Reference		
		0-4 years												
		1956	1957	1958	1959	1960	1955	1956	1957	1958	1959		1960	1961
<i>N. America</i>	> 30°N	—	—	—	—	—	0.4(2)	0.5(2)	1.6(2) 1.6 (9) (0.2-5.9)	1.8 (6) 0.89 (0.5-2.4)	—	—	—	319 ^a 13, 299
Canada		—	—	—	—	—	—	—	—	—	—	—	—	—
USA		—	0.6(30)	0.9(179)	1.2(241)	1.1(80)	0.6(17)	0.7(16)	1.2(74)	2.0(38)	2.3(24)	2.4(66)	—	319 ^a
<i>Europe</i>	> 30°N	—	1.6(10)	—	1.5(32)	—	—	—	3.2(15)	—	1.9(14)	—	—	37, 245 ^a 233
USSR		—	—	—	—	—	—	—	—	—	1.6(8)	—	—	—
Poland		—	—	—	—	—	—	—	—	—	—	—	—	—
UK		0.44(5)	0.6(50) (0.25-1.1)	0.65(114) (0.3-1.4)	1.2(148) (0.55-2.9)	0.89(101) (0.5-1.6)	1.2(1)	0.78(24) (0.15-1.6)	1.2(49) (0.3-3.2)	1.4(51) (0.2-3.1)	3.1(69) (0.4-9.5)	2.9(73) (0.9-5.5)	—	98, 99, 238, 321
Fed. Rep. of Germany		—	—	1.0(15) (0.4-2.1)	1.6(14) (0.4-5.3)	1.3(22) (0.6-2.7)	0.4(13)	0.4(13)	1.3(16)	2.0(21)	2.0(47)	2.0(28)	—	93, 319 ^a
The Netherlands		—	8.2(3) (1.2-16.6)	4.0(1)	—	—	—	—	1.9(3)	1.0(3)	1.8(3)	—	—	97
Denmark		—	—	0.64(5) (0.5-0.8)	1.0(20) (0.6-1.5)	0.8(8) (0.6-1.0)	0.3(1)	0.8(5)	2.1(5)	—	—	1.3(6)	—	96, 319 ^a
Switzerland		—	—	—	—	—	0.6(4)	0.9(9)	—	—	—	—	—	319 ^a
<i>Mediterranean</i>	> 30°N	—	—	—	—	—	—	—	1.4(3)	0.5(10)	0.4(1)	—	—	319 ^a
Israel		—	—	—	—	—	—	—	—	—	—	—	—	—
<i>Far East</i>	> 30°N	—	1.6(6) (0.02-4.8)	1.1(13) (0.02-5.3)	1.2(8) (0.2-3.2)	—	—	—	0.82(5) (0.4-1.5)	0.70(13) (0.2-1.7)	0.83(3) (0.4-1.2)	1.0(5) (0.22-1.17)	1.1(6) (0.2-1.5)	330
Japan		—	—	—	—	—	—	—	—	—	—	—	—	—
<i>C. America</i>	10-20°N	—	—	—	—	—	0.04(1)	0.5(1)	0.8(7)	0.7(34)	2.1(5)	2.7(10)	—	319 ^a
Puerto Rico		—	—	—	—	—	—	—	0.3(5)	0.6(1)	0.6(2)	0.6(28)	—	319 ^a
Guatemala		—	—	—	—	—	—	—	—	—	—	—	—	—
<i>Asia</i>	< 30°N	—	—	—	1.1(2)	—	0.5(1)	—	—	0.8(1)	—	—	—	94, 319 ^a
India		—	—	—	—	—	—	—	—	—	—	—	—	319 ^a
China (Taiwan)		—	1.0(9)	0.5(17)	—	—	0.8(1)	—	1.6(13)	0.7(4)	—	—	—	319 ^a
Hong Kong		—	—	—	—	1.2(13)	—	—	—	—	—	1.7(18)	—	313
<i>S. America</i>	10°N-10°S	—	—	—	—	—	—	—	—	—	—	—	—	—
Venezuela		—	—	—	—	—	0.5(10)	—	0.9(18)	—	—	—	—	319 ^a
Brazil		—	—	—	—	—	0.7(1)	—	0.3(1)	0.8(3)	1.0(34)	1.1(20)	—	319 ^a
Argentina	> 20°S	—	—	—	—	—	—	—	—	—	—	0.73(6) (0.55-0.82)	0.85(20)	6, 5
Chile		—	—	—	—	—	0.8(1)	0.4(5)	0.6(10)	0.6(8)	0.4(21)	0.4(33)	—	319 ^a
<i>Oceania</i>	> 20°S	—	—	0.35(10)	0.60(35)	0.51(73)	—	0.8(3)	0.5(1)	—	0.9(226)	0.6(114)	—	319 ^a
Australia		—	—	—	—	—	—	—	—	—	1.0(124)	0.96(172)	—	95, 320
<i>Africa</i>	~ 0°	—	—	—	—	—	—	—	0.6(4)	1.2(2)	—	—	—	319 ^a
Congo (Leopoldville)		—	—	—	—	—	—	—	0.6(11)	—	—	—	—	319 ^a
Union of South Africa	> 20°S	—	—	—	—	—	—	—	—	—	—	0.9(55)	—	—

TABLE XX. Sr⁹⁰ IN HUMAN BONE, 1955-1960 (continued)

Region, country or area	Latitude	5-10 years					10 years or more					Reference			
		1955	1956	1957	1958	1959	1960	1961	1955	1956	1957		1958	1959	1960
<i>N. America</i>															
Canada.....	> 30°N	—	—	0.45(4) (0.2-0.6)	0.76(12) (0.4-1.0)	—	1.4(35)	—	—	0.29(30) (0.05-0.6)	0.38(27) (0.07-0.8)	—	0.53(113)	—	13, 299
USA.....		0.5(16)	0.6(14)	0.6(67)	1.0(42)	1.1(17)	1.5(79)	—	0.07(125) 0.06(187)	0.12(335) 0.27(271)	0.23(31)	—	—	—	319 ^a
<i>Europe</i>															
USSR.....	> 30°N	—	—	—	—	1.4(5)	—	—	—	—	—	0.40(82)	—	—	37, 245
Poland.....		—	—	—	—	1.2(7)	—	—	—	—	—	0.38(63)	—	—	233
UK.....		0.27(4) (0.15-0.4)	0.78(24) (0.15-1.6)	0.44(18) (0.3-0.75)	0.75(20) (0.2-1.7)	0.90(23) (0.13-2.7)	1.1(54) (0.3-2.0)	—	0.22(7) (0.13-0.29)	0.24(4) (0.11-0.44)	0.31(11) (0.04-1.4)	0.29(28) (0.07-0.7)	0.66(20)	—	98, 99, 238
Fed. Rep. of Germany		0.2(19)	0.2(14)	0.3(4)	0.7(11)	0.9(33)	1.2(36)	—	0.12(60)	0.22(26)	0.36(105)	0.45(145)	0.51(42)	—	93, 319 ^a
The Netherlands....		—	—	0.37(2)	1.5(9)	0.4(4)	—	—	—	—	—	0.2(1)	—	—	97
Denmark.....		0.4(3)	0.3(7)	0.5(4)	0.35-4.0)	0.5-0.7)	1.3(3)	—	0.08(11)	0.13(9)	0.17(17)	—	—	—	96, 319 ^a
France.....		—	—	—	—	—	—	—	0.1(7)	—	—	—	—	—	319 ^a
Switzerland.....		0.4(8)	0.6(22)	0.3(1)	—	—	—	—	0.16(9)	0.16(29)	0.12(4)	—	—	—	319 ^a
Italy.....		—	—	—	—	—	—	—	0.19(7)	0.16(8)	0.22(3)	—	—	—	319 ^a
<i>Near East</i>															
Iran.....	> 30°N	—	—	—	—	—	—	—	0.06(1)	—	—	—	—	—	319 ^a
Israel.....		—	—	0.5(7)	0.2(3)	0.5(1)	—	—	—	—	—	—	—	—	319 ^a
UAR.....		—	—	—	—	—	—	—	—	0.18(33)	0.12(65)	0.13(28)	—	20.01(2)	229
<i>Far East</i>															
Japan.....	> 30°N	—	0.4(3)	0.6(9) 0.67(6) (10.2-1.8)	0.7(2) 0.62(12) (0.8-1.5)	0.6(1) 0.59(3) (0.2-1.0)	0.96(41) (0.1-2.6)	—	0.2(2) 3.0(2) (0.3-3)	0.16(19) 0.25(3)	0.14(38) 0.22(38) (0.1-0.8)	0.12(58) 0.90(20) (0.1-2.5)	0.16(20) 0.41(4) (0.1-0.7)	0.58(36) 0.46(39) (0.1-1.0)	319 ^a 101, 330 (0.1-1.0)
<i>C. America</i>															
Puerto Rico.....	10-20°N	0.2(1)	—	0.5(10)	0.9(11)	1.0(24)	1.2(17)	—	0.18(4)	0.18(47)	0.15(34) 0.13(49)	0.21(151) 0.14(56)	0.24(134) —	0.34(14) 0.15(34)	319 ^a 319 ^a
Guatemala.....		—	—	0.4(9)	0.4(3)	—	0.5(10)	—	—	—	—	—	—	—	—
<i>Asia</i>															
India.....	< 30°N	0.2(5)	0.1(4)	0.2(54)	0.3(2)	—	—	—	0.14(33)	0.11(31)	0.18(22)	0.13(1) 0.52(2)	—	—	319 ^a 94
China (Taiwan)....		0.5(3)	—	1.1(2)	0.7(4)	1.1(1)	—	—	0.15(10)	0.17(7)	0.14(6)	0.18(25)	—	—	319 ^a
Thailand.....		—	—	0.3(1)	0.4(1)	0.4(3)	—	—	—	—	0.28(33)	0.18(36)	0.22(46)	—	319 ^a
Viet-Nam, Rep. of.		—	—	—	—	1.0(1)	0.3(1)	—	—	—	—	0.5 (7)	0.4 (9)	—	319 ^a
<i>S. America</i>															
Colombia.....	10°N-10°S	0.1(1)	0.4(1)	0.1(2)	0.2(2)	—	0.2 (2)	—	0.10(7)	0.1(1)	0.07(3)	0.17(11)	0.12(8)	—	319 ^a
Venezuela.....		0.3(21)	0.2(3)	0.4(6)	—	—	—	—	0.16(35)	0.2(3)	—	—	—	—	319 ^a
Brazil.....		0.3(4)	0.1(9)	0.2(4)	0.4(12)	0.5(17)	0.7(6)	—	0.13(13)	0.08(40)	0.08(4)	0.15(23)	0.15(130)	0.24(70)	319 ^a
Ecuador.....		—	—	—	—	—	—	—	—	—	0.08(2)	—	—	—	319 ^a
Argentina.....	> 20°S	—	—	—	—	—	—	—	—	—	0.11(19)	—	—	—	319 ^a
Chile.....	> 20°S	0.2(18)	0.2(13)	0.3(37)	0.4(10)	0.4(22)	0.4(25)	—	0.20(40)	0.10(59)	0.06(24)	—	—	—	319 ^a
<i>Oceania</i>															
Australia.....	> 20°S	—	0.6(3)	0.5(2)	—	—	—	—	<0.1(13)	0.19(37)	—	0.15(460) 0.16(247)	0.22(247) 0.19(346)	—	319 ^a 95, 320
<i>Africa</i>															
Congo (Leopoldville)....	~ 0°	—	—	1.2(4)	0.4(1)	—	—	—	—	—	0.13(9) 0.43(12)	0.14(2)	—	—	319 ^a 319 ^a
Liberia.....		—	—	—	—	—	—	—	—	—	—	—	—	—	—
Union of South Africa.....	> 20°S	—	—	0.4(24)	0.9(32)	0.8(78)	1.0(73)	—	0.1(7)	0.18(39)	—	—	0.24(125)	—	319 ^a

^a Values from reference 319 below 1 μc/g. Ca are often stated as "less than" the value in which the bone sampled was not specified.

^b Normalized in accordance with footnote to paragraph 81 except Japan, USSR, Poland, quoted.

^a Values from reference 319 below 1 $\mu\text{Ci/g}$. Ca are often stated as "less than" the value quoted.

^b Normalized in accordance with footnote to paragraph 81 except Japan, USSR, Poland, in which the bone sampled was not specified.

TABLE XXI. SUMMARY OF THE REGIONAL MEANS OF Sr^{90} CONCENTRATION IN HUMAN BONES, 1959-1960
($\mu\text{c Sr}^{90}/\text{g calcium}$)

Area	Latitude	Age—years							
		Newborn		0—4		5—19		>19	
		1959	1960	1959	1960	1959	1960	1959	1960
America.....	> 30°N	1.2	1.1	2.3	2.3	1.1	1.5	0.3	0.3
N. Europe.....	> 30°N	1.4	1.1	2.5	2.5	0.9	1.2	0.4	0.6
S. Europe.....	> 30°N	1.5	—	1.9	—	1.3	—	0.4	—
Far East.....	> 30°N	—	—	0.4	—	0.5	—	0.1	—
Near East.....	> 30°N	1.2	—	0.8	1.0	0.6	0.9	0.3	0.6
Asia.....	< 30°N	1.1	1.2	—	1.7	0.5	0.3	0.3	0.2
Central America.....	< 30°N	—	—	0.6	0.6	—	0.5	—	0.2
South America.....	10°N–10°S	—	—	1.0	1.1	0.5	0.7	0.1	0.3
	> 20°S	—	—	0.4	0.6	0.4	0.4	—	—
Australia.....	> 20°S	0.6	0.5	0.9	0.8	0.6	0.6	0.2	0.2
Africa.....	> 20°S	—	—	—	0.9	0.8	1.0	—	0.2

TABLE XXII. A COMPARISON OF MEASURED RATIOS OF Sr^{90} TO CALCIUM ($\mu\text{c/g}$) IN TOTAL DIET (TABLE IV) AND MILK (TABLE VII)

Region and country	Year	Ratio (mean)	Total diet/milk (range)
(a) Values based on continued, often widespread, diet sampling			
<i>N. America</i>			
Canada.....	1959–1960	1.1	—
USA.....	1957–1960	1.3	0.9–1.7
<i>Europe</i>			
UK ^a	1957–1960	1.2	1.2–1.3
Fed. Rep. Germany.....	1959	1.8	—
Denmark ^a	1959–1960	2.9	—
Austria.....	1960	1.7	—
<i>Oceania</i>			
Australia.....	1957–1960	1.1	—
<i>Far East</i>			
Japan.....	1957–1960	2.2	1.4–3.6
(b) Values based on single, often very limited, diet samples			
<i>Central America</i>			
Five countries ^{a, b}	1957–1958	1.3	0.9–2.0
<i>S. America</i>			
Four countries ^b	1957–1959	2.7	1.9–3.3
<i>Africa</i>			
Rhodesia ^b	1959–1960	10–13	—

^a Excluding mineral calcium.

^b Based on limited sampling.

TABLE XXIII. CALCULATED RATIOS OF THE RATIO OF Sr^{90} TO CALCIUM IN THE TOTAL DIET TO THAT IN MILK FOR VARIOUS APPROXIMATE DIET TYPES FOR 1958-1960

Component	Milk	Percentage contribution of calcium to the diet				Ratio total diet to milk
		Cereal ^a		Veg. ^b	Fish ^c	
		Milled	Unmilled			
Ratio to milk.....	—	5	13	3	<0.1	
No. of observations.....	—	10	33	35	3	
Range.....		(2-10)	(1-43)	(1-12)		
Diet I ^d { (a).....	80	5	0	15		1.5
(b).....	80	3.5	1.5	15		1.6
(c).....	80	0	5	15		1.9
Diet II ^d { (a).....	40	20	0	40		2.6
(b).....	40	14	6	40		3.1
(c).....	40	0	20	40		4.2
Diet III ^d { (a).....	10	15	0	60	15	2.6
(b).....	10	10	5	60	15	3.0
(c).....	10	0	15	60	15	3.8

^a Including wheat, rye, maize and rice.

^b Vegetables of all kinds and fruit.

^c Marine fish only. If all the fish were from fresh water the ratio of total diet to milk might be increased by about 0.4. (Based on Japanese data, table XIX.)

^d Diet (a) contains only milled cereal, (b) 30 per cent unmilled cereal, (c) all unmilled cereal.

TABLE XXIV. COMPARISON OF MEASURED Sr^{90} TO CALCIUM IN BONE, 1959-1960, WITH LEVELS IN NEW BONE CALCULATED FROM DIET MEASUREMENTS, 1959-1960 (see text, para. 100)

All units $\mu\mu c Sr^{90}/g Ca$

Area	Assumed diet type	Latitude	Milk (a)	Total diet			New bone 1959-60		
				Measured (table IV) (b)	Calculated (c) ^a	Calculated (d) ^b	Calculated from diet (OR = 0.25) (e)	Calculated from bones of newborn 0-4-year-olds (f)	Measured as mean level in 0-4-year-olds (g)
N. America.....	I	> 30°N	9.5	12	13	14	3	2.3	2.3
W. Europe.....	I		8.1	11	11	12	3	2.5	2.5
E. Europe.....	I		9.1	—	13	14	3	3.0	1.9
Near East.....	II		—	3	—	—	1	—	0.4
Far East.....	III		5.1 ^a	13 ^a	—	13	3	2.4	1.0
Asia.....	II-III	< 30°N	3.5 ^a	7	—	9	2	2.3	1.7
Central America.....	—	< 30°N	1.6	1	—	—	0.3	—	0.6
S. America.....	I-II	> 0°S	2.3	4	—	3-6	1-2	—	0.6-1.0
Oceania.....	I	> 20°S	3.8	4 ^a	—	6	1	1.1	0.8
Africa.....	II	> 20°S	2.6	3-8	—	7	1-2	—	0.9

^a Based on the weighted mean of milk and measured ratio of total diet to milk in some countries (from table XXII).

^b Based on the weighted mean of milk and the ratios of total diet to milk for the approximate model diets (from table XXIII).

^c Based on one country only.

TABLE XXV. A COMPARISON OF THE RATIOS OF Sr^{90} TO Ca IN AVERAGE ADULT DIET AND BONE OF NEW-BORN OR FOETUS

The range of values is shown in parentheses. The data are taken from table IV (diet) and table XX (bone)

Country	Year	OR (foetus/mother's diet)
USA (New York).....	1957-1960	0.09 (0.07-0.10)
UK.....	1957-1960	0.12 (0.11-0.13)
Denmark.....	1959-1960	0.10 (0.09-0.11)
Fed. Rep. of Germany.....	1959-1960	0.12 (0.11-0.12)
Australia.....	1958-1960	0.10 (0.08-0.12)
Japan.....	1957	0.56
	1958	0.21
	1959	0.08

TABLE XXVI. ESTIMATED PROPORTIONALITY FACTORS FOR THE CALCULATION OF FUTURE LEVELS DERIVED FROM SURVEY MEASUREMENTS TO 1960

Country	Milk		Vegetables		Starchy roots		Cereals ^a	
	P _d	P _r	P _d	P _r	P _d	P _r	Unmilled P _r	Milled P _r
Argentina.....	0.24	0.54					30	—
Australia.....	0.71	1.5	1.5				18	9
Canada.....	0.30	0.66					20	6
Denmark.....	0.23	—	0.8	—	3	0	19, 148	—
Germany ^b	0.29	—	0.6	—	1.1	—	—	—
Japan.....	0.23	0.3					34 (47) ^c	
India.....	0.26	0.7						
New Zealand.....	0.80	—						
Norway.....	0.52	0.6						
S. Rhodesia.....	0.30	—						
USSR.....	0.40	1.1					20	4
UK.....	0.21	0.9	0.5	0.8	1.2	0	16	5
USA.....	0.27	0.7	1	0	0.8	1	25	16
Value adopted....	0.3	0.8	1	1	1	0	20	7

^a Mainly based on wheat; P_d is assumed as 0.5.

^b The value of F_d is assumed to be the same as in the UK.

^c Rice.

TABLE XXVII. SUMMARY OF PROPORTIONALITY FACTORS FOR PREDICTING FUTURE RATIOS OF Sr⁹⁰ TO Ca IN THE TOTAL DIET

Diet	Calcium ^a contribution	P _i immediate situation	P _i long-term situation	P _i ^b (with milled cereal only)	P _i ^b (with unmilled cereal only)
I and II.....	80:5:13:2	0.4	0.35	1.1	1.8
III.....	40:20:38:2	0.6	0.6	1.9	4.7
IV.....	13:15:50:7	0.7	0.7	1.7	3.6

^a From milk: cereals: green vegetables: starchy roots (based on potatoes). The contribution from fish has not been taken into account since, because of dilution of Sr⁹⁰ in the sea, the contribution is likely to remain small.

^b For calculation it has been assumed that 20 per cent of the cereal in the diet is unmilled.

TABLE XXVIII. SOME ESTIMATES OF THE MEAN DAILY INTAKE OF Cs¹³⁷ IN THE TOTAL DIET

	USA—1956–1957 (40)				Canada 1959 (108)			
			Cs ¹³⁷ intake				Cs ¹³⁷ intake	
	μμ Cs ¹³⁷ /g K	K intake g	μμ	Per cent	μμ Cs ¹³⁷ /g K	K intake g	μμ	Per cent
Milk and milk products.....	32	1.16	37	60	35	1.0	35	55
Vegetables except potatoes ^a	5	0.57	2.9	5	1	0.78	0.8	1
Potatoes.....	0	0.60	0		0	0.41	0.0	
Fruit.....	25	0.10	2.5	3	2.5	0.47	1.0	2.0
Meat.....	32	0.46	14.7	25	67	0.40	21.8 ^b	34
Fish.....	—	—	—	—	5			
Flour and cereals.....	24	0.20	4.8	7	23	0.22	5.1	8
		3.09	61.9			3.28	63.7	
Cs ¹³⁷ /K total diet.....			20				19.5	
Whole body.....			40				57	

^a Sampled on a very limited scale.

^b Assuming one-fifth of the potassium is from fish.

TABLE XXIX. Cs¹³⁷ IN MILK

Regular or widespread surveys (for description see table VIII)

Results as $\mu\text{C Cs}^{137}$ per g potassium, or as $\mu\text{C/litre}$ (italicized). Number of sites and range, where available, in parentheses.

Region	Latitude	Country	Area	1957	1958	1959	1960	1961	Reference
N. America	>30° N	Canada.....	Widespread	—	—	61 (12, 28-100)	55 (10, 26-115)	—	3, 40, 69, 71, 72
		USA.....	Widespread	33 (38, 12-59) ^a 34 (5) ^b	42 (33, 2-70) ^a 44 (5)	52 (33, 20-97) ^a 54 (12, 30-86)	32 (38, 7-70) ^a 28 (9)	15 (9, 10-25)	3, 40, 69, 71, 72, 251
Europe	>30° N	USSR.....	Widespread	—	—	—	30 (9, 13-59)	—	234
			Moscow	—	—	—	13 (2)	—	8, 227
		UK.....	Widespread	—	36 (9, 22-54) ^b	—	19 ^a	—	24, 25, 241
		Fed. Rep. of		—	—	—	—	—	—
		Germany....	Lindau	—	—	—	23 (1) ^b	—	—
		Italy.....	N. Italy	—	—	—	—	—	18, 228
		Denmark.....	Widespread	—	—	15 (11-22) ^b	12 (4, 8-14)	—	49, 42, 43
		Norway.....	S. Norway	19 (4, 12-23) ^b	31 (2, 25-38)	27 (2, 23-30) 149 (3, 47-270)	— 150 (11, 39-397)	—	231, 242
Far East	>30° N	Sweden.....	Mid-Sweden	27 (1) ^b	40 (1) ^b	46 (1) ^b	—	—	41
		Finland.....	Widespread	—	—	40 (22-80) ^b	—	—	54
				—	—	55 (19-220)	—	—	191
		Japan.....	—	18 (2) ^b	52 (4, 22-118) ^b	88 (10, 21-193) ^b	77 (8, 16-117) ^b	—	243
Asia	10-20° N	India.....	Widespread	—	9.4 (1)	18 (1)	11 (1)	10 (1)	88, 89
			Bombay	—	—	17 (21, 3-160) ^b	5.5 (16, 1.5-13) ^b	5.6 (7, 4-9)	89, 244, 302
S. America	>20° S	Argentina.....	Main production zone	—	—	—	19 ^a	20 ^a	44
Oceania	>20° S	Australia.....	Sydney	18 (1)	12 (1) ^b	18 (1)	19 (1)	—	40, 69, 71, 72, 73

^a Upper figure Los Alamos survey, lower figure U.S.P.H.S. stations.^b Not a complete year, or sampled irregularly.

* Countrywide bulked samples for part of year.

* Composite samples.

TABLE XXX. Cs¹³⁷ IN MILK; INFREQUENT OR SPOT SAMPLINGResults expressed as $\mu\text{C Cs}^{137}$ per g potassium

Figures in parentheses indicate number of samples

Region	Latitude	Country	1957	1958	1959	1960	1961	Reference
Europe	> 30°N	Denmark.....	—	39 (2)	—	—	—	69
		France.....	—	34 (2)	—	—	—	69
		Switzerland.....	—	77 (2)	—	—	—	69
		Fed. Rep. of Germany.....	54 (1)	54 (1)	39 (1)	50 (4)	—	23
Far East	> 30°N	Japan.....	80 (3)	29 (1)	74 (2)	—	—	33, 69, 72
Central America	10–20°N	Mexico.....	—	—	20 (2)	—	—	69
S. America	10°N–10°S	Colombia.....	—	6 (1)	16 (1)	—	—	69, 72
		Venezuela.....	—	1.2 (2)	—	—	—	69
		Brazil.....	—	26 (2)	36 (1)	—	—	71, 72
		Chile.....	—	66 (6)	40 (1)	—	—	69, 72

TABLE XXXI. THE Cs¹³⁷ CONTENT OF SOME FOODS

Category and type	Country	Year	Cs ¹³⁷		Reference		
			μμc/kg	μμc/gK			
Cereal							
Wheat grain.....	Canada	1957		35 ^a	114		
		1958		47 ^a	114		
Rice (brown).....	Japan (widespread)	1960	265	—	326		
		1961	90	54	326		
		1956	38	31	90		
		1957	55	44	90		
Rice (brown).....	Japan (Gunma)	1958	108	63	90		
		1959	63	37	90		
		Rice (brown).....	Japan (widespread)	1959	143	139	326
				1960	31	36	326
Barley.....	Japan (Gunma)	1956	80	34	90		
		1957	48	22	90		
		1958	89	35	90		
		1959	401	146	90		
Rice (boiled).....	India	1959	0.3	0.2	309		
		1959	10.4	4.9	309		
Vegetables							
Cabbage, etc.....	Japan (Gunma)	1957	13	6.0	90		
		1960	26	12	90		
Root vegetables.....	Japan (Gunma)	1957	18	7	90		
		1960	36	15	90		
Meat							
Beef.....	Japan (Gunma)	1960	92	32	90		
		1957	98	36	90		
Pork.....	Japan (Gunma)	1960	207	90	90		
		1960		180-1,760 (3)	231		
Reindeer.....	Sweden	1960	24,000		276		
Fish							
Cuttle fish.....	Japan (Pacific)	1957	21	11	90		
		1960	26	28	90		
Skipjack.....	Japan (Pacific)	1957	16	9	90		
		1960	87	43	90		

^a The Cs¹³⁷/K ratio in flour is not significantly different.

TABLE XXXII. THE Cs^{137} CONTENT OF MAN, MEASURED BY WHOLE BODY COUNTERResults as $\mu\mu\text{C Cs}^{137}$ per g potassium*The figures in parentheses indicate the number of observations*

Region	Latitude	Name or number of countries represented	1956	1957	1958	1959	1960	1961	Reference
N. America	> 30°N	USA	50 (279)	51 (294)	62 (461) 69 (576) (July-Dec.)	74 (280) 67 (777)	67 (279) 51 (646)	31 (245)	L. A. W. R.
		Canada			51 (30) (Dec.) 64 (2)	57 (20) (Spring) 94 (4) 79 (8)	49 (21) (Dec.) 92 (2) 55 (1)		107, 108 117 L. A. W. R.
Europe	> 30°N	UK	32 (14)	37 (18)	48 (14)	58 (30) *48 (94)	49 (47) *45 (88)	36 (26)	274, 298 104
		Fed. Republic of Germany					63 (1566)	42 (807)	116, 250, 253
		Sweden				66 (46) 73 (—)	65 (—) (June)	55 (87)	105 276
		7	32 (4)		70 (22)	87 (10)	85 (9)		L. A.
Near East	> 20°N	11			76 (47)	83 (122)	67 (208)	51 (43)	W. R.
		2			62 (1)		57 (2)		L. A.
		4			60 (2)	54 (1)	32 (5)	49 (2)	W. R.
Far East	> 30°N	2	25 (1)		44 (2)	64 (2)	109 (1)		L. A.
		5			75 (16)	67 (70)	49 (145)	29 (31)	W. R.
		Japan						29 (11)	278
Asia	0-30°N	4	20 (2)		66 (3)	42 (3)	51 (2)		L. A.
		6				60 (12)			W. R.
C. America	10°-30°N	3		14 (2)	47 (1)	99 (2)	27 (4)		L. A.
		3			78 (1)	49 (9)	54 (5)	28 (1)	W. R.
Caribbean	20°N	5			75 (1)	60 (3)	68 (1)	25 (4)	W. R.
S. America	< 10°N	7		14 (9)		47 (10)			L. A.
		5			35 (5)	49 (5)			W. R.
Africa	< 10°N	2			52 (2)	62 (1)			L. A.
		2				45 (2)		35 (1)	W. R.
Asia	< 10°N	2	11 (2)						L. A.
Oceania	< 10°S	2		50 (1)		103 (2)	68 (1)		L. A.
		2				54 (3)	34 (1)	36 (1)	W. R.

* Measurements made on former luminizers (female).
L.A. indicates data from the Los Alamos Scientific Laboratory.^{3, 6, 71, 72, 102}

W.R. from the Walter Reed Army Institute of Research.^{111, 240, 253}

TABLE XXXIII. MEAN CONCENTRATIONS OF Cs^{137} ($\mu\mu\text{C/PER G POTASSIUM}$) IN THE HUMAN BODY AS MEASURED BY WHOLE BODY COUNTING (from table XXXV)*The figures in parentheses indicate the number of observations*

Region	Latitude	1956	1957	1958	1959	1960	1961
North America	> 30°N	50 (279)	51 (294)	65 (1,069)	69 (1,089)	55 (949)	31 (245)
Europe	> 30°N	32 (18)	37 (18)	69 (83)	65 (302)	63 (1,891)	43 (963)
Near East	> 30°N	—	—	61 (3)	54 (1)	39 (7)	49 (2)
Far East	> 30°N	25 (1)	—	71 (18)	67 (72)	50 (146)	29 (42)
Asia	< 30°N	16 (4)	—	66 (3)	56 (15)	51 (2)	—
Central America	< 10°N	—	14 (2)	66 (3)	59 (14)	45 (10)	26 (5)
South America	—	—	14 (9)	35 (5)	48 (15)	—	—
Africa	—	—	—	52 (2)	51 (3)	—	35 (1)
Oceania	> 20°S	—	50 (1)	—	74 (5)	51 (2)	36 (1)

TABLE XXXIV. MEAN CONCENTRATION OF SHORT LIVED FISSION PRODUCTS IN MILK IN THE USA, 1957-1960

Values, expressed in $\mu\mu\text{C/litre}$, are from 5-12 stations of the US Public Health Service²⁵¹

<i>Year</i>	<i>Sr⁹⁰</i>	<i>Ba¹⁴⁰</i>	<i>I¹³¹</i>
1957 (second half).....	65	80	250
1958.....	50	15	40
1959.....	20	Not detectable	
1960.....	Not detectable		

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ANNEX F

ENVIRONMENTAL CONTAMINATION (continued)

PART III

Exposure data

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TABLES

REFERENCES

I. Introduction

1. The purpose of this section of the annex is to estimate the average doses of radiation received by the world population from fall-out.

2. Fall-out materials deposited on the ground are an external source of exposure to man. In addition to this, some radio-nuclides are taken into the body and become an internal source of radiation. Information on these two sources has been given in parts I and II of the present annex. To determine the average radiation dose received, a considerable amount of dosimetric and demographic data is also required.

3. This section of the annex presents "dose commitments"—the total doses which will be received by mankind in all generations (H 15-21)—from given periods of weapon testing. In addition, that fraction of the dose commitment that will be reached by the year 2000 is also given. The calculations have been based on the fact that testing was carried out from 1954-1958, and was

resumed in 1961, at an assumed constant annual rate of injection of 1 Mc of Sr⁹⁰ and 10²⁸ atoms of C¹⁴. On that basis, calculations have been made for tests up to the end of 1960 and up to the end of 1961, as well as for continued testing. Since the doses are necessarily based on many assumptions, they must be considered as estimates rather than precise determinations.

II. External exposure

WORLD AVERAGES OF FALL-OUT DEPOSIT

4. The average fall-out deposit per square km of the surface of the earth, \bar{F}_d , is obtained by integrating the local values of fall-out, F_d , over the total surface of the earth, S_0 , i.e.:

$$\bar{F}_d = \frac{1}{S_0} \int_{S_0} F_d dS$$

In order to get a measure of the mean effect of the global

fall-out, a population weighted average fall-out can be defined as

$$\overline{G} \overline{F}_d = \frac{\int_{S_0} N F_d dS}{\int_{S_0} N dS}$$

where N is the population density, and \overline{G} is called "the mean geographical factor" (figure 1).

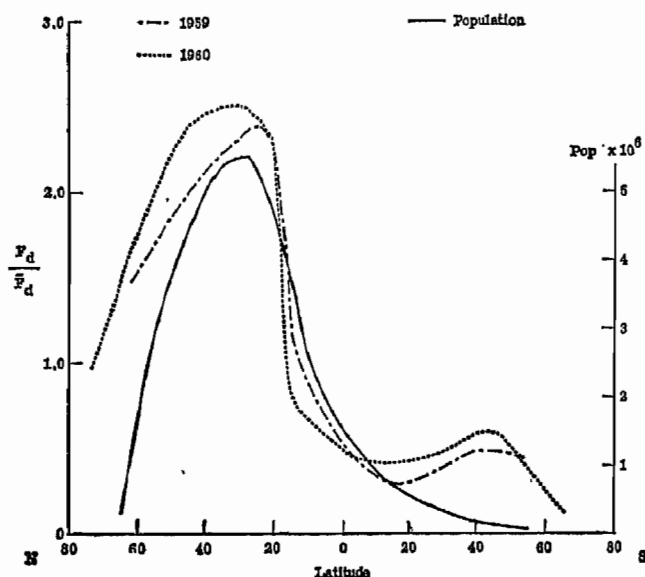


Figure 1. Geographical factor fall-out deposit

5. The values of the population weighted mean world geographical factor have risen from 1.6 to 1.9 in the years 1955-1960 owing to changes in the pattern of fall-out. It is therefore possible to use measurements in certain latitudes where F_d/\overline{F}_d is equal to about 1.9 to estimate the doses to the average member of the world population. This avoids the problem of attempting a total summation over the world's surface when insufficient data are available.

METHODS OF DOSE ESTIMATION

6. Various methods have been used to estimate the dose in air in the open from which the dose in specific organs of the body may be deduced. These may be summarized as:

(a) Direct measurements using ionization chambers and counters mounted about 1 metre above the ground;

(b) Indirect methods based on the determination of the radio-active fall-out products in soil either by gamma-ray spectroscopy or by chemical analysis. The cumulative deposition may also be deduced through similar analyses of fission products in rainfall, making allowance for radio-active decay;

(c) Calculations based on the fission product yields of nuclides and assumed residence times (paras. 12 and 13).

For both (b) and (c) above, one requires information regarding the dose from infinite plane sources of nuclides,

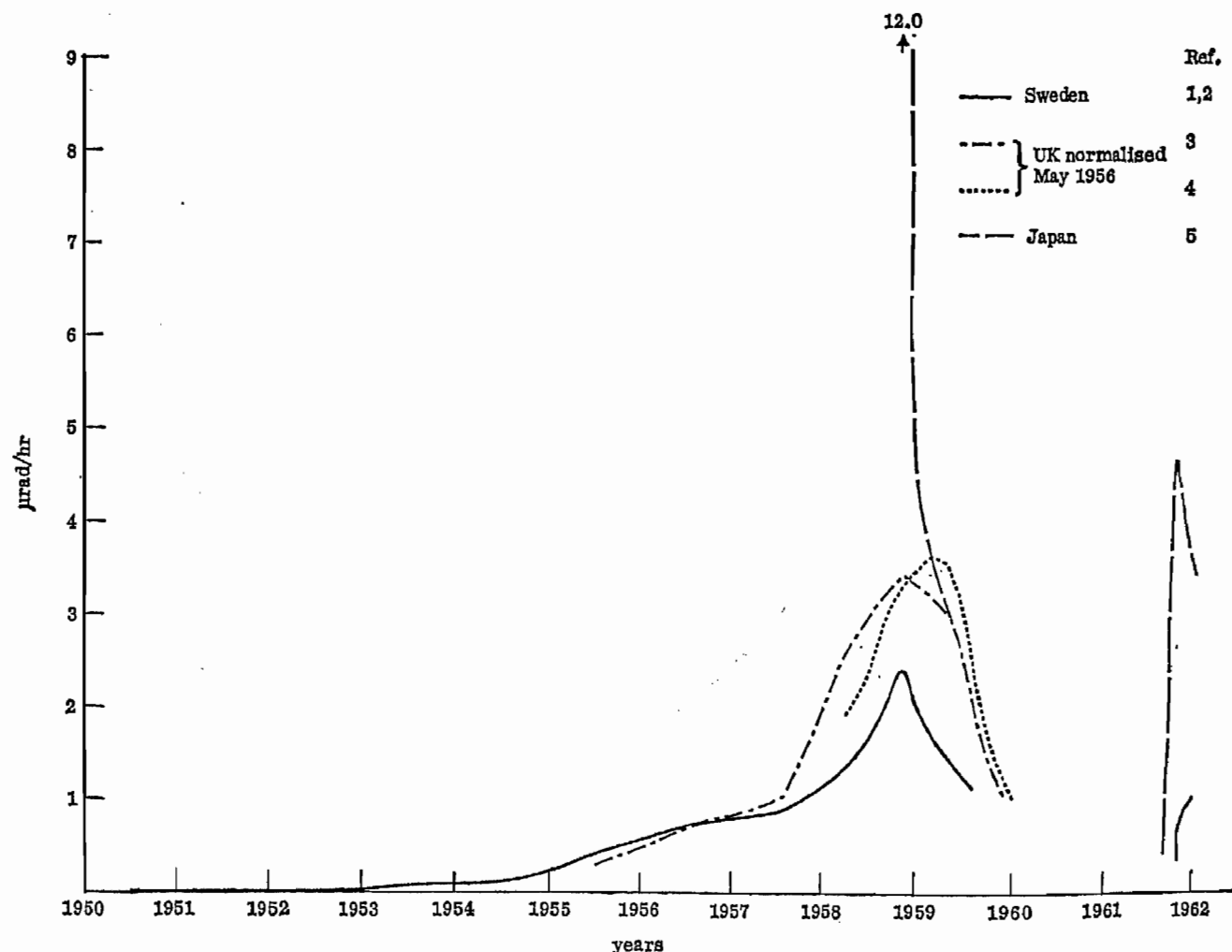


Figure 2a. Direct measurements—external dose measurements (100 mrad/y = 11.4 μrad/hr)

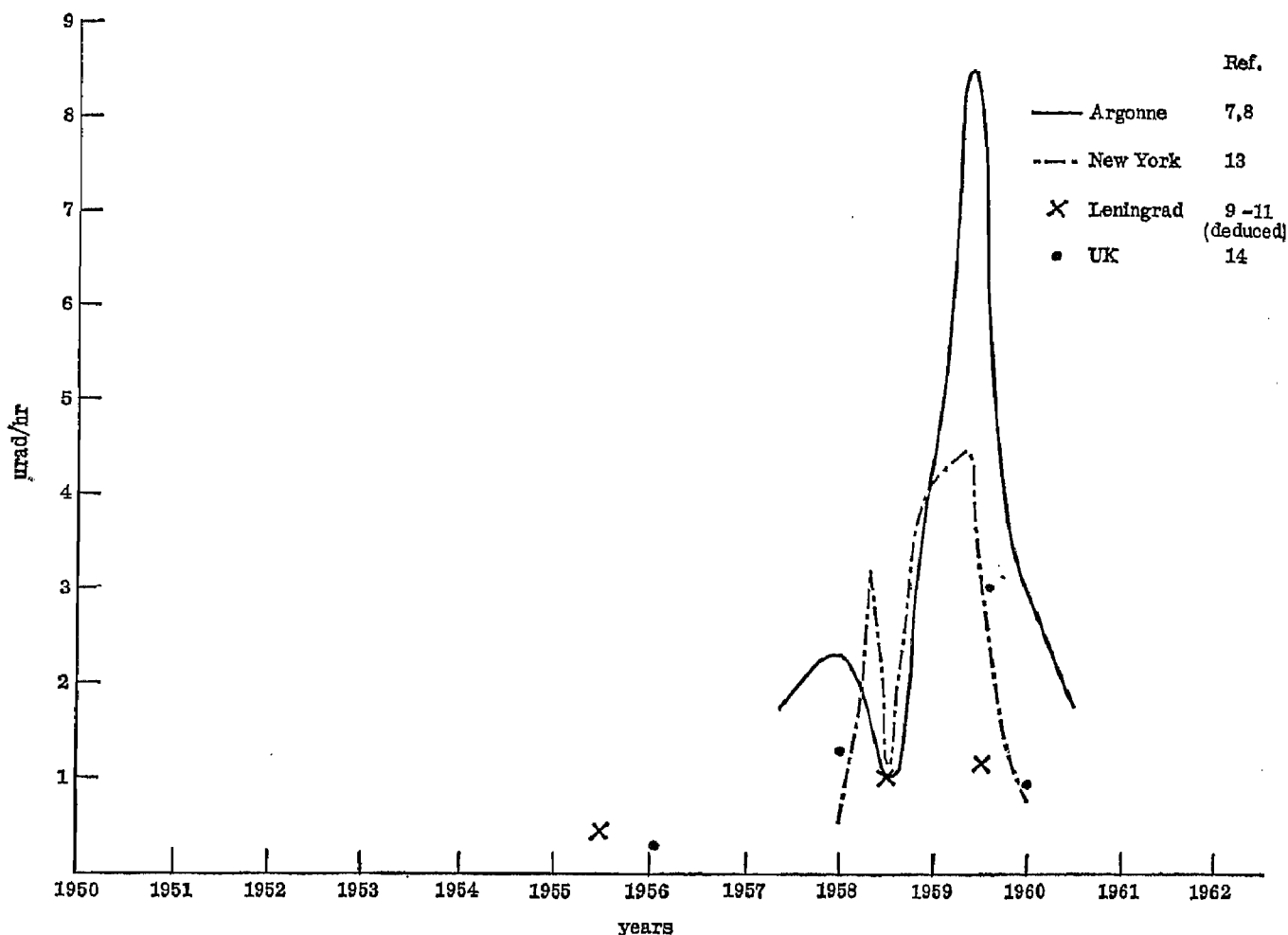


Figure 2b. Indirect measurements—external dose measurements (100 mrad/y = 11.4 μ rad/hr)

allowing for the scatter and absorption in the air and soil, and the relevant calculations of these are given in paragraphs 9-11.

Direct determination

7. The most comprehensive survey has been carried out in Sweden^{1,2} where high pressure ionization chambers have registered dose-rates from fission products since 1951. Measurements have also been made elsewhere³⁻⁵ using high pressure ionization chambers, geiger counters and plastic scintillators, respectively. These measurements are shown in figure 2a. The rapid fall in the Japanese measurements in 1959 indicates that these high levels were due to short-lived products.

Indirect methods

8. Many measurements⁶⁻¹³ using gamma-ray spectroscopy or chemical analysis have been reported and are shown in figure 2b. A comparison of figures 2a and 2b shows that there is reasonable agreement between direct and indirect estimates for the years 1954-1961. The Swedish data^{1,2} are lower than the others, as the measurements are made at a latitude higher than that of the peak shown in figure 1. Pearson and Salmon¹² have shown that calculations based on the cumulative deposition in rainfall of Cs^{137} and $\text{Zr}^{95} + \text{Nb}^{95}$ give results which are 70 per cent of those obtained using gamma-ray spectroscopy of soil, and other calculations on the same data show closer agreement.¹⁴ The difference

noted may be due to dry deposition of fall-out or to non-uniformity of site drainage.

9. To derive the values reported in figure 2b it is necessary to deduce the dose-rate of the particular gamma-emitting radio-isotopes when they are uniformly spread on an infinite plane in the concentrations derived by gamma-spectroscopy or other methods. These are based on calculations by several workers.¹⁵⁻²⁰ The dose-rate in air due to a deposit $F_d^j(t)$ of a certain gamma-emitting radio-isotope (j) spread uniformly on an infinite plane, can be considered as being governed by the relation:

$$\frac{dD_j}{dt} = k_j B_j F_d^j(t) \text{ mrad/y} \quad (1)$$

where

$\frac{dD_j}{dt}$ = dose-rate in air from the deposit $F_d^j(t)$ (mrad/y)

k_j = dose-rate from primary radiation (mrad/y/mc/km²)

B_j = ratio of total/primary radiation dose-rate (build-up factor)

$F_d^j(t)$ = deposit of isotope j (mc/km²)

The constants k_j and B_j have been considered for each of the important radio-nuclides and quite a wide range of values has been reported (table I). The values in columns 4 and 5 do not include the factor B_j and the values in column 6 have been chosen taking this into

account. The variations in the values are due to: (a) the variation of the gamma-ray spectrum used in deriving the values for each nuclide; (b) the values of the build-up factor and the methods of applying them; and (c) the assumption made as to whether Zr^{95} and its daughter product Nb^{95} are in secular equilibrium on the ground, or in a state of transient equilibrium.

10. The determination of the build-up factor which should be used for each particular isotope has been based mainly on the work of Goldstein *et al.*²¹ However, certain experimental investigations have been carried out using Cs^{137} and Co^{60} .^{22, 23} Davis²² compared scintillation counter measurements made about 1 m from the ground with the theoretically derived dose-rates after correcting for air absorption and build-up. The experimental values were 6 and 16 per cent lower than the theoretically derived values for Cs^{137} and Co^{60} respectively. The variation of the build-up factor with altitude was also measured and gave values at 1 m from the ground, extrapolated from about 100 m, of 0.8, 1.4 and 2.4 for I^{131} , Cs^{137} and Co^{60} respectively. Solon²³ obtained a value of 1.25 for Co^{60} from sources on the surface. Values of back scatter from a broad beam from infinite sources of the order of 20 per cent for radiation in the range 0.4-1 MeV have been computed.^{24, 25}

11. Lindell¹⁹ quotes a figure of build-up factor of 2 for Cs^{137} but this and other estimates are apparently all based on a homogeneous medium, and do not take into account the change of medium from earth to air. It would seem that the value of 2 used by some workers for the build-up factor may be an over-estimate when fall-out penetrates into the upper layers of the earth's surface. However, Gustafson¹⁸ in his determinations has taken account of both air absorption and the absorption by the soil due to penetration of the isotopes into the upper soil layers. The penetration of fall-out products into the soil has been estimated on the basis of measurements made in Chicago: 77 per cent activity for a depth up to 3.8 cm, 16 per cent for 3.8-7.6 cm and 7 per cent for 7.6-11.4 cm. Gustafson's method has been used to obtain the values for Sb^{125} , I^{131} and $Ba^{140} + La^{140}$ given in table I. The constants given in table I are calculated for a height above the ground equal to 1 m. The dose-rate changes little with height, being about 15 per cent higher at 0.5 m than at 1 m from the ground.¹⁹

Theoretical calculations of the total external dose

12. From the values of table I and the concentrations of individual nuclides on the ground the dose-rate from each nuclide may be estimated. The relative contributions to the total external dose from the nuclides present on the ground depend upon:

(a) The fission product yield of the particular nuclide. This may vary with both the fission element and the neutron energy. The yields of some nuclides, especially Ru^{106} and Sb^{125} may vary by a factor of up to 25 (F I, table I);

(b) The residence time in the atmosphere which determines whether any short-lived products that are formed at the time of the explosion will contribute to the ground level gamma-ray dose.¹⁴ As has been shown by Dunning²⁶ (figure 3) the ratio of the dose due to short-lived nuclides to the Cs^{137} dose over 30 years may vary from 10 to 0.4, depending upon whether the residence time is two weeks or ten years. The dose contributions are equal if the mean residence time is about 2.6 years;

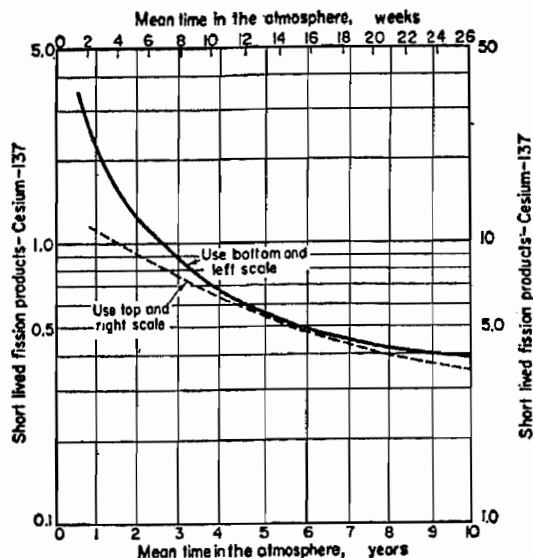


Figure 3. Theoretical relative 30-year doses for (short-lived fission products)/cesium-137

(c) The gamma-ray energy as well as the half-life of the particular isotope. The energy will also determine the relative importance of products present in the deeper soil layers since the greater the energy the less the absorption within the soil;

(d) The latitudinal variation of fall-out. The distribution of fall-out from the troposphere is not the same as that from the stratosphere (F I, 53).

13. To illustrate these effects on the dose at ground level, theoretical calculations of the dose-rates from various nuclides at equilibrium have been carried out for various atmospheric residence times. The yields given by Katcoff²⁷ for fast neutron fission of U^{235} have been assumed and the calculations are based on a constant fall-out rate of Sr^{90} of 2 mc per km^2/y which is approximately the world average over the surface of the earth for 1959. Assuming further that the rate of deposition of Cs^{137} is 1.7 times higher than that of Sr^{90} (F I, 81) and that the geographical factor is 1.9, this leads to a world population weighted mean fall-out rate of Cs^{137} in 1959 of approximately 6 mc per km^2/y . Table II gives the dose-rates in air which would arise from various nuclides if this fall-out rate continued until equilibrium conditions are set up on the ground. It will be seen that the shorter the atmospheric residence time the higher the dose-rate because of the effect of the short-lived products, especially $Zr^{95} + Nb^{95}$. Concentrations equal to 90 per cent of the equilibrium value will be reached in about one year or so for most of these short-lived products, whereas the equilibrium for Cs^{137} would only be reached after 33 or 100 years, depending on the assumption made as to the effective half-life of Cs^{137} on the ground.

FACTORS AFFECTING DOSE TO TISSUES

14. The doses reported so far give the external dose-rates measured in air. To estimate the actual doses that have been received or will be received by individuals, the following factors must be taken into consideration.

Weathering

15. Some of the fall-out material on the surface of the earth is transferred by rain into lower layers of soil and also washed off hard surfaces such as roads and pavements. Measurements made in the United King-

dom¹⁴ showed that the slow penetration of Cs¹³⁷ into undisturbed soil reduced the external dose-rate by 20 to 30 per cent over four to five years; thus the external dose-rate decreased with an effective half-life of about ten years. Agricultural procedures which cause fission products to become uniformly mixed in the first 20 to 30 cm of soil will cause a considerable reduction in the total external dose from Cs¹³⁷ but the dose will subsequently decrease with the 30-year half-life of the nuclide. The attenuation of the external exposure due to cultivation is not however taken into account in this assessment. The effect of weathering will not be so important in the case of the short-lived fission products which will have decayed before any appreciable penetration into the soil. Snow will reduce the dose-rate of external radiation, and measurements carried out by Sievert² are shown in figure 4. Calculations of this effect have also been carried out.^{19, 28}

Shielding by building structures

16. External radiation is absorbed by building materials, and therefore doses received inside buildings will be less than those outside. This dose reduction factor has been estimated by making measurements in many different places inside buildings, whilst a Co⁶⁰ source was passed through a continuous polythene tube laid over the roof of and ground adjacent to several different types of buildings.²⁸⁻³¹ Fixed arrays of cobalt and caesium sources have also been used.¹⁴ Table III shows the wide range of shielding factors which have been experimentally derived and indicate the importance of the contribution to the dose on the top floor of a building due to the fall-out products on the roof.

17. The shielding factors may be slightly larger for fall-out, as the average gamma energy from fall-out is 0.7 MeV^{32, 34} whilst the energy from Co⁶⁰ is 1.1-1.3 MeV. To estimate the reduction in daily dose due to this shielding, an assumption must be made regarding the time spent in and out of doors. According to the information given in the United Nations *Demographic Yearbook, 1960*,³⁵ it is estimated that one-third of the world's population live in urban and two-thirds in rural communities. Assuming that the time spent out of doors is three and nine hours per day, respectively, a world average time out of doors of 7 hours per day is obtained. A shielding factor of 5 has been taken as the world average value, and with an average time spent indoors of 17 hours the over-all reduction of dose due to shielding has been taken as 0.4.

Screening by the human body

18. To obtain the doses received by different body organs it is necessary to allow for the attenuation by the intervening body tissues. Measurements conducted by Spiers³⁶ using sources over a 3 π geometry gave values as in table IV. This shows the screening factors to marrow, testes, and ovary for different energies of radiation. The factors agreed well with those theoretically derived by O'Brien.³⁷ The values of the screening factor for the gonads and bone marrow given in table IV are sufficiently similar for the mean energy of fission products of 0.7 MeV to justify applying an average value of 0.6 both to gonads and to bone marrow.

Combined shielding and screening factors

19. The combined effect of shielding and screening therefore produces a dose reduction factor of 0.2 which

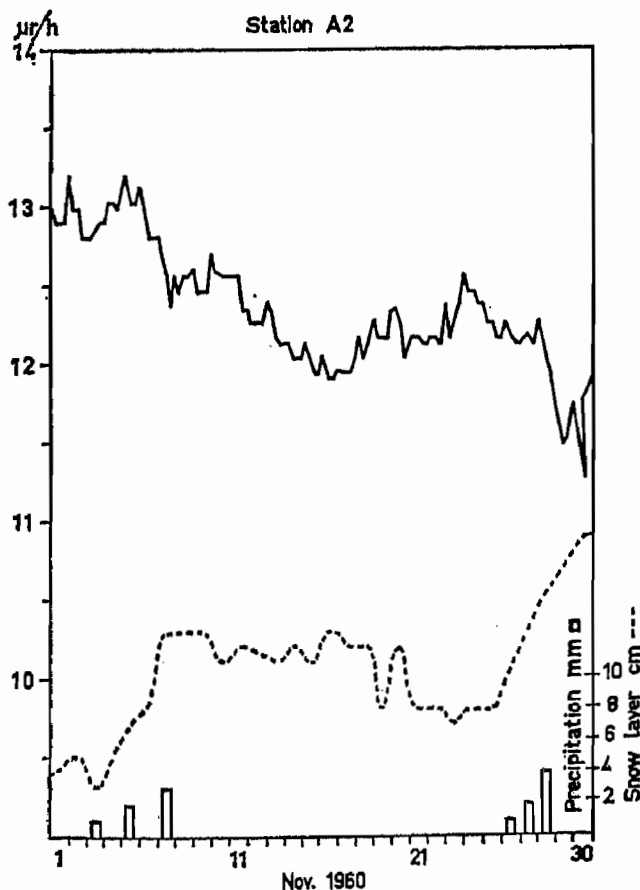


Figure 4a. Variations of the dose-rate during the falling of the snow

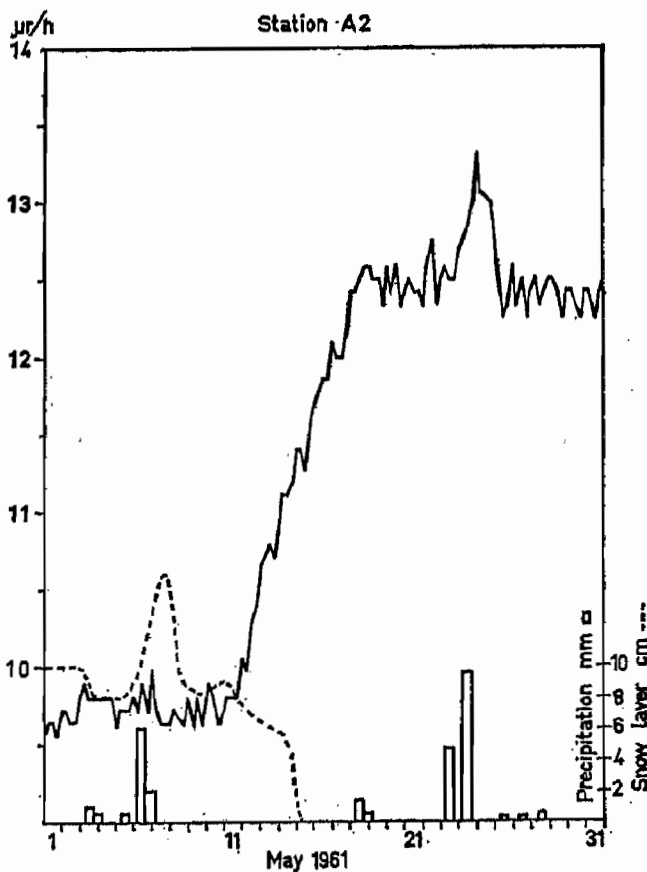


Figure 4b. Variations of the dose-rate during the melting of the snow layer

will be used to convert air doses to doses to the gonads and to the bone marrow. The value of 0.2 may be considered as a world average, and it must be emphasized that a wide range of values up to the maximum of 0.6 would obtain in particular countries, depending on the types of dwelling houses and the average time spent out of doors.

DOSES DUE TO EXTERNAL SOURCES

20. Comparison of published reports on doses is difficult owing to differing methods of calculation. The dose and dose-rate from fall-out have been given either from the total deposition on the ground or from the portion which has fallen out during a fixed period, ignoring past depositions.

21. The doses reported in the following sections are the population world average doses measured in air, and after presenting these the tissue doses will be derived by applying the shielding and screening factor of 0.2.

Total external dose in air received from testing from 1954 to August 1961

22. The measurements of the total external dose in Sweden and the United Kingdom given in figure 2a have been used to derive a population weighted external dose during this period. Graphical integration of these curves gives total air doses of 46 and 68 mrad respectively. These measurements were taken for areas in which the values for F_d/\bar{F}_d were approximately 1.5 and 1.9 for Sweden and the United Kingdom respectively. The mean population weighted external dose in air (for $\bar{G} = 1.9$) is therefore 63 mrad during this period. The total dose to the gonads and bone marrow during this period is therefore 13 mrem.

Total external dose commitment from testing up to the end of 1960 and the end of 1961

23. This estimate is made in two parts—the contribution from Cs^{137} and from short-lived products.

(a) *Caesium*¹³⁷. The estimate of ground level concentration of Cs^{137} may be deduced from annex F, part I, figure 37, which shows the total Sr^{90} deposit on the ground,* by using a relative yield factor for Cs^{137} of 1.7 and a geographical factor of 1.9. The air dose received up to the end of 1960 from Cs^{137} is therefore 10 mrad. Assuming an effective half-life of 10 years for Cs^{137} on the ground, the air dose received by mankind over all generations would be 80 and 92 mrad for testing ending in 1960 and 1961 respectively. The dose commitment for the gonads and bone marrow would therefore be 16 and 18 mrem for tests ending 1960 and 1961 respectively, and 92 and 94 per cent of these dose commitments would have been received by the year 2000.

(b) *Short-lived products*. It has been shown that the air dose up to August 1961 was 63 mrad and that Cs^{137} contributed 10 mrad, therefore it may be assumed that the dose commitment from short-lived products is $53 \times 0.2 = 10.6 \sim 11$ mrem for testing up to the end of 1960. The dose from short-lived products may be approximately calculated for further testing by using the ratios of the yields of Sr^{90} . Therefore the short-lived contribution due to testing up to the end of 1961, when according to the proposed model a further 1 Mc of Sr^{90} had been injected, would be $10.6 \times 7.6/6.6 \sim 12$ mrem.

* The Sr^{90} deposits have been estimated for a partial area of the earth of 471×10^6 sq km. F I, table XIV.

Combining the dose commitments from Cs^{137} and short-lived products, the total dose commitment due to external radiation would be 27 mrem and 30 mrem for tests ending 1960 and 1961 respectively.

Total external dose commitment which would be received under conditions of continued testing

24. (a) *Caesium*¹³⁷. From the continued testing conditions postulated in F I, 110 of 1 Mc Sr^{90} injected per year and allowing for an effective half-life of 10 years for Cs^{137} on the ground, an equilibrium deposit on the ground would exist when the fall-out rate of Cs^{137} equals the effective rate of removal of Cs^{137} from the superficial layer of the ground, i.e.

$$F_r = (\mu + \lambda) F_d(\infty)$$

where

μ = effective weathering constant

λ = radio-active transformation constant

$F_d(\infty)$ = fall-out deposit averaged over the surface of the earth

$$\text{i.e., } 3.4 = \frac{.693}{10} F_d(\infty)$$

$$\text{Therefore } F_d(\infty) = 49 \text{ mc/km}^2$$

Assuming that the geographical factor is 1.9 and the external dose rate from 1 mc/km² of Cs^{137} is 1 mrad/y, the air dose-rate would be 11 mrad/y. Therefore the dose commitment due to one year's testing would be 2.2 mrem (H 48).

(b) *Short-lived products*. The dose commitment 10.6 mrem has been received (paragraph 23) from injection of 6.6 Mc Sr^{90} and therefore the annual injection of 1 Mc Sr^{90} will give a dose commitment of 10.6 mrem from short-lived external deposit. No weathering factor needs to be used.

25. Therefore the total dose commitment from external radiation per year of testing is 3.8 mrem. It should be noted that the dose from short-lived products received in the immediately following years whereas the dose from Cs^{137} will extend over many years (table 1).

III. Internal exposure

26. Three types of internal exposure must be considered:

(a) Ingested radio-nuclides which are absorbed in the gastro-intestinal tract. The important fission products from this viewpoint are Sr^{90} and Cs^{137} and the short-lived radio-nuclides Sr^{89} , Ba^{140} and I^{131} . The manner in which they are absorbed and retained in the body is discussed in annex F, part II, paragraphs 2, 9-12, 31, 130-132, 153-154. In addition to fission products, neutron induced radio-nuclides C^{14} and H^3 must be considered, although the latter is of less importance;

(b) Ingested radio-nuclides in passage through the gastro-intestinal tract. These comprise those radio-nuclides which are either not, or only partially, absorbed and which cause irradiation of the mucosal lining of the GI tract;

(c) Inhaled radio-active particles. These will be deposited, depending on their size, into the upper or lower portions of the lungs where, if they are not removed by exhalation or ciliary action, they will irradiate lung tissue and particularly those cells in the immediate neighbourhood.

27. The appropriate basis for assessing the exposure of populations is discussed in annex H. A linear dose relationship is assumed; thus the mean tissue dose is used for estimating the risk to the population. On this basis the variation between individuals need not be considered. However, this would become important if a threshold concept were accepted.⁸⁸ Information on variability in intakes of Sr^{90} and Cs^{137} is given in annex F, part II, paragraphs 51-61. The problems associated with long-term retention and distribution of bone-seeking radio-nuclides in the skeleton, and with inhomogeneity of dose in individual bones are discussed in annex H. Observed variations in the concentration of Sr^{90} with age and in individual bones of the adult skeleton are described in annex F, part II, paragraphs 82-84.

Strontium-90

Concentrations in diet and bone

28. The data available up to the present time on the concentration of Sr^{90} in bone in children up to four years of age (F II, 80-89, tables XX, XXI) have been taken to represent the concentration in new bone in the population. It has been shown (F II, 31-36, 90, 91, table XXIV) that the ratio of Sr^{90} to calcium in this bone is about one quarter of that in diet. The OR (bone/diet) is therefore taken as 0.25. Hence future concentrations in new bone can be derived from the predicted levels in diet (F II, 103-107, 120, 121) which have been calculated from the models described previously (F I, 110).

Dose from Sr^{90} in bone

29. Several theoretical estimations of the dose received in bone and bone marrow from $1 \mu\text{Ci}$ of Sr^{90} per gram of calcium have been reported.²⁹⁻⁴⁵ These show that the dose to compact bone is about 2.7 mrem/y. The dose-rate at various distances from bone surfaces is shown in figure 5. For the purpose of the estimation of the β dose to cells lining bone surfaces it has been assumed in the present report that the β dose received is one half of the β dose within bone. The estimation of the dose in bone marrow cavities due to the incorporation of a β -emitting nuclide in the surrounding bone is complex. The energies of the β particles are distributed over a broad spectrum, and for each energy a specific range in bone and in soft tissues or a combination of the two must be considered. The dose to the bone marrow also depends on the size

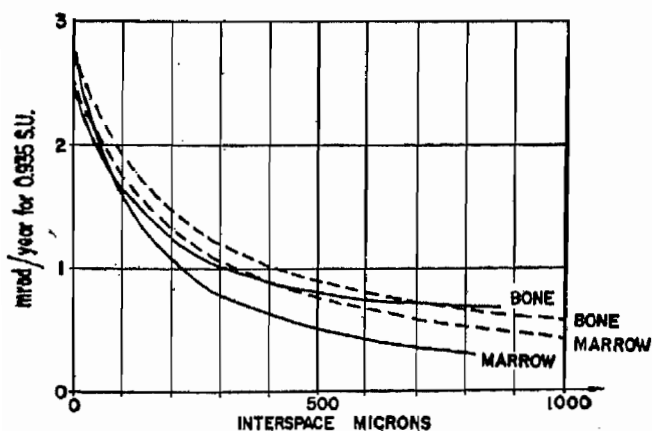


Figure 5. Central dose rates for infinite sandwich of bone slabs labelled with Sr^{90} , interleaved with 6 micron thick sheets of bone marrow.⁴⁴ The full lines give the data of Engström, Björnerstedt, Clemenson and Nelson,⁴⁰ the dotted lines the data of Libby.⁴⁵

of the marrow cavity and of the bone trabeculae. When the thicknesses of the trabeculae are less than the range of the β particles, electronic equilibrium conditions within the bone will not exist. The mean size of the marrow cavities in different bones varies, depending on the site, between 400-700 μ with maximum sizes as large as 1 mm in the vertebral bodies.⁴⁶ Table VI shows the comparison of bone marrow doses to bone doses for a 500 μ marrow cavity and three different trabeculae thicknesses. For $\text{Sr}^{90} + \text{Y}^{90}$ the mean value of the ratio bone marrow dose: compact bone dose for this size of marrow space is taken as 0.25, and the dose to bone marrow from $1 \mu\text{Ci}$ Sr^{90} /g calcium is taken as 0.7 mrem/y.

Method of estimation of mean population dose

30. Methods of estimation of the mean population dose due to long-term ingestion of Sr^{90} have been reported.^{10, 28, 47, 48} The estimation of mean population weighted doses to the above tissues has been carried out on the following basis. The major portion of the strontium is laid down during the growth years 0-20 and once deposited remains fixed after about the age of 2, except for the turnover of 1-10%/y due to exchange processes and bone resorption (F II, 81). Sr^{90} incorporated in the early years will therefore decay, leading to a total dose lower than if a constant new bone activity during the whole of the life is assumed. A factor F , called the dose increment factor, is introduced to take into account the rate of bone accretion and the radio-active decay of the nuclide. The factor F for Sr^{90} has been derived by Lindell,⁴⁹ and figure 6 shows the values for various conditions of bone growth and resorption. A value of $\bar{F} = 0.6$ is used in this report for Sr^{90} , representing the average value of the resorption rates. Therefore the bone dose actually received by an individual over his whole

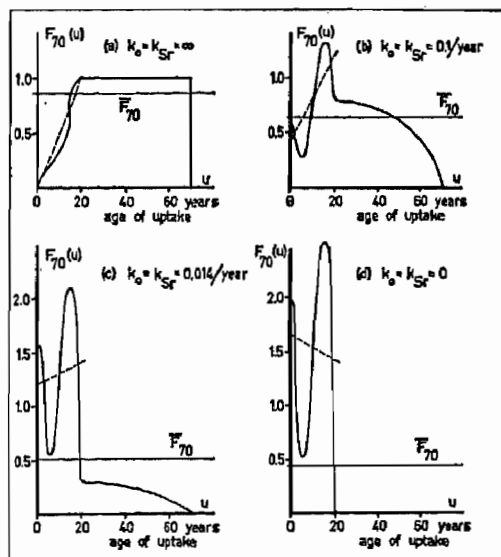


Figure 6. The dose increment factor $F_{70}(u)$ for an expected life span of 70 years, as a function of age of uptake.

- Extreme case of instantaneous equilibrium between bone and environmental Sr^{90} , with infinite turnover constant.
- Biological half life for Sr and Ca assumed to be 7 years ($k_{\text{Sr}} = 0.1/\text{year}$).
- Biological half life for Sr and Ca assumed to be 50 years ($k_{\text{Sr}} = 0.014/\text{year}$). Note the increasing importance of uptake and retention in childhood, and the reduced uptake in the adult.
- Essentially no Sr and Ca turn-over. Uptake only during bone growth in childhood.

lifetime, assuming a constant contamination, may be deduced from the following expression which also gives the dose commitment from any given pattern of contamination.

$$D_t = \bar{F} \gamma \int_0^t c(t) dt \quad (2)$$

where

D_t = total dose in mrem

\bar{F} = dose increment factor (assumed average value 0.6)

γ = dose-rate for unit concentration (2.7 mrem/y/ $\mu\mu\text{C Sr}^{90}$ /g Ca to bone, 0.7 mrem/y/ $\mu\mu\text{C Sr}^{90}$ /g Ca to bone marrow)

$c(t)$ = Ratio Sr^{90}/Ca in the salts entering bone ($\mu\mu\text{C Sr}^{90}$ /g Ca, assumed equal to $0.25 \times$ diet concentration)

31. Estimates of doses from Sr^{90} are based on data to be found in other sections of this annex. The total depositions and fall-out rates arising after various periods of testing are shown in annex F, part I, figures 37 and 38 respectively. The levels of Sr^{90} in bone in the years 1954-1960 are reported in annex F, part II, tables XX and XXIV. Future concentration in the three types of diet and in bone are given in annex F, part II, paragraph 121, and are based on the proportionality factors given in annex F, part II, table XXVII, and the future levels of Sr^{90} fall-out rate and deposit, assuming that for the latter there will be a 2%/y reduction due to the effects of weathering and agricultural procedures and to the removal of strontium from the soil by crops (F II, 120).

Dose commitment from Sr^{90} due to testing carried out up to the end of 1960 and the end of 1961

32. The bone dose received up to August 1961 has been estimated on the basis of the population weighted average values of the Sr^{90} to calcium ratio in the bones of children up to four years of age for each year from 1959-1960. These values have been calculated from the data of annex F, part II, table XX, and are given in table VII. Allowance has been made for the number of samples and the populations represented. The approximate nature of these values, in view of the large populations unrepresented, or represented by very few values, must however be recognized. The contribution to the dose commitment—formula (2)—received by bone cells is 12 mrem, by cells lining bone surfaces 6 mrem, and by the bone marrow 3 mrem.

33. Future levels of Sr^{90} in the approximate model diets are given in annex F, part II, paragraph 120, for tests up to 1960 and 1961. From these a world average concentration has been obtained by weighting the values for each diet by population and geographical distribution, assuming that the latitudinal distribution of fall-out will repeat the pattern observed so far. The diet types for populations and the F_d/\bar{F}_d ratios used are shown in table VIII. Obviously some gross assumptions have had to be made in view of the lack of more exact information, but it may be noted that the values of concentration calculated for different diets do not differ by more than a factor of 2 (F II, figure 6). The population weighted average diet is derived by adding together for each diet the values obtained by the following formula:

$$\frac{\sum N_i \times F_d/\bar{F}_d}{\sum N_i} \text{Concentration Diet}$$

where N_i is population given in table VIII, column 3, and F_d/\bar{F}_d , given in column 4, is defined in paragraph 4.

The composite population weighted diet and the corresponding bone concentrations in different years are given in figure 7.

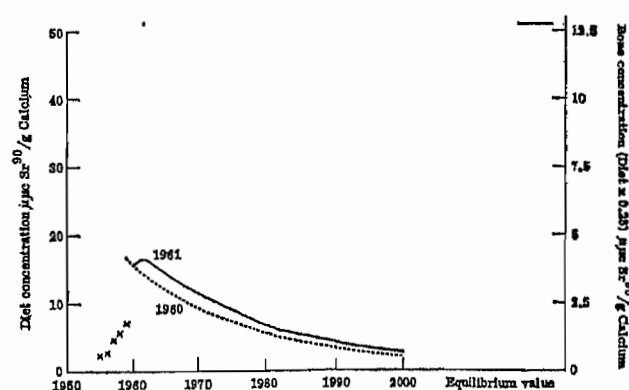


Figure 7. Population weighted concentrations of Sr^{90} in diet and bone for testing up to the end of 1960 and to the end of 1961
X Measured Sr^{90} in the bones of children 0-4 years old (F II, table XX)

34. The dose commitments to bone cells, to cells lining bone surfaces, and to the bone marrow, have been calculated using formula (2) and the graphically integrated curve of bone concentration given in figure 7. When combined with the contribution to the dose commitment derived from measured data up to 1960 (para. 32), the dose commitments to bone cells, cells lining bone surfaces and bone marrow are 133, 67, and 33 respectively, for testing up to the end of 1960. The dose commitments are 158, 79, and 40, respectively, for testing carried out up to the end of 1961 at the assumed rate. By the year 2000 some 91 and 92 per cent of the dose commitment would have been reached for tests ending in 1960 and 1961 respectively.

Dose commitment from Sr^{90} which would be received under conditions of continued testing

35. The population weighted world average concentration in diet and bone resulting from continued testing has been calculated from the predicted levels in the three approximate model diets using the method described previously, and is given in figure 7.

36. The dose commitment from one year of testing to bone cells, to cells lining bone surfaces, and to the bone marrow would be 21, 11 and 5 mrem, respectively. The dose commitments from Sr^{90} for the three conditions of testing are summarized in table XI.

Cs^{137} in whole body and bone

37. The biological half-life of Cs^{137} is four months, and therefore the body will reach an equilibrium with the diet after a few months' delay. The distribution is reasonably uniform throughout the whole of the soft tissues, but a slightly higher concentration in bone has been observed (F II, 130-133, 140-145). Dose estimates are therefore required both for the gonad dose and for the bone and bone marrow dose. Measurements⁴⁰ of the content of Cs^{137} in specimens from 114 subjects have shown a ratio of 2.2 between bone (including marrow) and muscle. This higher concentration of Cs^{137} in bone leads to a bone marrow dose 30 per cent higher than soft tissue doses if the same model of marrow cavity size as in paragraph 29 is used. The difference in concentration, however, has not been confirmed in other reports.

38. The dose calculations may be carried out in terms of the dose-rate from $1 \mu\mu\text{Cs}^{137}/\text{g}$ of soft tissue or that from $1 \mu\mu\text{Cs}^{137}/\text{g}$ of potassium. Values have been reported for the former in the range 7.3-11 mrem/^{29, 28, 50} and a mean value of 10 mrem/y will be used in the present report. The differences between these figures are due to the method of calculation of the gamma-ray contribution to the body dose. The dose-rates to bone cells and to bone marrow are therefore 22 and 13 mrem/y on the basis of the measurements reported⁴⁹ and the dose to cells lining bone surfaces has been taken as 18 mrem/y. Since there are about 140 g of potassium in a 70 kg man, $1 \mu\mu\text{Cs}^{137}/\text{g}$ potassium will deliver 0.044, 0.036 and 0.026 mrem/y to bone cells, cells lining bone surfaces and bone marrow respectively.

Dose commitment from internal exposure to Cs^{137} due to testing up to the end of 1960 and the end of 1961

39. The mean value of the whole body measurements for the years 1958-1960 was $60 \mu\mu\text{Cs}^{137}/\text{g K}$ (F II, table XXXIII). Assuming that this level had been maintained for five years, the contribution to the dose commitment to bone cells, cells lining bone surfaces, bone marrow, and to the gonads are 13, 11, 8 and 6 mrem respectively.

40. With a discontinuation of the tests, the levels of Cs^{137} in the body would be expected to decline in a manner similar to that observed in late 1959 and in 1960 (F II, 146-149). By extrapolation from the data in annex F, part II, figure 8, it can be estimated that the concentration of Cs^{137} in the body will be reduced to one-tenth in about 3 years after the cessation of tests. This corresponds to an effective mean life of Cs^{137} of 1.4 years. Therefore the dose commitment from Cs^{137} for testing up to the end of 1960 was 17, 14, 10 and 8 mrem for bone cells, cells lining bone surfaces, bone marrow and gonads, respectively. The dose commitment from testing up to the end of 1961 may be estimated by adding the dose commitment from one year of testing to these values (para. 41).

Dose commitment from internal exposure to Cs^{137} under conditions of continued testing

41. In annex F, part II, paragraph 150, limits have been set to the magnitude of the resultant internal radiation dose in relation to the external dose from this nuclide. The dose commitment for internal Cs^{137} from one year of testing is assumed to be equal to

$$\text{Internal } \text{Cs}^{137} \text{ dose 1959} \times \frac{\text{Cs}^{137} \text{ deposit at equilibrium}}{\text{Cs}^{137} \text{ deposit 1959}}$$

The dose commitment from one year of testing is therefore 6.6, 5.3, 3.9, 3.1 mrem for bone cells, cells lining bone surfaces, bone marrow and gonads.

C^{14} in whole body

42. The natural rate of formation of C^{14} is 3.22×10^{28} atoms C^{14}/y . The radiation doses to tissues from naturally occurring C^{14} in nature are given in annex E,

$$D_t = 0.25 r_o \int_0^t (0.96 e^{-0.0209t} + 0.04 e^{-0.000125t}) dt = 11.4 r_o (1 - e^{-0.0209t}) + 79 r_o (1 - e^{-0.000125t}) \quad (6)$$

This expression can only be expected to give approximate values, as it is based on a highly simplified model

paragraph 82. The average dose to the whole body is 1.06 mrem/y, and, as a consequence of their different carbon contents, the dose to bone is 1.64 mrem/y and that to soft tissue 0.71 mrem/y. Therefore the dose produced by a known amount of C^{14} formed during weapon testing may be estimated by direct comparison with the rates of production of naturally occurring C^{14} and with the resulting doses.^{47, 51-54} The dose commitment, which may be estimated with reasonable accuracy this way, will be received over many generations, as the mean life of C^{14} is 8,000 years, but estimates of the dose to this generation necessitate the use of the limited data described in annex F, part I, paragraph 118, regarding the distribution of C^{14} in nature.

43. The dose-rate r from N_I atoms of artificially produced C^{14} in reservoir I (i.e., the atmosphere and surface waters of the ocean) therefore will be

$$r = r_o \frac{N_I}{N_{I_o}} = \frac{r_o Q}{N_{I_o}} f(t) \quad (3)$$

where

r_o = annual dose from naturally occurring C^{14}

N_{I_o} = number of C^{14} atoms in reservoir I
= 86×10^{27} atoms C^{14}

Q = number of atoms formed

$f(t)$ = distribution of C^{14} into the other C^{14} reservoirs with time

Therefore the dose in a given time t may be obtained by integration

$$D_t = \frac{r_o Q}{N_{I_o}} \int_0^t f(t) dt \quad (4)$$

$\int_0^t f(t) dt$ is expressed algebraically in F I, 118, on the basis of the observed distribution of C^{14} in nature.

Dose commitment from C^{14} due to testing up to the end of 1960 and the end of 1961

44. The total C^{14} formed by weapon testing up to August 1961 is estimated as 22×10^{27} atoms (F I, table XVII). Therefore the dose commitment may be calculated from the naturally occurring C^{14} formation rate and consequent dose-rates. Using the symbols given in paragraph 43

$$D_\infty = r_o \frac{Q}{\beta} \quad (5)$$

where $\beta = 3.22 \times 10^{28}$ atoms C^{14}/y . Therefore the dose commitment due to testing up to the end of 1960 to the bone cells, cells lining bone surfaces, bone marrow and gonads is 111, 80, 48 and 48 mrem respectively. Similarly, the dose commitment due to testing to the end of 1961 when, according to the model, a further 10^{28} C^{14} atoms have been injected, would be 162, 116, 70 and 70 mrem respectively to the same tissues. The portion of the dose commitment received in any period of time may be estimated by using formula (4). It is shown in annex F, part I, paragraph 118, that for an injection of 22×10^{27} atoms this equation is as follows:

of the transport of the C^{14} in the atmosphere and oceans. The gonad dose given by formula (6), which will be

received by the year 2000, is 5 mrem, i.e., 10 per cent of the dose commitment.

Dose commitment from C^{14} due to continued testing

45. Under conditions of continued testing it is assumed in annex F, part I, paragraph 119, that 10^{28} C^{14} atoms are injected annually. From one such injection the dose commitment is 51, 37, 22, 22 mrem to the bone cells, cells lining bone surfaces, bone marrow and gonads respectively. Only 10 per cent of this dose however will be received in the next fifty years.

Reduction of dose from C^{14} due to combustion of fuels

46. The increasing combustion of fossilized fuels, such as oil and coal, results in a reduction in the specific activity of the C^{14} in the atmosphere due to the addition of " C^{14} -free" carbon dioxide. This effect is called the Suess effect and is described in annex F, part I, paragraph 68.

47. According to Suess⁵⁵ the average rate of combustion of these fuels since 1950 is 82×10^{11} kg/y. This rate is increasing with a doubling time of 20 years so that by the year 2000 the rate may be 5-6 times higher.

48. The total CO_2 content of the atmosphere is 21×10^{14} kg, and, since the start of industrial coal combustion, some 14 per cent of this amount has been injected into the atmosphere. With the above input rates it is estimated that the total amount of carbon added by the year 2000 will be 50 per cent of the atmospheric reservoir. The average residence time given by Suess for a carbon atom in the atmosphere is only 10 years before it is transferred to the ocean. Therefore the present decrease in specific activity of the atmosphere due to this cause is only about 2 per cent which corresponds to a total input of 14 per cent. By integration, it is calculated that the decrease in specific activity by the year 2000 will be about 6 per cent corresponding to the 50 per cent total input. This effect would therefore cause a corresponding reduction in the gonad doses from C^{14} which may be received by the year 2000.

H^3 in the body

49. The natural level of tritium in water is 5×10^{-18} tritium atoms per hydrogen atom, and the soft tissue dose corresponding to this level is 1.8×10^{-8} mrem/y. Tritium is formed in the process of the explosion of a fusion type weapon (F I, 18). On several occasions since 1953, in the northern hemisphere the tropospheric concentration of tritium in rain water⁵⁶⁻⁵⁹ has been observed to be approximately a hundred times greater than the normal. However, these levels are greatly reduced by dilution in the mixed surface layers of the ocean. This effect, as well as the relative short half-life of 12 years and the low energy beta-radiation of tritium, accounts for the dose levels to soft tissue being very low.⁴⁷

Short-lived isotopes

50. Consideration is given here to the doses to the GI tract, to the lungs, as well as to the concentrations in the body of Sr^{89} , $Ba^{140} + La^{140}$ and I^{131} .⁶⁰⁻⁶² These have half-lives of 51, 12, 8 days respectively. The concentrations of the short-lived isotopes in milk follow the pattern of weapons testing (F II, 151-155) but vary depending on the time involved between the explosion and contamination of the vegetation. The available information on the levels of short-lived fission products in man is not sufficient for accurate estimation of the radiation doses. Many of the following dose calculations are based on

the estimated levels of these nuclides in the diet.

Sr^{89} in bone

51. Because the metabolism of Sr^{89} is the same as that of Sr^{90} , the radiation dose from Sr^{89} can be estimated from that for Sr^{90} on the basis of the ratio of the two nuclides in diet and the relative magnitude of the tissue doses caused by the ingestion of 1 μ c of each nuclide.

52. The radiation dose-rate from 1 μ c Sr^{89} /g Ca maintained in bone is 1.5 mrem/y and 0.33 mrem/y to bone marrow. This latter value is interpolated from the data given by Björnerstedt⁴⁸ who showed that for a 0.5 MeV β -emitter the average dose to bone marrow is 17 per cent of the dose to bone, whilst for $Sr^{90} + Y^{90}$ it is 25 per cent (para. 29). The mean dose increment factor \bar{F} for Sr^{89} is .005.

53. During the years 1955-1960 the mean concentration of Sr^{90} in bone was 1.3 μ c/g Ca and the average world concentration of Sr^{89} in rainfall was about ten times that of Sr^{90} .⁶³ The Sr^{89}/Sr^{90} ratio in milk measured in the United Kingdom, Canada and the United States during 1958 showed that the activity in milk approached half of that in rain.⁶⁴ Assuming the level in milk corresponds to that in diet type I, and that the concentration in bone depends mainly on the rate of fall-out, the total dose can be calculated from formula (2) (para. 30) for the years 1954-1960 in which 6.6 Mc Sr^{90} were injected into the stratosphere. The resulting population weighted dose to bone due to Sr^{89} from an injection of 1 Mc Sr^{90} would be 0.05 mrem and that to bone marrow 0.01 mrem. These values represent the dose commitment from Sr^{89} since the total dose from this isotope is received in one year. They are less than 1 per cent of the dose commitment from Sr^{90} .

54. There are very few data on the Sr^{89}/Sr^{90} ratio in bone. A series of United Kingdom measurements for the latter half of 1957 showed an average value of 2.3 for post-mortem specimens from some 60 children in age range 0-4 years.⁶⁵ At the time of death the resulting dose-rate from Sr^{89} in this bone was therefore approximately equal to that from Sr^{90} . In view of the ratios of their half-lives, the dose commitment for Sr^{89} would thus be less than 1 per cent of that for Sr^{90} . This is in reasonable conformity with the dietary estimates given in the previous paragraph.

Ba^{140} and La^{140} in bone

55. Since the metabolism of barium is very similar to that of strontium, the dose to bone from Ba^{140} and La^{140} can be considered in the manner adopted for Sr^{89} in paragraph 53. The fission yields of Ba^{140} and Sr^{89} are very similar, although the disintegration energy of $Ba^{140} + La^{140}$ is about twice that of Sr^{89} . However, the uptake of barium from the GI tract both in the cow and in man is much smaller than that for strontium and the shorter half-life will make for greater decay before its entry into diet.^{61, 62} On account of these considerations, the dose commitment from $Ba^{140} + La^{140}$ is much smaller than that from Sr^{89} and is accordingly neglected.

I^{131} in thyroid

56. Measurable levels of I^{131} have been found in the thyroid glands of man and animals soon after the detonation of nuclear weapons.⁶⁶⁻⁷⁰ I^{131} enters the body mainly in fresh foods; milk is the predominant source in many areas. As a result of tests conducted in the autumn of 1961, the average concentrations in milk produced in the United Kingdom⁷¹ and the United

States^{72, 73} were 110 and 135 $\mu\text{C}/\text{l}$ respectively over a period of ten weeks. Thereafter the levels declined rapidly (F II, figure 11).

57. The radiation dose to the thyroid varies greatly depending on the age of the subject and the nature of the diet. Because of their higher absorption of iodine and of the smaller size of their thyroid glands infants receive a considerably larger dose than adults from the same intake of I^{131} .¹⁴ Furthermore, if infants are fed on fresh milk, their intake of I^{131} may exceed that of adults. However, even in countries where milk is a major component of their diet, many children are fed largely or entirely on prepared milk products in which the I^{131} will have decayed so that the exposure of their thyroid glands is correspondingly reduced.

58. The pattern of distribution of short-lived activities is very different from that of long-lived materials and consideration is here confined to areas where the deposition of iodine is appreciable. Moreover, the pattern of deposition of iodine may be very different for different conditions of explosion. For reasons explained in annex F, part I, paragraph 37, it is assumed that the pattern of deposition of I^{131} observed in the autumn of 1961 will occur with each annual injection of 1 Mc Sr^{90} . This deposition led to a mean level of 125 $\mu\text{C}/\text{l}$, as averaged over a period of ten weeks in the United States and the United Kingdom, and this figure is used as a basis for calculation (table IX). Children under the age of one year who consumed 0.5 litre per day of fresh milk may have received a total dose of about 170 mrem, while adults taking half this quantity of milk have received only 4 mrem. In some countries the intake of fresh milk by young children appreciably exceeds the value assumed in table IX though elsewhere their intake is considerably lower.

Mixed fission products in the GI tract

59. The dose to the GI tract is determined by the quantity of fission products entering the body by ingestion and inhalation. No direct measurements of this quantity are available, however. Some gamma spectrometer measurements of faecal samples⁷⁴ were carried out in the United Kingdom in April-May 1959, which was the period of highest fall-out contamination in air in that year. The United Kingdom measurements showed an average daily excretion of 150 $\mu\text{C}/\text{day}$ in 214 g faeces in addition to the total natural potassium activity of 577 $\mu\text{C}/\text{day}$. Allowing for there being some beta-active nuclides that are not gamma-emitters, the dose-rate in the faecal material would be about 10 $\mu\text{rad}/\text{day}$ and about half this for the adjacent tissue in the lower large intestine, which is the part of the GI tract sustaining the greatest dose. The estimated excretion of Zr^{95} , which is not appreciably taken up through the GI tract, was 10 $\mu\text{C}/\text{day}$ and it is noteworthy that the average inhalation of this isotope over the period January-June 1959 was 12 $\mu\text{C}/\text{day}$. During this period also the total inhalation averaged 100 $\mu\text{C}/\text{day}$ beta activity compared with the estimated excretion of 150 $\mu\text{C}/\text{day}$ of gamma activity in the two-week period of the measurements; the intake during this period may well have been higher than the average.

60. The measurements suggest that the dose-rate to the lower large intestine was less than 2 mrem/y during this period of very high air contamination, and that the average dose over the five-year period 1955-1959 was less than 1 mrem per year. These calculations suggest

that the dose to the lower large intestine from this cause is negligible.

61. An alternative approach would be to use the fact that during 1958-1959 in the United Kingdom less than 10 per cent of the body intake of Sr^{90} arose from contamination of water and air. If it is assumed that the intake of strontium arising from air and water was accompanied by mixed fission products of age greater than one month, the dose to the GI tract can be computed by the method of Greitz⁷⁵ as about 1 mrem/y. This value is in conformity with that derived in the previous paragraph.

ENTRY OF RADIO-ACTIVITY INTO THE BODY THROUGH INHALATION

62. The average daily inhalation of certain fission products in the United Kingdom during the years 1957-1960 is given in table X¹⁴ and the concentration in ground level air is presented in annex F, part I, figures 10 and 11. The average daily amounts of Ce^{141} , Ce^{144} and Zr^{95} inhaled in March to June 1958 have been reported as 8.8, 6.6 and 8.9 μC respectively.⁷⁶⁻⁷⁸

63. When particles are inhaled into the lungs, some are exhaled again, whilst of the remaining ones the larger are mainly swallowed and ingested and the finer may be retained within the lung tissues for considerable periods of time. Knowledge of their movement within the lungs, however, is very limited. Because of the small range of β -rays, very high doses occur in tissue in contact with these particles.⁷⁹

64. The average dose-rates to the lungs may be deduced following the approach used by the ICRP.⁸⁰ The average dose to the lungs from the concentrations of Ce^{141} , Ce^{144} and Zr^{95} reported above would be 0.14, 2.6 and 0.7 mrem/y respectively. From the world average concentration of Sr^{90} in ground level air (F I, 56) the annual dose-rate would be about 1 mrem/y. Analyses of a number of post-mortem specimens^{80, 81} showed in 1959 that lungs contained total activities of Zr^{95} , Ru^{103} , Ce^{144} of 0.36, 0.6 and 0.02 $\mu\text{C}/\text{g}$ respectively. These would give average dose-rates to the lungs of 3.2, 1.3 and .05 mrem/y respectively.

65. A dose-rate to the lungs of 5 mrem/y may occur during periods of testing but further information is required to obtain the average dose over prolonged periods of time.

66. Some measurements have also been made of concentrations in pulmonary lymph nodes,¹⁴ and concentrations 12-64 times those of lung tissue have been reported.⁸¹

SUMMARY OF RADIATION DOSES TO TISSUES DUE TO FALL-OUT

67. Table XI shows the dose commitments to the population (H 15-21) for the periods of testing 1954-1960 and 1954-1961, respectively. The values for these two periods differ owing to the assumption made in the illustrative model proposed in annex F, part I, paragraphs 110 and 119 that an injection of 1 Mc Sr^{90} and the formation of 10^{28} atoms of C^{14} occurred in the year 1961. The fraction of the dose commitment reached by the year 2000 is also given. This fraction represents the dose received by a particular tissue to that date plus the dose that will be received from radio-active materials which

are already incorporated within the tissue. It excludes however any dose due to radio-active materials in the environment which have not yet been incorporated into body tissues. The last column of the table gives the dose commitments due to one year's injection according to the proposed model. These may therefore be used as

units to derive dose commitments from a given practice of testing when the actual injections of Sr^{90} and formation of C^{14} are known. The values given in the table must be considered as indicative rather than as accurate estimates because of the many assumptions on which the computation rests.

TABLE I. PRODUCT OF GAMMA-RAY DOSE CONSTANTS $k_1 \times B_1$ FOR CERTAIN RADIO-ISOTOPES BY VARIOUS WORKERS

Isotope	$k_1 \times B_1$ in mrad/y per mc/km ²				
	Gustafson ⁷	Loutifi ¹⁴ et al.	Mahmoud ^{15*}	Collins ^{12*} et al.	Suggested value
Zr ⁹⁵	0.14**	0.129	0.082	—	—
Nb ⁹⁵		0.137	0.085	—	—
Zr ⁹⁵ + Nb ^{95***}		(0.46)	(0.29)	0.35	0.5
Ru ¹⁰³	0.046	0.091	0.055	—	0.1
Ru ¹⁰⁶	0.019	0.031	0.018	0.025	0.04
Sb ¹²⁵	—	—	—	—	0.06
I ¹³¹	—	—	—	—	0.05
Cs ¹³⁷	0.056	0.11	0.06	0.077	0.12
Ba ¹⁴⁰ + La ¹⁴⁰	—	—	—	—	0.03 + 0.13
Ce ¹⁴¹	0.005	0.008	0.008	—	0.01
Ce ¹⁴⁴	0.004	0.009	0.003	0.008	0.01

* Does not include contribution due to build-up factor, i.e., values are for k_1 only.

** Contribution due to 1 mc Zr⁹⁵ plus 1 mc Nb⁹⁵.

*** Contribution due to 1 mc Zr⁹⁵ plus 2.4 mc Nb⁹⁵ (transient equilibrium conditions).

TABLE II. AIR DOSE-RATES AT 1 METRE FROM GROUND FROM RADIO-NUCLIDES IN EQUILIBRIUM FOR VARIOUS ATMOSPHERIC RESIDENCE TIMES AND CONSTANT Cs¹³⁷ FALL-OUT RATE OF 6 mc/km²/y.

Atmospheric residence time		mrem/y									
Half- days	Mean- years	Zr ⁹⁵ -Nb ⁹⁵	Ru ¹⁰³	Ru ¹⁰⁶	Sb ^{125**}	I ¹³¹	Ba ¹⁴⁰ -La ¹⁴⁰	Ce ¹⁴¹	Ce ¹⁴⁴	Total	Cs ¹³⁷
25.....	0.1	85.7	15.7	4.3	0.58	0.3	5.3	1.7	1.7	115.3	31.2* or 12
63.....	0.25	45.5	5.8	3.9	0.55	—	0.3	0.7	1.6	58.4	
126.....	0.5	17.3	1.2	3.3	0.51	—	—	0.1	1.3	23.7	
247.....	1.0	2.5	0.5	2.3	0.43	—	—	—	0.8	6.5	
2.5y.....	3.6	—	—	0.4	0.18	—	—	—	0.1	0.7	
90% equilibrium set up after years		0.6	0.4	3.3	6.7	0.07	0.12	0.3	2.6		100 or 33*

* These values depend on whether a 30 y or a 10 y half-life is assumed for Cs¹³⁷, i.e., if weathering is not or is allowed for. The equilibrium concentrations would be 261 and 97 mc/km² respectively.

** The value used for the yield of Sb¹²⁵ is 0.24 which is a mean value of the yield between the fission neutron and 14 MeV neutron fission of U²³⁵ (F I, table I).

TABLE III. SHIELDING FACTORS

	Floor	Construction		Shielding factors
		Wall thickness	Roof thickness	
Large building ^{30*}	Basement	41cm concrete		500-10,000
	First†	20cm concrete 11 cm brick		80-100
	Second	20cm concrete 11cm brick		200-300
	Third	20cm concrete 11cm brick		250
	Floor directly under roof		20cm concrete	100
			5cm insulation 10cm concrete 5cm insulation	50
Houses				
Concrete block ³¹	Basement	15cm concrete		14
	First†			3.9
Brick ³⁴		22cm brick		8-35 (av. 20)
Cemento and wood ^{31**}	Basement	4cm concrete and 1.3cm wood, or	2.5cm asphalt paper	12.2
	First†	4cm wood above windows	2.5cm insulation 1.3cm plaster	2.5
Wood frame ^{31***}	Basement	5cm wood		13
	First†			2.5
Light shielding Japanese house ³²				1-2

† The first floor is the floor at ground level or just above in case of semi-basement house.

* Average conditions exist beyond 8 ft. from inner surface exterior wall. Dose rate $\times 5-10$ times higher inside of window opening $\div 2$ on first floor below window-sill level.

** Average of 4 houses assuming contribution from infinity.

*** Average of two houses.

Note: The effect of sloping ground has little effect on the shielding factors. The effect of having sources close to buildings only, ignoring remote sources, increases the figures up to plus 1.

TABLE IV. SCREENING FACTORS OF THE HUMAN BODY DETERMINED BY 3π GEOMETRY WITH OMNIDIRECTIONAL RADIATION

	MeV				
	0.2	0.5	1.0	1.5	2.0
Marrow.....	0.57	0.61	0.65	0.69	0.75
Testes.....	0.57	0.61	0.67	0.73	0.78
Ovary.....	0.47	0.50	0.56	0.61	0.66

TABLE V. POPULATION WEIGHTED GONAD AND BONE-MARROW DOSES (ASSUMED EQUAL) DUE TO EXTERNAL RADIATION FROM FALL-OUT ($G = 1.9$)

	Short-lived mrem	Cs^{137} mrem	Total mrem
Doses received from 1954-August 1961 (based on measurements).....	11	2	13
Estimated dose commitment from testing up to the end of 1960.....	11	16	27
Fraction by year 2000.....	1.0	0.94	0.97
Estimated dose commitment from testing up to the end of 1961.....	12	18	30
Fraction by year 2000.....	1.0	0.92	0.95
Total dose received by mankind in all generations per year of testing (1 Mc Sr^{90} /y).....	1.6	2.2	3.8

TABLE VI. RATIO OF MARROW DOSE TO BONE DOSE FOR BONE CONTAINING Sr^{90}

Size of marrow cavity	Thickness of trabeculae	Marrow dose Bone dose	Source
500 μ	70 μ	0.23	Björnerstedt (Theoretical) ⁴⁴
500 μ	125 μ	0.26	Spiers (Experimental) ⁴⁹
500 μ	100 μ	0.28-0.31	Libby (Theoretical) ⁴⁵

TABLE VII. THE CONCENTRATION OF Sr^{90} IN 0-4 y OLD BONE BASED ON
ANNEX F, PART II, TABLE XX

$\mu\text{c/g Ca}$		$\mu\text{c/g Ca}$	
1955.....	0.6	1958.....	1.4
1956.....	0.7	1959.....	1.8
1957.....	1.2	1960.....	1.8

TABLE VIII. ASSUMED DIET TYPES, POPULATIONS AND F_d/\bar{F}_d RATIOS USED TO COMPUTE
A POPULATION WEIGHTED WORLD DIET (F II, table XXIV)

Assumed diet type	Area	Population N_i $\times 10^6$	F_d/\bar{F}_d
I	N. America	220	2.3
	Europe	622	2.0
	Oceania	15	0.5
II	Near East	65	2.3
	Asia (India)	400	2.3
	S. America	136	0.5
	Africa	247	0.6
III	Asia and Far East	765	2.3
—	C. America	40	1.5

From these values a population weighted world average diet is derived as the sum of concentration diet I $\times 0.7$, concentration diet II $\times 0.5$, concentration diet III $\times 0.7$.

TABLE IX. ESTIMATED DOSES TO THE THYROID GLAND FROM I^{131}

It is assumed that the average level of I^{131} in milk is 125 $\mu\text{c/l}$ over a period of ten weeks (para. 58).

Age y.	Quantity of fresh milk consumed per day (litres)	Thyroid dose mrem	Age y.	Quantity of fresh milk consumed per day (litres)	Thyroid dose mrem
0.5.....	0.5	170	10.....	0.25	25
3.....	0.25	45	Adult.....	0.25	4

TABLE X. AVERAGE DAILY INHALATION OF FALL-OUT NUCLIDES IN VARIOUS YEARS IN THE UNITED KINGDOM

	Micro-microcuries per day						
	1955	1956	1957	1958	1959 Jan.-June	1959 July-Sept.	1959 Oct.-Dec.
Total beta fission products.....	13.3	20	32	57	100	17	4
Cs^{137}	0.22	0.24	0.26	0.36	1.1	0.43	0.12
Sr^{90} (calc.).....	0.13	0.14	0.15	0.21	0.65	0.25	0.07
Zr^{95}	—	—	3.9 ^a	6.2	12	0.8	0.06
I^{131}	—	—	—	3 ^b	—	—	—
Pu^{239} (calc.).....	0.0020	0.0021	0.0023	0.0032	0.010	0.0038	0.0011

^a August-December.

^b October-November.

TABLE XI. DOSE COMMITMENT FROM NUCLEAR TESTING

Tissue	Source of radiation		Para.	Dose commitment for period of testing 1954-1960		Dose commitment for period of testing 1954-1961		Dose commitment per year of testing ^a mrem
				Total mrem	Fraction of dose com- mitment 2,000	Total mrem	Fraction of dose com- mitment 2,000	
Gonads.....	External	Short-lived	23,24	11	1.0	12	1.0	1.6
		Cs ¹³⁷	23,24	16	0.92	18	0.94	2.2
	Internal	Cs ¹³⁷	39-41	8	1.0	11	1.0	3.1
		C ¹⁴	44,45	48	0.10	70	0.10	22
				83	0.47	111	0.42	29
Cells lining bone surfaces.....	External	Short-lived	23,24	11	1.0	12	1.0	1.6
		Cs ¹³⁷	23,24	16	0.92	18	0.94	2.2
	Internal	Sr ⁹⁰	32-36	67	0.92	79	0.91	10.5
		Cs ¹³⁷	39-41	14	1.0	19	1.0	5.3
		C ¹⁴	44,45	80	0.10	116	0.10	37
		Sr ⁸⁹	53	0.15	1.0	0.17	1.0	0.03
				188	0.58	244	0.54	57
Bone marrow.....	External	Short-lived	23,24	11	1.0	12	1.0	1.6
		Cs ¹³⁷	23,24	16	0.92	18	0.94	2.2
	Internal	Sr ⁹⁰	32-36	33	0.92	40	0.91	5.3
		Cs ¹³⁷	39-41	10	1.0	14	1.0	3.9
		C ¹⁴	44,45	48	0.10	70	0.10	22
		Sr ⁸⁹	53	0.07	1.0	0.08	1.0	0.01
		118	0.61	154	0.56	35		

^a For details of model see annex F, part I, paragraphs 110 and 119.

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ANNEX F

ENVIRONMENTAL CONTAMINATION (*continued*)

PART IV

Disposal of radio-active wastes and releases from accidents in nuclear reactors

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I. Disposal of radio-active wastes

INTRODUCTION

1. The problems of waste disposal have arisen with civilization and have become increasingly complex with its development. The use of atomic energy has increased the already complicated problems of disposing of the wastes arising from human communities. Radio-active materials could be transmuted into non-radio-active materials by further neutron capture, but this procedure would not be economic. Chemical treatment merely transfers wastes to a more convenient form while leaving a lower concentration of radio-activity in the treated wastes. With the continuing extension of isotope technology in industry and medicine and the development of nuclear power, there will be larger quantities of radio-activity to be stored and there will also be an increase in the amount of low activity wastes released into man's environment. It will therefore become more and more important to control these releases and to assess the contribution they make to man's exposure to radiation.

CLASSIFICATION OF RADIO-ACTIVE WASTES

2. According to their physical state, radio-active wastes are classified as solid, liquid and gaseous. Though no fixed classification system has been agreed upon, liquid wastes can be arbitrarily divided into three groups according to their specific activity: low-, intermediate- and high-level wastes.¹⁻⁴ These terms are used to describe the approximate concentration of activity in the particular waste materials and their quantitative definition varies from one establishment to another. Low-level wastes are those having a range of activity from a trace amount up to one microcurie per litre; intermediate-level wastes have concentration up to three curies per litre; and high-level wastes have specific activities up to hundreds of curies per litre.¹

METHODS OF DISPOSAL

3. Methods of waste disposal must aim at reducing, as

far as practicable, the radiation dose to man. Two basic methods are available to achieve this aim. The first is to contain the waste in shielded areas and to absorb most of the radiation in the shield. If special attention is paid to the problems of siting, containment and shielding, any quantity of radio-activity can be dealt with in this way. The second method is to disperse the radio-activity in the environment so that most of the radiation energy is absorbed by the diluting material, and again the radiation dose to man can be kept low. There is, however, a limit to the capacity of the environment to accept wastes without causing excessive radiation dose to man. Broadly speaking, therefore, the first method is the appropriate one for high-level wastes, and the second is satisfactory for low-level wastes. Intermediate-level wastes must be considered on their merits and are usually partly contained and partly dispersed.

ORIGIN AND NATURE OF RADIO-ACTIVE WASTES⁵⁻¹⁵

4. Radio-isotopes originate from three different sources: natural radio-active isotopes with their decay products, fission products and radio-isotopes obtained as a result of activation. By far the greatest quantity of radio-activity in the form of wastes produced at the present time originates from the reactor-fuel cycle. A general flow-sheet indicating the types of waste produced during the nuclear fuel cycle complex is given in figure 1.⁷ Smaller amounts of radio-activity occur in the wastes from medical and industrial uses of isotopes. Although these releases are small, they take place in a very large number of establishments and the disposal problems thus posed are by no means negligible.

GASEOUS AND AIRBORNE WASTES

5. Gaseous and airborne radio-active wastes are produced during feed material production, isotope separation, fuel element fabrication, fuel reprocessing and reactor operation. During the re-processing of shortly-cooled fuel elements, fission product gases are released,

including Kr⁸⁵, Xe¹³⁵ and I¹³¹. Where air is used as a coolant for reactor cores or shields, the short-lived isotope A⁴¹ appears in large quantities. C¹⁴ may be produced in a reactor by irradiation of the graphite moderator, or of the carbon dioxide used as a coolant, and by irradiation of nitrogen.

6. Before being discharged into the atmosphere, airborne and gaseous wastes may have to be partly decontaminated through various devices.¹⁶ Isotopes of the noble gases are diluted by meteorological processes and the dose to man can be adequately controlled by the selection of a suitable stack height. Kr⁸⁵ may in the future give rise to significant exposures if improved methods of treating gaseous effluents are not developed. Other materials, notably isotopes of iodine, are deposited from the air and may be substantially reconcentrated by agricultural processes. This introduction of radio-activity into the food chain is usually likely to contribute more to the radiation dose to man than direct exposure to the airborne waste.

7. Quantitative information on the amounts of radio-activity discharged in gaseous wastes is extremely sparse, but both the United Kingdom and the United States have published some information relating to atomic energy installations. Some of these data are summarized in table I.¹⁷ Because of the various ways in which gaseous discharges can cause radiation exposure to man, the discharge figures in table I cannot be used directly to assess the environmental consequences of the discharges. However, in many cases, detailed assessments have been made of the resultant radiation doses to man and it has been found that these are very small.¹⁸ It is reasonably certain that gaseous wastes from all sources make a very small contribution to man's total radiation dose.

HIGH-LEVEL RADIO-ACTIVE LIQUID WASTES

8. Wastes of high activity must be stored for long periods of time so as to prevent their release into the environment. At present, all high-level activity wastes from the re-processing of reactor fuel are kept in a concentrated liquid state in tanks. These tanks are either placed in buildings above ground or, more commonly, underground.

9. Despite a number of shortcomings, such as self-heating, radiolysis and corrosion with leakage as a possible consequence, storage of liquid high-level activity wastes in tanks can be considered as satisfactory. Nevertheless, research is being carried out to make possible the storage and disposal of high-level activity wastes in the solid state, as this will provide their safe fixation for a long period. The conversion of high activity wastes to the solid form has some disadvantages including particularly the production of additional low- and intermediate-level wastes and of gaseous wastes. The additional processing required also causes additional radiation doses. However, the increased safety of the finally stored or disposed waste may well outweigh these disadvantages. The methods of conversion of liquid wastes into solid substances are given in table II.¹⁹

10. The per cent fraction of total radio-activity contributed by certain fission products of biological interest after various times of cooling is given in table III.⁷ Serious attention should be given to the proposal²⁰ that Cs¹³⁷, Sr⁹⁰ and other long-lived isotopes be removed from high-level wastes, so that the residue can be finally disposed of after a period of about fifteen years. Additional

problems are posed by the presence of alpha-emitting transuranic isotopes of long half-life.²¹

LIQUID WASTES OF INTERMEDIATE- AND LOW-LEVEL ACTIVITY

11. Low activity wastes can often be disposed of directly in the soil, rivers or seas. The quantity of waste which can be disposed of in this way depends on the radio-active components of the waste and on the capacity of the environment to absorb or disperse these components without causing excessive radiation dose to man or harm to the environment. If the amount of waste for disposal exceeds the estimated capacity of the environment, then the waste must be treated to remove part of the radio-activity through concentration. The concentrate can then be stored or transferred to other parts of the environment better able to receive the radio-activity. Intermediate-level wastes almost always require treatment in this way. A relatively complete decontamination can be achieved only by using a combination of methods, the choice of which depends on the composition of the wastes. The efficiency of decontamination methods is given in table IV.²²

SOLID WASTES

12. Solid wastes include contaminated equipment, process wastes such as slags, contaminated laboratory wastes, and the concentrates from some types of treatment of liquid wastes. Depending on the activity and the available environmental conditions, solid wastes are either permanently stored, e.g. in concrete-lined trenches, or buried with or without containers, or dumped on the sea-bed in drums or concrete containers. They are often processed to reduce their volume and to simplify the subsequent disposal operations. Such processing includes incineration and baling and usually produces secondary gaseous or liquid wastes which have proved to be of little hazard.

13. Typical quantities of liquid and solid radio-active wastes discharged into rivers, seas and oceans from some of the establishments of the United Kingdom Atomic Energy Authority and United States Atomic Energy Commission are given in table V.¹⁷

DISPOSAL OF RADIO-ACTIVE WASTES INTO RIVERS

14. Studies of the biology of river waters into which radio-active wastes are discharged have indicated that radio-nuclides are strongly concentrated by river organisms, both plant and animal. As examples, observations made at Hanford and at Chalk River will be reported.²³⁻²⁵

15. Low-activity cooling water from the reactors at Hanford is discharged, after a short delay, in retention basins into the Columbia River. The activity decreases at points downstream from the discharge point because of radio-active decay and adsorption onto sediments.²³ Estimates have been made of the radiation doses to people living in downstream communities and it has been found that in spite of some very high concentration factors²⁴ in individual river organisms the principal sources of radiation dose to man are drinking water and a species of whitefish. The use of the river for irrigation and the transfer of radio-active materials to the sea and their reconcentration in marine organisms have been shown to contribute extremely small radiation doses to man.²⁵

16. At the Chalk River plant the effluent is diluted by large volumes of water used for cooling the reactors before it enters into the Ottawa River. The concentration of the beta-gamma emitting radio-nuclides is equal to $2 \times 10^{-8} \mu\text{c/cc}$ upstream from the plant; at a distance of 1.6 km downstream from the plant, the concentration is $3 \times 10^{-8} \mu\text{c/cc}$.²⁵ Sr^{90} in excess of that attributable to fall-out was occasionally observed in fish caught in the locality of the reactor outfall.

DISPOSAL OF RADIO-ACTIVE WASTES INTO SEAS AND OCEANS²⁶

17. Two methods of disposal of radio-active wastes into seas and oceans are used at the present time. The first consists of the direct discharge of liquid wastes from atomic plants into coastal waters; the second of the dumping of solid wastes on the bottom of the sea after sealing in appropriate containers, thus delaying the entrance of radio-active substances into the water masses. In this connexion the oceans can be considered from two points of view: as a dilution medium for radio-active waste and as an area of temporary isolation in which radio-activity can decay before escaping to the water and ultimately returning to man.

18. While the possibilities of the ocean as a medium for dilution are great, it is obvious that uniform dilution of the global quantities of radio-active wastes in the ocean is highly improbable both because of the slow rate of mixing of water and because of concentrating effects. Among the factors which influence the fate of radio-active wastes in sea water are the physical and chemical state of radio-nuclides and also oceanographic conditions. The possible physical states of elements in sea water are: ionic, colloidal, and particulate.²⁷ Elements in ionic form will be diluted better, but as they remain longer in solution they may enter in zoo- and phytoplankton. Elements in particulate form or those which tend to be absorbed by particulates in the sea will have a tendency to settle on the sea-bed, which will lead to a higher concentration of radio-activity at the bottom as compared with the rest of the sea. Radio-nuclides in particulate form may then be removed by filter-feeding marine life and so become available to the larger marine fishes. Thus, radio-active materials may enter bottom sediments and in some form become available to bottom-dwelling marine life.

MIXING PROCESS BETWEEN DEEP WATER AND SURFACE WATER OF THE OCEANS AND "BIOCIRCULATION"

19. In considering disposal of radio-active wastes by burial in ocean depths, it is necessary to examine the possibility of exchange between deep and surface waters of the ocean. Two points of view exist.²⁸ The first maintains that the replacement of deep waters in the ocean takes place comparatively rapidly, in perhaps forty to fifty years. This point of view is supported by observations and calculations regarding dissolved oxygen and phosphate, and other factors present in the ocean. The other point of view holds that the replacement of deep waters in the ocean, and consequently the time required for any contamination from the depths to come to the surface, takes place much more slowly, over a period of several hundred years, or even 1,000 or 1,500 years. This opinion is supported by studies conducted with carbon-14 and radium. In addition to the movement of radio-active nuclides due to vertical transfer of water layers, "biocirculation"²⁹⁻³⁰ also must play a role.

20. It is now clear that the deep waters of the oceans

cannot be regarded as isolated from the surface waters. Waste disposal in the deep water in containers must therefore be treated as a form of temporary storage, the storage period depending both on the life of the container and on the rate of transfer to the surface waters. In addition, the process of transfer will result in substantial dilution.

21. Experiments³¹ have indicated that the expected life period of metal drums because of corrosion in sea waters is not more than ten years, whereas concrete containers may last as long as thirty years. One container described in the literature³¹ is capable of withstanding high pressures and corrosion, so that its expectation of life at the sea bottom is 1,000 years.

22. Since 1946 the United States Atomic Energy Commission has been disposing of relatively low-level radio-active waste products at sea off the Atlantic and Pacific coasts of the United States. Most of these wastes were packaged in 200 l. steel drums with encased concrete drums, and preformed, reinforced concrete boxes were used in some instances. During three oceanographic cruises³² in March, April and November 1960, samples of sea water, sediments and marine life were collected for the purpose of measuring their radio-activity level. Bottom photographs were taken and documentary motion pictures of the April cruise were filmed. Different seasons of the year were chosen for the cruises in order to detect seasonal differences in levels of contamination. Water depth at all sites was 1,800 m. or greater. The three areas of survey were two disposal sites and the control area off Point Arguello, between the two disposal sites. In general, the results indicated that within experimental error, no radio-activity was detected in excess of the background levels.

23. At the present time, since many factors are still unknown to us and few data on the question of disposing of sealed wastes in ocean depths are available, it is difficult to reach definite conclusions on the suitability of such practices for all types of waste. At present, however, only small amounts of radio-active material are being deposited in the ocean and before this practice could be extended to the high activity waste from large-scale nuclear power programmes, much more investigation would be required into the processes of dispersion and reconcentration. There is still substantial disagreement³³⁻³⁶ on the validity of deep ocean disposal, but even with the assumption of a very rapid mixing of the deep water and the surface water the present practices have so far given rise to exceedingly small radiation doses to man.

DISPOSAL OF RADIO-ACTIVE WASTES ON LAND

24. Like the ocean the land also can be considered both as a place for ultimate disposal through isolation in special geological formations and as a medium for dispersion of low-level radio-active wastes. In the latter case there is also some degree of isolation by adsorption of the radio-activity on to the soil as well as dispersion and dilution in the ground water. In rare cases substantially all the radio-activity is retained by the soil and only a purified waste reaches the ground water. This situation occurs at Hanford where some quantities of radio-activity are released into the ground and no fission products have been observed to penetrate into the river waters.²⁸ Direct disposal of low-level liquid and solid wastes into the ground is practised at the present time, and the isolation into special geological formations is in the state of development.

DIRECT DISPOSAL OF LOW-ACTIVITY WASTES INTO SUPERFICIAL PERMEABLE LAYERS OF THE GROUND

25. Disposal of low-level liquid radio-active wastes to the ground is founded on the ability of various earth materials to remove and retain fission product cations. Some years of practical experience in the controlled disposal of wastes to the ground at the Hanford Works, Oak Ridge National Laboratory, and Savannah River Plant have demonstrated the feasibility, safety and economy in the disposal of at least limited volumes of some types of liquid wastes.⁸⁷

26. The binding capacity of soil for radio-nuclides depends on the composition of the soil and on the properties of the discharged wastes. Strontium is well sorbed by montmorillonite, kaolinite, mica, hydromicas, peat, phosphorite and nepheline syenites.⁸⁸ Caesium, as a rule, is very well retained by soils, and the extent to which it is retained depends on the mineral content of the soil. It has been established that the most suitable types of soil columns for the decontamination of liquid wastes are those composed of vermiculite overlaying solid phosphates, which in turn lie on coarse-grained gravel.⁸⁹

ISOLATION IN SPECIAL GEOLOGICAL FORMATIONS

27. It has been proposed to discharge liquid wastes even of high activity into various rocks, salt formations, limestone, shale formations, gypsum, sandstone and other impermeable geological formations.⁴⁰⁻⁴¹ All these methods are at the experimental stage. Of all the indicated geological formations, the most promising are sandstone and salt formations.

28. Deep well injections of radio-active materials into porous geological formations⁴⁰⁻⁴⁸ are suitable for regions which have porous rock, such as sandstone, under which is a layer of impermeable material such as shale. Sandstone possesses several desirable properties, such as considerable heat conductivity, stability in acids; its porosity reaches 10-30 per cent; it has a fairly high ion-exchange capacity (20-30 milligram equivalents per 100 g.).

29. Disposal into natural salt formations provides one of the most interesting possibilities.⁴⁴⁻⁴⁶ The method has several geological and operational advantages and is expected to provide a high degree of isolation. Analytical studies indicate that it is possible to store two-year-old 10,000 megawatt-day/ton, 3,200 litre/ton waste in a sphere about 3 m. in diameter. Structural properties and thermal conductivity of rock salt are not changed to any significant extent under the influence of high doses of radiation. The chemical interaction of liquid wastes with salt produces chlorine and other gaseous compounds, but their quantity is not very great.

CONCLUSION

30. Information on the contamination of the environment through disposal of radio-active wastes is very limited and only for few areas are relevant data published periodically. In even fewer cases is the published information sufficient to allow any assessment of the resultant radiation doses to man. These cases represent major releases of radio-activity into the environment and it has been shown that the resultant radiation doses to man are small.¹⁸ Other releases of radio-active waste result in even smaller doses and present waste disposal does not make a significant contribution to man's exposure to radiation.

31. The problem of disposing of radio-active waste will assume increasing importance with the development of atomic energy which is expected in the next few decades. It has been estimated⁴⁷⁻⁴⁸ that the thermal power produced by atomic plants will reach 700,000 megawatts by the year 2000 and will be accompanied by billions of curies of accumulated radio-activity. Almost all the resulting radio-active material will be sent to permanent storage and improved storage methods are being investigated. It is also likely that there will be an increase in the amount of radio-activity dispersed into the environment not only from fuel-reprocessing plants but also from the increasing uses of isotopes in industry and medicine. The control of such discharges and the assessment of the resulting radiation doses to man will thus become increasingly important.

32. Most of the present practices for the disposal of low activity wastes are satisfactory provided that they are subject to close and continued control. In some cases this control should include appropriate environmental monitoring and the primary aim of this monitoring should be to establish that the disposals cause no unacceptable radiation doses to man. In the case of the majority of the industrial and medical applications of isotopes, simple procedures controlled by suitable sanitary standards⁴⁹⁻⁵³ can be used for disposing of radio-active wastes without the need for a complex environmental monitoring programme.

33. The release into the environment of the principal fission-product wastes from the large scale production of nuclear power cannot be considered until substantially more information is available on the behaviour of such fission products in the environment.

II. Releases from accidents in nuclear reactors

34. The release of radio-active materials as a result of nuclear accidents represents a situation that must be considered in connexion with its potential effects on man and his environment. Of the six major nuclear accidents to date⁶⁴ only the accidents at Windscale and at Chalk River led to a substantial release of radio-active nuclides.⁵⁵⁻⁵⁸

35. The accident at Windscale was caused by local overheating of the uranium fuel elements during the annealing of the graphite moderator of an open air-cooled reactor. The amount of radio-activity released during the accident is not known precisely, but approximate estimates were made from the measurements of the radio-active iodine deposited on the ground and from measurements on air filters obtained both in the United Kingdom and in Continental Europe. The following list shows estimates of the amounts of various isotopes released:

	Curies
Iodine-131	20,000
Tellurium-132	12,000
Caesium-137	600
Strontium-89	80
Strontium-90	2

36. During the six weeks after the accident, over 3,000 samples of milk were analysed. The I^{131} content of milk rose to a maximum three days after the accident when the highest levels recorded were $1.4\mu\text{C/l}$. The levels of I^{131} in samples of drinking water obtained from reservoirs, and from streams feeding reservoirs and water taps, varied from below the threshold of detection (about

100 $\mu\text{C}/\text{l}$) to about 1,000 $\mu\text{C}/\text{l}$. Samples of eggs, vegetables and meat from the more highly contaminated areas were examined. They also were shown to be contaminated with I^{131} , but contributed much less to the diet of the population than did milk.

37. Before the accident the ratio of Sr^{90}/Ca was 44 $\mu\text{C}/\text{g}$ in milk from a farm within a quarter of a mile of the perimeter of the Windscale Works. Shortly after the accident values up to 115 $\mu\text{C}/\text{g}$ Sr^{90}/Ca were observed in milk from the farm nearest the plant. It was also found that in the area of highest contamination, the maximum levels of Cs^{137} , Ru^{103} and Ru^{106} , and Zr^{95} in grass were 0.25, 0.21 and 0.3, $\mu\text{C}/\text{m}^2$ respectively.

38. The only control measure needed as a result of the accident was the control of the consumption of milk and vegetables from an area of approximately 500 square kilometres. The opinion was expressed in the official report following the accident that this control measure had been adequate and that it was highly unlikely that any harm was done to anybody as a result of the accident.

39. Most reactor accidents have taken place in experimental reactors or in reactors cooled by the old-fashioned flow-through system rather than in the more modern power generating facilities where the coolant is recirculated. The probability of other types of accidents occurring can only be assessed on the basis of past experience. This is still limited but suggests that releases of such a nature as to cause concern for the health of individuals in the population are extremely rare. It is also

likely that carefully planned emergency measures can substantially reduce the radiation doses which would otherwise result from accidental releases.

TABLE I. SOME EXAMPLES OF RELEASES OF GASEOUS WASTE FROM ATOMIC ENERGY PLANTS

Site	Amount of waste and radio-active content
<i>United Kingdom</i>	
Springfields (feed material production plant)	Approx. 1 c/y, alpha
Capenhurst (gaseous diffusion plant)	Approx. 0.1 c/y, alpha (uranium)
Calder Hall (nuclear power station)	10 c/hr, A^{41}
Chapelcross (nuclear power station)	10 c/hr, A^{41}
Dounreay (reactor research centre)	0.5 mc/hr, A^{41}
Harwell (nuclear research centre)	30 mc/y; beta; 1 mc/y, alpha; 50 c/hr, A^{41}
Amersham (isotope production plant)	15 mc/wk, I^{131}
Aldermaston (nuclear weapon research centre)	20 mc/y, beta; 3 mc/y, alpha
<i>United States of America</i>	
Hanford (plutonium production plant)	1 c/d, I^{131}
Idaho (reactor testing station)	100,000 c/y beta, mainly very short half-life, and noble gases
ORNL (reactor development and chemical processing laboratory)	0.25 c/y, alpha (uranium)
Brookhaven (nuclear research centre)	700 c/hr, A^{41}

TABLE II. POSSIBLE METHODS OF CONVERSION OF WASTES TO SOLID FORMS

Preparation containing fission products	Metal oxides dried at 200-250°C	Metal oxides calcinated at 500-700°C	Calcinated clays	Cement blocks	Molten salts	Preparation type glass
Difficulties in the preparation process	Considerable dust	Dust	Limited exchange capacity of clays	Must be mixed	Corrosion of the equipment	High temperature (> 1000°C)
Volume variations	Reduction up to 100 times	Reduction up to 100 times	Reduction up to 50 times	Increase up to 30-50%	Reduction up to 70 times	Reduction up to 350 times
Separation of gaseous products in radiolysis	Yes	No	No	Yes	Yes	No
Heat resistance	High	High	High	Medium	Low	Very High
Heat conduction kilocalorie/metre/h/°C	0.05	0.03	0.05		About 1	Up to 2
Transfer of fission products into water	Considerable	Appreciable	Small	Small	Soluble	Very small

TABLE III. COMPOSITION OF FISSION PRODUCT MIXTURE AFTER ONE-YEAR IRRADIATION OF FUEL ELEMENTS BY 3×10^{18} THERMAL NEUTRON FLUX AND VARIOUS TIMES OF COOLING

Isotope	Half-life	Approximate % of total FP activity after cooling		
		100 days	3 years	30 years
Cs^{137}	26.6 years	< 2	15	~ 49
Sr^{90}	28.0 years	< 2	15	~ 49
Pm^{147}	2.6 years	3	15	< 1
Ce^{144} - Pr^{144}	290 days	45	50	—
Kr^{86} (gas)	10.3 years	< 1	1	< 1
I^{131} (gas)	8.1 days	< 1	—	—
Zr^{96} - Nb^{96}	63 days	33	—	—
Ba^{140} - La^{140}	12.8 days	< 1	—	—
Ru^{103} - Rh^{103}	41.0 days	5	—	—
Ru^{106} - Rh^{106}	1.0 year	2	3	—
Sr^{89}	54 days	7	—	—
Xe^{138} (gas)	5.27 days	< 1	—	—

TABLE IV. EFFICIENCY OF DECONTAMINATION METHODS OF LIQUID WASTES

Treatment	Unspecified alpha-removal	Unspecified beta-gamma-removal
FeCl ₃	97%	50%
BaCl ₂ + Fe ₂ (SO ₄) ₃	99%	98%
Lime soda-softening process....	70-99%	50-80%
40-80 ppm Al + activated silica (5-10 ppm SiO ₂).....	80%	65%
20 ppm Al + lime or Na ₂ CO ₃ ...	90%	70%
40 ppm Na ₂ PO ₄ + lime + tannic acid.....	98%	75%
100 ppm Na ₂ PO ₄ + lime or NaOH	95%	75%
Phosphate treatment followed by sulphide treatment.....	99%	90%
Phosphate treatment followed by vermiculite columns.....	99.95%	99.36%
Precipitation and electro-de-ionization.....	99-100%	99-100%
Ion-exchange resins.....	10 ² -10 ⁵	10 ² -10 ⁴
Mixed bed.....	10 ⁵	10 ⁵
Evaporation.....	10 ⁴ -10 ⁵	10 ⁴ -10 ⁵

TABLE V. EXAMPLES OF LIQUID AND SOLID WASTE DISPOSAL FROM SOME ATOMIC ENERGY INSTALLATIONS

Site	Type of waste	Amount and radio-active content	Method of disposal
<i>United Kingdom</i>			
Springfields.....	Liquid	2.5 × 10 ⁶ m ³ /y; 50 c/y alpha; 1,500 c/y beta	Pipeline to tidal estuary
Capenhurst.....	Liquid	2 × 10 ⁶ m ³ /y; 1 c/y alpha (uranium)	Open brook to tidal estuary
Windscale and Calder..	Liquid	8 × 10 ⁶ m ³ /y; 90,000 c/y beta; 40,000 c/y Ru; 1,500 c/y Sr ⁹⁰ ; 70 c/y alpha	Pipeline to open sea
Chapelcross (1960)....	Liquid	3 × 10 ⁶ m ³ /y; 4.5 c/y alpha and beta; 80 mc/y Sr ⁹⁰	Pipeline to tidal estuary
Dounreay (1959-60)....	Liquid	10 ⁶ m ³ /y; 40,000 c/y beta; 20 c/y Sr ⁹⁰ ; 5 c/y alpha	Pipeline to open sea
Harwell.....	Liquid	7 × 10 ⁶ m ³ /y; 15 c/y beta; 0.5 c/y Sr ⁹⁰ ; 0.02 c/y alpha	Pipeline to River Thames
	Solid	800 tons/y; 80 c/y beta; 4 c/y alpha	Dump in light drums on bed of English Channel
Aldermaston.....	Solid	50 tons/y; 1,000 c/y beta; 200 c/y alpha	Dump in strong drums on bed of Atlantic Ocean
	Liquid	5 × 10 ⁴ m ³ /y; 0.02 c/y beta; 0.06 c/y alpha	Pipeline to River Thames
	Solid	400 tons/y; 2 c/y alpha; 0.5 c/y beta	Dump in light drums on bed of English Channel
Brookhaven (1957-58)..	Solid	50 tons/y; 200 c/y alpha; 15 c/y beta	Dump in strong drums on bed of Atlantic Ocean
<i>United States of America</i>			
Hanford (1959).....	Liquid	3,000 c/d beta; 1,200 c/d Cr ⁵¹ ; 70 c/d Zn ⁶⁵ ; 0.2 c/d Sr ⁹⁰	Pipeline to river
ORNL (1954-57).....	Liquid	10 ⁶ m ³ /y; 250 c/y beta; 50 c/y Sr ⁹⁰	Discharge to local stream
Brookhaven (1957-58)..	Liquid	5 × 10 ⁶ m ³ /y; 0.1 c/y beta	Discharge to stream
	Solid	1,000 c/y	Dump in drums on bed of Atlantic Ocean

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ANNEX G

MEDICAL, OCCUPATIONAL AND OTHER EXPOSURES

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I. Introduction

1. This annex deals mainly with information and data radiation doses to individuals and populations as a result of exposure to ionizing radiation of:

- (a) Patients undergoing medical radiological procedures—medical exposure;
- (b) Workers as a consequence of their work—occupational exposure;
- (c) Persons from miscellaneous man-made sources and abnormal exposure to natural radiation, when the exposures do not belong to (a) or (b)—other exposures.

2. The term "medical exposure" is taken to apply to types of exposure (except occupational) resulting from radiation administered by radiologists, general practitioners, dentists, obstetricians, osteopaths, chiropractors, etc.

3. The term "occupational exposure" is, in the present annex, taken to apply to all activities involving exposure of workers to ionizing radiation in the course of their work, regardless of whether the workers are directly engaged in radiation work or not.^{1,2}

4. Data concerning radiation doses to specific organs and tissues, and to the whole body may be used for the purpose of:

- (a) Risk estimates; this implies adequate knowledge of the dose-effect relationship;
- (b) Education, which, by presenting comparative data, might result in improved standards of operation and a reduction of doses;
- (c) Guiding epidemiological studies.

5. The concept of significant dose for the evaluation of a specific biological risk was considered by the Com-

mittee in its 1958 report (chapter II, para. 26)⁸ in the following way:

"Any specific biological effect of irradiation must be evaluated from physical factors such as the distribution of tissue dose (expressed in rem) in space and time and from biological factors such as radiosensitivity, latent period, recovery and repair. The simplest situation is that in which a dose-effect relation for a biological effect is known, making it possible for the probability or degree of this effect to be calculated. Whether the effect eventually may manifest itself in the form of deleterious consequences, however, depends on individual circumstances such as expectation of life, or, in the case of genetic injury, expectation of children. For this reason, the potential effect indicated by a direct application of an assumed dose-effect relation must be weighted according to these individual circumstances."

As has been pointed out earlier in the present report, quantitative risk estimates presuppose assumptions regarding the dose-effect relationship. As long as the true mode of dose-effect relationship is not known, any use of the presented dose data for risk estimates must be made with the recognition of the necessary assumptions and the awareness of the uncertainty of the result. In any circumstances only comparative risk estimates may be made on the basis of the presented data and they should be limited to considerations of exposures to the same organs or tissues.

6. The present annex deals with the following types of radiation dose:

- (a) Genetically significant dose;
- (b) Mean dose to the active bone-marrow;
- (c) Doses to organs and tissues of special interest.

Data on radiation exposure to the gonads are presented using the accepted definition of the genetically significant dose (para. 9) with the intention that they may be used for comparative risk estimates of the radiation-induced genetic effect, following the procedures outlined in the 1958 report. However, in the cases of radiation exposures to the bone-marrow and to other organs and tissues of special interest the data are not given with the intention that they be used for risk estimates but for educational purposes and as a guide for epidemiological studies as mentioned in paragraph 4 above. Medical exposure is dealt with in paragraphs 7-99, occupational exposure in paragraphs 100-116 and other exposures in paragraphs 117-126.

II. Medical uses of ionizing radiation

7. Medical exposure arises from the following types of procedures:

- (a) X-ray diagnosis;
- (b) Radio-therapy by X-rays and sealed radio-active sources;
- (c) Administration of unsealed radio-isotopes for diagnostic, therapeutic and research purposes; radiation exposures also result from the use of contrast media containing radio-active materials, e.g. thorium dioxide.

8. Data on the frequencies of radiological procedures in various countries and areas are presented in tables I, II and III. The frequency figures are obtained as the annual number of procedures per 1,000 individuals of the population under study:

(a) Table I deals with X-ray diagnosis. Although the frequencies are based on sample studies, nine of the twelve countries which had carried out comprehensive surveys had similar amounts of radiography and fluoroscopy (excluding mass surveys and dental exposures). Their annual frequencies range between 260 and 410 examinations per 1,000 individuals. The frequency figures in the cities tend to be higher than those based on the whole country, not only because cities usually have more X-ray facilities, but also because many patients are examined there without being residents of the city itself or the surrounding suburban area.

(b) Table II, which sets out the frequencies of cases treated with X-rays and sealed radio-active sources, shows large differences between the various countries and areas.

(c) Table III gives the frequency of the administration of radio-active isotopes to cases for either diagnostic or therapeutic reasons. The number of patients undergoing diagnostic procedures is four to ten times higher than the number undergoing therapeutic procedures. The table also gives the annual consumption for medical use of I^{131} , P^{32} and Au^{198} . The contribution to the amounts of radio-active isotopes from the diagnostic use may be disregarded, as compared to the amounts used for therapeutic purposes. The information usually originates from the distributors. The figures given for the amounts should be regarded as maximum estimates in view of the disintegration of the radio-active isotopes in transit and because the total amount of requested isotopes may not have actually been used for medical purposes.

THE GENETICALLY SIGNIFICANT DOSE

Definitions and calculations

9. In the 1958 report the genetically significant dose was defined (chapter II, para. 27) as

"... the dose which, if received by every member of the population, would be expected to produce the same total genetic injury to the population as do the actual doses received by the various individuals".

This definition was based upon the following assumptions and considerations:

(a) The relevant tissue dose is the accumulated dose to the gonads;

(b) The dose-effect relation is linear, without a threshold;

(c) The individual gonad dose is weighted with a factor which takes into account the future number of children expected of the irradiated individual compared with an average member of the population (in this connexion the foetus is treated as such an irradiated individual and not as a child to be expected).

10. Evidence has lately been obtained that although the dose-effect relation for the production of most genetic damage might be linear at any given dose-rate, it has a lower slope for low dose-rates than for high ones. (C, 84-87) There are also indications that the genetic damage to future generations at any given dose or dose-rate may differ with sex and with the cell-stage of a gamete, depending on a difference in the radio-sensitivity of the male and female gametes and on a difference in the possibility of transferring the damage to future generations. This means that the weighting of the individual gonad dose should, in addition to the factor for future number of children, include weighting factors for the dose-rates to the gonads and for the difference both be-

tween the sexes and the cell-stages. Since these new weighting factors are not yet known, it is not possible to incorporate them in the calculation of the genetically significant dose.

11. It is still justifiable to use the formulas for the calculation of the genetically significant dose as they were presented in the previous report. The derivations of these formulas are therefore repeated in the appendix.*

12. Available information on genetically significant dose and its parameters is given under the heading "Data", with the following subdivisions: X-ray diagnosis; radio-therapy by X-rays and sealed radio-active sources; administration of radio-active isotopes.

Data

13. During the last few years many investigations have been performed to determine the genetically significant dose arising from medical exposure. Though most of these were performed along the lines presented in the appendix, using either formula 8 or 11 for the calculations, the sampling techniques and the modes of measurement or estimation of the gonad doses vary. Because of this, short explanatory statements of the investigations presented are given below in paragraphs 17 to 30.

X-ray diagnosis

(a) National surveys

14. Tables XVIII and XIX present the average gonad dose for each of the ten most significant examinations for each of the countries submitting information, with the reservations of paragraph 15. Table XVIII gives the values for examinations of male patients and table XIX the information for female patients. Table XX presents the values for the foetal gonad dose during examinations of the obstetric abdomen and pelvimetry. Only the Federal Republic of Germany (Hamburg) and the United Kingdom presented separate values of foetal gonad doses for the other examinations. Some countries assumed that the foetal gonad dose was the same as the female gonad dose for these other examinations. The variation in the values shown in these tables demonstrate that for any one examination a wide range of gonad doses may be obtained. This is due to varying techniques, for example the amount of fluoroscopy carried out as part of an examination and the size of the incident skin fields. Reductions in both of these will greatly reduce gonad dose in an examination. Table XXI presents the total genetic dose contribution for each examination for each of the countries submitting information. Similarly, table XXII gives the same information but presented as the percentage of the total genetic dose of each country, whilst the totals are summarized in table XXIII.

15. Further details of the genetic dose computations and data for each country may be obtained by reference to the national tables presented as tables IV-XVI. In these tables the ten types of examination which contribute most to the genetically significant dose originating from X-ray diagnosis are set out in descending order of their contribution. All other types of examination are presented as a whole. As an exception to this principle, the two types of obstetrical examination, e.g., pelvimetry and obstetric abdomen, are always individually presented, although their contribution to the genetically sig-

nificant dose does not always justify this. They are then placed at the bottom of the table, replacing the ninth and tenth types of examination. It should be mentioned that although the genetically significant dose is referred to as the "annual" dose, the validity of the figures is limited to the year or years to which the surveys relate.

16. The doses to the gonads and the annual genetically significant doses are presented in mrem. The dose-rates being the dose averaged over the exposure time are presented in mrem per sec and for the purposes of this annex it is assumed that for X-, β - and γ -radiation 1 r corresponds to 1 rad and to 1 rem.

17. *Argentina (Buenos Aires)*. Table IV is based on a report by Placer.⁴ His investigation is limited to radiography. Studies on the numbers of different types of radiographs and their distribution by sex of the patients radiographed were undertaken in a total of eighty-six hospitals and medical centres. The dose measurements were made with ionization chambers and film badges attached to the skin of the patients. Depth dose data were used for computing the gonad doses. The genetically significant dose was calculated from formula 11. The mean age of child-bearing was set as thirty. It should be emphasized that Placer's report deals with numbers of radiographs and not examinations. An estimate of the contribution to the genetically significant dose caused by radiography in private clinics and practices has been made, assuming the distribution of the radiographs in various types of examination to be the same as in the hospitals.

18. *Denmark*. The figures presented in table V are taken from the investigation published by Hammer-Jacobsen.⁵ The figures on the numbers of various types of examination are based upon a sample inquiry. Information on sex and age distribution of the patients was obtained from a special study on 139,000 examinations. Measurements on the doses to the gonads were made with ionization chambers on 2,475 patients during the actual course of examination. Data on doses to the foetus were obtained by measurements in a phantom. The genetically significant dose was calculated by means of formula 8 in the appendix. The fertility factors used were calculated from the official vital statistics of the population.

19. *Federal Republic of Germany (Hamburg)*. The data in table VI are taken from the investigation published by Holthausen, Leetz and Leppin.⁶ The genetically significant dose was calculated by means of formula 8. Information on the number of examinations of various types, subdivided by sex and age of the patients, was collected by means of questionnaires, compiling all examinations during the period from November 1957 to October 1958. Measurements were made on the gonad doses to adults in the course of examinations belonging to the types which were expected to give the highest contribution to the genetically significant dose. In addition, gonad doses to children and to adults were taken from an investigation made by Seelentag.⁷ The figures for d_j in table VI are, according to the original paper, mean figures including all age groups. They were obtained by means of formula 8 after the detailed calculation of the annual genetically significant dose had been made. The fertility factors were computed from the official vital statistics of the population. For comparative purposes figures are presented for the annual genetically significant dose using formula 11 and a figure for the annual per capita dose for the whole population, disregarding fertility factors.

* Although, for editorial reasons, the pertinent paragraphs are not directly quoted, they are substantially a quotation from the Committee's 1958 report, annex C, para. 6-17.

20. *France*. Table VII is based upon data published by Reboul *et al.*⁸⁻¹⁰ The sample study of the number of different types of examinations and their subdivision with regard to sex and age of the patients, was performed in Bordeaux during 1957, and comprised 36,000 examinations. By means of the records of the Sécurité sociale the results obtained from the sample study were extrapolated to cover the whole of France. Measurements of the gonad doses were made during the examinations. For the female patients, the ionization chambers were placed on the skin at the level of the ovaries. The factors for the ratio of ovary dose to skin dose were determined by measurements in cadavers and phantoms. The genetically significant dose was computed with the use of formula 11.

21. *Italy (Rome)*. Table VIII is based on an investigation published by Biagini, Barilla and Montanara.¹¹ The numbers of examinations of various types, subdivided by sex and age of the patients, are based upon a year-long study of the number of examinations performed in certain selected hospitals and clinics. A special correction was made, to exclude the examinations on patients who were not residents of Rome. Using ionization chambers the authors arrived at gonad doses through measurements in a phantom and in patients during the examinations. In order to account for the variations in the gonad doses as a consequence of differences in technique and physical parameter, figures on gonad doses were obtained as mean figures from pertinent data presented by ten authors. The genetically significant dose was calculated from formula 8. The fertility factors were computed from official vital statistics of the population.

22. *Japan*. Table IX is based upon data from a Japanese report.¹² This investigation is based upon two sample studies, the first covered seven districts comprising around 80,000 examinations and the second was representative of the whole of Japan, in which details of 66,000 examinations were obtained. The sample studies for the collection of numbers of examinations lasted for one week each. During this period, information was also obtained on the sex and age distribution of the patients. The gonad doses to adults and children were obtained by measurements with ionization chambers in body-shaped phantoms. The influence on the gonad doses as a consequence of variations in physical parameters was investigated. No measurements were made of doses to the foetal gonads. Fertility factors were determined from official statistics. The genetically significant dose was calculated according to the principles set out in formula 8. The contribution to the genetically significant dose from the exposure of foetal gonads was computed only for obstetrical examinations.

23. *Netherlands (Leiden)*. Table X presents data obtained from Beekman and Weber.¹³ The numbers of roentgen examinations of various types are based upon a study of the records from 30,000 examinations. Information on sex and age distribution in different types of examination was also collected. The gonad doses were obtained from measurements with ionization chambers in a body-shaped phantom. The influence on the gonad doses was studied in relation to variations in examination techniques and physical dose parameters. The figures presented for gonad doses are averaged with regard to the existing ranges of techniques and parameters. The annual genetically significant dose was calculated by means of formula 8. For comparative purposes, formula 11 was used, under the assumption that the mean age of child-bearing was thirty years. In addition, a per capita

annual gonad dose was calculated without regard to the fertility factors. The fertility factors were obtained from the official vital statistics of Leiden.

24. *Norway*. The data set out in table XI are extracted from an investigation performed by Flatby.¹⁴ Information on the numbers of examinations of various types was obtained during 1957 and 1958 from all the establishments in Norway where X-ray diagnosis was performed. The subdivision of the number of examinations by sex and age of the patients was based on a study comprising four diagnostic departments (40,000 examinations). The gonad doses were measured directly with ionization chambers during the examination. In addition, doses to the ovaries were also assessed by measurements in a body-shaped phantom. The dose measurements comprised around 1,300 patient and 100 phantom measurements. The fertility factors were determined from the official vital statistics of the population. The genetically significant dose was calculated by means of formula 8.

25. *Sweden*. Table XII summarizes the data on genetically significant dose presented in the Committee's previous report. The data are based on the investigation published by Larsson.¹⁵ Information on the numbers of examinations of various types, subdivided by sex and age of the patients, was collected from a sample of hospital records (40,000 examinations) and corrected by an estimate of the numbers of examinations performed by private practitioners. Only around 5 per cent of the total number of examinations were carried out by these practitioners. These were mainly chest and small bone examinations. Around 1,900 measurements of the doses to the male and female gonads were performed with ionization chambers during the actual course of examination. Only the doses to foetal gonads were obtained by measurements in a phantom. The fertility factors were computed from the official vital statistics of the population. The genetically significant dose was calculated from formula 8.

26. *Switzerland*. Table XIII is based on an investigation performed by Zuppinger, Minder, Sarasin and Schaer.¹⁶ Through a sample study, lasting for three weeks in 1957 and comprising around 65,000 examinations, information was gained regarding the numbers of examinations of various types, subdivided by sex and age of the patients. The doses to the gonads were obtained partly from the authors' own measurements with ionization chambers in patients and a body-shaped phantom, and partly, when appropriate, from dose data published in other countries. Since the Swiss investigation started with the original intention of computing the genetic dose to individuals below the age of forty but later changed to a determination of the genetically significant dose according to formula 8, the calculations were not made directly with the use of this formula, although the principles were the same. The fertility factors were determined from official statistics.

27. *United Arab Republic*.^{17,18} Investigations carried out in Alexandria and Cairo during the years 1955-1961 are presented in tables XIV and XV. They are representative of the whole of Alexandria and the area west and south-west of Cairo. Phantom measurements were carried out on a selection of units used in these cities. The calculations were made on the basis of formulae 8 and 11 and the results presented as a weighted mean. The survey showed that some 17 per cent of the annual examinations were for investigations of the urinary tract. This is due to the investigation of the endemic disease, schistosomiasis.

28. *United Kingdom.* The material presented in table XVI has been taken from the report of the Adrian Committee.¹⁹ The comprehensive survey covered all medical radiology carried out in the United Kingdom, except Northern Ireland. The numbers of examinations of various types and their distribution by sex and age of the patients are based on two nation-wide sample studies in 1957, each one lasting for one week, and together comprising around 310,000 examinations. The whole country was divided into nineteen regions and in each measurements were carried out in a sample of six hospitals. The gonad doses were obtained for 5,400 examinations by measurements with ionization chambers. The methods used for making these measurements were:

(i) Male patients: by a direct dose measurement made with the chamber in contact with the scrotum during the examination;

(ii) Female patients: by an indirect method, using the dose to the skin at the level of the iliac crest, measured during the course of examination, and the ratio of the corresponding skin dose and the ovary dose, as obtained from dose measurements in body-shaped phantoms;

(iii) Foetus: by calculations based upon dose data derived from body-shaped phantoms.

The fertility factors were computed from official statistics. A separate statistical investigation was made to determine the average number of future children to be born to a pregnant woman. While the accuracy of this estimation is low, the general indication is that the fertility factor for a pregnant woman is higher than that for a woman in the population at large. These higher fertility factors, although admittedly approximate, have been used solely in computations on examinations made in connexion with a pregnancy, viz. pelvimetry and obstetric abdomen examinations. The genetically significant dose was calculated by the use of formula 8.

(b) Other investigations

29. *United States of America.* Most of the national surveys are performed in countries with small populations. In countries with large populations, a small-scale study may not truly reflect the situation, especially when there are great variations within the country in the parameters that determine the genetically significant dose. For the United States, Laughlin and Pullman²⁰ made an estimate of the annual genetically significant dose, on the basis of those data in the literature up to 1955, using formula 11. They arrived at a figure of 50 ± 25 mrem as a minimum estimate and a more probable estimate of 140 ± 100 mrem. With the same formula, Norwood *et al.*²¹ calculated the annual genetically significant dose caused by X-ray diagnosis for the inhabitants of a small American town to be 45 mrem. Another United States investigation²² covers the employees of the Oak Ridge National Laboratory who were regarded as patients. The annual genetically significant dose from X-ray diagnosis was found to be 50 mrem (13 mrem caused by exposure of male patients and 35 mrem by exposure of female patients). The results of the two later investigations are within the range of the minimum estimate obtained by Laughlin and Pullman.

30. *USSR.* In the USSR no calculations of the genetically significant dose arising from medical X-ray diagnosis have yet been published. However, Pobedinsky²³ has published data on the doses to the gonads during diagnostic X-ray examinations, e.g. chest, stomach (barium meal), kidneys, gall bladder, pelvic region, lumbar spine and lumbosacral region. The data, which are based

upon dose measurements in a body-shaped phantom, are within the ranges of the individual gonad doses presented in tables XVIII and XIX. Data have also been published by Viktorina.²⁴ Provided there are not significant differences in the age distribution of the patients and in the numbers of examinations of various types, it is reasonable to believe that the annual genetically significant dose from X-ray diagnosis in the USSR is of the same order of magnitude as the doses presented in the summary table, XXIII.

(c) Mass survey examinations of the chest

31. Since mass survey examinations of the chest are frequently performed in many countries, current interest has been devoted to the doses associated with this type of examination. In table XVII data have been collected from various countries and areas for gonad exposure in this type of survey examination. In most countries these examinations are performed as mass miniature radiography (photo-fluorography). The table shows that these radiographic examinations, in spite of their high numbers, give a very low genetically significant dose. In some countries, however, survey examinations are performed by means of fluoroscopy. These examinations give individual gonad doses which are up to 100 times higher than those given by mass miniature radiography. Even if the doses to the gonads are much lower than in many other types of examination, the high number of these fluoroscopic examinations among individuals in the pre-fertile and fertile ages may cause a considerable contribution to the genetically significant dose. Therefore, in order to reduce the dose, mass miniature radiography should be used when practicable rather than mass survey fluoroscopy.

(d) Comments

32. Certain types of examination, mainly those of the pelvic region, together contribute 85-95 per cent of the genetically significant dose. This is shown in table XXII. However, in terms of numbers of examinations, these examinations represent only about 15 per cent of the total in those countries where the contributions from chest and mass survey examinations are small.

33. The following points from the national tables require further explanation:

(i) In table VI, relating to Hamburg, the colon examinations are responsible for a third of the total genetically significant dose. Holthusen *et al.*⁸ have explained this as being the result of a special technique used in Hamburg for colon examinations, involving extensive fluoroscopy.

(ii) In Japan¹² stomach and colon examinations cause 50 per cent of the genetically significant dose. Table IX shows high gonad doses for the fluoroscopy in these two types of examination, which form 23 per cent of the total number of Japanese examinations.

(iii) In the Netherlands (Leiden) (table X),¹³ pelvimetric examinations are never performed and the number of obstetrical abdomen examinations is very low. Although the investigation reflects only Leiden, this statement is valid for the whole of the Netherlands.

(iv) Table XII, relating to Sweden,¹⁵ shows a high contribution to the genetically significant dose caused by foetal exposure during pelvimetry. Since the investigation was made, the examination technique for pelvimetry has been changed in Sweden with the result that the dose to the foetal gonads has been decreased to a small fraction of the previous dose.²⁵

(v) Table XVI (United Kingdom) shows that obstetrical abdomen examinations form nearly 70 per cent of the genetically significant dose caused by foetal exposure.¹⁹

34. In table XXIII, the annual genetically significant doses arising from X-ray diagnostic procedures in various countries and areas are brought together. The contributions to the genetically significant dose caused by diagnostic exposures of males, females and foetuses are given separately. For some countries and areas, estimates are also given of the uncertainty in the determination of the genetically significant dose.

35. Table XXIII gives information covering populations that together comprise over 200,000,000 individuals (6.7 per cent of the total population of the world).

36. Some estimates of the genetically significant dose arising from X-ray diagnosis do not include the contribution from dental radiography. However, available data show that this contribution is very small with values ranging from 0.01 to 0.15 mrem/y.

37. In the investigations from the Federal Republic of Germany (Hamburg)⁹ and from the Netherlands (Leiden)¹⁸ comparisons were made between the genetically significant dose computed according to formulas 8 and 11 in the appendix. The figures are set out in table XXIII. There is good agreement between the figures derived by the use of formula 8, which accounts for the relative child expectancy of the average individual for each type of examination, and by the simplified formula 11, which considers only the examinations performed on patients below the mean age of childbearing (usually thirty years). The per capita dose was also computed for Leiden and Hamburg. In these two cities the per capita dose is much higher than the genetically significant dose, which means that the relative child expectancy factor (w_1/w) is considerably less than unity for most of those types of examination that contribute most to the genetically significant dose. In other countries the per capita gonad dose may be of the same magnitude as the genetically significant dose as indicated in the last report. This depends upon the age distribution of the patients within the various types of examination and the future number of children expected to be conceived after the exposure.

(e) Consideration of the dose-rate effect

38. As was pointed out in paragraph 10, there is now experimental evidence with mice and insects that the genetic effect caused by irradiation is governed not only by the magnitude of the dose but also by the rate at which the dose is delivered. Table XXIV presents probable dose-rates to the gonads during some types of examination and during fluoroscopy and radiography. Because of the difference in the sites of the testes and the ovaries, the dose-rate to the ovaries is lower than to the testes when the gonads are in the primary beam. Since examinations usually consist of several radiographs of various sites and in different projections, and sometimes of both radiography and fluoroscopy, the dose-rate may vary considerably during an examination, by a factor of 1,000 and even more. Although table XXIV presents only probable dose-rates, these range from 0.005 mrem/sec to 2,000 mrem/sec, which is a difference of a factor 10⁵. The lowest dose-rate presented in the table is still 1,000 times higher than the dose-rate by which the natural radiation is delivered. The range of dose-rates used

by Russell in his experiments are quoted in table XXIV. These dose-rates, which were used in obtaining experimental evidence for dose-rate dependence, are within the range of dose-rates which occur in X-ray diagnosis.

39. Except for examinations consisting of only one radiograph, or continuous fluoroscopy, the dose to the patient strictly must be regarded as fractionated, even though for most examinations the duration is short compared with the time cycle of cells. An exception is the general film series taken over the alimentary tract. This type of examination may be conducted over a period of twenty-four hours, during which radiographs are taken at intervals of minutes or hours. The rate of delivery of the dose may either be represented by the actual dose-rate for each exposure, which usually does not last more than ten seconds, or by the average dose-rate over the total time for the examinations, e.g. twenty-four hours. The computed rate will thus differ by a factor of 10⁴, depending upon the criterion used.

40. Since Russell's experiments were carried out on mice with continuous irradiation, with a constant rate of dose delivery at doses of 100-1,000 rem, it is not possible to use his results for a quantitative determination of weighting factors for the dose-rate dependence in the calculation of the genetically significant dose arising from X-ray diagnosis. Neither is there information sufficient to take into account the variation in the sensitivity with the cell stage of the gamete.

(f) Reduction of the genetically significant dose

41. It is obvious that efforts to reduce the genetically significant dose should be devoted to the types of examination which give the highest dose contribution. Since the genetically significant dose (formula 8) caused by a type j examination (D_j) is the product of the frequency of conducting the examination (N_j/N), the relative child expectancy of the individuals examined (w_1/w) and the gonad dose (d_j), a decrease in the genetically significant dose may be achieved by a reduction in N_j , w_1 or d_j :

(i) N_j may be decreased by lowering the number of type- j examinations, which means more rigorous indications for the examinations;

(ii) w_1 may be lowered by a reduction of the number of examinations of young patients;

(iii) In general, however, the greatest effect in the reduction of the genetically significant dose can be obtained by lowering the dose to the gonads, d_j .

42. The ways of reducing the gonad dose are well known and are recommended in most of the papers on which the tables are based and they are summarized as follows:²⁰

(i) To reduce the number of radiographs per patient;

(ii) To reduce the length of time and the intensity of exposure;

(iii) To avoid, as much as possible, pre-set schemes of radiological examinations;

(iv) When fluoroscopy is not essential, to take radiographs only;

(v) To use the appropriate physical parameters, with special emphasis to the use of the smallest field size;

(vi) To avoid the inclusion of gonads within the primary beam;

(vii) To protect the testicles by adequate shielding of scrotum during male pelvic radiologic examinations; and

(viii) To train properly the staff engaged in X-ray diagnostic examinations.

43. The Adrian Committee¹⁹ states that the result of bringing the techniques in the 10 per cent of hospitals showing the highest doses up to the standard of the average technique of all the other hospitals would in total reduce the genetically significant dose to 70 per cent of the present one. If the techniques used by the 25 per cent of the hospitals in the survey showing the lowest doses were used by all hospitals it would mean a reduction of the genetically significant dose to less than 20 per cent of the present value. For Sweden, Larsson¹⁵ estimates that an increased use of already existing examination techniques, which give low gonad doses, would mean a reduction of the genetically significant dose to 40 per cent of its existing value. Such reduction may be achieved without detriment to the diagnostic information to be obtained from the examinations.

External radio-therapy by X-rays and sealed radio-active sources

44. As compared to those for X-ray diagnosis, there are few data for gonad doses and genetically significant dose caused by exposure of patients undergoing external radio-therapy. One of the reasons for this is that the first investigations showed that the contribution from external radio-therapy to the genetically significant dose was less than the contribution from X-ray diagnosis. However, detailed data on gonad doses and genetically significant dose arising from external radio-therapy have recently been obtained from the Federal Republic of Germany (Hamburg), France and the United Kingdom. To make estimates of the average gonad dose received during the treatment of any one disease is more difficult than for one diagnostic examination since a disease such as eczema may affect any area of the body and the details of the actual treatment are not always available. Therefore details of the treatment of a large number of patients are required to get a representative distribution of the sites affected by a particular disease.

45. Radio-therapy is used in the treatment of non-malignant and malignant conditions. It is necessary to consider in any calculation of genetically significant dose from radio-therapy the effect of the disease itself and the irradiation on the relative child expectancy. It may be assumed that neither the non-malignant conditions nor the radiation doses, with the possible exception of those in the regions of the gonads, affect the fertility of the patients. However, for patients suffering from malignant conditions the life expectancy is usually shorter than in the general population and in each age group of such patients a lesser number of children will be conceived as compared to the statistics for the whole population. The irradiation itself may cause decreased fertility, which would also reflect upon the number of children to be expected.

(a) National surveys

46. *Federal Republic of Germany (Hamburg):* The investigation performed by Holthusen, Leetz and Leppin⁶ also covers radio-therapy. The number of patients treated for various conditions, subdivided by sex and age, and the individual gonad doses were arrived at by the same methods as were used for X-ray examinations (para. 19). In their calculations Holthusen *et al.* have taken the fertility factors to be zero for patients who have been irradiated for malignant diseases, and presume that the genetically significant dose caused by

external radio-therapy arises only from irradiation for non-malignant conditions. The annual genetically significant dose is presented in tables XXV and XXIX in which the genetically significant dose is subdivided by various locations of treatment. The individual gonad doses and the numbers of patients treated are also set out. The genetically significant dose was calculated from formula 8. For comparative purposes, Holthusen *et al.* also calculated the genetically significant dose, using formula 11, and the per capita dose for the whole population (para. 19).

47. *France.* The figures for France in tables XXVI and XXIX are based upon an investigation by Reboul *et al.*²¹ who determined the number of patients who underwent external radio-therapy for various conditions in a large hospital. By means of information from the Sécurité sociale, these numbers, subdivided by sex and age, were extrapolated to cover the whole of France. The doses to the gonads in various types of treatment were measured with ionization chambers in the same way as has been described in paragraph 20. The genetically significant dose was calculated according to formula 11. In the cases of non-malignant conditions, only around 7 per cent of the dose, expressed by $\Sigma N_j \cdot d_j$, was estimated to have been given to patients below the age of thirty. When the contribution to the genetically significant dose from the treatment of malignant conditions was calculated, the cases with the most severe prognoses were disregarded. Also, the cases where the irradiation was expected to have caused sterility were disregarded. From the remaining cases, the numbers of patients below thirty years of age were estimated by means of their hospital records. These patients together form around 6 per cent of all those treated for malignant conditions.

48. *Netherlands.* The data presented in tables XXVII and XXIX are from an investigation by Scholte *et al.*²⁸ for the period 1942-1951 based on radio-therapy treatments in three large hospitals in The Hague, Leiden and Rotterdam. The survey does not include any contribution from dermatology. The calculations were made according to formula 8 and it was possible to use the actual number of children born to the patients up to 1960. The number of children conceived by the patients who received high gonad doses from pelvic region irradiation were only 53 per cent of those which would be expected from the number of legitimate live births in the period 1955-1959 in the Netherlands. Even though these statistics are not strictly comparable they emphasize the effect of the diseases and the irradiation itself on the relative child expectancy compared with that based on average values of the population.

49. *United Kingdom.* The data presented in tables XXVIII and XXIX have been taken from the report of the Adrian Committee¹⁹ which covers the United Kingdom except Northern Ireland. The numbers of patients treated for various conditions, subdivided by sex and age, were calculated from a sample study during three months in 1957 of all treatments carried out in United Kingdom hospitals and comprising around 30,000 patients. The doses to the gonads were calculated from information on the dose parameters used in various hospitals and private clinics and the results of dose measurements in a phantom under various conditions. The genetically significant dose was calculated according to the principles set out in formula 8. In the calculations of the contribution from radio-therapy of non-malignant conditions, it was assumed that the child expectancy was zero for all patients in whom an artificial menopause was

induced. For all other non-malignant conditions the fertility factors obtained from population statistics were used. In the calculation of the genetically significant dose caused by external radio-therapy of malignant conditions, due attention was paid to the changes in the fertility factors, as determined from official statistics, that are caused by the shortening of the patients' life expectancy and by the reduction in fertility, due to the radiation received by the gonads.

(b) Other investigations

50. In the United States, Clark²⁹ estimated the annual per capita dose of the total population due to external radio-therapy to be 12 mrem. He assumed that the gonad doses arising from irradiation for malignant conditions were of no genetic significance. A survey of the individual gonad doses received has also been carried out by Bailey.³⁰

51. A survey by Purser and Qvist³¹ yields an estimate of the annual genetically significant dose in Denmark (Copenhagen) of 1 mrem. In the Danish estimate, reduced fertility as a consequence of the severity of the prognosis of the disease and of the actual irradiation was allowed for by subdividing the patients into three groups, with the fertility factor being zero, one-fifth of normal, and normal, respectively. Twenty-two per cent of the genetically significant dose was assumed to arise from treatments of malignant disease.

52. For Australia, Martin^{32, 33} estimated the annual genetically significant dose from external radio-therapy to be 28 mrem. The estimate was made using the appropriate survival rates from the Central Cancer Registry. It was assumed that the prospects of parenthood were not impaired by the treatment, except for those patients receiving doses which would cause sterilization.

53. In the United Arab Republic (Cairo) a survey has been carried out in 1959-1960 of the frequency of treatments by X-rays.^{34, 35}

(c) Comments

54. Compared to the genetically significant dose originating from X-ray diagnosis (table XXIII) the genetically significant dose from external radio-therapy (table XXIX) is small. However, the individual gonad doses received from external radio-therapy are larger than from an X-ray diagnosis examination.

55. It is the practice in some countries to use radiation for so termed ovarian stimulation in cases of subfertility. Little data are available regarding the numbers of such treatments but a report³⁶ shows that, in 33 institutions surveyed in Buenos Aires, 222 cases were treated in 1960 representing some 2 per cent of the total number of patients treated by radio-therapy for non-malignant and malignant conditions. The radiation used was generated at 200-250 kV and the average dose to the ovary was 60 rem with a range of doses from 35-110 rem.

56. In the German investigation⁶ the annual genetically significant dose was calculated according to both formula 8 and formula 11. The per capita dose for the whole population was also calculated. On the basis of the data from investigations in France²⁷ and the United Kingdom¹⁹ the per capita dose to the population arising from the treatment of non-malignant conditions in each of the two countries has been estimated. The figures are set out in table XXX. As expected, the per capita doses are higher than the genetically significant doses.

Clark's figures for the United States of America,²⁹ 12 mrem, should be compared with the figures in the last column of table XXX, which are 6.5, 21 and 9 mrem in the Federal Republic of Germany (Hamburg), France and the United Kingdom respectively. The explanation for the difference between the figures for per capita dose and genetically significant dose is the same as was given in paragraph 37.

57. Both in the Federal Republic of Germany (Hamburg) (table XXV) and the United Kingdom (table XXVIII) the major part of the genetically significant dose caused by external radio-therapy for non-malignant conditions originates from treatments of the skin (around 55 and 75 per cent respectively). In France (table XXVI) the bulk of the corresponding genetically significant dose arises from treatment to the lumbar spine and the hips.

(d) Consideration of the dose-rate effect

58. For the reasons indicated in paragraphs 10 and 38 the probable dose-rates to the gonads during external radio-therapy of certain treatment areas, are given in table XXXI. The dose-rates have been calculated assuming a maximum dose-rate at the treatment site of 50 rem per minute. Since high doses to the gonads may cause sterility or reduced fertility, treatment sites have not been included in this table when the dose to the gonads during a complete treatment is estimated to exceed 200 rem. The dose-rates range between 0.002 mrem/sec and 50 mrem/sec, which means that the highest dose-rate is around 10^4 times greater than the lowest one. This range of dose-rates covers the lower portion of the range used by Russell in his experiments.

59. In most instances external radio-therapy is administered in fractionated doses. In external therapy for non-malignant conditions a total dose seldom exceeds 3,000 rem given over a period of two to three weeks, while for malignant conditions doses to the treated volume of up to 7,000 rem may be given. The period of treatment is varied, dependent on the total dose, up to about seven weeks. If the gonad dose-rates are calculated as mean dose-rates over these periods, the figures in table XXXI should be divided by a factor of around 10^3 . The lowest dose-rates would then be of the same magnitude as the delivery rate of natural radiation (3.10^{-6} rem/sec).

60. In radio-therapy, as in X-ray diagnosis (para. 40), it does not seem possible to use Russell's results for a quantitative determination of weighting factors for the dose-rate dependence in the calculation of the genetically significant dose. Neither is there information sufficient to take into account the variation in the sensitivity with the cell-stage of the gamete.

(e) Reduction of the genetically significant dose

61. In contra-distinction to X-ray diagnosis, where the radiation is a means for producing an image on a screen or a film, the dose in radio-therapy to be delivered to an actual part of the body is determined with regard to the effect that is sought by the treatment. With reference to paragraph 41, N_j , w_j and d_j govern the genetically significant dose. Regarding malignant conditions, where there are strong indications for treatment, N_j and w_j cannot be expected to undergo changes in favour of reduced genetically significant dose. For non-malignant conditions, it might be possible to reduce N_j and w_j by using stricter criteria for the treatment of non-malignant

conditions, especially among young patients. Reductions in the individual gonad doses, d_1 , when the gonads are not the sites of the irradiation, may be obtained as follows:

(i) By the use of strictly appropriate physical conditions of exposure, placing emphasis on the smallest possible radiation field and, for instance, the use of low energy radiation and beta-emitting sources in skin therapy;

(ii) By satisfactory shielding against leakage radiation;

(iii) By the use of scrotum protection;

(iv) By adequate positioning of the patients during treatment so that the gonads are as far away as possible from the primary beam.

Administration of radio-isotopes

62. Only a few national surveys exist on the contribution from the medical use of unsealed radio-isotopes to the genetically significant dose. It is assumed that this contribution is even less than the contribution from external radio-therapy. The number of cases to whom the isotopes were administered and the total quantities of isotopes are given in table III.

63. Since unsealed radio-isotopes are used for both malignant and non-malignant conditions, the same allowance described in paragraph 45 has to be made for possible changes in the fertility factors among patients. This means, for instance, that Au^{198} , although used in considerable quantities for treatment (table III) has been considered to be of no genetical significance.

(a) National surveys

64. In the present annex, national surveys and estimates of genetically significant dose are presented from Canada, the Federal Republic of Germany (Hamburg), the United Kingdom and the United States of America (table XXXII).

65. *Canada.* The figures in table XXXII are taken from an investigation published by Johns and Taylor.⁸⁷ They considered patients below thirty years of age (formula 11) but did not make any correction with regard to severe prognoses for malignant conditions. I^{131} formed 75 per cent and P^{32} 25 per cent of the genetically significant dose from the administration of radio-active isotopes.

66. *Federal Republic of Germany (Hamburg).* Holthausen *et al.*⁶ have studied the genetically significant dose from I^{131} (table XXXII). The dose was calculated according to formula 8 but the malignant conditions were disregarded (cf. para. 46).

67. *United Kingdom.* The Adrian Committee's results¹⁹ are presented in table XXXIII. The genetically significant dose was calculated from formula 8 and the normal fertility factors were modified for some of the malignant conditions. In table XXXIII the annual genetically significant dose is subdivided into the diagnostic use of radio-isotopes and their use for the treatment of malignant and non-malignant conditions. I^{131} delivers 60 per cent and P^{32} 40 per cent of the genetically significant dose from the administration of radio-active isotopes.

68. *United States of America.* Chamberlain⁸⁸ has estimated the annual genetically significant dose from the medical use of unsealed radio-isotopes. His results

are presented in table XXXII. The dose was calculated according to the principles of formula 11 and the genetical significance of treatment for conditions with severe prognoses was considered. It was estimated that only the use of I^{131} gave a dose of genetical significance.

69. In the national surveys presented above (paras. 65-68), calculation of the gonad doses was based on existing information regarding deposition in various organs and tissues and the effective half-lives of the radio-isotopes in question. In table XXXIV, some results are presented for gonad doses arising from the administration of 1 mc I^{131} or P^{32} .^{37, 39-41} Weijer *et al.*⁸⁹ obtained their results from measurements on patients with different diseases, thus allowing for disturbances in the normal distribution of I^{131} in the body. Regarding I^{131} , Johns and Taylor⁸⁷ found that the beta and gamma components formed 50 per cent each of the gonad dose. The figures in table XXXIV, or results from other investigations, can be used for estimating the genetically significant dose arising from the medical use of unsealed radio-isotopes in various countries.

(b) Comments

70. The contribution from the administration of radio-isotopes to the genetically significant dose is small (table XXXII) as compared to X-ray diagnosis (table XXIII) and external radio-therapy (table XXIX). Between 5 and 15 per cent of the genetically significant dose caused by the administration of radio-isotopes originates from their use for diagnostic purposes. The individual gonad doses are estimated to range between 25 mrem and 200 rem.

(c) Consideration of the dose-rate effect

71. The dose to the gonads from a deposited radio-isotope is received through continuous irradiation, with a decreasing rate of delivery as a consequence of the excretion and the decay of the radio-isotope. The initial dose-rate to the gonads per millicurie administered I^{131} or P^{32} is of the order of 10^{-8} mrem/sec. This estimate does not allow for differences in dose-rates as a consequence of various distances from the gonads to the deposits of activity in the body. Since the administered amounts of radio-isotopes usually range between around 5 μ c in diagnosis and 200 mc in therapy, dose-rates may range between 5.10^{-6} mrem/sec to 0.2 mrem/sec.

72. Although these dose-rates should be regarded as rough estimates, they are lower than the ones used by Russell in his experiments. It is not possible at the present time to take into account variations of dose-rate or of the cell-stage of the gamete.

(d) Reduction of the genetically significant dose

73. Since the administration of radio-isotopes contributes only 1 or 2 per cent to the genetically significant dose caused by medical exposure, there is no urgent need for improvements aimed at lowering this contribution. The amounts of radio-isotopes used can be decreased in diagnostic investigation by further improvement of the sensitivity of the measuring instruments and by the use of *in vitro* rather than *in vivo* tests. Particular care is necessary when labelled substances are used which are incorporated into the chromosomes, such as thymidine, for these may result in high radiation doses to the genetic material. In therapy, deposits of radio-isotopes in organs and tissues which are not objects of treatment, can sometimes be reduced by special measures. For instance, high fluid intake following I^{131} administration induces fre-

quent micturition, thus reducing the residual time in the bladder of the excreted radio-isotope.³⁹ This causes a decrease in the dose to the gonads.

Summary

74. The annual genetically significant dose from medical exposure has been shown to be in the range 6-58 mrem from diagnostic radiology for those countries given in table XXIII. The contribution from radio-therapy and the use of radio-active isotopes has been shown in tables XXIX and XXXII to be in the ranges 2-13 mrem and 0.18-0.42 mrem respectively. Due to the many national and international reports on the subject which have been issued in the last seven years there is a greater awareness of the desirability of reducing the genetically significant dose. This has resulted in many countries in a downward trend in the levels estimated. For the purposes of making comparisons of risk in annex H, it has been accepted according to table XXIII that a representative value of the genetically significant dose would be 30 mrem/y from diagnostic exposure and 5 mrem/y from radio-therapy.

EXPOSURE OF THE BONE-MARROW

75. This section of the annex summarizes the data regarding the doses received by the active bone-marrow of patients undergoing radiological examinations or treatments. This tissue is regarded as the significant one in respect to the induction of leukaemia by radiation (D, 254-271, 485-489). It has been suggested (H, 8) that the mean dose to a tissue should be used, in the light of present knowledge, for the assessment of the effects of radiation at these dose levels. The term "mean marrow dose" is defined as the dose received by any portion of the active marrow averaged over the whole mass of active marrow. The mean marrow dose can either be given for an irradiated individual or as a per capita dose for a population.

Determination of the mean marrow dose

76. The marrow doses presented below are given as individual mean marrow doses for various types of radiological procedure. Mean marrow doses are usually obtained from dose measurements with small ionization chambers placed either on the skin in the radiation field or at the actual site of the primary irradiated bone-marrow. In the latter case, the measurements are made in phantoms which undergo the irradiation procedures. The phantoms should represent as closely as possible, in size, shape and material, the radiation conditions *in vivo*. Since measurements with ionization chambers express exposure doses in roentgens under given conditions, the absorbed doses have to be calculated with the application of appropriate conversion factors. When calculations are based on exposure doses to the skin, the dose figures have to be multiplied by the percentage depth dose at the location of the bone-marrow in question, corrected for the shielding effect of the bone surrounding the bone-marrow.

77. In soft tissues adjacent to bone, the absorbed dose is increased by secondary electrons, which are generated in the bone. This should be allowed for in the calculation of the absorbed dose to the bone-marrow. A discussion of this effect is included in the report of the ICRU.⁴² A typical example from this report shows that within a marrow cavity of size 400 μ , irradiated by radiation of

photon energy 50 keV, there is a 13 per cent increase in the dose received by soft tissue remote from bone.

Distribution of active bone-marrow

78. The calculation of the mean marrow dose presupposes knowledge of the distribution in the body of the active bone-marrow. A comprehensive study was carried out by Mechanik⁴³ of the quantitative distribution of the total bone-marrow in adults. A summary of his data has been published by Woodard and Holodny.⁴⁴ These studies do not, however, give any information on the distribution of the active marrow. Studies on the distribution of the active marrow have shown that before birth the liver and spleen are the major erythropoietic organs, the activity of the liver being equal to that of the bone-marrow at 7½ months. At birth all bones which contain marrow have active red marrow; however with increasing age this is gradually replaced in some bones by inactive yellow marrow. By the age of eighteen to twenty years little red bone-marrow exists in the limb bones, except for the proximal epiphysis of femur and humerus.⁴⁵ A gradual replacement also takes place in all adult bones with increasing age and measurements of this effect have been given by Custer⁴⁶ for the ribs, sternum and vertebrae. Ellis⁴⁷ has calculated from the data of Mechanik and Custer the distribution of total and active marrow in the adult (table XXXV). This table also gives the set of distribution figures that was presented in the Committee's 1958 report.

79. Further research on the distribution of the bone-marrow is needed, for it is well known that the distribution of active marrow varies very much between adult individuals. Also diseases or other conditions which impose a stress on the haematopoietic system cause the red marrow to reappear in the limb bones. Large radiation doses to local volumes of active marrow may also cause variations in the active bone-marrow distribution.⁴⁸

Dose data

80. There are few available data on mean marrow doses from medical exposure.

X-ray diagnosis

81. In its 1958 report the Committee presented mean marrow doses calculated on the basis of assumed average practice and available information for various types of examination—number of radiographs, skin doses and depth dose data. Several of these dose figures are set out in table XXXVI, together with the results from a Danish investigation performed by Buhl,⁴⁹ and from measurements by Epp *et al.*^{50, 51} A national survey has been conducted in the United Kingdom (para. 28) and extensive phantom measurements at eleven marrow sites are being used to derive a per capita mean marrow dose.

82. Even though the investigations presented in table XXXVI show differences between the dose figures in each of several types of examination, the order of the types of examination with regard to the size of the dose is nearly the same in the investigations. These types are examinations of the upper and lower gastro-intestinal tract (barium meal and barium enema), the gall bladder, dorsal and lumbar spine, and the lumbosacral region. Pelvimetry also belongs to those types of examination giving among the highest mean marrow doses. The differences in the dose figures reported for any one examination are due to the variations in the assumed extent and techniques of the particular examination and the values of percentage depth doses used.

83. It is obvious that the mean marrow dose will depend upon the field size and the incident skin dose. Another parameter that influences the magnitude of the mean marrow dose is the quality of the radiation used. For radiography of the chest, Epp, Weiss and Laughlin⁵⁰ showed that a low kilovoltage technique (60 keV, 1-2 mm Al filter) gives 50 per cent greater mean marrow dose than kilovoltages between 80 and 120 (2-3 mm Al filter), for which the mean marrow dose is nearly constant. Weber⁵² has reported similar results for radiography of the stomach (barium meal) and abdomen. He found 50 per cent higher mean marrow doses at 70 keV (2 mm Al filter) than at 90 keV (3 mm Al filter).

84. In paragraph 31 it was pointed out that in some countries mass survey examinations of the chest are performed by means of either fluoroscopy or radiography (table XVII). Skin doses to patients from fluoroscopy may amount to more than 100 times the skin dose when radiography is used.⁵³ While reported mean marrow doses for mass survey examinations of the chest using radiography range between 50 and 100 mrem, it has been calculated that mass survey fluoroscopy in Austria, France and Spain gives mean marrow doses averaging 1,900, 1,200 and 1,300 mrem respectively.⁵³ For Belgium and Switzerland, the corresponding doses were reported to be 380 and 230 mrem respectively. The doses are set out in table XXXVII. Owing to differences between apparatuses and the duration of the fluoroscopy, the individual mean marrow doses range from around 200 mrem up to around 4,000 mrem. Since many of the examinations in France¹⁰ are made on young people (40 per cent on individuals below the age of twenty) the figures for the mean marrow doses, calculated by means of distribution figures for the active marrow in adults, may be rather uncertain (para. 78). It is obvious from this table that in order to reduce the dose, mass miniature radiography should be used rather than mass survey fluoroscopy (cf. para. 31).

85. In the 1958 report of the Committee (annex C, para. 50) an estimate of the population per capita bone-marrow dose was made and it was suggested that it might be of the order of 50-100 mrem/y. The Committee has no reason to alter this estimate, as little information has been obtained since the last report.

External radio-therapy by X-rays and sealed radioactive sources

86. Few data on bone-marrow doses are available at present for patients who have undergone radio-therapy. Comprehensive measurements of the radiation doses to the spinal marrow in a phantom were carried out by Jones and Ellis⁵⁴ as part of the survey by Court Brown and Doll⁵⁴ on patients irradiated for ankylosing spondylitis. Maudal⁵⁵ has also made measurements of doses to organs and tissues for several sites of treatment. The latter investigation also gives data regarding the dose received by sites outside the primary beam. Further measurements have also been conducted in the United Kingdom as part of the national survey. All these measurements give the dose at the particular site in terms of 100 rem incident at the skin. Table XXXVIII gives representative values of the mean marrow dose received during such treatment.

87. Holodny, Lechtman and Laughlin⁵⁶ have reported mean marrow doses arising from the treatment of cervix carcinoma with radium applicators. Their results, presented in table XXXVIII, are based on measurements of the doses in a body-shaped phantom at different sites

of the bone-marrow. They calculated the mean marrow doses by means of Ellis's distribution figures for active marrow.

88. Mean marrow doses to children below two years of age who were treated with radium skin applicators for haemangioma have been reported by Nordberg.⁵⁷ Dose measurements were made in a phantom which, in shape and size, corresponded to a child below the age of two. It was assumed that the active bone-marrow is distributed throughout the skeleton. The mean marrow doses were calculated by means of the data on the distribution of marrow space given by Woodward and Holodny⁴⁴ assuming that the distribution of marrow space in children is the same as in adults. The results are given in table XXXVIII and the distribution figures used are presented in a footnote to the table.

Administration of radio-isotopes

89. The data at present available to the Committee on relevant parameters for I¹³¹, P³² and Au¹⁹⁸ do not suffice for estimating the individual mean marrow doses with any certainty. The estimates of the total dose to the blood following administration of these isotopes give a first approximation of the mean marrow dose.^{37, 39}

Comments

90. The mean marrow doses caused by external radio-therapy are, of course, much higher than the ones caused through X-ray diagnosis. A diagnostic examination of the lumbar spine results in a mean marrow dose of 100-400 mrem, but the treatment of this site for non-malignant conditions may give a mean marrow dose that is 100 times greater. In certain types of radio-therapy for malignant conditions, the mean marrow doses may be even higher.

DOSE TO OTHER ORGANS AND TISSUES OF SPECIAL INTEREST

General remarks

91. The organs and tissues which, in addition to the gonads and the bone-marrow, are usually considered of special interest with regard to radiation doses are the foetal tissue, the lenses of the eyes, the thyroid, skin, and the liver. Information regarding the effects caused by the irradiation of these organs are given in annex D together with analyses of the radiation doses which have caused them. Other information is given in the report of the meeting, held at the Committee's invitation, of the ICRP/ICRU Study Group in 1960.⁵⁸

Data

92. Table XXXIX gives a few examples of the radiation doses which may be received by these selected tissues as a consequence of various radiological procedures. The doses must not be considered as being the results of extreme circumstances but as figures obtained from radiological procedures at present or recently used in various countries. Particular points regarding each tissue are given in the following paragraphs.

Foetal tissue

93. During the first two months after conception, it may happen, because of unawareness of pregnancy, that women undergo various kinds of radiological procedures which would not have been performed if the pregnancy had been known. Because of the small dimensions of the

foetus at this stage, the foetal dose can be regarded as the same as the dose to the maternal gonads. Data regarding the incidence of malignancies following irradiation *in utero* are given in annex D, paragraphs 277-285, and table VII.

Lens of the eye

94. Full mouth examination and encephalography are two X-ray diagnostic procedures which may give substantial doses to the lens of the eye. Similarly, treatment of lesions of the eye, or in the region of the eye, may also contribute high doses. Data regarding the formation of cataract or lens opacity is given in annex D, paragraphs 91-93, 289-307 and 443-445.

Thyroid

95. Tests of thyroid functions are frequently performed in most countries. The dose to the normal adult thyroid is about 1.5 rem per μ C administered I^{131} . Barium swallow and examination of the cervical spine are assumed to be the two types of commonly performed X-ray diagnostic procedure which give the highest dose to the thyroid. The treatment of hyperthyroid conditions and heart conditions with I^{131} gives doses of the order of 10,000 rem to the thyroid (see para. 96 below) (D, 286, 402-404).

Thymus

96. In some countries enlarged thymus glands have been treated by radiation with doses of the order of 200 rem. In annex D, paragraphs 263-272, 485 and table VI, data are given regarding surveys carried out on the incidence of leukaemia and thyroid cancer in these patients.

Liver

97. The use of thorotrast as a contrast medium in diagnostic radiology has been curtailed since its possible deleterious effects have been recognized. The effects observed are sequelae at the site of injection and the induction of liver malignancies. Reports of surveys of patients injected with thorotrast have been given by Hursh *et al.*,⁵⁹ Baserga,⁶⁰ Looney⁶¹ and Blomberg *et al.*,⁶² Studies of the radiation doses received have been carried out by Rotblat and Ward⁶³ and Rundo.^{64, 65} A comparison of the doses to various body tissues over twenty years from an injection of 20 ml thorotrast is given in table XL from Marinelli.⁶⁶

Reduction of doses to various organs and tissues including the bone-marrow

98. Earlier in this annex (paragraphs 41, 42, 61) the Committee has considered ways of reducing the doses to the gonads. Most of these measures are also applicable for the reduction of doses to other organs and tissues and can be summarized as follows:

- (a) Improved methods of radiological procedure;
- (b) The use of strictly appropriate physical conditions of exposure, including the smallest possible radiation field and good collimation of the beam;
- (c) The reduction of the incident skin dose, e.g. by reducing fluoroscopy time;
- (d) Satisfactory shielding against leakage radiation;
- (e) The use of radio-active isotopes in diagnostic investigations utilizing *in vitro* rather than *in vivo* tests and the use of the nuclide with the shortest half life consistent with the requirements of the investigation; for

example, I^{132} may be used rather than I^{131} for some thyroid investigations.

(f) Well-trained staff of all categories for the performance of the procedures.

FIELDS OF RESEARCH

99. The present state of knowledge requires that consideration should be given to the following items and that research in these fields should be encouraged:

- (a) The promotion of statistical studies concerning the number of people medically exposed;
- (b) Follow-up studies on the offspring of pregnant patients having radiological examinations or treatments of the pelvic region;
- (c) Follow-up studies of patients having had (i) radio-therapy for non-malignant conditions such as ankylosing spondylitis and enlarged thymus; (ii) I^{131} treatment, or (iii) diagnostic examinations using thorotrast as a contrast medium;
- (d) Investigations aimed at defining good practices in diagnostic radiology so that minimum gonad doses are received;
- (e) Investigations of the effect of dose-rate on the production of mutation;
- (f) More quantitative information on the distribution of active marrow and how it varies with age;
- (g) Investigations of the dose received by the bone marrow during radiological procedures.

III. Occupational exposure

100. In the introduction to the present annex (para 3) the Committee considered the term "occupational exposure" as being applicable to all activities involving exposure of individuals to ionizing radiation in the course of their work, regardless of whether they are directly engaged in radiation work or not.

NUMBER OF INSTALLATIONS AND RADIATION WORKERS

101. Work with ionizing radiation is usually subdivided with regard to the purpose of the work as follows: medical (diagnosis and therapy), dental, veterinary, industrial, research and educational, and atomic energy. Table XLI gives the range of the number of X-ray installations* per thousand of total population for these purposes in the Netherlands,⁶⁷ New Zealand,⁶⁸ Norway,⁶⁹ Sweden,⁷⁰ Switzerland,⁷¹ and two areas of the United States of America, New York City⁷² and California.⁷³ Most of the installations for medical and dental purposes have X-ray apparatus only. The number of X-ray installations used for veterinary, industrial, and research and educational purposes, is at present very small compared with those used for medical purposes.

102. Only a few data exist on the number of installations where radio-isotopes are used. In California, work with radio-isotopes is performed in 6 per cent of the total number of installations and most of this work is done where X-ray work also is performed.⁷² Even in work with radio-isotopes is carried out in the majority of hospitals and of industrial and research installations: the large number of private medical and dental practices.

* "Installation" covers any department or private practice. If a hospital has a central X-ray department as well as X-ray facilities in various other sections of the hospital, each one is counted as an installation.

tioners using X-ray apparatuses exclusively, keeps the figure low as compared to X-ray installations. It does not seem likely that in any country the number of installations where radio-isotopes are used would surmount 10-20 per cent of the total number of installations.

103. Table XLI also gives the ranges of the numbers of individuals per 1,000 of the population directly occupied in radiation work in the countries listed in paragraph 101.

RECOMMENDATIONS ON THE CONDITIONS OF WORK

104. Recommendations regarding the exposure of workers to ionizing radiation have been made by the ICRP.¹ The doses to which their suggested limits apply do not include the contributions from natural sources of radiation, or from the exposure of the workers for medical reasons. The maximum permissible levels of exposure are kept under constant surveillance and the present recommendations state that for the dose "accumulated in the gonads, the blood forming organs and the lenses of the eyes, at any age over 18, shall be governed by the relation $D = 5 (N-18)$ rem where D is tissue dose in rem and N is age in years". The ICRP goes on: "To the extent the formula permits, an occupationally exposed person may accumulate the maximum permissible dose at a rate not in excess of 3 rem during any period of 13 consecutive weeks". Exposure limited to certain parts of the body, such as the extremities, or to single organs, as in the case of internal exposure, is subject to special recommendations allowing somewhat higher doses. Based on these recommendations many national and international organizations have produced their own rules and recommendations.

DOSE INFORMATION FROM INDIVIDUAL MONITORING

105. Table XLII sets out average figures for the annual occupational exposure to individuals from external X- and γ -ray sources in various kinds of radiation work in Argentina,⁸⁰ Canada,⁷⁹ the Netherlands,⁸¹ Norway,⁷⁴ and the United Kingdom.⁷⁶ In Norway and the United Kingdom, for which doses are given separately for diagnosis and therapy, the annual doses in therapeutic work are higher than in diagnosis. This may be explained by the fact that therapeutic work involves the handling of radium applicators. It is necessary that there be a continuous improvement of protection devices, especially for work with radium applicators.

106. Even though the average values received by workers are of interest, the distribution of doses and the number of personnel exceeding the recommended annual level is of more importance. A comprehensive analysis of the doses received by the 12,000 workers in the Federal Republic of Germany has been given by Wachsmann⁷⁶ and shows for the years 1952 to 1959 the gradual reduction in the number of persons exceeding the recommended level. In 1952, 23 per cent exceeded 0.4 rem/mo while in 1958 only 4 per cent were observed. The division of these into medicine, industry and research showed that 31 per cent, 12 per cent, and 14 per cent respectively of the personnel working in these fields exceeded 5 rem/y. It is known that there has been over the last decade a great improvement in the doses received by workers so that reports^{87, 76, 77} show that only 0.1-0.5 per cent of the dose measurements show doses of such a magnitude that the individual, if these doses continued to be recorded, would exceed the maximum permissible annual or quarterly levels.

107. For atomic energy work, detailed results have been published on the extensive monitoring of individuals for occupational exposure. Table XLIII gives data on occupational exposure from penetrating radiation at Oak Ridge National Laboratory, United States,⁷⁸ the establishments of the United Kingdom Atomic Energy Authority,⁷⁶ Argentina,⁸⁶ Canada⁷⁹ and the United Arab Republic.⁸⁰

Internal contamination

108. As far as occupational exposure caused by internal contamination of the body by radio-isotopes is concerned, surveys are frequently made on the radio-activity in the air and water and by whole body counting and urine surveys the inhaled or otherwise absorbed radio-isotopes may be estimated. During usual working conditions the surveys have given concentrations far below the highest permissible concentrations, corrected to allow for occupational exposure by external radiation. At Oak Ridge National Laboratory⁷⁸ the level of air contamination in the laboratories during 1959 was only 0.4 per cent of the assumed maximum permissible concentration (10^{-9} $\mu\text{C}/\text{cm}^3$ of air). Regarding surveys of body burdens of radio-isotopes, practically no concentrations beyond the maximum permissible ones have been detected for radio-isotopes other than uranium.^{76, 81}

Mining: industrial processing of uranium and thorium

109. High concentrations of radon and thoron and daughters exist in mines. In areas of poor ventilation where high-grade uranium ores or radium enriched residues are stored, the radon concentrates may be as high as 10^{-4} to 10^{-6} $\mu\text{C}/\text{cm}^3$ of air.⁸² Experience has shown, however, that the concentrations of radon daughter products can be greatly reduced by forced ventilation.⁸³ During the industrial processing of uranium and thorium, fine dusts are often produced and precautions must be taken to prevent inhalation of them.^{84, 85} Consideration of these hazards is given in the report of the United States National Academy of Science on the effects of inhaled radio-active particles,⁸³ which also gives data regarding the radon concentration in seventy-five uranium mines surveyed in Utah. Information is also available for the Argentinian,⁸⁶ Canadian,⁸⁸ French,⁸⁷ and South African⁸⁸ uranium mines, and the phosphate mines in the United Arab Republic.⁸⁹ Since uranium is excreted very rapidly from the body, concentrations of the isotope can easily be detected in man. In the workers in Argentinian⁸⁰ mines mean levels of uranium in the urine vary from 2-29 micrograms excreted per 24 hours.

Luminizing industry

110. Total body burdens of 273 persons employed in the luminizing industry have been measured in the United Kingdom.⁷⁶ Ten of these were found to have body burdens in excess of 0.1 μC radium, the highest being 0.6 μC . Twenty-nine persons had burdens between 0.05 μC and 0.1 μC and 234 had burdens less than 0.05 μC . All those persons having burdens above 0.05 μC were employed before the introduction, in 1942, of the first regulations. An incident involving the occupational contamination from Sr^{90} used in the luminizing industry has been reported from Czechoslovakia.⁹⁰

ESTIMATES OF OCCUPATIONAL EXPOSURE IN HIGH ALTITUDE AIRCRAFT

111. Cosmic radiation increases with altitude. Commercial jet aircraft fly at an altitude of 8-12 km (25,000-

40,000 feet), while military jet aircraft may reach an altitude of 16 km (50,000 feet). According to estimates in the United Kingdom⁷⁵ and in the United States,⁹¹ the annual radiation dose to a crew at 16 km amounts to 400-500 mrem. At an altitude of 12 km, the corresponding dose is around 300-350 mrem. Dose figures relate to a northern latitude of around 40°, assuming 80 hours' flying time per month.

112. It is anticipated that supersonic transport aircraft, if and when they become commercially available, may fly at altitudes of up to 26 km (85,000 ft). Aircraft crews might be expected to fly a maximum of 40 hours per month at these altitudes. It has recently been calculated by Foelsche⁹² that at a latitude of N 50° a crew, under these assumptions, would be exposed to an annual dose of approximately 1,500 mrem. However, during intense solar flares a few hours' supersonic flight at an altitude of 24 km may cause a dose of 8,000 mrem. If these solar flares can be predicted in advance, aircraft flying at very high altitudes would be able to descend to lower altitudes before the peak activity is reached.

113. The contribution to the dose from contamination of an aircraft by surrounding radio-active particles can be disregarded, although the exposure of maintenance staff has received some consideration.^{91, 93}

114. Consideration⁹⁴ has been given to the computation of the radiation likely to be received by space crews and also to the problem of determining the dose due to protons in solar flares.^{95, 96}

GENETICALLY SIGNIFICANT DOSE

115. By the use of dose information obtained from individual monitoring, the genetically significant dose from occupational exposure has been reported from a number of countries. Allowance has been made for the age distribution of the workers. The estimated annual genetically significant doses calculated from formula 11 (see appendix) give the following results:

	Dose mrem	Year of Estimation
Austria ¹¹⁹	0.2	1955
Netherlands ⁸⁷	0.3	1960
United Kingdom ⁷⁵	0.4	1959

In the United Kingdom, the contribution to the genetically significant dose from atomic energy establishments has been calculated to be 0.15 mrem. There is no reason at present to assume that the genetically significant dose from occupational exposure in other countries would considerably exceed the figures listed above.

MEAN MARROW DOSE

116. No data are available on the actual mean marrow dose from occupational exposure. However, the values given in table XLII may be regarded as the dose at the skin and therefore the bone marrow doses will be considerably smaller.

IV. Other exposures

117. In addition to the doses received by individuals, either as patients undergoing medical radiological procedures or by radiation workers during working hours, irradiation may come from other man-made sources.* These comprise such sources as X-ray fluoroscopy for

shoe fitting, luminous markings in clocks and watches and other luminous devices, and television sets. The public living in the vicinity of radiological installations and passengers in aircraft may also receive additional radiation. Some of the more important sources are considered in the following paragraphs.

RADIOLOGICAL INSTALLATIONS

118. Members of the general public living near or having access to these installations may receive small doses mainly from scattered radiation. The Committee notes that the ICRP¹ has made recommendations that such people should not receive from such exposure more than 500 mrem per year in the gonads, the blood forming organs and the lenses of the eyes.

X-RAY FLUOROSCOPY FOR SHOE FITTING

119. A survey by Seelentag and Peck⁹⁷ has comprehensively reviewed the literature regarding the doses received from these machines. They also report measurements on ten different units. The average annual genetic dose to the population of the Federal Republic of Germany was estimated as 4-7 microrem per year. The Medical Research Council of the United Kingdom⁷⁵ estimated in 1956 that the annual genetic dose in that country from this source was not more than 0.1 per cent of that received from natural background and that after the full implementation of present legislation (by 1963) the dose would be reduced to some 0.01 per cent. In several countries fluoroscopy for shoe fitting has been prohibited since it is regarded as causing unnecessary radiation exposure.

LUMINOUS MARKINGS IN CLOCKS AND WATCHES

120. Reports of the activities of watches and clocks have been made in Germany,⁹⁸ Norway,⁹⁹ Sweden,¹⁰⁰ Switzerland¹⁰¹ and the United Kingdom.⁷⁵ These show that there is a wide variation in activities of watches and clocks up to about 0.5 microgram of radium with a mean value of about 0.1 microgram. Estimates of the annual genetically significant dose from this source are 2.6 mrem,⁹⁸ 1-3 mrem,¹⁰⁰ 8 ± 3 mrem,¹⁰¹ and 0.5 mrem.⁷⁵ The annual dose to the sales staff has been estimated as 90 mrem.⁹⁸

TELEVISION SETS

121. The ICRP¹ has recommended that the dose-rate at any accessible point 5 cm from the surface of any set used in the home or place where the public is likely to be shall not exceed 0.5 mrem/hr under normal operating conditions. Braestrup and Wycoff¹⁰² have shown that at 15 kV, the normal operating voltage of home television sets, the dose-rate at the surface of the screen is about 1 mr/hr. However, most sets are provided with a further plastic or glass sheet which reduces the dose-rate, but when these sets are operated above normal voltages, for testing purposes for example, then the dose-rate may be increased greatly. Operation at 24 kV increased the dose-rate by a factor of 1,000. It has been pointed out that colour television tubes operate at about this voltage so that further shielding is required to conform to the ICRP recommendation.

122. The dose-rates received by the operators of projection TV units working at 80 kV may be of the order of 10 mrem/hr, but high dose-rates of the order of 1 r/hr have been measured close to the tubes. However, these are not in the direction of the audience.¹⁰²

* Environmental contamination is dealt with in Annex F.

123. Braestrup¹⁰⁸ has estimated that the average gonad dose from home television is much less than 1 mrem/yr.

PASSENGERS IN AIRCRAFT

124. The enhanced cosmic radiation experienced in aircraft makes a negligible contribution to the total dose received by the population at the present time.

USE OF NUCLEAR POWER IN SHIPS

125. Information has been given of the predicted radiation levels to the workers and public from the use of nuclear propulsion in ships.^{104, 105} The doses received by occupationally exposed workers were on the average

about 0.5 rem/y and were up to a maximum of 1-2 rem/y.¹³⁰ The activities discharged as waste from these vessels are unlikely at the present time to make any contribution to the dose received by the general public.

GENETICALLY SIGNIFICANT DOSE

126. The use of these miscellaneous sources is likely to contribute about 2 mrem/y, mainly from the use of luminizing of clocks and watches. However, with the increasing uses of miscellaneous sources of radiation, none of which individually contribute an appreciable dose, the total genetically significant dose may be expected to increase slightly.

Appendix

1. A general definition of genetically significant dose has been given in paragraph 9 above. Approximations must be made to calculate this dose, the most obvious being consideration of groups rather than individuals. It is convenient to start with the approximate definition*

$$D = \frac{\sum_j \sum_k (N_{jk}^{(F)} w_{jk}^{(F)} d_{jk}^{(F)} + N_{jk}^{(M)} w_{jk}^{(M)} d_{jk}^{(M)})}{\sum_k (N_k^{(F)} w_k^{(F)} + N_k^{(M)} w_k^{(M)})} \quad (1)$$

where

D = (annual) genetically significant dose,
 N_{jk} = (annual) number of individuals of age-class k ,
 subjected to class j exposure,
 N_k = total number of individuals of age-class k ,
 w_{jk} = future number of children expected by an exposed individual of age-class k subsequent to a class j exposure,
 w_k = future number of children expected by an average individual of age-class k ,
 d_{jk} = gonad dose per class j exposure of an individual of age-class k ,
 (F) and (M) denote "female" and "male" respectively.

2. For the practical work, formula 1 can be simplified considerably, the first step being to replace the denominator by $w \cdot N$, where

$$w = \frac{N^{(F)}}{N} \cdot w^{(F)} + \frac{N^{(M)}}{N} \cdot w^{(M)} \quad (2)$$

and

$$w^* = \frac{1}{N^*} \sum_k w_k^* N_k^* \quad (3)$$

In the last expression, * denotes the sex. N is the total number of individuals of the population. It should be noticed that $w \cdot N$ is about twice the future number of children expected by the present population even though the value of w may be as low as 0.8.

3. As formula 1 has w^* in both the numerator and denominator, the numerical value of w has no direct relevance, and all terms can be expressed by help of the ratio w_{jk}/w . For understanding of the demographic background, however, it is valuable to realize that w must be calculated from the sum of the age-group products $w_k^* \cdot N_k^*$ for a population, which means that an assumption has to be made regarding the expected

future number of children (w_k^*) of an individual in any specified age-group.

4. The assumption could be that the average individual will have a future annual child-expectancy expressed by the present specific annual birth rate. This makes it possible to calculate, by summation, the total future expected number of children of an individual of any age, and hence also the mean for any age-group. If significantly less than unity, the probability of an individual of age a to reach age t should also be considered. This gives

$$w_a^* = \sum_{t=a}^{\infty} c_t^* \cdot \Delta t \cdot P_a^*(t) \quad (4)$$

where

w_a^* = expected future number of children of an individual of age a . With knowledge of the function w_a^* of age, the average w_k^* for any age-group k can be calculated,

c_t^* = age-specific annual birth rate, i.e., annual expected number of children of an individual of age-group t ,

Δt = number of years included in age-group t ,

$P_a^*(t)$ = probability of an individual of age a to reach age (group) t .

5. It must be noted that c_t^* may have a tendency to change considerably before an average individual of a specified age has reached the age-group in question. As it is, however, difficult to predict the values for the future, c_t^* has been assumed not to vary with time.

6. $W^* = w_{a \rightarrow 0}^*$ is the number of children expected by the average individual during his whole life. The range of w^* is normally 0.8-2, and the range of W^* is 2-4 for most developed countries. The ratio W/w ranges from 1.5 to 3.

7. The female and male contribution to the genetically significant dose can both be written

$$D^* = \frac{1}{wN} \sum_j \sum_k N_{jk}^* w_{jk}^* d_{jk}^* \quad (5)$$

8. If the gonad dose due to an examination of type j is nearly uniform for all age-classes k , then

$$d_{jk}^* = d_j^* \quad (6)$$

approximately for all k , and formula 5 reduces to

$$D^* = \frac{1}{wN} \sum_j d_j^* \sum_k N_{jk}^* w_{jk}^* \quad (7)$$

or

$$D_j^* = d_j^* \cdot \frac{1}{wN} \sum_k N_{jk}^* w_{jk}^*$$

* The degree of approximation involved in the use of formula 1 depends on the definition of classes j . In theory, there need be no approximation since the classes may be made so restrictive as to include only one individual per class.

where D_j^* is the contribution from type j examination of the specified sex to the genetically significant dose. This again can be written as

$$D_j^* = d_j^* \cdot \frac{N_j^*}{N} \cdot \frac{w_j^*}{w} \quad (8)$$

which is the expression for numerical calculations.

9. The necessary information to make it possible to calculate D_j^* by help of formula 8 is:

- (a) d_j^* = the mean gonad dose per individual undergoing class j examination;
- (b) N_j^*/N = the relative frequency of class j examination, i.e., the number of examinations per capita, per year;
- (c) w_j^*/w = the relative child-expectancy of the average individual undergoing class j examination.

The formula is applicable also to foetal exposure ($w_j = W$) which must not be overlooked.

10. Often d_j varies considerably from hospital to hospital. Most of the uncertainty in estimates of D_j is probably due to the difficulty of estimating a reliable average of d_j for a population.

11. If there are no data on the child-expectancy of the patients, an approximate estimate of D_j^* may be made, under the assumption that the child-expectancy is not influenced by the nature of the condition for

which the patient is examined. w_j^* can then be calculated from the age-distribution of the patients and the normal child-expectancy for each age-group,

$$w_j^* = \frac{\sum_k w_{jk}^* N_{jk}^*}{N_j^*} \approx \frac{\sum_k w_k^* N_{jk}^*}{N_j^*} \quad (9)$$

where w^* can be taken from formula 4. If w_j^*/w is not given in the primary material, it may be recalculated from N_j^*/N , d^* and this approximation of D_j^* , but will in that case reflect only variations in the age-distribution of the patients examined and not indicate any dependence of child expectation on type of examination.

12. In the case where the age-distribution in an examination class is not known, a yet more simplified assumption may be used, namely

$w_k^* = W^*$ for all persons below mean age of child-bearing,

$w_k^* = 0$ for all persons above mean age of child-bearing. If n is the total number in the population below the mean age of child-bearing, it follows from formula 3 that

$$w^* = \frac{n}{N^*} \cdot W^* \quad (10)$$

which is also, indirectly, a definition of the "mean age of child-bearing". Formula 8 reduces approximately to

$$D_j^* = \frac{n_j}{n} \cdot d_j^* = \frac{N}{n} \cdot \frac{n_j}{N} \cdot d_j^* \quad (11)$$

TABLE I. ANNUAL FREQUENCIES OF X-RAY EXAMINATIONS

Country or area	Year of study	Population at time of study	Annual number of x-ray examinations per 1,000 of total population					Reference
			Examinations, except mass surveys and dental		Mass surveys		Dental	
			Radiography	Fluoroscopy	Radiography	Fluoroscopy		
Argentina (Buenos Aires)	1950-1959	6,000,000 ^a	270 ^b	No data	80 ^b	Not applicable	No data	4
Australia	1955-1957	9,500,000	480 ^a	— ^d	190 ^a	Not applicable	No data	32, 33
Austria	1955-1958	6,974,000	67 ^a	310 ^a	25	25	No data	53,119
Belgium	1958	8,924,000	No data	No data	130	21	No data	53
Canada	1958	17,048,000	220 ^a	30 ^a	90	Not applicable	No data	106, 107
Denmark	1956	4,466,000	260	— ^d	140	Not applicable	40	5
Federal Republic of Germany (Hamburg)	1957-1958	1,755,000	560	— ^d	130	Not applicable	80	6
France	1957-1958	42,000,000	150	— ^d	40	570	No data	8-10
Israel	1959	2,062,000	300	110	170	Not applicable	20	108
Italy (Rome)	1957	1,875,000	500	— ^d	80	Not applicable	No data	11
Japan	1958-1960	90,000,000	410	— ^d	320	Not applicable	10 ^b	12, 53
Netherlands (Leiden)	1959	110,000	350	200 ^f	130	Not applicable	40 ^b	13
New Zealand	1957	2,221,000	340 ^a	— ^d	90 ^a	Not applicable	240 ^a	68
Norway	1958	3,525,000	390	— ^d	210	Not applicable	100	14
Sweden	1958	7,300,000	290	— ^d	140	Not applicable	No data	15
Switzerland	1957	5,160,000	310	330	130	60	140	16
United Arab Republic:								
Alexandria	1959-1960	1,361,700 ^a	36	— ^d	4	Not applicable	0.3	17
Cairo	1955-1961	2,640,000 ^a	40	— ^d	5	Not applicable	2	18
United Kingdom (except Northern Ireland)	1957-1958	50,000,000	280	— ^d	95	Not applicable	40	19
United States of America	1955-1956	162,000,000	250 ^a	80 ^a	135 ^a	Not applicable	400 ^a	20

^a Including commuters.

^b Figures relate to films and not to examinations.

^c Data are taken from the 1958 report of the United Nations Scientific Committee on the Effects of Atomic Radiation.³

^d Fluoroscopy is generally performed only in connexion with

radiography.

^e Figures relate to hospitals only.

^f Fluoroscopy of the chest not connected with radiography but not mass surveys.

^g Population served by hospitals surveyed.

TABLE II. ANNUAL FREQUENCIES OF CASES TREATED BY X-RAYS AND SEALED RADIO-ACTIVE SOURCES

Country or area	Year of study	Population at time of study	Annual number of cases per 1,000 of total population			Reference
			Malignant	Non-malignant	Total	
Austria.....	1955-1957	6,974,000	4	10	14	119
Canada.....	1958	17,048,000	No data	No data	1.9 ^a	106
Czechoslovakia (Prague).....	1958	990,000	No data	7.7	—	109
Federal Republic of Germany (Hamburg).....	1957-1958	1,755,000	4.0	8.3	12.3	6
France.....	1957	42,000,000	3.7	2.2	5.9	27
Israel.....	1959	2,062,000	0.6 ^{a, b}	3.5 ^{a, b}	4.1 ^{a, b}	108
Italy (Rome).....	1957	1,875,000	No data	1.3	—	110
Lebanon.....	1956-1960	1,500,000	0.2	0.1	0.3	111
United Arab Republic:						
Alexandria.....	1956-1961	1,361,700	0.25	0.21	0.46	18
Cairo.....	1959-1960	2,640,000	0.6	0.7	1.3	34, 35
United Kingdom (except Northern Ireland).....	1957	50,000,000	1.2	1.2	2.4	19

^a Figures relate to hospitals only.^b For non-malignant conditions around 70 per cent of all cases. For malignant conditions around 80-85 per cent of all cases.TABLE III. ANNUAL FREQUENCIES OF ADMINISTRATIONS OF RADIO-ACTIVE ISOTOPES FOR MEDICAL REASONS AND THE ANNUAL AMOUNT OF I¹³¹, P³² AND Au¹⁹⁸ FOR MEDICAL USE

Country or area	Year of study	Population at time of study	Annual number of cases per 1,000 of total population		Annual amounts of radio-active isotopes for medical use (curies) ^a			Reference
			Diagnosis	Therapy	I ¹³¹	P ³²	Au ¹⁹⁸	
Argentina.....	1960	20,956,000	0.30	0.03	6.0 ^a	0.8 ^a	No data	36
Australia.....	1959-1960	9,800,000	0.65 ^b	0.09 ^b	8.2	2.1	4.4	112
Canada.....	1958-1960	17,048,000	No data	0.04 ^a	55.0	5.1	23.8	106, 113
Federal Republic of Germany (Hamburg).....	1957-1958	1,755,000	1.1 ^d	0.20 ^d	No data	No data	No data	6
Israel.....	1959	2,062,000	1.7	0.16	2.5	0.3	3.4	108
Lebanon.....	1956-1960	1,500,000	0.1	0.01	0.3	<0.1	No data	11
Norway.....	1960	3,500,000	No data	No data	2.1	0.5	5.7	69
United Arab Republic:								
Cairo.....	1961	2,640,000	0.33	0.42	1.3	0.07	1.1	18
United Kingdom (except Northern Ireland)...	1957	50,000,000	0.5	0.08	50 ^a	4.2 ^a	88 ^a	20
United States of America.....	1959	180,000,000	1.2	0.3	No data	No data	No data	114

^a See paragraph 8 (c) above.^b Minimum estimate.^c Figures refer to hospitals only.^d Figures refer to the use of I¹³¹ only.^e Figures refer to the quantities actually administered.

TABLE IV. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1950-1959

Argentina (Buenos Aires)^a

Type of examination	$\frac{N^*}{N} \times 1,000^a$		$d_i^* \text{ (mrem)}^a$			$D_i^* \text{ (mrem)}$			D_i	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus	mrem	Percent-age
A. HOSPITALS AND CITY CENTRES (RADIOGRAPHY)										
Urography (descending pyelography).....	2.7	2.2	700	900	No data	1.9	2.0	No data	3.9	16
Hip, upper femur.....	2.8	3.0	600	600	No data	1.7	1.8	No data	3.5	14
Colon (barium enema) lower GI	2.7	2.7	300	450	No data	0.8	1.2	No data	2.0	8
Lumbar spine.....	2.4	3.7	200	400	No data	0.5	1.5	No data	2.0	8
Mass miniature radiography...	58	18*	10	15	No data	1.3	0.6	No data	1.9	7
Pelvis.....	1.1	1.6	600	700	No data	0.7	1.1	No data	1.8	7
Obstetrical abdomen.....	—	1.0*	—	800	No data	—	1.8	No data	1.8	7
Lumbosacral region.....	1.2	2.3	230	600	No data	0.3	1.4	No data	1.7	7
Pelvimetry.....	—	0.6*	—	900	No data	—	1.2	No data	1.2	5
Retrograde (ascending) pyelography.....	1.0	0.6	600	800	No data	0.6	0.5	No data	1.1	4
SUB-TOTAL	72	36				7.8	13.1		20.9	83
Other types of examination ^b ...	67	56				1.7	2.7		4.4	17
SUB-TOTAL	139	92				9.5	15.8		25.3	100
B. PRIVATE CLINICS AND PRACTICES (RADIOGRAPHY)^d						4.5 ^d	7.5 ^d		12 ^d	
TOTAL						14	23		37	100

^a Figures are related to radiographs and not to examinations.^b Does not include dental radiography.^c Does not include contribution from foetal exposure.^d Estimated figures (see para. 17).^e Below mean reproductive age, i.e., (n_j^n).

TABLE V. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1956-1958

Denmark^a

Type of examination	$\frac{N^*}{N} \times 1,000$		$d_i^* \text{ (mrem)}$			$D_i^* \text{ (mrem)}$			D_i	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus	mrem	Percent-age
Intravenous pyelography.....	4.3	4.3	1,019	565		4.3	2.4		6.7	24
Retrograde pyelography.....	0.9	0.4	2,580	1,136		2.3	0.5		2.8	10
Cystography.....	0.4	0.4	5,078	437		2.3	0.2		2.5	9
Hip and femur.....	2.2	2.5	980	58		2.2	0.1		2.3	8
Pelvimetry.....	—	2.2	—	822		—	1.8		1.8	7
Urethrography.....	0.4	—	3,709	—		1.7	—		1.7	6
Pelvis.....	2.5	0.7	567	210		1.4	0.1		1.5	5
Spine lumbar.....	4.3	3.4	104	222		0.4	0.7		1.1	4
Abdomen obstetric.....	—	2.0	—	190		—	0.4		0.4	2
Abdomen A.P.....	0.4	0.4	610	85		0.3	0.1		0.4	2
SUB-TOTAL	15.4	16.3				14.9	6.3		21.2	77
Foetal contribution								5.0	5.0	18
Other types of examination..	244					0.7	0.6		1.3	5
TOTAL		260				15.6	6.9	5.0	27.5	100

TABLE VI. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1957-1958

Federal Republic of Germany (Hamburg)^a

Type of examination	$\frac{N^*}{N} \times 1,000$		\bar{d}_j^* (mrem)			D_j^* (mrem)			D_j	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus	mrem	Percentage
Colon (barium enema) lower GI	3.7	4.0	890	2,530	2,740	1.87	4.03	0.19	6.09	34
Hip, upper femur.....	2.6	3.2	1,520	214	255	3.15	0.17	0.01	3.33	19
Urography (descending pyelography).....	5.1	3.6	241	439	476	0.70	0.71	0.04	1.45	8
Lumbar spine.....	11.2	10.2	63	183	178	0.52	0.72	0.04	1.28	7
Pelvis.....	3.8	3.7	275	94	166	0.90	0.24	0.01	1.15	7
Obstetrical abdomen.....	—	0.32	—	680	677	—	0.22	0.54	0.76	4
Stomach (barium meal) upper GI	23.9	16.9	65	67	63	0.11	0.47	0.02	0.60	3
Retrograde (ascending pyelography).....	1.2	1.1	311	657	720	0.21	0.27	0.02	0.50	3
Abdomen.....	4.6	2.9	88	128	167	0.27	0.20	0.01	0.48	3
Pelvimetry.....	—	0.05	—	600	2,900	—	0.03	0.37	0.40	2
SUB-TOTAL	56	46				7.73	7.06	1.25	16.04	90
Other types of examination....	369	299				1.07	0.61	0.02	1.70	10
TOTAL	425	345				8.80	7.67	1.27	17.74	100

^a Denotes mean figures of gonad dose. After detailed calculation of D_j^* formula 8 was used for obtaining d_j^* .

TABLE VII. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1957-1958

France⁸⁻¹⁰

Type of examination	$\frac{N^*}{N} \times 1,000$		\bar{d}_j^* (mrem)			D_j^* (mrem)			D_j	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus	mrem	Percentage
Chest (heart, lung).....	340	230	30 ^b	No data	No data	38 ^a	No data	No data	38	65
Abdomen.....	3.7	4.4	1,500	1,300	No data	5.58	4.62	No data	10.20	18
Hip, upper femur.....	2.1	1.7	1,200	180	No data	2.61	0.23	No data	2.84	5
Urography.....	2.1	1.8	390	4,500	No data	0.32	2.30	No data	2.62	4
Lumbar spine.....	3.0	2.4	250	700	No data	0.48	0.80	No data	1.28	2
Obstetrical abdomen.....	—	0.2	—	1,600	No data	—	0.80	No data	0.80	1
Urethrocytography.....	0.7	0.5	1,900	1,800	No data	0.24	0.23	No data	0.47	1
Stomach (barium meal) upper GI	5.9	3.8	90	300	No data	0.14	0.29	No data	0.43	1
Colon (barium enema) lower GI	2.0	2.5	134	264	No data	0.14	0.23	No data	0.37	1
Pelvimetry.....	—	0.02	—	1,200	No data	—	0.02	No data	0.02	0
SUB-TOTAL	360	247				9.51	9.52		57.03	98
Other types of examination ^d ...	84	65				0.22	0.96		1.18	2
TOTAL	444	312				9.73	10.48		58.21	100

^a Does not include contribution from foetal exposure.^b Mean value for the dose to testes and ovaries.^c Since d_j is given only as mean figure for the gonads the dose

figure cannot be split into male and female dose.

^d Does not include dental radiography.

TABLE VIII. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1957

Italy (Rome)¹¹

Type of examination	$\frac{N^*}{N} \times 1,000$		d_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus ^a	mrem ^b	Percentage
Digestive tract.....	27.8	14.2	123	411	No data	3.08	5.25		8.33	19
Hip, femur.....	6.1	7.0	586	223	No data	3.93	1.09		5.02	12
Urography (descending pyelography).....	5.2	3.4	940	1,060	No data	2.44	2.52		4.96	11
Pelvis.....	5.0	4.7	1,130	330	No data	3.38	1.40		4.78	11
Lumbar spine.....	7.9	4.8	234	570	No data	2.03	2.19		4.22	10
Barium enema.....	4.7	2.4	239	1,050	No data	1.01	2.27		3.28	8
Cholecystography.....	9.1	11.6	12	156	No data	0.12	1.27		1.39	3
Abdomen.....	5.2	3.4	141	210	No data	0.66	0.64		1.30	3
Obstetrical abdomen.....	—	0.8	—	399	No data	—	0.59		0.59	1
Pelvimetry.....	—	0.1	—	1,250	No data	—	0.23		0.23	1
SUB-TOTAL	71	52				16.65	17.45		34.10	79
Foetal contribution ^a								2.59	2.59	6
Other types of examination ^a ..	276	174				4.15	2.57		6.72	15
TOTAL	347	226				20.80	20.02	2.59	43.41	100

* No figures subdivided into various types of examination are available.

contributions.

^a Does not include dental radiography.

^b The figures for D_1 are the sum of the male and female

TABLE IX. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1958-1960

Japan¹²

Type of examination	$\frac{N^*}{N} \times 1,000$		d_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus	mrem	Percentage
Stomach (barium meal) upper GI	53	33	4.3 ^a (28)	74 ^a (2,660)	No data	0.69	10.92	No data	11.61	30
Colon (barium enema) lower GI	5.0	4.5	220 ^a (2,390)	81 ^a (4,320)	No data	4.01	4.28	No data	8.29	21
Lumbar spine.....	7.6	3.6	767	121	No data	4.36	0.19	No data	4.55	12
Lumbosacral region.....	3.7	1.6	1,700	116	No data	4.44	0.06	No data	4.50	12
Hip, upper femur.....	4.7	6.0	691	30.5	No data	1.93	0.46	No data	2.39	6
Pelvis.....	1.6	1.5	1,490	80	No data	1.58	0.08	No data	1.66	4
Chest (heart, lung).....	103	65	1.0 ^a (0.6)	8.0 ^a (78)	No data	0.41	1.07	No data	1.48	4
Urography (descending pyelography).....	3.6	2.6	631	92	No data	1.27	0.13	No data	1.40	4
Obstetrical abdomen.....	—	1.1	—	162	162 ^b	—	0.12	0.30	0.42	1
Pelvimetry.....	—	0.15	—	322	322 ^b	—	0.03	0.09	0.12	0.3
SUB-TOTAL	182	119				18.69	17.34	0.39 ^d	36.42 ^d	96
Other types of examination ^a	74	37				1.82	0.79	No data	2.61	4
TOTAL	256	156				20.51	18.1	0.39 ^d	39.0 ^d	100

* Dose figures relate only to the radiographical part of the examination. In around 8 per cent of chest, 38 per cent of stomach and 50 per cent of colon examinations, fluoroscopy is performed. The figure within brackets denote the gonad doses arising from fluoroscopy. The values of D_1^* refer to the total from both radio-

graphy and fluoroscopy.

^b The dose is assumed to be the same as to the maternal ovaries.

^c Does not include mass miniature and dental radiography.

^d The figure implies contribution from foetal exposure only from obstetrical examination.

TABLE X. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1959-1960

Netherlands (Leiden)¹³

Type of examination	$\frac{N^*}{N} \times 1,000$		d_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus ^a	Male	Female	Foetus	mrem	Percentage
Urography (descending pyelography)	5.6	3.0	512	604	604	1.16	0.62	0.08	1.86	27
Hip, upper femur	1.6	2.1	3,323	140	140	1.48	0.04	n	1.52	22
Colon (barium enema) lower GI	3.7	2.6	25	613	613	0.03	0.50	0.08	0.61	9
Lumbosacral region	1.9	1.5	60	790	790	0.07	0.46	0.07	0.60	9
Pelvis	3.4	3.4	157	142	142	0.35	0.19	0.01	0.55	8
Urethrocytography	1.1	0.3	423	1,608	1,608	0.11	0.30	0.03	0.44	6
Abdomen	3.7	2.6	92	132	132	0.18	0.16	0.01	0.35	5
Lumbar spine	4.5	3.3	16	47	47	0.03	0.06	0.01	0.10	2
Obstetrical abdomen ^b	—	0.1	—	100	100	—	0.01	0.02	0.03	<1
Pelvimetry	—	0	—	—	—	—	0	0	0	0
SUB-TOTAL	26	19				3.41	2.34	0.31	6.06	89
Other types of examination ^c	282	222				0.32	0.36	0.05	0.73	11
TOTAL	308	241				3.73	2.70	0.36	6.79	100

^a Doses are the same as for female.^b The position is not justified by the magnitude of the dose.^c Does not include mass miniature radiography and dental

radiography.

n = negligible.

TABLE XI. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1958

Norway¹⁴

Type of examination	$\frac{N^*}{N} \times 1,000$		d_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus ^a	Male	Female	Foetus	mrem	Percentage
Lumbosacral region	11.9	9.2	130	592	592	0.78	1.81	0.12	2.71	27
Lumbar spine										
Colon (barium enema) lower GI	3.0	3.4	185	2,050	2,050	0.16	1.19	0.09	1.44	15
Pelvis	5.7	5.9	376	135	135	0.92	0.29	0.01	1.22	12
Urography (descending pyelography)	3.8	3.5	217	403	403	0.37	0.51	0.03	0.91	9
Hip	3.4	6.0	384	159	159	0.61	0.20	n	0.81	8
Pelvimetry	—	0.3	—	800 ^b	900 ^b	—	0.19	0.50	0.69	7
Femur	1.4	1.4	407	10	10	0.58	0.01	n	0.59	6
Obstetrical abdomen	—	0.3	—	400 ^b	600 ^b	—	0.10	0.34	0.44	4
Abdomen	3.3	3.0	65	178	178	0.12	0.27	0.01	0.40	4
Stomach (barium meal) upper GI	14.4	11.2	2.8	17.5	17.5	0.05	0.07	n	0.12	1
SUB-TOTAL	47	44				3.59	4.64	1.10	9.33	93
Other types of examination	320	294				0.30	0.32	0.02	0.64	7
TOTAL	367	338				3.89	4.96	1.12	9.97	100

^a Except for obstetrical examinations, the doses are the same as for female.^b Estimate and calculation based on exposure data. n = negligible.

TABLE XII. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1955-1957

Sweden¹⁵

Type of examination	$\frac{N^*}{N} \times 1,000$		\bar{d}_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus ^a	Male	Female	Foetus	mrem	Percent-age
Lumbosacral region.....	9.1	7.0	940	490	490	6.30	1.36	0.14	7.80	21
Lumbar spine.....	—	0.6	—	1,080	4,500	—	0.28	6.40	6.68	18
Pelvimetry.....	5.3	3.8	1,240	925	925	3.48	1.77	0.16	5.41	15
Urography.....	4.1	4.2	870	200	200	2.70	0.40	0.03	3.13	8
Pelvis.....	2.5	2.4	1,360	1,150	1,150	1.78	0.93	0.11	2.82	7
Abdomen.....	4.1	5.0	310	1,520	1,520	0.56	2.03	0.21	2.80	7
Colon.....	2.6	4.4	1,090	260	260	2.19	0.25	0.01	2.45	6
Hip.....	1.0	0.2	3,700	1,940	1,940	1.57	0.14	0.02	1.73	5
Urethrocytography.....	1.8	0.9	830	35	35	1.40	0.02	0.01	1.43	4
Femur.....	—	0.6	—	265	910	—	0.06	1.20	1.26	3
Obstetrical abdomen.....										
SUB-TOTAL	31	29				20.0	7.2	8.3	35.5	94
Other types of examination ^b ...	186	188				0.3	1.8	0.2	2.3	6
TOTAL	217	217				20.3	9.0	8.5	37.8	100

^a Except for obstetrical examinations the doses are the same as for female.^b Does not include dental radiography.

TABLE XIII. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1957

Switzerland¹⁶

Type of examination	$\frac{N^*}{N} \times 1,000$		\bar{d}_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus	mrem	Percent-age
Urography (descending pyelography).....	3.7	4.0	1,000	1,000		1.93	2.14		4.07	18
Obstetrical abdomen.....	—	1.1	—	700	800	—	1.73	1.96	3.69	17
Pelvis.....	2.8	2.4	1,200	300		2.55	0.55		3.10	14
Lumbar spine.....	7.4	7.4	150	500		0.48	1.62		2.10	9
Colon (barium enema), lower GI	6.9	6.9	150	200		0.90	1.20		2.10	9
Retrograde (ascending pyelography).....	0.8	1.2	1,000	1,000		0.42	0.62		1.04	5
Chest.....	190.0	188.0	2	1		0.69	0.35		1.04	5
Hip, upper femur.....	4.1	3.5	100	300		0.27	0.70		0.97	4
Stomach (barium meal), upper GI	31.1	26.5	20	50		0.31	0.65		0.96	4
Pelvimetry.....	—	0.24	—	700	800	—	0.34	0.38	0.72	3
SUB-TOTAL	247	241				7.55	9.90	2.34	19.8	88
Other types of examination....	290	194				1.78	0.73		2.5	12
TOTAL	537	435				9.33	10.63	2.34	22.3	100

TABLE XIV. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT
DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1956-1960

United Arab Republic (Alexandria)¹⁷

Type of examination	$\frac{N^*}{N} \times 1,000$		d_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus*	Male	Female	Foetus*	mrem	Percentage
Urinary tract.....	3.7	4.6	500	320	—	1.85	1.47	—	3.32	47
Lumbosacral spine.....	3.2	3.1	255	270	—	0.82	0.84	—	1.66	24
Lower GI tract.....	2.3	2.2	100	600	—	0.2	1.3	—	1.5	21
Upper GI tract.....	0.7	0.8	70	470	—	0.05	0.36	—	0.41	6
Mass radiography.....	7.2	10.7	5	5	—	0.04	0.05	—	0.09	1
Chest.....	3.6	7.4	5	5	—	0.02	0.04	—	0.06	1
Cervical spine.....	2.4	2.4	—	1	—	—	0.002	—	0.002	<1
Skull.....	1.1	1.2	—	1	—	—	0.001	—	0.001	<1
Obstetrical abdomen*	—	—	—	—	—	—	—	—	—	—
Pelvimetry*	—	—	—	—	—	—	—	—	—	—
SUB-TOTAL	24	32				2.98	4.06	—	7.04	100
Other types of examination. . .	—	—				—	—	—	—	—
TOTAL		36				2.98	4.06		7.04	100

* No data.

TABLE XV. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT
DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1955-1961

United Arab Republic (west and south-west of Cairo)¹⁸

Type of examination	$\frac{N^*}{N} \times 1,000$		d_1^* (mrem)			D_1^* (mrem)			D_1	
	Male	Female	Male adults	Female adults	Foetus*	Male	Female	Foetus*	mrem	Percentage
Urinary tract.....	4.1	5.1	500	320	—	2.08	1.9	—	3.98	57
Lower GI tract.....	1.5	1.8	100	600	—	0.13	1.10	—	1.23	17
Upper GI tract.....	1.0	1.1	70	470	—	0.05	1.13	—	1.18	17
Lumbosacral spine.....	0.9	0.9	255	270	—	0.23	0.23	—	0.46	7
Mass radiography.....	5.7	8.4	5	5	—	0.02	0.04	—	0.06	1
Chest.....	5.0	10.0	5	5	—	0.02	0.05	—	0.07	1
Cervical spine.....	0.9	0.9	—	1	—	—	0.001	—	0.001	<1
Skull.....	2.6	2.9	—	1	—	—	0.003	—	0.003	<1
Obstetrical abdomen*	—	—	—	—	—	—	—	—	—	—
Pelvimetry*	—	—	—	—	—	—	—	—	—	—
SUB-TOTAL	22	31				2.53	4.45		6.98	100
Other types of examination. . .	22	4				—	—		—	—
TOTAL	44	35				2.53	4.45		6.98	100

* No data.

TABLE XVI. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

Survey, 1957-1958

United Kingdom (except Northern Ireland)¹⁰

Type of examination	$\frac{N^*}{N} \times 1,000$		d_j^* (mrem)			D_j^* (mrem)			D_i	
	Male	Female	Male adults	Female adults	Foetus	Male	Female	Foetus	mrem	Percentage
A. NATIONAL HEALTH SERVICE HOSPITALS										
Obstetrical abdomen	—	1.5	—	367	723	—	1.12	2.27	3.39	24
Pelvis	1.8	2.0	370	392	536	1.72	1.17	0.22	3.11	22
Lumbosacral region	2.2	2.3								
Lumbar spine	3.5	3.1								
Urography (descending pyelography)	2.3	2.0	765	585	843	0.96	0.69	0.09	1.74	12
Retrograde (ascending pyelography)	0.3	0.4	740	102	154					
Hip, upper femur	2.0	2.9				1.33	0.14	0.01	1.48	11
Pelvimetry	—	0.4	—	745	885	—	0.55	0.60	1.15	8
Abdomen	3.0	3.0	105	183	281	0.22	0.32	0.06	0.60	4
Stomach (barium meal), upper GI	6.0	4.3	44	333	448	0.11	0.36	0.04	0.51	4
Chest (heart, lung) (excluding mass miniature radiography) .	63	61	2.75	5.4	5.5	0.14	0.29	0.05	0.48	3
SUB-TOTAL	84	83				4.48	4.64	3.34	12.46	88
Other types of examination . . .	52	40				0.35	0.39	0.04	0.78	6
TOTAL	136	123				4.83	5.03	3.38	13.24	94
B. DIAGNOSTIC X-RAY EXPOSURE OUTSIDE NATIONAL HEALTH SERVICE HOSPITALS										
General diagnostic examinations	22					No data			0.83	6
Mass miniature radiography . . .	95		0.09	0.09	0.09	No data			0.01	
Dental radiography	40		0.3	0.3	0.3	No data			0.01	
TOTAL genetically significant dose									14.1	100

TABLE XVII. DATA FROM VARIOUS COUNTRIES AND AREAS ON GONAD EXPOSURE FROM MASS SURVEY EXAMINATIONS OF THE CHEST

Country or area	Population at time of study		Number of examinations per 1,000 of total population		Number of examinations per 1,000 of population below age 30		Gonad dose adults (mrem)		Genetically significant dose (mrem)		Reference
	Total	Below age 30	Radiography	Fluoroscopy	Radiography	Fluoroscopy	Male	Female	Male	Female	
Argentina (Buenos Aires).....	6,000,000	2,770,000	76	—	166	—	10	15	1.3	0.6	1.9 ^b
Australia.....	9,500,000	—	190	—	No data	—	No data	No data	No data	No data	0.2 ^b
Austria.....	6,984,000	2,990,000	25	25	37	28	R 0.3	No data	No data	No data	0.02 ^b
							F 7	18	No data	No data	0.36 ^b
Belgium.....	8,924,000	3,797,000	128	26	226	48	R 0.2	0.6	No data	No data	0.09 ^b
							F 5	13	No data	No data	0.45 ^b
Canada.....	17,048,000	9,300,000	90	—	86	—	0.7	12	0.03	0.5	0.53 ^b
Denmark.....	4,466,000	2,080,000	140	—	120	—	0.25	0.15	0.03	0.02	0.05
Federal Republic of Germany (Hamburg).....	1,755,000	—	130	—	No data	—	0.16	0.32	0.02	0.03	0.05
France.....	43,600,000	20,000,000	40	—	71	—	R 0.25	0.6	No data	No data	0.02 ^b
Italy (Rome).....	1,875,000	—	77	—	No data	—	5.5	11	0.33	0.60	0.93
Japan.....	90,000,000	—	322	—	No data	—	0.05	0.4	No data	No data	0.08 ^b
Netherlands (Leiden).....	110,000	58,400	80	—	53	—	0.4	0.4	0.01	0.01	0.02
Norway.....	3,525,000	—	211	—	No data	—	0.13	1.0	0.02	0.06	0.08
Spain.....	29,000,000	16,000,000	2	5	4	6	R 0.3	0.8	No data	No data	0.002 ^b
							F 12	31	No data	No data	0.13 ^b
Sweden.....	7,300,000	—	140	—	No data	—	0.8	1.6	0.1	0.3	0.4
Switzerland.....	5,160,000	2,300,000	130	60	155	70	R 0.2	0.5	No data	No data	0.05
							F 0.6	1.5	No data	No data	0.07 ^b
United Arab Republic:											
Alexandria.....	1,361,700	787,000	4	—	7	—	5	7	0.04	0.05	0.09
Cairo.....	2,640,000	1,527,000	5	—	6	—	5	7	0.03	0.04	0.07
United Kingdom (except Northern Ireland).....	50,000,000	—	95	—	No data	—	0.09	0.09	No data	No data	0.01
United States of America.....	162,000,000	82,000,000	135	—	90	—	1	3	0.05	0.13	0.18 ^b

R = Radiography.

F = Fluoroscopy.

^a Not applicable.^b Genetically significant dose calculated according to formula 11, e.g. assuming the mean age of child-bearing to be 30.

TABLE XVIII. GONAD DOSES AS SUBMITTED BY COUNTRIES AND EXAMINATIONS (MALES)

(mrem)

	Mass survey, chest	Chest, heart, lung	Cholecystography	Stomach, barium meal	Urography descending	Retrograde pyelography	Abdomen	Colon, barium enema	Pelvis	Lumbar spine	Lumbo-sacral	Hip, upper femur
Argentina (Buenos Aires) ^a	10	5	60	60	700	600	150	300	600	200	230	600
Denmark	0.3	0.4	2	20	1,019	2,580	610	40	567	104	555	980
Federal Republic of Germany (Hamburg)	0.2	0.5	4	65	241	311	88	890	275	63	555	1,520
France	30 ^d	30 ^d	45	90	390	1,900	250	134	1,500	250	1,200	1,200
Italy	6	0.5	12	123	940	631	141	239	1,130	234	1,700	—586—
Japan	0.1	1	2	13	631	423	220	1,310	1,490	767	1,700	691
Netherlands (Leiden)	0.1	2	3	4	512	15	92	25	157	16	60	3,233
Norway	0.1	1	3	3	15	217	65	185	376	—130 ^b —	60	384
Sweden ^c	0.8	2	6	14	1,240	3,700	1,360	310	870	—940 ^b —	—	407
Switzerland	0.4	10	—	20	1,000	1,000	—	150	1,200	150	255	830
United Arab Republic	5	5	8	70	500	—	105	100	1,200	—	—	100
United Kingdom	0.1	3	8	44	—765—	—	—	146	—	370	—	740

^a Radiographs, not examinations.^b In these countries the two types of examinations are combined.^c Hip only; femur only.^d Estimate from contribution due to fluoroscopic examinations in private practice.

• Including urethrocytography.

TABLE XIX. GONAD DOSES AS SUBMITTED BY COUNTRIES AND EXAMINATIONS (FEMALES)

(mrem)

	Mass survey, chest	Chest, heart, lung	Cholecystography	Stomach, barium meal	Urography descending	Retrograde pyelography	Abdomen	Obstetrical abdomen	Pelvimetry	Colon, barium enema	Pelvis	Lumbar spine	Lumbo-sacral	Hip, upper femur
Argentina (Buenos Aires) ^a	15	10	90	90	900	800	200	800	900	450	700	400	600	600
Denmark	0.2	0.1	16	9	565	1,136	85	190	822	20	210	222	58	58
Federal Republic of Germany (Hamburg)	0.3	0.7	35	67	439	657	128	680	600	2,530	94	183	402	214
France	105	30 ^d	105	300	4,500	1,800	375	1,600	1,200	264	1,300	700	—	180
Italy	11	1.0	156	411	1,060	—	210	399	1,250	1,050	330	570	—	—223—
Japan	0.4	13	80	1,108	92	604	49	162	322	2,200	80	121	116	31
Netherlands (Leiden)	0.4	2	4	6	604	1,608	132	100	613	613	142	47	790	140
Norway	1	2	8	18	125	403	178	400	800	2,050	135	—592 ^b —	—	159
Sweden ^c	1.6	4	17	29	925	1,940	1,150	265	1,080	1,520	200	—490 ^b —	—	10
Switzerland	1.0	5	5	50	1,000	1,000	—	1,500	1,500	200	300	500	270	35
United Arab Republic	5	5	299	470	320	—	183	367	745	600	—	—	—	300
United Kingdom	0.1	5	—	333	—585—	—	—	—	—	464	—	392	—	102

^a Radiographs, not examinations.^b In these countries the two types of examinations are combined.^c Hip only; femur only.^d Estimate from contribution due to fluoroscopic examinations in private practice.

• Including urethrocytography.

TABLE XX. FOETAL GONAD DOSES AS SUBMITTED BY COUNTRIES FOR OBSTETRICAL EXAMINATIONS

(mrem)

	Obstetrical abdomen	Pelvimetry	Obstetrical abdomen	Pelvimetry
Federal Republic of Germany (Hamburg).....	677	2,900	Sweden.....	910
Netherlands (Leiden).....	100	—	Switzerland.....	800
Norway.....	600	900	United Kingdom.....	723
				835

TABLE XXI. TOTAL ANNUAL GENETICALLY SIGNIFICANT DOSE FROM X-RAY DIAGNOSIS SUBMITTED BY COUNTRIES AND EXAMINATIONS

(mrem)

	Mass survey, chest	Chest, heart, lung	Cholecys- tography	Stomach, barium meal	Urography descending	Retrograde pyelo- graphy ^a	Abdomen	Obstetrical abdomen	Pelvimetry	Colon, barium enema	Pelvis	Lumbar spine	Lumbo- sacral	Hip, upper femur	Femur	Others	Total ^b
Argentina ^d	2.8	0.3	0.3	1.2	5.7	1.6	1.3	2.6	1.8	2.9	2.6	2.9	2.5	5.1		3.4	37
(Buenos Aires).....					6.7	7.0	0.4	0.4	1.8		1.5	1.1		2.3		6.3	27.5
Denmark.....				0.60	1.45	0.50	0.48	0.76	0.40	6.09	1.15	1.28		3.33		1.70	17.7
Federal Republic of Germany (Hamburg)		38 ^c		0.43	2.62	0.47	10.2	0.80	0.02	0.37		1.28		2.84		1.18	58.2
France.....			1.39	8.33	4.96		1.30	0.59	0.23	3.28	4.78	4.22		5.02		6.72	43.4
Italy.....		1.48		11.61		1.40	0.35	0.42	0.12	8.29	1.66	4.55	4.5	2.39		2.61	39.0
Japan.....					1.86	0.44	0.40	0.03	0.61	0.61	0.55	0.10	0.60	1.52		0.73	6.8
Netherlands (Leiden)...				0.12	0.91		0.40	0.44	0.69	1.44	1.22	—2.71 ^b		0.81	0.59	0.64	10.0
Norway.....					5.41	1.73	2.82	1.26	6.68	2.80	3.13	—7.8 ^b		2.45	1.43	2.3	37.8
Sweden.....		1.04		0.96	4.07	1.04		3.69	0.72	2.1	3.1	2.1		0.97		2.5	22.3
Switzerland.....																	
United Arab Republic:	0.09	0.06		0.41	3.32		0.60	3.39	1.15	1.5			1.66				7.0
Alexandria.....	0.06	0.07		1.18	3.98					1.23			0.46				7.0
Cairo.....		0.48		0.51	1.53	0.21						—3.11—		1.48		1.63	14.1
United Kingdom.....																	

^a Rounded-off total from national figures.^b In these countries the two types of examinations are combined.^c Includes contribution from fluoroscopic examinations in private practice.^d These values include the contribution from private clinics and practices.^e Includes urethrocytography.

TABLE XXII. COMPARISON OF PERCENTAGE TOTAL GENETIC DOSE FROM DIAGNOSTIC RADIOLOGY BY COUNTRIES AND EXAMINATIONS

	Mass survey, chest	Chest, heart, lung	Cholecystography	Stomach, barium meal	Urography, descending	Retrograde pyelography ^b	Abdomen	Obstetrical abdomen	Pelvimetry	Colon, barium enema	Pelvis	Lumbar spine	Lumbo-sacral	Hip, upper femur	Femur	Sub-total	Others	Total
Argentina (Buenos Aires)	8	1	1	3	15	4	4	7	5	8	7	8	7	14		92	8	100
Denmark.....					24	25	2	2	7		5	4		8		77	23	100
Federal Republic of Germany (Hamburg)																		
France.....		65 ^a		3	8	3	3	4	2	34	6	7		19		89	11	100
Italy.....			3	19	4	1	18	1	1	1	11	2		5		98	2	100
Japan.....				30	4		4	1	0.3	21	4	10		—12—		79	21	100
Netherlands (Leiden)....					27	6	5	1	6	9	4	12	12	6		96	4	100
Norway.....				1	9		4	4	7	15	12	2	9	22		89	11	100
Sweden.....					15	5	7	3	18	7	8	—27—	21	8	6	93	7	100
Switzerland.....		5		4	18	5		17	3	9	14	9		6	4	94	6	100
United Arab Republic:														4		88	12	100
Alexandria.....	1	1		6	47					21			24					100
Cairo.....	1	1		17	57					17			7					100
United Kingdom.....		3		4	12	1	4	24	8		—	22	—	10		87	13	100

^a Includes contribution from fluoroscopic examination in private practice.

^b Includes urethrocytography.

TABLE XXIII. COMPARISON OF THE ANNUAL GENETICALLY SIGNIFICANT DOSE ARISING FROM X-RAY DIAGNOSTIC EXPOSURE IN VARIOUS COUNTRIES AND AREAS

Country or area	Genetically significant dose (mrem)								Reference table
	Male		Female		Fetus	Total			
	A	B	A	B		A	B	C	
Argentina (Buenos Aires).....		14 ^a		23 ^a	No data		37 ^a		IV
Austria.....	No data		No data		No data			16-25	
Denmark.....						28 ^a			V
Federal Republic of Germany (Hamburg).....	8.8		7.7		1.3	18	17	29	VI
France.....		10 ^b		10 ^b	No data		58		VII
Italy (Rome).....	21		20		2.6	43 ± 35			VIII
Japan.....	21		18		0.4	39 ^{a, d}			IX
Netherlands (Leiden).....	3.7		2.7		0.4	6.8 ^a	5.7 ^a	18.7 ^a	X
Norway.....	3.9		5.0		1.1	10 ± 3			XI
Norway.....	20		9		8.5	38 ± 10			XII
Switzerland.....	10 ^d		12 ^d		No data	22 ^d			XIII
United Arab Republic: Alexandria.....	3		4			7			XIV
United Arab Republic: Cairo.....	2.5		4.5			7			XV
United Kingdom (except Northern Ireland).....	5.1 ^a		5.3 ^a		3.6 ^a	14 ± 1			XVI

A is computed according to the formula $D = \sum \frac{N_j}{N} \cdot \frac{w_j}{w} \cdot d_j$

B is computed according to the formula $D = \sum \frac{n_j}{n} \cdot d_j$

C is computed according to the formula $D = \sum \frac{N_j}{N} \cdot d_j$

^a Arising from radiography only.

^b Except for chest examinations in private practice which include a contribution of 38 mrem to the genetically significant dose and which cannot be split into male and female figures.

^c Does not include mass miniature radiography.

^d Includes a contribution from foetal exposure arising from obstetrical examinations.

^e 0.85 mrem, arising from examinations outside the National Health Service hospitals, are distributed among male, female and foetus.

TABLE XXIV. PROBABLE DOSE-RATES TO THE GONADS DURING VARIOUS TYPES OF X-RAY EXAMINATIONS

Type of examination	Dose rate (mrem/sec)	
	Testes	Ovaries
<i>Fluoroscopy</i>		
Chest.....	0.005-0.02	0.01-0.04
Stomach (barium meal).....	0.05-0.2	0.1-0.3
Colon (barium enema).....	1-100 ^a	3-20
<i>Radiography</i>		
Chest.....	10-30	30-50
Stomach.....	4-8	10-50
Colon.....	30-2,000 ^{a, c}	40-200
Lumbar spine } AP.....	40-500 ^{a, d}	20-80
Lumbosacral joint } Lateral.....	50-100	30-100
Pelvic region.....	100-1,500 ^{a, c}	100-400
Urinary bladder.....		
Natural radiation.....	3.10 ⁻⁶	

Note: Russell's experiments cover the following dose-rate range 0.014-1400 mrem/sec.^b

^a The testes in the primary beam.

^b See annex C, table X.

^c With scrotum protection ~ 10 mrem/sec.

^d With scrotum protection 2-3 mrem/sec.

TABLE XXV. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM EXTERNAL RADIO-THERAPY FOR NON-MALIGNANT CONDITIONS

Survey, 1957-1958

Federal Republic of Germany (Hamburg)¹

Location	Number of patients treated per 1,000 of total population		Gonad dose (mrem) Average figures		Annual genetically significant dose (mrem)			
	Male	Female	Male	Female and foetus	Male	Female	Foetus	Total
Skin (various conditions)	1.52	1.63	0.1 ^a 390	3 ^a 6,900	0.05	1.40	0.01	1.46
Spine	0.46	0.72	800	6,000	0.05	0.25	0.02	0.32
Other sites	1.48	2.43	40 ^a 3,000	70 ^a 10,000	0.18	0.22	n	0.40
TOTAL	3.5	4.8			0.28	1.87	0.03	2.2

^a The dose ranges are due to various conditions and different sites treated.

n denotes less than 0.005 mrem.

TABLE XXVI. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM EXTERNAL RADIO-THERAPY FOR NON-MALIGNANT CONDITIONS

Survey, 1957

France^{2,3}

Location	Number of patients treated per 1,000 of total population		Gonad dose (mrem) Average figures		Annual genetically significant dose (mrem) ^a			
	Male	Female	Male	Female	Male	Female	Foetus	Total
Skin (various conditions)	0.31	0.38	5 ^b 100	20 ^b 200	n	n	No Data	n
Spine:								
Cervical	0.16	0.22	900	1,500	0.02	0.04	No Data	0.06
Dorsal	0.04	0.07	2,800	4,500	0.01	0.04	No Data	0.05
Lumbar	0.25	0.16	14,200	49,600	0.5	1.0	No Data	1.5
Hip	0.04	0.04	91,500 100 ^b	99,500 20 ^b	0.5	0.5	No Data	1.0
Other sites	0.26	0.29	17,000	8,000	0.2	0.3	No Data	0.5
TOTAL	1.1	1.2			1.2	1.9		3.1

^a Reboul has calculated that 6.8 per cent of ΣN_d originates from patients below age 30. The subdivision into locations is made under the assumption that this percentage is valid for all locations.

^b The dose ranges are due to various conditions and different sites treated.
n denotes less than 0.01 mrem.

TABLE XXVII. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM EXTERNAL RADIO-THERAPY FOR NON-MALIGNANT CONDITIONS

Survey, 1942-1951

Netherlands^{2,8}

Condition treated	Number of patients treated per 1,000 of total population		Gonad dose (mrem) Average figures		Annual genetically significant dose (mrem)		
	Male	Female	Male	Female	Male	Female	Total
High gonad doses	0.65	0.33	70	110	1.16-5.03 ^a (2.57-8.02) ^b	1.63 (3.76) ^b	2.79-6.66 ^a (6.33-11.78) ^b
Low gonad doses	1.4	(1.4) ^a	1	(1) ^a	0.17	(0.17)	0.34
TOTAL	2.1	1.7					3.1-12.1

^a Based on actual number of children born to patients.

^b Based on total expected number of children averaged throughout population.

^a Female assumed equal to male.

TABLE XXVIII. DATA ON THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM EXTERNAL RADIO-THERAPY FOR NON-MALIGNANT CONDITIONS

Survey, 1957-1958

United Kingdom (except Northern Ireland)¹⁸

Condition treated	Number of patients treated per 1,000 of total population		Gonad dose (mrem) Average figures		Annual genetically significant dose (mrem)			
	Male	Female	Male	Female and foetus	Male	Female	Foetus	Total
Skin conditions.....	0.46	0.57	150- ^a 32,000	300- ^a 6,000	1.55	0.93	0.03	2.52
Ankylosing spondylitis..	0.03	0.01	50,000	20,000	1.07	0.08	n	1.15
Arthritic and rheumatic conditions.....	0.02	0.02	23,000	160,000	0.04	0.18	0.05	0.27
Other non-malignant conditions.....	0.02	0.07	40- ^a 6,000	20- ^a 50,000	0.04	0.49	n	0.53
TOTAL	0.5	0.7			2.70	1.69	0.08	4.47

^a The dose ranges are due to various conditions and different sites treated.

n denotes less than 0.005 mrem.

TABLE XXIX. COMPARISON OF THE ANNUAL GENETICALLY SIGNIFICANT DOSE ARISING FROM EXTERNAL RADIO-THERAPY IN VARIOUS COUNTRIES AND AREAS

Country or area	Annual genetically significant dose (mrem)								Total	Reference
	Non-malignant conditions				Malignant conditions					
	Male	Female	Foetus	Sub-total	Male	Female	Foetus	Sub-total		
Federal Republic of Germany (Hamburg).	0.28	1.87	0.03	2.2	0 ^a	0 ^a	0 ^a	0	2.2	6
France ^b	1.2	1.9	No data	3.1	—2.5 ^c		No data	2.5	5.6	27
Netherlands.....	1.33–8.19	1.8–3.93	No data	3.1–12.1	0.5	(0.5) ^d	No data	1.0	4.1–13.1	28
United Kingdom except Northern Ireland....	2.70	1.69	0.08	4.47	0.41	0.11	0	0.52	5.0	19

^a Fertility factors regarded as zero.

^c Not subdivided into sexes.

^b Genetically significant dose calculated according to formula

^d Female assumed equal to male.

TABLE XXX. COMPARISON OF GENETICALLY SIGNIFICANT DOSE AND PER CAPITA DOSE CAUSED BY EXTERNAL RADIO-THERAPY FOR NON-MALIGNANT CONDITIONS

Country or area	Mode of calculation (doses in mrem)		
	$\sum \frac{N_j}{N} \cdot \frac{w_j}{w} \cdot d_j$	$\sum \frac{n_j}{n} \cdot d_j$	$\sum \frac{N_j}{N} \cdot d_j$
Federal Republic of Germany (Hamburg).....	2.0	2.0	6.5
France.....	—	3.1	21
United Kingdom (except Northern Ireland)....	4.5	—	9

TABLE XXXI.^a ESTIMATED DOSE-RATES TO THE GONADS FROM EXTERNAL RADIO-THERAPY FOR NON-MALIGNANT AND MALIGNANT CONDITIONS^b

Location	Dose rate (mrem/sec)	
	Testes	Ovaries
Head.....	0.01-0.05	0.01-0.05
Thorax.....	0.5-3	2-5
Abdomen and pelvic region.....	5-15	20-50
Skin (various sites).....	0.002-0.5	0.008-1
Natural radiation.....	3.10 ⁻⁸	

^a Russell's experiments cover the following dose-rate range—0.014-1400 mrem/sec.

^b Estimated on the assumption of 50 rad/min at the treatment site.

TABLE XXXII. COMPARISON OF THE ANNUAL GENETICALLY SIGNIFICANT DOSE FROM THE ADMINISTRATION OF RADIO-ACTIVE ISOTOPES IN VARIOUS COUNTRIES AND AREAS

Country or area	Year of study	Genetically significant dose (mrem)		Source	Reference
		Diagnosis	Therapy		
Canada.....	1956	0.02 ^a	0.40 ^a	I ¹³¹ , P ³²	37
Federal Republic of Germany (Hamburg).....	1957-1958	0.01	0.18	I ¹³¹	6
United Kingdom (except Northern Ireland).....	1957	0.03	0.15	I ¹³¹ , P ³²	19
United States of America.....	—	0.01 ^b	0.24 ^b	I ¹³¹ ₀	38

^a Computed according to formula 11. No allowance made for the influence on fertility from the severity of the disease.

^b Computed according to formula 11.

^c Other radio-isotopes considered to be of no significance.

TABLE XXXIII. ANNUAL GENETICALLY SIGNIFICANT DOSE FROM THE ADMINISTRATION OF RADIO-ISOTOPES

Survey, 1957		United Kingdom (except Northern Ireland) ¹⁹		
Use	Radio-isotope	Genetically significant dose		
		mrem	Percentage	
Diagnosis				
Test doses.....	{ I ¹³¹ P ³²	0.016 0.012	9 6	
Therapy				
Non-malignant conditions.....	{ I ¹³¹ P ³²	0.049 0.059	27 33	
Malignant diseases.....	I ¹³¹	0.045	25	
TOTAL		0.18±0.18		

Note. The contribution from other radio-isotopes is negligible.

TABLE XXXIV. GONAD DOSES IN MREM PER ADMINISTERED MILLICURIE OF I¹³¹ OR P³²

Radio-isotope	Gonad dose (mrem)	Remarks	Reference
I ¹³¹	450	Normal physiological conditions	37
	450 (130-1,170)	20 patients: 10 thyroid cancer 7 hyperthyroidism 3 others	39
	600±300	Normal physiological conditions	40
P ³²	2,600	Normal physiological conditions	37
	7,000	Normal physiological conditions	41

TABLE XXXV. MARROW DISTRIBUTION IN THE ADULT

Site	Bones	Total marrow in g ^a	Fraction active marrow ^b	Total active marrow in g ^a	Active marrow per cent	
					Ellis ^c	1958 report of the committee ^d
Head.....	Cranium, mandible	182	0.75	140	13	10
Upper limb girdle.....	Scapulae, clavicles, head and neck of humeri	116	0.75	85	8	5 ^d
Thorax.....	Sternum	39	0.6	25	2.5	25
	Ribs 1 to 12	207	0.4	85	8	
Spine.....	Cervical vertebrae	47	0.75	35	3.5	40
	Dorsal vertebrae	197	0.75	150	14	
	Lumbar vertebrae	152	0.75	115	11	
	Sacrum	194	0.75	150	14	
Lower limb girdle.....	Pelvic bones, coccyx, head and neck of femora	364	0.75	270	26	20 ^e

^a Mechanik⁴³, and Woodard and Holodny.⁴⁴

^b Custer⁴⁶ for ribs, sternum and vertebra at age 40. Other values assumed in study.

^c Ellis.⁴⁷

^d Half the contribution of 10 per cent from "other" (e.g. in

extremities, etc.) in the 1958 report of the Committee (annex C, para. 44).

^e The contribution from pelvis and half the contribution of 10 per cent from "other" (e.g. in extremities, etc.) in the 1958 report of the Committee (annex C, para. 44).

TABLE XXXVI. MEAN MARROW DOSES FROM DIAGNOSTIC X-RAY EXPOSURE (EXCLUDING MASS SURVEYS OF THE CHEST)

Examination	Mean marrow dose (mrem)		Epp et al. U.S.A. ^a 50	
	1958 Report of the Committee ^b	Buhl ⁴⁸ Denmark ^b	AP	Lat.
Head.....	50	—	—	—
Spine.....	—	—	—	—
Cervical.....	50	—	10	3
Dorsal.....	400	200	30	90
Lumbar.....	400	100	50	180
Lumbosacral region.....	300	—	—	—
Pelvis.....	20	30	70	180
Hip, incl. upper femur.....	30	20	35	—
Arm and hand.....	2	0.2	—	—
Thorax (ribs and sternum).....	200	150	—	—
Chest (regular).....	40	20	PA 1.3	4.5
Gall bladder.....	400	150	—	—
Stomach (barium meal), upper GI.....	500	200	—	—
Colon (barium enema), lower GI.....	700	200	—	—
Abdomen.....	50	30	—	—
Urography.....	200	80	—	—
Retrograde pyelography.....	100	30	—	—
Urethrocytography.....	300	—	—	—
Pelvimetry.....	800	—	—	—
Obstetrical abdomen.....	100	—	—	—
Hysterosalpingography.....	100	25	—	—
Dental.....	20	—	—	—

^a Radiography only.

^b In Buhl's investigation the dose calculations are based upon the figures for the distribution of active marrow presented by the Committee^a.

^c The technical factors used are those of the Memorial Hospital, New York. The doses are those that arise from well collimated and aligned fields. The dose due to the scatter outside the direct beam has been included but not the effect due to the photo-electrons from the bone.

TABLE XXXVII. INDIVIDUAL AND PER CAPITA MEAN MARROW DOSES IN SOME COUNTRIES ARISING FROM MASS SURVEY FLUOROSCOPY OF THE CHEST AND COMPARISON WITH CALCULATED PER CAPITA DOSES FROM RADIOGRAPHY

Country	Number of examinations per 1,000 of total population ^a	Mean marrow dose (mrem)		
		Individual	Per capita in total population	Per capita dose if radiography is used instead of fluoroscopy ^b
Austria.....	25	2,000	50	2.5
Belgium.....	26	380	10	2.6
France.....	570	1,200	680	57
Spain.....	5	1,300	8	0.5
Switzerland.....	60	230	14	6

^a Figures taken from table XVII.

^b Mean marrow dose per examination assumed to be 100 mrem.

TABLE XXXVIII. EXAMPLES OF MEAN MARROW DOSES IN EXTERNAL RADIO-THERAPY^a

Site or condition	Type of radiation	Mean marrow dose (rem)		
		Per 100 r skin dose	Total treatment	Reference
Cervical spine, 10 × 15 cm.....	X-rays (170 keV, filter 0.5 mm Cu)	2.6	— ^b	
Lumbar spine, 10 × 15 cm.....	X-rays (170 keV, filter 0.5 mm Cu)	5.5	— ^b	54, 55
Hip, one side, 10 × 15 cm.....	X-rays (170 keV, filter 0.5 mm Cu)	2.5	— ^b	
Carcinoma of cervix.....	Radium (applicators containing 50, 75 or 87.5 mg Ra)	—	60-100	56
Haemangioma ^c	Radium (applicators containing Ra ranging between 80-130 mg)	—	0.5-25 ^d	57

^a With the exception of those for haemangioma Ellis's figures for the distribution of active bone-marrow have been used (table XXXV).

^b The values of total skin doses used in references 54 and 55 range from 300 rem to several thousand rem delivered over more than one course of treatment.

^c Children below two years age. According to paragraph 78, it is assumed that only red bone-marrow exists. The distribution of the active marrow is taken from Woodard and Holodny⁴⁰

under the assumption that the distribution of marrow space in children and adults is the same. The following distribution figures were used: upper limbs 12%, lower limbs 39%, ribs 7%, head 7%, spine 15%, scapulae 2%, clavicles 1%, sternum 1%, pelvis 16% of total marrow space.

^d The range covers various sites of the haemangioma. The highest figures are received when the haemangioma are situated on the skin of the abdomen and the thigh.

TABLE XXXIX. EXAMPLES OF RADIATION DOSES IN VARIOUS KINDS OF RADIOLOGICAL PROCEDURE TO ORGANS AND TISSUES OF SPECIAL INTEREST

Tissue	Diagnosis		Radio-therapy		
	Examination	Dose rem	Non-malignant condition	Dose rem	Malignant condition
Foetal tissue (a) age < 2 months.... (b) age > 7 months.... Lens of the eye..... Thyroid..... Thymus..... Liver.....	See tables in this annex—assume foetal dose is same as maternal gonad dose Pelvimetry Obstetric Abdomen Dental (full mouth) Encephalography Uptake from 25 µc I ¹³¹ Ba Swallow 20 cc Thorotrast	1-3 ~0.5 5-25 5-20 40 2-10 2,100-5,400 (over 20 years)	Cervical spine Tonsillitis Thyrotoxicosis I ¹³¹ Enlarged gland	400-1,200 150 10,000 ~200	Retinoblastoma (dose to unaffected eye) Head lesions ~200 100-1,500

TABLE XL. ESTIMATES OF RADIATION DOSES IN THOROTRAST PATIENTS (20 ml injection)

Estimates of Th²³² activity¹¹⁷: 0.0217 µc/ml (German), 0.0244 µc/ml (U.S.A.)

Tissue	Radio-active source	Average dose-rate rad/y	Accumulated rem ^a (20 years)	Reference
Skeleton.....	Th ²³² + d	1.4-3.0	600	116
Marrow.....	Th ²³² + d	1.2-2.9	580	59
Bronchi.....	Thoron + daughter	12-19	3,800	117
Lungs.....	Thoron + daughter	0.8-1.9	380	117
Liver.....	Th ²³² + d	27	5,400	118
Spleen.....		71	14,000	118

^a The RBE value used in this report for α particles is 10, but Marinelli⁶⁶ suggested that the range of RBE values in this case may be between 4-10.

TABLE XLI. RANGE OF NUMBERS OF INSTALLATIONS AND OCCUPATIONALLY EXPOSED PERSONS PER 1,000 OF THE POPULATION

	Number of installations per 1,000 of total population	Number of workers directly engaged in radiation work (per 1,000 of total population)	Contribution to the annual genetically significant dose (mrem)
Medical:			
Diagnosis.....	0.1-0.7	0.3-0.5	0.1-0.3
Therapy.....	0.02-0.1		
Dental.....	0.1-0.8	≈ 0.9	
Veterinary.....	0.004-0.03		
Industrial.....	0.003-0.02	0.05-0.06	0.1-0.2
Research and educational.....	0.01-0.03	≈ 0.02	
Atomic energy.....	—	0.1-0.3	

TABLE XLII. MEAN ANNUAL DOSES (IN MREM) OF EXTERNAL X- AND γ-RADIATION TO VARIOUS GROUPS OF OCCUPATIONALLY EXPOSED PERSONS

Type of work	Argentina ³⁶ (1959-1960)	Canada ³⁵ (1959)	Netherlands ⁶⁷ (1960)	Norway ⁴¹ (1960)	United Kingdom ⁷⁵ (1959)	
					Male	Female
Medical:						
Diagnosis.....		150-225 ^a	300-1,400 ^b	{ 50-380 2,000	440	500
Therapy.....					1,900	1,600
Dental.....		70		170		
Veterinary.....				400		
Industrial.....		640	400-1,000 ^b	110 (1,900) ^d	1,100 ^c	380
Research and educational.....		180			40	27
Atomic energy.....	430		100-800 ^b		420	

^a The lower figure concerns private practitioners; the higher, hospitals.

^b The range of observed values is given.

^c Both X-ray and gamma-radiography.

^d The dose within brackets concerns gamma-radiography only.

TABLE XLIII. RESULTS FROM MONITORING RADIATION WORKERS AT THE OAK RIDGE NATIONAL LABORATORY, USA, THE ESTABLISHMENTS OF THE UNITED KINGDOM ATOMIC ENERGY AUTHORITY, ARGENTINA, CANADA AND THE UAR (Penetrating radiation)

	Oak Ridge National Laboratory ⁷⁸ (1959)		United Kingdom Atomic Energy Authority ⁷⁸ (1959)		Argentina ³⁶ (1959-1960)		Canada ⁷⁹ (1959)		UAR ⁸⁸ (1961)	
	No. of persons	Per cent	No. of persons	Per cent	No. of persons	Per cent	No. of persons	Per cent	No. of persons	Per cent
Total wearing dose meters or films.....	4,695	100	16,374	100	579	100	423	100	600	100
Annual dose (rem)										
> 1.....	441	9.4	1,492 ^a	9.1	12.4		9	2	4	1
> 2.....	179	3.8			4.5		6 ^c	1		
> 3.....	74	1.6	417	2.6	2.0					
> 4.....	35	0.75	133	0.81	0.6					
> 5.....	10	0.21	43	0.26						
> 6.....	8	0.15	22	0.13						
> 7.....	2	0.04	6	0.04						
> 8.....	1	0.02	3	0.02						
> 9.....	0	0	3 ^b	0.02						

^a Annual dose > 1.5 rem.

^c In range 2.0-4.9 rem.

^b Three individuals received annual doses of 17.2, 10.3 and 10.7 rem.

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ANNEX H

COMPARISON OF DOSES AND ESTIMATES OF RISK

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I. Introduction

1. Much information has been reported since 1958 on dose levels and effects of radiation in animals and man but there are still many gaps in knowledge. It is not possible to determine with desired precision the effect on the world population of the doses from natural radiation (annex E), medical and occupational exposure (annex G) or from fall-out from weapon testing (annex F, part III).

2. Accurate assessment of the late effects of low dose exposure requires a full knowledge of the relevant effects, of the tissue or tissues involved and of the dose-response relationships. At the present time there is a lack of information with regard to each of these factors and also, of course, uncertainty regarding future levels of radiation. In the present annex various of the problems will be reviewed. The first part of the annex deals with the general problems involved in making risk estimates, and presents a method for comparing the risks from various sources of exposure. The second part discusses the problems associated with the assessment of biologically significant doses, estimates of which are presented in the third part. Finally, genetic and somatic risks from the various sources of man's exposure are compared.

II. Problems associated with risk estimation

3. Knowledge of the late effects of radiation comes from clinical and experimental data at much higher levels of dose (and often of dose-rate) than those of

natural radiation, fall-out and many types of medical exposure.¹⁻⁴ The types of effect, or their dose-response relationships, will not necessarily be the same at low as at high dose levels.

4. The estimation of risk at low dose levels requires answers to three basic problems:

- (a) The effects to be considered;
- (b) The critical tissue for each of these effects;
- (c) The function of dose, dose-rate and dose distribution to be taken as the relevant exposure parameter for each of these effects.

EFFECTS AND RELEVANT TISSUES

5. Both genetic and somatic effects have to be considered. The genetic effect is the production of mutations and the critical organs are the gonads. Possible late somatic effects which have given rise to most concern are the induction of leukaemia, malignant bone tumours, and the reduction of life expectancy. The significant tissue for the induction of leukaemia is generally considered to be the active bone marrow. With bone tumours, early pre-malignant changes have been reported⁵ in the connective tissue lining endosteal surfaces or trabeculae and in the loose connective tissue in bone marrow spaces between trabeculae; these are therefore probably the tissues of importance. There is as yet no information concerning tissues important in the reduction of life expectancy. Therefore no estimates will be made of the risk associated with this effect. Although limited exposure data are available for other organs such as thyroid, gastro-intestinal tract and lung, these tissues will

not be used for risk estimates because of uncertainties in dose-effect and dosimetric parameters. More information, including the specification of the relevant effect, would be required for any careful assessment of risk to foetal tissue.

DOSE-EFFECT RELATIONSHIP

6. There are two considerations concerning the exposure parameter to be used: (a) what is theoretically justifiable? (b) what is practicable? For genetic effects experimental data justify the use of a linear dose relationship at low doses and dose-rates. No such generalization can be made about late somatic effects of radiation. In radiation carcinogenesis at high dose levels many different mechanisms may play a part, including various kinds of interactions between damaged cells and tissues, effects of vascular and hormonal changes, as well as specific radiation-induced changes in cells. Also there may be several different ways in which the same macroscopic effect can be brought about, so that the equivalence of macroscopic effect does not imply equivalence of primary mechanism. Carcinogenicity, at these high levels of radiation dose, could only be described by a very complex function of dose and other exposure factors.

7. One would expect, however, that the mechanisms of production of any late effects are simpler at lower doses because interactions between damaged cells, as well as general systemic effects of radiation, will play a smaller part. Although the possible importance of subtle generalized changes in tissue cannot be ruled out, it is likely that, if serious late effects can arise at these low dose levels, they will result predominantly from specific changes induced in individual cells.

8. If it is assumed that even the smallest dose entails a finite probability of effect, can any statement be made about the shape of the dose-response curve near the origin? For certain radiobiological effects which have a non-linear relationship at high dose levels (e.g. certain types of chromosomal change induced by radiation), it is probable that the slope of the dose-effect curve near the origin is linear. However, the range of effective linearity may be very limited. Formally, if the dose function which determines the incidence of the effect includes a linear dose term, however small, it is this term which will be controlling at the lowest doses. The assumption of a linear dose-effect relationship normally implies that mean accumulated dose, i.e., cell-rad, within the tissue of interest can be taken as the significant dose parameter for calculation of incidence of late effects. Protraction of exposure and non-uniformity of dose within the tissue of interest can be ignored. However, if a non-linear dose relationship holds, a mean dose cannot be used to estimate the incidence of effects. Also with a non-linear dose-effect relationship, the dose-rate might be an important factor.

9. The assessment of risk of specific late somatic effects on the basis of a given dose-effect relationship must take into account the way in which injury is distributed over time. In the time-incidence curve the important parameters will be the shortest latent period L before any effect is manifest and the subsequent shape of the curve. For example, figure 1 shows the time-incidence curve deduced from data on the incidence of leukaemia after radiation therapy for ankylosing spondylitis.⁶

10. If the probability of the induction of a specific late effect (figure 2a) has fallen to zero after a given dose of

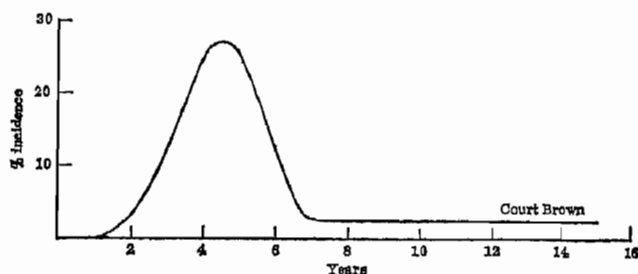


Figure 1. Time incidence curve of leukaemia

radiation in a time which is short compared with the mean life span of an individual (curve 1), a linear dose-effect relationship implies that the area under the curve, i.e., the total incidence of injury, is proportional to dose. If with a reduction in dose there is an increase in the length of the shortest latent period or a change in the shape of the time-incidence curve (curve 2) so that the probability of induction of the effect has not dropped to zero at the end of life, any statement about the dose-effect relationship—linear or otherwise—cannot be made without consideration of life expectancy.

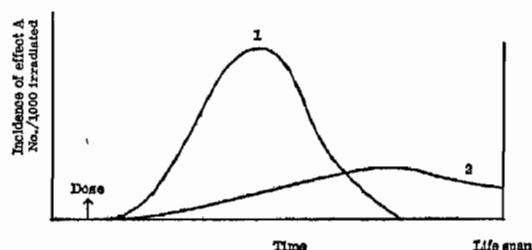


Figure 2a (see para. 10)

11. Similarly if, whatever the dose, the effect has a finite probability to the end of life (figure 2b), any simple statement concerning linear relationship can only be made if the shortest latent period does not change with the dose, and if the probability of injury at any later time is proportional to the dose.

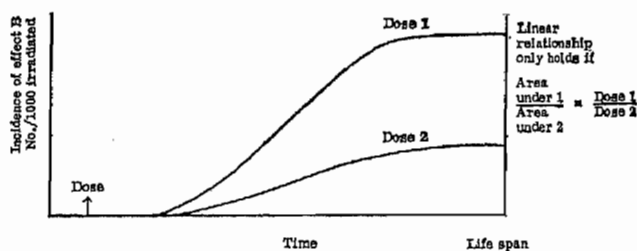


Figure 2b (see para. 11)

12. In the present state of knowledge, mean tissue dose is the only parameter that can be used to estimate risks in populations. If the dose-effect relationship is non-linear the use of a per capita mean tissue dose will be inapplicable, and individual dose and dose distribution would need to be considered; this would be a much more difficult task.

13. So far as an absolute assessment of risk is concerned, that is, an estimate of the actual number of effects from a given radiation exposure, a clear distinction must be made between the genetic and somatic problems. For radiation-induced genetic changes there is good experimental evidence that the dose-effect relationship is linear; the difficulty of making absolute assessments for

a human population lies in lack of knowledge of the slope of the dose-effect curve under various conditions, and uncertainty about the way in which an increased mutation rate will be expressed in a human population.

14. For somatic effects there are no experimental data relevant to the form of the dose-effect curve at low doses and, even at high doses, as indicated in annex D, there are very few reliable dose-response data for late effects. Thus, although the assumption of a linear dose-effect relationship at low doses may be made, there is no means at present of arriving at the actual value of the slope. However, even if adequate dose-response data were available at high doses, any extrapolation to low doses would involve large assumptions on: (a) the dose-effect relationship; (b) the latent period for manifestation of the effects; and (c) dose-rate dependence. For these reasons it is felt that the use of mean dose as the risk parameter can be used only to estimate the comparative risk from various sources, and not absolute risk.

BASIS OF RISK COMPARISON

15. In using the mean dose in calculations of comparative risk of natural radiation, fall-out and medical exposure, it is necessary to take into account that: (a) the yearly dose from natural radiation is constant; (b) the yearly dose from medical exposure is varying; and (c) the yearly dose from fall-out not only varies but the radiation exposure continues long after the event.

16. It is suggested that the basis of comparison should be the number of injuries resulting from procedures carried out during any given period of practice. For natural radiation and medical exposure the period of practice and the period of radiation exposure will coincide. For environmental contamination the period of radiation exposure will greatly exceed the period of practice.

17. This method of treatment permits comparison of total numbers of injuries occurring over all time. To obtain information on the yearly incidence in a population, or on the risk to a given individual, other methods of treatment would be required which, in the present state of knowledge, would involve so many assumptions as to be of little value.

18. The term "dose commitment" is used for the radiation dose resulting from procedures carried out during a given period of practice. For natural background and medical exposure the dose commitment will be the dose actually received during the period of practice. For environmental contamination the dose commitment will be the dose received during the selected period together with that received subsequently as a result of events during the period, i.e., an integration of dose to infinite time.

19. The term "dose commitment" is applied not to individuals but to populations only and represents the mean tissue dose (i.e., the dose to the total pool of specified cells) within the population.

20. Although the dose commitment from environmental radiation due to a given period of practice involves an integration to infinite time, the major fraction of the dose, apart from the contribution from C^{14} , will have been delivered within fifty years. This implies, of course, that a considerable fraction of whatever somatic effects may arise from a given test will have appeared within about fifty years. Any more detailed statement

than this on the rate of appearance of somatic effects would require a knowledge of the time-incidence relationships at the relevant levels of dose and dose-rate.

21. In the present annex, dose commitments will be based on world-wide averages of dose from the various sources and, for the comparative risk estimation, the ratio of the respective dose commitments will be used.

WEIGHTING FACTORS FOR POPULATION

22. When considering the genetic effect of uniform irradiation of the population, each increment of time, and therefore of dose to the gonads, contributes an equal number of mutations to the population so long as the age distribution of the population remains the same. However, when only certain individuals in a population are irradiated, as in medical radiology, the gonad doses will have varying importance depending on the age of the individual, as the probable number of children to be born to the individual must be taken into account. The term "genetically significant dose" is defined (G, 9-12) as that dose which, if received by every member of the population, would be expected to produce the same genetic injury to the population as do the actual doses received by the various individuals. This population dose is obtained by weighting the individual gonad doses by a relative child expectancy factor so as to make possible comparisons with doses from sources to which populations are uniformly exposed.⁹⁻¹²

23. It is very probably that there is a considerable age dependence in the development of late somatic effects of radiation, but there is at present no information on which to base appropriate weighting factors. In the present calculations it has been assumed that the average latent period, for the somatic effects considered, is short compared with the normal life span, and has not therefore been taken into account.

24. The growth of world population also has to be considered. The expression "cell-rad" implies the product of two terms, one related to numbers of cells, and the other to dose. In the case of the risk comparison between medical exposure and exposure from natural radiation the "cell" term will be identical for each dose commitment, and the comparison can be based solely on the ratio of the doses. However, the dose commitment from nuclear testing will be delivered during a period of time in which the size of population (and thus the number of cells) will increase. Ideally, this increase would have to be taken into account in the calculation of the dose commitment. In view of the uncertainty of the estimates of future world population, this factor has not been taken into account in the comparison of risks.

III. Problems associated with the estimation of the dose received by body tissues

25. As has been explained above, comparative risk assessments will be made for genetic effects, induction of leukaemia and induction of bone tumours. Radiation doses from the various sources must therefore be calculated for the relevant critical tissues.

26. The estimation of the radiation doses to any tissue must include contributions from external and internal sources. The conversion of exposure dose measured outside the body to absorbed dose in the relevant tissues can be made by calculation, but often only

with major assumptions. Alternatively, measurements may be made on tissue-equivalent "phantoms", but these will also have limitations since phantoms can only approximately simulate man.

27. In determining the contribution from internally deposited radio-nuclides it is necessary to recognize that the mean dose to the relevant tissue will not necessarily be the same as the mean dose to the organ containing that tissue, if dose distribution throughout the organ is not uniform.

28. This problem does not arise with the gonads since it may normally be assumed that the distribution of radio-nuclides is uniform throughout the gonads and the dose in all parts of the gonads, including the germinal cells, will be the same.

29. The dose to bone from bone-seeking radio-nuclides, such as Sr^{90} , may not be uniform. There is the additional complication, in estimating dose to bone surfaces, in that the lack of electron equilibrium near the surface has to be taken into account. With single injections of bone-seeking nuclides the problems of dose estimation may be very severe since there will be "hot spots", i.e., high local concentrations of radio-activity, in areas of bone growth and remodelling. However, with continuous intake of radio-nuclides, non-uniformity will be much less, particularly with beta-emission of relatively long range (e.g. $\text{Sr}^{90} + \text{Y}^{90}$).

30. For continuous uniform ingestion of radio-active materials during steady bone growth, as in young children, the distribution of activity in a given bone is relatively even. In the adult there will be greater non-uniformity, but there is much still to be learned about the effect of age. The effect of such variations on the dose to bone and bone marrow has been discussed.⁷ There is evidence from recent studies of a substantial variation between different bones, but presumably this will become less marked with prolonged ingestion.

31. Another factor affecting the calculation of bone dose from internally deposited radio-nuclides in the adult is the degree of mineralization of bone, which also may change considerably with age. This again is a subject on which much further information is required.

32. In the present calculations the major problem, in determining the internal dose to the bone surface and bone marrow, is the contribution from Sr^{90} derived from fall-out. There is some contribution in natural radiation from the α -emitters, but this dose represents only about 10 per cent of the total from natural sources.

33. Assuming no gross non-uniformity in dose distribution in bone, the Sr^{90} contribution to the mean dose at the surface of bone will be approximately one half of the mean Sr^{90} skeletal dose derived in annex F, part III. With regard to the bone marrow dose from Sr^{90} in the bone, it is shown in annex F, part III, that the mean bone marrow dose within trabeculae will be approximately one-quarter of the mean skeletal dose. These factors have been used in the present calculations.

THE PROBLEM OF RBE (RELATIVE BIOLOGICAL EFFECTIVENESS)

34. As has been shown in annexes B and D, the value of the RBE of ionizing radiations of different characteristics, e.g. neutrons and X-rays, depends on the biological effect considered.^{8,9} For the assessment of any given biological effect, it is clear that a precise analysis requires an RBE for each of the radiation conditions as

well as for each effect under consideration. However, values of RBE that have been obtained experimentally apply only to the conditions under which the measurement was made. At the present time there is no information on the RBE values appropriate to the production of specific late effects in man, and without this information there is no alternative but to use the values adopted by ICRP. The values of RBE quoted by the ICRP, reproduced in annex A, have been chosen as those which are unlikely to be exceeded under conditions of occupational exposure.

EFFECT OF TRANSMUTATION OF C^{14}

35. One further outstanding problem is that associated with the interpretation of the effects of the incorporation of C^{14} into body tissue. Carbon atoms make up about 37 per cent of the deoxyribonucleic acid (DNA) which is an important constituent of chromosomes and is associated with the genes. Hence if a C^{14} atom becomes incorporated into a DNA molecule and later disintegrates, the DNA molecule may be damaged not only by the ionizing beta particle emitted and the recoiling nucleus, but also by the transmutation of the C^{14} atom to N^{14} , a process which might also give rise to a gene mutation (annex B).

36. Estimates of the magnitude of the transmutation effect vary from one tenth to many times the effect due to ionization¹⁰⁻¹³ and more experimental data are needed before a reliable assessment of this effect can be made.

IV. Comparison of doses

37. With the reservations outlined in the previous sections and in the relevant sections of the other annexes, the doses to present and future generations are summarized in the following paragraphs.

DOSES FROM NATURAL RADIATION

38. Natural radiation includes cosmic rays, radiations from radio-active nuclides in the earth and in building materials, and radiations from internal radio-activity. The yearly population doses to gonads and bone marrow are given in table I. These represent only average values of natural radiation; they do not reflect the large variations throughout the world.

DOSES FROM MEDICAL EXPOSURE

39. Table I also gives representative values of the yearly dose due to medical exposure. During the next decade the availability of X-ray facilities will be much greater throughout the world, and information will be required regarding the doses to the larger numbers of people being examined or treated. This expansion cannot be predicted, nor can the possible development of more conservative procedures. For the purpose of this annex, the doses to the population will be assumed to be constant. Although much smaller, the doses from occupational exposure and miscellaneous sources of radiation are included in table I.

DOSES FROM FALL-OUT

40. The world average doses (weighted for population distribution) resulting from fall-out do not include the doses from local fall-out within the first few hundred miles from megaton surface nuclear explosions.

41. The estimation of the dose from current fall-out is possible with some accuracy on the basis of observed data. However, when one attempts to predict levels of activity on the ground or in foodstuffs due to past and future testing, and to derive the ensuing doses, the unknowns make any estimate extremely difficult.

42. In the case of external exposure and internal exposure from substances with rapid turnover, the dose-commitment from a given period of practice can be calculated as the dose actually received up to the present date plus the dose to be expected in the future. For isotopes, such as Sr^{90} , with slow turnover, the same calculation is more difficult. As has been shown in annex F, part III, the dose-commitment from Sr^{90} can be derived from an integral of the environmental contamination

$$D_{\infty} = k \int_{t_0}^{\infty} c(t) dt$$

If experimental data are available for the period t_0 to t_1 , the dose commitment can be written

$$D_{\infty} = k \left(\int_{t_0}^{t_1} c(t) dt + \int_{t_1}^{\infty} c(t) dt \right)$$

where the first integral can be evaluated from the measured values of $c(t)$ and the second integral has to be derived from a predicted future environmental contamination. It should be realized that the dose actually received during the period t_0 to t_1 is only part of the first integral (F III, 67).

43. The dose-commitments given in table II have been calculated on the following assumptions with regard to testing conditions:

(a) *Testing up to the end of 1960.* The dose-commitments can partly be derived from experimental data (cf. para. 42). The future doses have been calculated on the basis of a total atmospheric injection of 6.6 Mc Sr^{90} and 2.2×10^{28} atoms of C^{14} .

(b) *Future testing.* As a model to be used for the calculation of the doses from possible future testing, it has been assumed that the yearly rate would involve the injection of 1 Mc Sr^{90} and 10^{28} atoms of C^{14} into the atmosphere;

(c) *Testing during the period 1954 to 1961 inclusive.* Since the experimental data do not permit an assessment of the atmospheric injection of Sr^{90} and C^{14} during 1961, it has been assumed for the purpose of the dose estimates that the total injection during the period 1954-1961 (8 years) was $(6.6 + 1) = 7.6$ Mc Sr^{90} and $(2.2 + 1) 10^{28} = 3.2 \times 10^{28}$ atoms of C^{14} . It is shown in annex F, part I, that this is the most reasonable estimate that the Committee can at present venture to make.

V. Comparative genetic and somatic risk estimates

44. The period of practice for which the dose commitments have been calculated is the period 1954-1961 (eight years). It has been assumed that all the weapon tests were carried out during this period and none previously. This period has been used because it is difficult to analyse the measurements of fall-out to determine the actual doses likely to be received from any one series of nuclear testing, but only the doses arising from the total testing so far carried out.

45. The dose commitments to all generations due to nuclear weapon testing during this period are given in

table III for the genetic risk and for the selected somatic risks (induction of leukaemia or bone tumours). These dose commitments are compared to the dose commitments from natural radiation and medical and occupational exposure during the same period. For these two latter sources, the dose commitment for any one year is equal to the dose actually experienced during the same year.

46. It can be seen from table III that, for the period chosen (i.e., 1954-1961), the comparative genetic risk from fall-out is about one-tenth of that from natural sources. The genetic risk from medical exposures* is about one-third of that due to natural sources. Fall-out contributes to the dose commitment for the induction of leukaemia and bone tumours between one-quarter and one-sixth of that from natural sources.

47. If no further testing is carried out, the relative importance of the dose commitment due to previous tests will decrease in comparison with the accumulated doses from natural sources and medical exposure. The figures in table III indicate that the whole series of tests during 1954-1961 will give a dose commitment corresponding to about one to one and a half years of exposure from natural radiation.

48. In the event of continued testing at a constant rate of injection, equilibrium conditions would obtain in about 100 years, except for C^{14} . For this nuclide equilibrium conditions would imply many thousands of years of testing. The dose commitment from one year of injection is numerically equal to the yearly dose under equilibrium conditions at the same rate of injection. The dose commitments per year of testing at the assumed rate are compared with the dose commitments due to one year of natural irradiation and medical and occupational exposure in table III, columns 5-7.

49. If the dose commitment is derived from an integration of future doses to infinite time, the dose from C^{14} will be found to contribute more than 60 per cent of the total dose from fall-out. If, however, the integration is only carried out to the year 2000, the contribution from C^{14} is only about 5 per cent of the dose from fall-out.

SUMMARY

50. The assumption of a linear dose-effect relationship and the use of the mean tissue dose have been used to estimate the comparative risk of the doses from the various sources of radiation to which the population is exposed, but there are insufficient data to make absolute risk estimates at the present time.

* See table I, footnote.

TABLE I. AVERAGE YEARLY DOSE TO THE POPULATION

	Genetically significant dose (mrem)	Bone marrow dose (mrem)	Cells lining bone surfaces (mrem)
Natural radio-activity	125	122	130
Medical exposure*			
Diagnostic	30	50-100	?
Therapeutic	5	?	?
Occupational and miscellaneous exposure	~ 2	?	?

* Based on the values reported in annex G.

TABLE II. DOSE COMMITMENT FROM NUCLEAR TESTING

Organ	Contribution	Tests 1954-1961		Future tests
		Dose commitment (mrem)	Fraction of dose commitment reached by 2000	Dose commitment per year of testing (mrem)
Gonads.....	All sources but C ¹⁴	41	0.97	7
	C ¹⁴	70	0.10	22
	TOTAL	111	0.42	29
Cells lining bone surfaces.....	All sources but C ¹⁴	128	0.94	20
	C ¹⁴	116	0.10	37
	TOTAL	244	0.54	57
Bone marrow.....	All sources but C ¹⁴	84	0.94	13
	C ¹⁴	70	0.10	22
	TOTAL	154	0.56	35

TABLE III. COMPARISON OF RISK^a
(Dose commitment to all generations)

	Tests 1954-1961						Future tests					
	Dose commitment (mrem)						Dose commitment per year of testing (mrem)					
	Gonads		Cells lining bone surfaces		Bone marrow		Gonads		Cells lining bone surfaces		Bone marrow	
Natural sources....	1,000	(1.00)	1,040	(1.00)	1,000	(1.00)	125	(1.00)	130	(1.00)	125	(1.00)
Medical and occupational ^b	300	(0.30)	?		400-800	(0.4-0.8)	37	(0.30)	?		50-100	(0.4-0.8)
Fall-out:												
All but C ¹⁴	41	(0.04)	128	(0.12)	84	(0.08)	7	(0.06)	20	(0.15)	13	(0.10)
C ¹⁴	70	(0.07)	116	(0.11)	70	(0.07)	22	(0.18)	37	(0.28)	22	(0.18)
Total fall-out.....	111	(0.11)	244	(0.23)	154	(0.15)	29	(0.23)	57	(0.43)	35	(0.28)

^a Figures in parentheses indicate contribution relative to natural sources.^b See table I, footnote.

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ANNEX I

LIST OF OFFERS TO ASSIST IN MEASUREMENTS OF SAMPLES

1. The Governments of the following Member States informed the Committee before 10 March 1962 that they had made known to other Governments the extent to which they are prepared, at the request of other Governments, to receive and analyse samples in accordance with the programme of work of the Committee, in response to section IV of General Assembly resolution 1376 (XIV) of 17 November 1959: Argentina, Australia, Belgium, Canada, Denmark, France, India, Israel, Italy, Japan, Norway, Sweden, Union of Soviet Socialist Republics, United Kingdom of Great Britain and Northern Ireland and United States of America.

2. Similar communications were received from the International Atomic Energy Agency and the World Health Organization.

ANNEX J

LIST OF REPORTS SUBMITTED TO THE COMMITTEE

1. This annex lists reports received by the Committee from Governments, specialized agencies, the International Commission on Radiological Protection and the International Commission on Radiological Units and Measurements.

2. All those reports are included of which a sufficient number of copies for distribution in the A/AC.82/G/R. and A/AC.82/G/L. document series were received before 10 March 1962.

3. The first 213 reports received by the Committee are listed in annex I of its first comprehensive report.*

* *Official Records of the General Assembly, Thirteenth Session, Supplement No. 17 (A/3838).*

<i>Document No.</i>	<i>Country and title</i>	<i>Document No.</i>	<i>Country and title</i>
A/AC.82/G/R.		A/AC.82/G/R.	
	ARGENTINA		BRAZIL
214	Descontaminación y potabilización de las aguas del Río de la Plata luego de una explosión nuclear.	228	Radio-active products in the soil and in the atmosphere.
	UNITED STATES		CZECHOSLOVAKIA
215	Detection of radiation effects on hair roots of the human scalp.	229	Measurements of radio-active fall-out on the territory of the Czechoslovak Republic.
216	Fission product radio-activity in the air along the 80th meridian January-June 1957.	230	The role of deoxiribonucleotides in irradiation sickness.
217	The biological effects of atomic radiation. The effects of radiation on oceanography and fisheries.	231	Damage of the liver cell produced by a small dose of radiation.
	CANADA		UNITED STATES
218	Consanguineous matings as a means of evaluating the effect of deleterious recessive genes on fertility in humans.	232	Common strontium content of the human skeleton.
	DENMARK	233	Current strontium-90 level in diet in United States.
219	Gonad-dose-measurements in Denmark.	234	Long-term fall-out, a summary of measurements made through June 1957 by the gummed-film network of the AEC.
220	Risk of parenthood and risk of subsequent parenthood. Denmark, 1955 and 1956.	235	Environmental contamination from weapons tests.
221	Genetically significant radiation doses from diagnostic radiology in Denmark.	236	The shorter-term biological hazards of a fall-out field.
	ARGENTINA		GERMANY
222	Distribución geográfica del calcio y potasio solubles del suelo en la República Argentina.	237	Tables of radiological data.
	UNITED STATES		ITALY
223	Tabulated results of radio-strontium analyses.	238	Data on radio-active fall-out, collected in Italy (January-June 1958).
224	Strontium-90 in man, II.		POLAND
225	Manual of standard procedures.	239	Measurements of radio-active fall-out and airborne radio-activity in Warsaw and Cracow during the year 1957.
225/ Add.1	Addendum to above document.		UNITED STATES
225/ Add.2	Addendum to above document.	240	Some measurements of the radio-activity of the air during 1957.
225/ Add.2/ Corr.1	Corrigendum to above document.		A/AC.82/G/L.
225/ Add.3	Addendum to above document.		UNITED KINGDOM
225/ Add.4	Addendum to above document.	241	The deposition of long-lived fission products from nuclear test explosions.
225/ Add.5	Addendum to above document.		UNITED STATES
225/ Add.6	Addendum to above document.	242	Critique of the linear theory of carcinogenesis.
225/ Add.7	Addendum to above document.	243	Geochemical scavenging of strontium.
226	Leukemia in Hiroshima City atomic bomb survivors.	244	Uptake of waste Sr ⁹⁰ and Cs ¹³⁷ by soil and vegetation.
	UNITED KINGDOM	245	Beneficiation of soils contaminated with strontium-90: beneficial effects of potassium.
227	Radio-active and natural strontium in human bone. UK results for 1957.	246	The distribution of radio-activity from rain.

<i>Document No.</i>	<i>Country and title</i>	<i>Document No.</i>	<i>Country and title</i>
A/AC.82/G/L.		A/AC.82/G/L.	
	UNITED STATES (<i>continued</i>)		UNITED STATES
247	Radiation dose rate and mutation frequency.	268	Atmospheric aspects of strontium-90 fall-out.
248	Retention of radio-active bone-seekers.	269	Accidental radiation excursion at the Y-12 Plant.
249	Hazard to man of carbon-14.	270	The acute radiation syndrome.
	UNITED KINGDOM	271	Strontium program quarterly summary report.
250	A preliminary survey of radiostrontium and radiocaesium in drinking water in the United Kingdom.		BELGIUM
	UNITED STATES	272	Mesures des doses aux gonades reçues lors d'examens radiologiques.
251	Radiation exposures from nuclear tests at the Nevada test site.		UNITED KINGDOM
252	Genetic and somatic effects of carbon-14.	273	Radio-active and natural strontium in human bone—UK results for early 1958.
253	Radiochemical analyses of air-filter samples collected during 1957.	274	Radio-active and natural strontium in human bone—UK results for mid- and late 1958.
254	Cs ¹³⁷ biospheric contamination from nuclear weapons tests.		UNITED STATES
255	Determination of tungsten-185, strontium-90, barium-140, and cesium-137 in fall-out samples.	275	Quarterly statement on fall-out by the US Atomic Energy Commission—September 1959.
256	Entry of radio-active fall-out into the biosphere and man.		ILO
257	Radiocarbon from nuclear tests.	276	The protection of workers against ionising radiations.
258	Analysis of stratospheric strontium-90 measurements.		UNITED STATES
259	Nuclear-critical accident at the Los Alamos Scientific Laboratory on December 30, 1958.	277	Quarterly statement on fall-out by the US Atomic Energy Commission, October 1959.
260	Atmospheric radio-activity studies at the US Naval Research Laboratory.	278	Strontium program quarterly summary report.
261	Gamma radio-activity of people and milk.		GERMANY
	ITALY	279	The recent increase in the C ¹⁴ content of the atmosphere, the biosphere and the ocean.
262	Data on radio-active fall-out, collected in Italy (July–December 1958).		UNITED STATES
	FRANCE	280	Stratospheric carbon-14, carbon dioxide, and tritium.
263	Quelques données récentes sur la conversion roentgen-rad dans l'os et le muscle.		CANADA
	BELGIUM	281	Contamination of the NRU reactor in May 1958.
264	Comparative sensitivity to radiation of seeds from a wild plant grown on uraniferous and non-uraniferous soils.		ITALY
	CANADA	282	Data on environmental radio-activity, collected in Italy (January–June 1959).
265	Levels of strontium-90 in Canadian milk powder samples up to the end of December 1958.		NORWAY
	UNITED KINGDOM	283	Cesium-137 in milk.
266	Strontium-90 in human diet in the United Kingdom, 1958.		CANADA
	DENMARK	284	The analysis of the strontium-90 levels in Canadian milk up to 1958.
267	Therapeutic abortion on account of X-ray examination during pregnancy.		INDIA
		285	Strontium-90 in milk and human bone in India.

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	UNITED KINGDOM		SWEDEN (<i>continued</i>)
286	The deposition of fission products from distant nuclear test explosions: results to mid-1959.	306	Dosage implications based on microscopic distribution.
	UNITED STATES	307	A method for determination of the strontium distribution in human bone.
287	Industrial radio-active waste disposal.	308	A method for photographic identification of microscopical radio-active particles.
287/ Add.1	Addendum to above document.		NORWAY
	FAO	309	Wet and dry deposition of fall-out materials at Kjeller.
288	Radio-active materials in food and agriculture.		ARGENTINA
288/ Corr.1	Corrigendum to above document.	310	Fall-out en la República Argentina durante 1959.
	FRANCE	311	Estudio de la contaminación del Prochilodus platensis (Sábalo) con productos de fisión.
289	Activité de l'atmosphère due au krypton-85.	312	La precipitación radiactiva atmosférica en la República Argentina en el período Enero 1957-Julio 1958.
290	Radioactivité artificielle dans la stratosphère.		UNITED STATES
291	Modifications de la radioactivité naturelle due au carbone-14.	313	Measurements of the air concentration of gross fission product radio-activity during the IGY—July 1957–December 1958.
292	Polution de l'air et irradiation au sol dues au panache d'un réacteur en fonctionnement normal.		NEW ZEALAND
293	Mesure du rayonnement γ du corps humain.	314	Environmental contamination.
	INDIA	315	Notes on measurements of alpha-particle activity of soils, fertilizers, plants and animals.
294	Measurements on the ground deposition of fission products from nuclear test explosions.		AUSTRALIA
295	Airborne fall-out measurements in India.	316	Strontium-90 in the Australian environment.
296	Measurements of cesium-137 in Indian and foreign milk.		UNITED STATES
	CANADA	317	Radiochemical analyses of air-filter samples collected during 1958.
297	Automatic linkage of vital records.	318	Effect of soil nutrients on plant uptake of fall-out.
	SWEDEN	319	Symposium on occupational health experience and practices in the uranium industry.
298	Gamma radio-activity of Swedish people measured during May and June 1959.	320	Press release HEW-L6. US Dept. of Health, Education and Welfare, regarding radio-activity in milk, dated 20 August/59.
299	Fractionation phenomena in nuclear weapons debris.	321	Press release HEW-L44. US Dept. of Health, Education and Welfare, regarding radio-activity in milk, dated 3 October/59.
300	Cs ¹³⁷ in Swedish milk and soil.	322	Fall-out from nuclear weapons tests, volume 1.
301	Determination of Sr ⁹⁰ in dried milk, milk and soil.	322/ Add.1	Addendum to above document.
301/ Add.1	Addendum to above document.	322/ Add.2	Addendum to above document.
302	Cs ¹³⁷ in Swedish milk—results up to June 1959.		
303	The fission products Zr ⁹⁵ and Nb ⁹⁵ in Swedish milk.		
304	Recent fall-out measurements in Sweden.		
305	Gamma radiation from nuclear weapons fall-out.		

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	USSR		UNITED KINGDOM
323	Определение загрязнений биосферы продуктами ядерных испытаний (сборник статей).	342	Radio-strontium and radio-caesium in drinking water in the United Kingdom.
324	О чувствительности нервной системы к слабым радиационным воздействиям.		SWEDEN
325	Опухоли у крыс, возникшие после внутрибрюшинного введения азотнокислого плутония (Pu-239).	343	Physical aspects of the radio-active fall-out over Scandinavia, especially during the period October 1958–October 1959.
326	Некоторые данные о влиянии ионизирующих излучений на нуклеиновые вещества в живом организме.	344	The increase of γ -radiation from the ground in Sweden (1950–1959) caused by fall-out from nuclear weapon tests.
327	О биологическом действии ионизирующей радиации в малых дозах.	345	A method for the automatic recording of ionizing radiation.
328	О некоторых закономерностях возникновения остеогенных сарком, индуцированных радиоизотопами.	346	The radio-active fall-out in Sweden 1957–1958.
329	О нейрогуморальной регуляции клеточного деления.		UNITED STATES
330	Выпадение стронция-90 на поверхность территории СССР.	347	An investigation of the late clinical findings following thorotrast (thorium dioxide) administration.
331	Задачи экспериментальной техники лучевых воздействий и некоторые радиобиологические данные.		GERMANY
332	Действие ионизирующей радиации на бактериальные вирусы.	348	Estimate of future Sr ⁹⁰ —deposition.
	FRANCE		FINLAND
333	Radioactivité de l'air et des précipitations au niveau du sol dans la région parisienne.	349	Measurements of the amount of radio-active fall-out in Finland.
334	Etude autoradiographique du métabolisme du 131 iode chez le rat.		UNITED STATES
	UNITED STATES	350	Natural aerosols and nuclear debris studies. Progress Report II.
335	Health and Safety Laboratory strontium program quarterly summary report HASL-77, dated 1 January 1960.		SWEDEN
	NORWAY	351	The transfer of strontium-90 from mother to fetus in mice.
336	Radio-active fall-out in Norway, 1959.		UNITED STATES
	GERMANY	352	Press release HEW-M46, dated 4 February 1960.
337	Sonderausschuss Radioaktivität—Radioaktive Partikel.		SWITZERLAND
	UNITED STATES	353	Bericht der eidgenössischen Kommission zur Überwachung der Radioaktivität zuhanden des Bundesrates.
338	Radio-activity of surface waters of the United States.		UNITED KINGDOM
339	Press release HEW-M9. US Department of Health, Education and Welfare, dated December 31, 1959.	354	Strontium-90 in milk and agricultural materials in the United Kingdom, 1958–1959.
340	Quarterly statement on fall-out, by the US Atomic Energy Commission.	354/ Add.1	Addendum to above document.
	FRANCE		WHO
341	Rapport sur le problème des doses aux gonades résultant de l'utilisation médicale des radiations ionisantes en France.	355	Methods of radio-chemical analysis.
		356	Effect of radiation on human heredity: investigations of areas of high natural radiation.
			CANADA
		357	Gonadal exposure dose to adults in diagnostic radiography.

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	UNITED STATES		UNITED KINGDOM (<i>continued</i>)
358	The biological effects of atomic radiation. (Summary reports 1960.)	375	The radio-activity of the atmosphere near ground level due to distant nuclear test explosions.
358/ Add.1	Addendum to above document.		UNITED STATES
359	Critical analysis of measurements of the gross fission product activity in the air at ground level.	376	Fall-out program quarterly summary report (March 1, 1960 through June 1, 1960).
360	Health and Safety Laboratory fall-out program quarterly summary report.		UNITED KINGDOM
	FRANCE	377	Radio-active and natural strontium in human bone, UK results for 1959. Part I.
361	Evolution de la teneur du lait et des végétaux en radioéléments artificiels dans l'est de la France (période du 1 ^{er} janvier 1958 au 1 ^{er} octobre 1959).	378	Bibliography of papers published in the United Kingdom from January 1959 to May 1960 on radio-biological and allied subjects—MRC.60/735.
	UNITED KINGDOM		JAPAN
362	Strontium-90 in human bone in the United Kingdom (1956-1958).	379	Radio-active contamination in the upper atmosphere.
	UNITED STATES	380	On the radio-activity and particle analysis of airborne dust in the troposphere.
363	Leukemia in Hiroshima atomic bomb survivors.	380/ Corr.1	Corrigendum to the above document.
	SWEDEN	381	Behavior of radio-active fall-out and air- masses around Japan.
364	The genetic background to the reactions of various mouse strains to X-rays.	382	The residence time in the atmosphere of the debris from atomic test explosions.
365	Distribution of S ³⁵ in mice after injection of S ³⁵ -cysteamine.	383	Radio-activity of airborne dusts and atmospheric pressure patterns.
	DENMARK	384	Sr ⁹⁰ deposition and meteorological fac- tors.
366	Environmental radio-activity at Risø, April 1, 1957-March 31, 1958.	385	Deposition of radio-active dust and atmospheric conditions.
367	Environmental radio-activity at Risø, April 1, 1958-March 31, 1959.	386	Radio-active fall-out in Japan and its bearings on meteorological conditions.
368	Environmental radio-activity at Risø, Report No. 14, 1959.	387	Strontium-90 in Western North Pacific surface waters.
	ITALY	388	Cesium-137 and strontium-90 in fall-out deposits.
369	Data on environmental radio-activity, collected in Italy (July-December 1959).	389	Local changes in Sr ⁹⁰ deposition in the soil as observed in Hokkaido Island, Japan.
	INDIA	390	Neptunium-239 content in the radio- active rain water collected in Japan dur- ing the period 1954-1958.
370	Evaluation of future levels of radio-active fall-out.	391	Recent variation in the atmospheric radio-carbon and the problem of transfer of radio-carbon into hydrosphere.
	NORWAY	392	Research on radio-activity in stock rain water of lighthouses in Japan.
371	On the transportation and deposition of fall-out materials.	393	Radio-active contamination of milk and milk products in Japan.
372	Fall-out over Norway from high-yield nuclear explosions.	394	Radio-active contamination of marine products in Japan.
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373	Programme "Evolution du Sr ⁹⁰ dans les sols et les végétaux".		
	UNITED KINGDOM		
374	Training in radiological health and safety.		

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	UNITED STATES		UNITED KINGDOM (<i>continued</i>)
358	The biological effects of atomic radiation. (Summary reports 1960.)	375	The radio-activity of the atmosphere near ground level due to distant nuclear test explosions.
358/ Add.1	Addendum to above document.		UNITED STATES
359	Critical analysis of measurements of the gross fission product activity in the air at ground level.	376	Fall-out program quarterly summary report (March 1, 1960 through June 1, 1960).
360	Health and Safety Laboratory fall-out program quarterly summary report.		UNITED KINGDOM
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	UNITED KINGDOM		
374	Training in radiological health and safety.		

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395	The rapid radio-chemical determination of caesium-137.
396	The concentration of cesium-137 in human tissues and organs.
397	Measurements of radiation doses due to background gamma rays by plastic scintillators.
398	Cytological effect of hot rain.
399	Effects of radiations on mitoses studied by <i>Tradescantia</i> test <i>in vivo</i> . I. X-ray irradiations by small doses.
400	Statistical observations on leukemias in Hiroshima during the past fourteen years (1946-1959).
401	Optimum mutation rate and degree of dominance as determined by the principle of minimum genetic load.
402	Relative applicability of the classical and the balance hypotheses to man, especially with respect to quantitative characters.
403	Human genetic study in Japan.
	USSR
404	Отдаленные последствия поражений, вызванных воздействием ионизирующей радиации.
405	Влияние ионизирующих излучений на плодovitость самок некоторых видов грызунов.
406	Генетическая опасность малых доз радиации для человека и их эффект на наследственность обезьян и грызунов.
407	Контролирование естественного мутационного процесса.
408	Влияние малых доз ионизирующей радиации на частоту возникновения сцепленных с полом рецессивных летальных мутаций у дрозофилы.
409	Радиочувствительность разных стадий сперматогенеза у <i>Drosophila melanogaster</i> .
410	Защитный эффект цистеаминa (β -меркаптоэтиламина) на хромосомные перестройки в тканях обезьян и мышей.
411	Генетический эффект радиации у микроорганизмов при различных перестройках ядерных структур.
412	Обратимость цитогенетических повреждений, вызванных радиацией.
413	Биологическая опасность от повышения концентрации C^{14} в результате взрывов ядерных бомб.
414	Причины радиоустойчивости растений.
415	Относительная генетическая радиочувствительность различных видов млекопитающих и дрозофилы.

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416	Генетическая радиочувствительность клеток разных видов млекопитающих.
417	Эффект малых доз радиации на хромосомные перестройки при облучении клеток в культурах эмбриональных тканей человека.
418	Влияние генотипа организма на чувствительность ядерного аппарата к малым дозам ионизирующей радиации.
419	Роль наследственных особенностей в радиочувствительности животных.
420	Об экспериментальной обратимости ядерных повреждений в облученных клетках млекопитающих.
421	Сравнительное изучение эффективности однократного и фракционированного рентгеновского облучения семенников мыши.
422	Сравнительная радиочувствительность личинок обезьян <i>Macaca mulatta</i> и мышей при облучении рентгеновыми лучами.
423	Эффективность биологического действия C^{14} при его включении в живые структуры.
424	Цитогенетическая радиочувствительность половых клеток обезьян и мышей на уровне малых и других доз.
425	Цитологические доказательства физиологической защищенности аутотетраплоидов гречихи (<i>Fagopyrum esculentum</i> <i>moenke</i>) от действия ионизирующей радиации.
426	Радиационное поражение рыб.
427	Особенности индуцированного мутационного процесса у микроорганизмов.
	SWEDEN
428	The concentration of some fission product nuclides in ground-level air during the period September 1957-December 1959.
	UNITED STATES
429	Secretion of dietary strontium-90 and calcium in human milk.
430	X-ray induced chromosome aberrations in mammalian cells <i>in vivo</i> and <i>in vitro</i> .
431	Sex-linked recessive lethals in <i>Drosophila</i> whose expression is suppressed by the Y-chromosome.
432	X-ray sensitivity of primary spermatocytes of the mouse.
433	Summary of available data on the strontium-90 content of foods and of total diets in the United States.
434	Mutation frequency at low radiation intensity.

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435	Factors causing a high frequency of mice having the XO sex-chromosome constitution.
436	Genetic control of physiological processes: The genetics of radiation toxicity in animals.
437	Radio-activity of invertebrates and other organisms at Eniwetok Atoll during 1954-1955.
438	Ratio of cesium-137 and strontium-90 radio-activity in soil.
439	The error hypothesis of mutation.
440	Strontium-90 in North Atlantic surface water.
441	Leukemia in Nagasaki atomic bomb survivors.
442	Neoplasms among atomic bomb survivors in Hiroshima City.
443	Special report on high altitude sampling program.
444	Evaluation of radiological conditions in the vicinity of Hanford for 1959.
	AUSTRIA
445	Data compiled by the Bundesstaatliche Bakteriologisch-Serologische Untersuchungsanstalt in Linz, the Bundesanstalt fuer Wasserbiologie und Abwasserforschung at Wien-Kaisermuehlem and the Zentralanstalt fuer Meteorologie und Geodynamik in Vienna as to the degree of radio-activity in air and water.
445/ Add.1	Addendum to previous document.
445/ Add.2	Addendum to previous document.
445/ Add.3	Addendum to previous document.
445/ Add.4	Addendum to previous document.
445/ Add.5	Addendum to previous document.
445/ Add.6	Addendum to previous document.
445/ Add.7	Addendum to previous document.
445/ Add.8	Addendum to previous document.
445/ Add.9	Addendum to previous document.
	IAEA
446	Radiation damage in bone.
	DENMARK
447	Excerpt from draft-report on the activities of the Danish AEC for the period from 1 April 1959 to 31 March 1960.

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448	Strontium-90 in human bone.
449	Information regarding levels of Sr ⁹⁰ and Cs ¹³⁷ in rainfall up to the end of 1959.
	UNITED STATES
450	Consanguineous marriages in the Chicago region.
451	Radiation dose rate and mutation frequency.
452	Influence of dose rate on radiation effect on fertility of female mice.
453	Acute radiation response of mice from a cross between radio-sensitive and radio-resistant strains.
454	Effects of incorporated radio-carbon, C ¹⁴ , on somatic flower-color variations and morphological changes in the snapdragon, <i>Antirrhinum majus</i> .
455	Annual report for 1959 on the radio-active fall-out study program.
456	Quarterly report of the radio-active fall-out study program—January-March 1960.
	GERMANY
457	The 90-strontium content of the diet of children and juveniles in 1959.
	NORWAY
458	Meteorological fractionation of nuclear bomb debris.
459	Determination of fall-out radio-activity in the atmosphere by means of an air-borne filter.
	INDIA
460	Fall-out observations in India after the first French atomic test in Sahara.
	ARGENTINA
461	Radioestroncio en la Leche.
	UNITED STATES
462	Dependence of mutation rate on radiation intensity.
463	Some prompt and delayed effects of X-rays on growth of human amnion cells (strain FL) in tissue culture.
464	Damage and recovery of mouse testis after 1,000 r acute localized X-irradiation with reference to restitution cells, sertoli cell increase, and type A spermatogonial recovery.
	JAPAN
465	Delayed radiation effects in survivors of the atomic bombings.
466	Further studies in radiation conditioned behavior.

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467	The use of ionizing radiation as a motivating stimulus.	484	Atmospheric radio-activity in Bucharest from January to June 1960.
468	Accumulation of radio-active materials by fishery organisms.		UNITED STATES
	UNITED STATES	485	Fall-out program quarterly summary report, HASL-95.
469	Research in radio-biology.	486	Summary of gummed film results through December 1959, HASL-93.
	ARGENTINA		UNITED KINGDOM
470	Informe sobre mediciones radioquímicas de la precipitación radioactiva.	487	Strontium-90 in human diet in the United Kingdom, 1959.
	CZECHOSLOVAKIA		SWEDEN
471	Action of chloramphenicol on the change in capacity of <i>Escherichia coli</i> B cells irradiated with X-rays for phage T3.	488	The content of Cs ¹³⁷ and (Zr N b) ⁹⁵ in Swedish soils.
472	The significance of the intensity of metabolic processes and of weight for the radio-sensitivity of the organism.	489	The Cs ¹³⁷ and Sr ⁹⁰ content in dried milk samples from 1958 and 1959, FOA 4, Rapport A 4141-456, June 1960.
	JAPAN		AUSTRALIA
473	The summary of researches in Japan particularly related to document A/AC.82/R.87.	490	Results of strontium-ninety determinations on samples from Lucas Heights and Richmond, N.S.W., 1959-1960.
	UNITED STATES		SWEDEN
474	Measurement of bone marrow and gonadal dose from the chest X-ray examination as a function of field size, field alignment, tube kilovoltage and added filtration.	491	Autoradiographic and microscopic examination of nuclear-weapon debris particles.
	SWITZERLAND	492	Summary report on upper-air radio-activity measurements, 1956-1960.
475	Die Belastung des Menschen durch ionisierende Strahlen.	493	An approach to the question of computing doses and effects from fall-out.
	JAPAN	494	Radio-active fall-out in Sweden through May 1960.
476	The concentration of cesium, rubidium and potassium in human body with reference to cesium-137.		UNITED STATES
477	Annual and geographical change of Sr ⁹⁰ dietary intake of Japanese.	495	A selected list of references on marine and aquatic radiobiology.
478	Sr ⁹⁰ in human bone in Japan, during 1954-1960.	496	Radiological Health Data, Pb 161371-4, quarterly report, July 1960.
479	The environmental increase of cesium-137 since 1957 to 1960.	497	Radiological Health Data, Pb 161371-7, quarterly report, October 1960.
	UNITED STATES	498	Radiological Health Data, Pb 161371-6, monthly report, September 1960.
480	Interim report of studies of Sr ⁹⁰ in adult beagles.	499	Initial depletion and subsequent recovery of spermatogonia of the mouse after 20 r of gamma rays and 100, 300 and 600 r of X-rays.
481	The determination of internally deposited radio-active isotopes.	500	Radiation and the sex ratio in man.
	DENMARK	501	The ORINS human radiation counters, Orins-38.
482	Caesium-137 in spray-dried Danish milk.		CZECHOSLOVAKIA
	ROMANIA	502	The role of cellular cytoplasm in the development of primary effect of radiation.
483	Atmospheric radio-activity in Bucharest and Iassy in the Romanian People's Republic.	503	Strontium-90 in milk, 1957 to 1960, and its relation to radio-active fall-out in Central Europe.

<i>Document No.</i>	<i>Country and title</i>	<i>Document No.</i>	<i>Country and title</i>
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	CZECHOSLOVAKIA (<i>continued</i>)		MEXICO (<i>continued</i>)
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505	The time dependence of the man-made radio-activity of atmospheric precipitation.	524	Contador 4 π con circuito de anticoincidencia doble.
506	Polyvalent immunological tolerance in homologous radiation chimaeras.	525	Análisis químico empleando protones con energías de 1.5 mev.
507	A brief survey of results of measurement of fall-out and rainfall strontium-90 in fall-out and milk.	526	Yodación de la seroalbúmina con yodo-131.
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509	Changes in the catalase activity of the liver in mice after X-irradiation.	527	Report to the Danish National Health Board on the irradiation studies in progress at the Copenhagen University Institute for Human Genetics.
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	UNITED STATES	528	Fuerzas de Wigner y el modelo de capas del núcleo.
511	Radio-active iodine concentration in the fetal human thyroid gland from fall-out.	529	Fuerzas nucleares con centro repulsivo y el modelo de capas del núcleo. Efectos de segundo orden.
	UNITED KINGDOM	530	El efecto del reflector en los reactores heterogéneos.
512	The deposition of fission products from distant nuclear test explosions—results to the middle of 1960.	531	Sobre la generación de funciones transferentes por medio de distribuciones.
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	INDIA	536	Geomagnetic coordinates and cosmic radiation.
515	Cesium-137 in milk.	537	The simple cones of albedo of cosmic rays.
	UNITED KINGDOM	538	Short range forces and nuclear shell theory.
516	Radio-active fall-out in air and rain.	538/ Add.1	Addendum to above document.
	NORWAY	539	Velocity-dependent forces and nuclear structure. II. Spin-dependent forces.
517	Radio-active fall-out in Norway—July 1959 to July 1960.		UNITED KINGDOM
	MEXICO	540	Bibliography of papers published in the United Kingdom from June to November 1960 on radiobiological and allied subjects.
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519	Producción mesónica de mesones.	541	Radio-active fall-out in Ghana.
520	Métodos de cálculo de la precipitación radioactiva.		BELGIUM
521	Resonancia del F ¹⁸ por bombardeo de O ¹⁶ con deuterones.	542	La retombée radioactive à Mol et au Congo.
522	Métodos de determinación del estroncio-90.		

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552	Применение трития в биологических исследованиях.	573	Radiological Health Data, monthly report, February 1961, PB 161371-12, Volume II, No. 2.
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	SOUTH AFRICA	577	The 90-strontium content of human bone and tissues in 1958, 1959 and 1960.
556	Radio-active fall-out over South Africa.		SWEDEN
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584	Dietary levels of strontium-90 and cesium-137.
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586	Caesium-137 in air, precipitation, drinking water, milk and beef in Norway during 1959 and 1960.
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587	Strontium-90 in milk and agricultural materials in the United Kingdom, 1959–1960.
	FRANCE
588	Mesures de la contamination radio-active de la chaîne alimentaire.
	INDIA
589	Strontium-90 in milk and human bone in India.
	ARGENTINA
590	Contaminación por radioestroncio durante el año 1960.
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594	Data on environmental radio-activity, collected in Italy (July–December 1960).

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611	Dominant lethal effects of high intensity X-irradiation of mouse spermatogonia.		при воздействии на организм малых доз ионизирующей радиации в условиях внутреннего облучения.
612	Sex chromosome loss in mice following irradiation of the fertilised egg.	629	Флуоресцентные исследования изменений нуклеопротеидов и их дериватов в облученных клетках.
	INDIA	630	О действии рентгеновского облучения на окислительное фосфорилирование в митохондриях растений.
613	Radiochemical procedures for the assay of low levels of strontium-90 activity in milk, human bone and water.	631	Действие многократного рентгеновского облучения в малых дозах на деятельность высших отделов центральной нервной системы животных.
	USSR	632	Значение регенерационных процессов в реакции тканей на облучение.
614	Уровень загрязнения приземного слоя атмосферы продуктами испытаний ядерного оружия по измерениям в Подмоскowie с 1955 по 1959 год.	633	Изменения условнорефлекторной деятельности собак, вызванные хроническим общим облучением предельно допустимой дозой рентгеновых лучей.
615	Глобальное распространение в атмосфере и выпадение на землю радиоактивных продуктов ядерных взрывов.	634	Белковый обмен и иммунологические особенности клеточных органоидов при острой лучевой болезни.
616	Состав и концентрация радиоактивных загрязнений воздуха в Индийском и Тихом океанах в 1959-1960 годах по материалам экспедиции на Э/С «Витязь».	635	О подавлении регенерационных процессов в кости при различных условиях облучения животных.
617	Воздействие ионизирующей радиации на нуклеиновый обмен половых клеток самцов-производителей в связи с развитием мужских и женских особей в их потомстве.	636	Экспериментальное изучение первичного механизма действия радиации на ядро клетки.
618	Количественная характеристика чувствительности центральной нервной системы к ионизирующему излучению.	637	Некоторые вопросы экспериментально-биологического обоснования максимально-допустимых количеств радиоактивных изотопов при попадании их в организм.
619	О роли радиационного повреждения внутриклеточных поверхностей раздела в биологическом действии ионизирующих излучений.	638	Спектрофотометрическое и радиометрическое исследование препаратов дезоксирибонуклеиновой кислоты, выделенных из печени крыс после поражения стронцием-90.
620	Ритмика окислительных процессов и ее нарушение при действии радиации.	639	О начальных механизмах биологического действия ионизирующих излучений.
621	Переход Sr ⁹⁰ от матери к потомству и изменения нервной и сердечно-сосудистой системы у последних.	640	О некоторых механизмах влияния малых доз хронического общего рентгеновского облучения на высшую нервную деятельность и некоторые вегетативные функции белых крыс.
622	Природа первичных цитогенетических лучевых повреждений и каталитическая активность хромосом.	641	Особенности хронического поражения, вызванного стронцием-90.
623	О «кислородном эффекте», наблюдаемом при лучевом повреждении растительных и животных клеток.	642	О характере изменения полимерного спектра ДНК при γ-облучении ее растворов.
624	К вопросу об обратимости различных форм радиационного поражения у диплоидных дрожжевых клеток.	643	О двух видах радиационного последствия, выявляемых у семян ячменя.
625	О некоторых проблемах современной радиобиологии.	644	О передаче стронция-90 самками крыс детенышам.
626	Реакция коркового слоя надпочечников при воздействии на организм малых доз ионизирующей радиации в условиях внутреннего облучения.	645	К вопросу о характеристике синтеза белков в органоидах клеток тканей нормальных и облученных белых крыс.
627	Анализ действия основных физических факторов, изменяющих радиочувствительность.		
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	GERMANY	662	Annex to paper of estimation of gonad dose in radiotherapy of benign conditions.
647	Research on fundamental radiobiology and somatic effects of radiation of Germany, 1954-1960.	663	Report on exposure of workers of Atomic Energy Establishment of United Arab Republic.
648	Major radiogenetical studies carried out in the Federal Republic of Germany during 1953 to 1960.	664	Fall-out over United Arab Republic from the fourth French nuclear test over Algerian Sahara.
	SWEDEN	665	Strontium-90, stable strontium and stable calcium in soil, food items, water and human bone in Egypt (UAR).
649	Distribution of radiocesium in mice. An autoradiographic study.	666	Committee on the Effects of Atomic Radiation on Man. Detailed annual report No. 2, Cairo, July 1961.
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651	Radiocesium and potassium in Norwegians.	667	Assay of strontium-90 in human bone in the United Kingdom. Results for 1960, Part I with some further results for 1958 and 1959. Medical Research Council Monitoring Report, Series No. 2.
652	Cs ¹³⁷ burdens in Swedish Laplanders and reindeer.	668	Human bone metabolism deduced from strontium assays.
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653	Strontium-90 in fall-out and in man in Australia, January 1959-June 1960.	669	Fall-out in Norwegian milk in 1960. Norwegian Defence Research Establishment, Intern Rapport S-0006.
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654	Chronic occupational exposure to Sr ⁹⁰ and Ra ²²⁶ .	670	The protective effect of cysteamine against genetic damages by X-rays in spermatozoa from mice.
655	Results of systematic measurement of fall-out in Hradec Králové and Plzen, Czechoslovakia.	671	Sex-ratio—an unreliable method for estimations of radiation hazards.
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656	Bericht der eidgenössischen Kommission zur Überwachung der Radioaktivität zuhanden des Bundesrates.	672	Radiological Health Data, Vol. II, No. 7, July 1961, quarterly report. US Department of Health, Education and Welfare.
	FRANCE	673	Radiological Health Data, Vol. 22, No. 8, August 1961, monthly report.
657	Détermination du rapport rad/r dans l'os et le muscle par la méthode des gaz équivalents.	674	Assessment on the radiation dose due to fall-out.
658	Deux ans de contrôle de la radio-activité du Rhône et de la nappe phréatique.	675	The dose-response relation in radiation-induced cancer.
	CANADA		UNITED KINGDOM
659	Strontium-90 and cesium-137 in Canadian wheat (1957-1959).	676	Radiostrontium and radiocaesium in drinking water in the United Kingdom. Results to December 1960.
	UNITED STATES		UNITED STATES
660	Applications of radio-isotopes and radiation in the life sciences. Summary-analysis of hearings held on March 27, 28, 29 and 30, 1961 before the Sub-committee on Research, Development and Radiation of the Joint Committee on Atomic Energy Congress of the US, June 1961.	677	Offsite ecological research of the Division of Biology and Medicine—terrestrial and freshwater.
660/ Add.1	Addendum to above document.		

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	UNITED STATES (<i>continued</i>)		FAO
678	Radiological Health Data, Vol. II, No. 9, September 1961, monthly report.	699	The organization of surveys for radio-nuclides in food and agriculture.
679	US Atomic Energy Commission Health and Safety Laboratory fall-out program quarterly summary report for October 1, 1961. HASL-115.		UNITED KINGDOM
680	Bioenvironmental features of the Ogotoruk Creek area, Cape Thompson, Alaska. A first summary by the Committee on Environmental Studies for Project Char-iot. December 1960, TID-12439.	700	Medical X-ray exposure history of the parents of children with Down's syndrome (mongolism).
681	Atmospheric radio-activity at Kodiak and Wales, Alaska, NRL Report 5658.	701	Surveys of radio-activity in human diet and experimental studies.
682	Evaluation of the ground-water contamination hazard from underground nuclear explosion. UCRL-5538, April 8, 1959.		USSR
683	Distribution of radio-activity from a nuclear excavation. UCRL-6249-T, October 26, 1960.	702	Интенсивное радиоактивное выпадение в Симеизе (Крым) в результате ядерного взрыва в Сахаре 13 февраля 1960 года.
684	Proceedings of the Second Plowshare Symposium May 13-15, 1959, San Francisco, Calif. Part I. Phenomenology of underground nuclear explosions. UCRL-5675, May 15, 1959.	703	Исследование радиоактивных загрязнений в районе Черного моря в 1959 году.
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685	Strontium-90 and cesium-137 in fall-out deposits and implications of their ratio.	705	Содержание Sr^{90} в костной ткани людей, проживающих на территории Советского Союза.
686	Cesium-131 and strontium-90 in sea water.	706	Выпадения долгоживущих продуктов деления на территории СССР в 1959-1960 годах.
687	A new method of measurement of absorption dose rate from terrestrial background radiation.	707	Содержание Sr^{90} и Cs^{137} в пробах молока, взятых в разных районах СССР в 1960 году.
688	Deposition of Cs^{137} and Sr^{90} in Tokyo.		FRANCE
689	Measurement of the carbon-14 concentration in essential oil using the liquid scintillation spectrometer.	708	Etude de la vocation des sols en place à la rétention du radiostrontium.
690	The concentrations of Sr^{90} and Cs^{137} in land waters in Japan.	709	Méthode d'étude de la contamination radioactive des sols en place.
691	Cesium-137 levels in human body, August 1958-August 1960.		DENMARK
692	Measurements with a whole body counter.	710	Environmental radio-activity in Denmark 1960.
693	Natural concentration of krypton-85, carbon-14 and tritium in recent years.		BELGIUM
694	Physical aspect of fall-out in the troposphere.	711	La retombée radioactive à Mol—Rapport d'avancement 1er semestre 1960.
695	Influence of radio-activity of the atomic explosion in Sahara desert.		UNITED KINGDOM
696	The peak in radio-active fall-out in the temperate zone of the northern hemisphere.	712	Radio-active fall-out in air and rain; results to the middle of 1961.
697	Penetration of artificial radio-activity in deep waters of the Pacific and vertical diffusion rate of sea water.		UNITED STATES
698	Seasonal variation of radio-active fall-out.	713	Radiological Health Data, Volume II, Number 10, October 1961, quarterly report.
		714	Radiological Health Data, Volume II, Number 11, November 1961.
		715	Fall-out from 1957 and 1958 nuclear test series.
		716	The latent period, incidence, and growth of Sr^{90} -induced osteosarcomas in CFI and CBA mice.
			CANADA
		717	The effect of radiation dose rate upon the

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	CANADA (<i>continued</i>)		JAPAN (<i>continued</i>)
	production of eye colour mutations in the <i>Chalcid dahlbominus</i> .	733	The distribution of active marrow in the bones of normal adult.
	UNITED KINGDOM	734	Mutation rates at low level irradiation in <i>Drosophila melanogaster</i> .
718	Strontium-90 in bones of infants in Hong Kong.	735	The genetically significant dose by the X-ray diagnostic examinations in Japan.
719	Bibliography of papers published by the United Kingdom sources from May to October 1961, on radiobiological and allied subjects.		UNITED STATES
720	Assay of strontium-90 in human bone in the United Kingdom—Part II.	736	Fission product radio-activity in the air along the 80th meridian (West) during 1960.
	BELGIUM	737	Health and Safety Laboratory, fall-out program, quarterly summary report, September 1, 1961 through December 1, 1961, HASL-117.
721	La retombée radioactive à Mol—Rapport d'avancement 2ème semestre 1960.	738	Sr ⁹⁰ in man and his environment, Volume III: Publications.
	UNITED KINGDOM	739	Sr ⁹⁰ in man and his environment, Volume II: Analytical data.
722	Radio-activity in milk in the United Kingdom 1961: preliminary report.	740	Radiological Health Data, Volume II, No. 12, December 1961.
723	Some provisional estimates of radio-active fall-out in the United Kingdom—autumn 1961.	741	HASP second special report on high altitude sampling program.
	INDIA		NORWAY
724	Observations of fall-out in India during the period of cessation of nuclear tests.	742	Caesium-137 and strontium-90 in precipitation, soil and animals in Norway.
725	A study of washout of radio-active fall-out and particulate matter in individual rain showers.		UNITED STATES
726	Gamma-ray analysis of fall-out samples collected in India during October 1958 to March 1960.	743	Radiological Health Data, Volume III, No. 1, January 1962.
727	Cesium-137 and strontium-90 in milk.	744	Fall-out from USSR 1961 nuclear tests.
728	Seasonal variations of cesium-137 in the ground level air.		AUSTRALIA
	MEXICO	745	Measurements of strontium-90 in the Australian environment.
729	Quinto informe sobre estudios de la precipitación radioactiva.		ARGENTINA
	UNITED STATES	746	Radiocesio en la dieta humana.
730	The effect of deposition rate and cumulative soil level on the concentration of strontium-90 in US milk and food supplies. AEC TID-13945.		UNITED STATES
	JAPAN	747	Criticality accidents in Vinca, Yugoslavia, and Oak Ridge, Tennessee.
731	A shift of sex-ratio in the progeny from irradiated males in <i>Drosophila melanogaster</i> (preliminary note).	748	Health and Safety Laboratory—Preliminary data on fall-out from the fall 1961 USSR test series. Staff report, February 27, 1962, HASL-121.
732	On the incidence of leukemias in Hiroshima during the past fifteen years from 1946 to 1960.		SWEDEN
		749	Late effects of thorotrast in cerebral angiography.
		750	On the Hiroshima and Nagasaki experience of nuclear weapons initial radiation LD ₅₀ for man.

ANNEX K

LETTER SENT AT THE REQUEST OF THE COMMITTEE BY ITS SECRETARY TO STATES MEMBERS OF THE UNITED NATIONS AND MEMBERS OF THE SPECIALIZED AGENCIES AND OF THE IAEA ON 7 APRIL 1960

Sir,

I have the honour to inform you that the Scientific Committee on the Effects of Atomic Radiation has now completed its seventh session. The Committee has received during the course of its past work, and is continuing to receive, substantial data from Governments and United Nations agencies, and assistance continues to be rendered to the Committee by them, by international non-governmental and national scientific organizations and by individual scientists. The Committee is greatly indebted to all of these and welcomes all information relevant to its work on the effects of atomic radiation on man and his environment. It wishes to ensure continuation of the flow of such material so that nothing significant in the knowledge available in the world as a whole should by any mischance escape its notice.

A primary objective of the Committee is to assess the effects of radiation on the world population. In any attempt at this assessment it is necessary to know the world-wide levels in food products and in the human body of radio-active debris from the testing of nuclear devices. Data obtained now is of particular value in assessment of the present and prediction of the future situation, because of the period that has elapsed since the latest high yield nuclear tests.

In pursuit of this aim the Committee on 3 July 1959 addressed an invitation to States Members of the United Nations and members of the specialized agencies and of the International Atomic Energy Agency to send any further data of the type already contained in its comprehensive report, so as to enable this report to be kept up to date or extended. This invitation outlined the principal categories of information sought by the Committee, including those of immediate significance to its programme. The Committee was subsequently requested by resolution 1376 (XIV), adopted by the General Assembly on 17 November 1959, to consider and study, in consultation with certain agencies of the United Nations and other interested organizations, appropriate arrangements for the purpose of stimulating the flow of such information and data, and for encouraging genetic, biological and other studies.

In the course of its studies of appropriate arrangements for stimulating the flow of relevant information and data, the Committee noted that at the present time there is a substantial part of the globe regarding which there is little information concerning levels of radio-active contamination in soils, water, food products and the human body. The Committee would like to obtain data for these areas and would suggest that countries in them initiate sampling programmes, especially on the following topics:

(a) Levels of Sr^{90} in human bones classified by age groups: for example—still-born, 0-1, 1-2, 2-3, 3-5, 6-10, 11-20 years;

(b) Levels of Sr^{90} and Cs^{137} in diet: this involves measurement of the mean levels in the principal contributing food products and in the total diet. Corresponding data on natural radio-activities would also be desirable;

(c) Data "linking" rainfall and deposition of Sr^{90}

The Committee also noted that Member States in need of assistance in the field of sampling and analysis are able to obtain it from a number of other Member States or from interested agencies of the United Nations that have offered such assistance: these offers are listed in annex 1 to the present letter. The Committee recognizes that it is desirable for close co-operation between the Committee, Member States and participating agencies of the United Nations to be maintained in consideration of these arrangements and collation of scientific information obtained. The Committee would appreciate receiving in all cases full information on the manner in which data was obtained; and it emphasized that collections should be made by methods which ensure that data is precise and representative.

The Committee invites all those who can do so to submit by 31 July 1960 data on Sr^{90} and Cs^{137} levels to December 1959.

The Committee was also requested by General Assembly resolution 1376 (XIV) to consider and study appropriate arrangements for encouraging genetic, biological and other studies that will elucidate the effects of radiation exposure on the health of human populations. The Committee recognized that any fundamental advances in knowledge of biological mechanisms will be relevant to the understanding of the genetic and somatic effects of ionizing radiation on living tissue. Fundamental advances can be best facilitated by bringing together scientists of experience and distinction and making them aware of each others' needs for information and data. Progress also requires the provision of necessary equipment to enable ideas to be tested. Whilst new and significant advances in basic science can never be guaranteed it is possible nevertheless for scientific institutes and individual scientists to develop and expand information in fields where knowledge is lacking. Sometimes this lack comes about not through a deficiency of method to elicit information but through paucity of data provided by single individual or unit. In its own area, the Committee is especially conscious that although means have been developed for measuring:

(i) The mutation-rate, natural and radiation-induced at specific loci in mammals such as the mouse;

(ii) The radio-biological effects of radio-active elements such as Sr^{90} in mammals;

(iii) The induction of specific new growths such as lymphoma by gamma-rays at defined dose-rates, the accumulation of data in these and related areas adequate for statistical appraisal is extremely time-consuming.

ing and expensive. Thus close collaboration between laboratories all working within a defined and agreed framework is eminently desirable.

The Committee feels that Governments might well wish at this time to re-examine the ways and means whereby its requests for relevant information can best be channelled, in their respective countries, to the appropriate national scientific organizations and committees, as well as to individual scientists. It would welcome information from Governments concerning the names of individual scientists or members of panels to whom its requests are referred: such information would enable it to communicate requests with the specificity and detail appropriate to the scientists concerned, through the usual Governmental channels.

Conscious of the need to establish and maintain such contact with scientists and scientific bodies, the Committee decided to request Governments to bring to their notice a statement which it prepared at its seventh session. This could be done either by direct distribution, by diffusion in scientific journals or by any other appropriate means. This statement is attached to the present letter as annex 2.

May I, in connexion with the Committee's requests for information, draw your attention to the fact that 150 copies of each report are required for distribution and circulation to the Committee, as distinct from deposition in the Committee's library. The reports should be addressed to the Secretary of the Scientific Committee on the Effects of Atomic Radiation, United Nations, New York.

ANNEX 1

[The list originally given in the present annex has been superseded by the one contained in annex I to the report.]

ANNEX 2

Statement addressed to scientists in the radiation field by the United Nations Scientific Committee on the Effects of Atomic Radiation

The United Nations Scientific Committee on the Effects of Atomic Radiation* is indebted to the many scientists throughout the world whose work contributed directly or indirectly to the Committee's first report published in 1958. It recognizes that much research pertinent to its area of concern is being carried on now, and that almost any aspect of biology contributes to knowledge of radiation effects in man. The Committee wishes

* The General Assembly, at its tenth session, established by resolution 913 (X) the United Nations Scientific Committee on the Effects of Atomic Radiation consisting of the following members: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt (now part of the United Arab Republic), France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics, United Kingdom of Great Britain and Northern Ireland, United States of America.

to obtain reports of all work in relevant fields, and is anxious that no results of relevant research carried out in laboratories of Member States escape its attention, whether or not those States are at present represented on the Committee.

The Committee is neither carrying on its own research, nor directly sponsoring research, but rather depends on the work of other scientists which it studies and collates for the guidance of the United Nations and the information of all scientists.

In July 1959 the Committee invited Member States to send it data on a wide variety of physical and biological topics. Among these were the following:

1. Physical data relevant to radiation levels and accumulated doses from both natural and man-made sources:
 - Medical, industrial and research uses of ionizing radiations and radio-active materials;
 - Radio-active fall-out:
 - Measured contamination of air, ground, foodstuffs and man by strontium-90 and caesium-137;
 - Computation of external doses from fall-out deposit, including short-lived isotopes;
 - Significant disposals of radio-active wastes;
- Other significant sources of ionizing radiations;
2. Methods of measurements and radiological standards;
3. Fundamental radiation biology;
4. Somatic effects of ionizing radiation;
5. Genetic effects of ionizing radiation.

At its last meeting the Committee reviewed the present state of knowledge in its area of concern and discussed certain specific areas where additional information would be particularly welcome at the present stage of its work. In view of the need for this information the Committee brings to the notice of scientists those areas where an intensification of scientific effort would seem to be most helpful.

In the biological field the Committee noted the need for more extensive statistical data concerning:

- (i) The mutation-rate, natural and radiation-induced, at specific loci in mammals such as the mouse;
- (ii) The radio-biological effects of radio-active elements such as Sr⁹⁰ in mammals;
- (iii) The induction of specific new growths such as lymphoma by gamma-rays at defined dose-rates.

In the physical field the Committee would like to obtain data on the following topics, especially for those parts of the globe for which there is little information available at present:

- (a) Levels of Sr⁹⁰ in human bones classified by age groups: for example—still-born, 0-1, 1-2, 2-3, 3-5, 6-10, 11-20 years;
- (b) Levels of Sr⁹⁰ and Cs¹³⁷ in diet: this involves measurement of the mean levels in the principal contributing food products and in the total diet. Corresponding data on natural radio-activities would also be desirable;
- (c) Data "linking" rainfall and deposition of Sr⁹⁰.

However, all data pertinent to evaluation of effects of radiation, particularly in the low dose and dose-rate range, remain of interest to this Committee and would be appreciated because of the assistance that would thereby be rendered to it in its work.

The Committee receives reports through Governments which have been invited to forward them to the Secretary of the Committee.

APPENDIX I

LIST OF SCIENTIFIC EXPERTS, MEMBERS OF NATIONAL DELEGATIONS

The scientific experts who took part in the preparation of the present report while attending Committee sessions as members of national delegations are listed below:

ARGENTINA

Dr. D. Beninson (*Representative*)
Dr. J. Flegenheimer
Dr. A. Placer

AUSTRALIA

Mr. D. J. Stevens (*Representative*)
Professor A. M. Clark

BELGIUM

Professor J. A. Cohen (*Representative*)
Professor M. Errera
Professor F. H. Sobels
Dr. J. Blok
Mr. J. F. Bleichrodt
Miss Z. M. Beekman

BRAZIL

Professor C. Pavan (*Representative*)
Professor C. Chagas (*Representative*)
Dr. L. R. Caldas
Dr. O. Frota-Pessôa
Dr. N. Libanio
Dr. A. Paes Carvalho
Dr. E. Penna Franca
Father F. X. Roser, S.J.

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Dr. F. D. Sowby
Dr. W. E. Grummitt
Dr. H. B. Newcombe
Dr. P. M. Bird
Dr. G. H. Josie
Dr. B. B. Migicovsky
Mr. H. Cameron

CZECHOSLOVAKIA

Professor Dr. F. Herčík
(*Representative*)
Professor Dr. F. Běhounek
Dr. M. Hašek
Dr. L. Novák
Dr. M. Vojtišková

FRANCE

Professor L. Bugnard (*Representative*)
Dr. H. Jammot
Mr. J. Labeyrie

Mr. G. Lambert
Dr. G. Lejeune
Mr. L. Facy

INDIA

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Dr. V. R. Khanolkar (*Representative*)
Mr. A. S. Rao (*Representative*)
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Dr. K. G. Vohra

JAPAN

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Dr. M. Tsuzuki (*Representative*)
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Dr. Y. Hiyama
Dr. Y. Miyake
Dr. M. Kimura
Dr. R. Ichikawa
Dr. Y. Tajima

MEXICO

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Dr. F. Alba Andrade
Dr. A. Moreno y Moreno
Dr. H. Zalce

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Dr. A. Nelson (*Representative*)
Professor R. M. Sievert
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Dr. B. Lindell
Dr. B. Aler
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Professor K. G. Luning
Dr. K. Edvarson

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Dr. A. A. Prokofyeva-Belgovskaya
Dr. Y. M. Shtukkenberg
Dr. M. A. Arsenieva
Dr. V. I. Terentiev
Dr. V. T. Kozlov
Mr. G. I. Apollonov

UNITED ARAB REPUBLIC

Dr. M. E. A. El Kharadly
(*Representative*)
Dr. K. A. Mahmoud
Dr. M. M. Mahfouz

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Dr. E. E. Pochin (*Representative*)
Dr. W. G. Marley
Dr. A. C. Stevenson
Professor L. F. Lamerton
Dr. R. S. Russell
Dr. J. F. Loutit
Mr. P. J. Meade

UNITED STATES OF AMERICA

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