UNITED NATIONS

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

**GENERAL ASSEMBLY**
OFFICIAL RECORDS : THIRTEENTH SESSION
SUPPLEMENT No. 17 (A/3838)

New York, 1958

UNITED NATIONS

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

**GENERAL ASSEMBLY**
OFFICIAL RECORDS : THIRTEENTH SESSION
SUPPLEMENT No. 17 (A/3838)

*New York, 1958*

## NOTE

Throughout this report and its annexes cross-references are denoted by a letter followed by a number: the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

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.

# TABLE OF CONTENTS


| *Chapter* | | *Page* |
|---|---|---|
| I. | INTRODUCTION | 1 |
| II. | GENERAL | 3 |
| III. | PHYSICAL DATA | 8 |
| IV. | FUNDAMENTAL RADIOBIOLOGY | 17 |
| V. | SOMATIC EFFECTS OF RADIATION | 22 |
| VI. | GENETIC EFFECTS OF RADIATION | 30 |
| VII. | SUMMARY AND CONCLUSIONS | 36 |
| *Annexes* | | |
| A. | DEFINITIONS OF QUANTITIES, UNITS AND SYMBOLS | 47 |
| B. | RADIATION FROM NATURAL SOURCES | 49 |
| C. | MAN-MADE SOURCES (Other than environmental contamination) | 60 |
| D. | ENVIRONMENTAL CONTAMINATION | 98 |
| E. | METHODS OF MEASUREMENT | 124 |
| F. | FUNDAMENTAL RADIOBIOLOGY | 127 |
| G. | MAMMALIAN SOMATIC EFFECTS | 153 |
| H. | THE GENETIC EFFECTS OF RADIATION | 172 |
| I. | LIST OF REPORTS SUBMITTED TO THE COMMITTEE | 205 |
| *Appendix* | | |
| | LIST OF SCIENTIFIC EXPERTS | 227 |
| MAP | | *at end of Report* |

# Chapter I
# INTRODUCTION

1. Living beings have always been exposed to ionizing radiation from various natural sources. Nevertheless, the discovery of X-rays by Roentgen in 1895, and of radioactivity in uranium salts by Becquerel in 1896, brought, in addition to very great benefits, unforeseen hazards. Considerable damage resulted until the first measures of precaution were adopted. Indeed, within only five years, 170 cases of radiation injury were recorded.

2. The medical use of X-rays increased considerably during the First World War; this increased the incidence of over-exposure. By 1922 about 100 radiologists had died from its effects. The discovery of radioactivity was followed by a rapid development in knowledge of the characteristics and properties of radioactive substances, their separation and their applications, so that the hazard became extended to those undertaking chemical work with radioactive materials.

3. As exposure of human beings and of animals led progressively to knowledge of the gross effects of radiation, national and international conferences were held to discuss possible methods of protection against the radiations emitted by X-ray tubes and radium. The year 1921 marks the birth of national organizations for radiological protection and the publication of their first recommendations. International action was first taken during the Second International Congress of Radiology, which met at Stockholm in 1928; there, the International Commission on Radiological Protection was established, members of which were elected according to their recognized ability in this field, independent of their nationality.

4. Progress in experimental physics since the beginning of the twentieth century has also brought about new sources of radiation such as man-made radioactivity and powerful accelerators. Following the discovery of nuclear fission in 1939 and its applications, radiation hazards and protection problems increased very extensively and the atomic explosions in Hiroshima and Nagasaki caused many human deaths from radiation. The contamination of the environment by explosions of nuclear weapons, the discharge of radioactive wastes arising from nuclear reactors, and the increasing use of X-rays and of radioisotopes for medical and industrial purposes extend the problem to whole populations and also raise new international questions. In 1955, the General Assembly of the United Nations decided to include in the agenda of its tenth session an item entitled "Effects of atomic radiations".

### Constitution of the Committee

5. The General Assembly, as a result of debates held in the First Committee from 31 October to 10 November 1955, adopted resolution 913 (X) on 3 December 1955 and thereby established a Scientific Committee consisting of Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt*, France, India, Japan, Mexico, Sweden, the Union of Soviet Socialist Republics, the United Kingdom of Great Britain and Northern Ireland and the United States of America.

6. 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 radioactivity 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 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."

### Sessions of the Committee and progress reports

7. The first session of the Committee was held from 14 to 23 March 1956 and the second session from 22 October to 2 November 1956. A first yearly progress report was submitted to the General Assembly at its eleventh session (A/3365) and covered those two first sessions. The second yearly progress report of the Committee to the General Assembly at its twelfth session (A/3659) dealt with the third session of the Committee held from 8 to 18 April 1957. The text of the present report was drafted by the Committee in the course of its

* Now in the United Arab Republic.

fourth session held from 27 January to 28 February 1958, and finally approved at the fifth session held from 9 June to 13 June 1958.

### Organization of the work of the Committee

8. At its first session, the Committee elected Dr. C. E. Eddy of Australia as its Chairman and Professor Carlos Chagas of Brazil as its Vice-Chairman. Following the untimely death of Dr. Eddy, the Committee, at its second session, elected Professor Chagas as its Chairman and Professor Zénon Bacq of Belgium as its Vice-Chairman. At the third session, Professor Bacq and Dr. E. A. Watkinson of Canada were elected respectively Chairman and Vice-Chairman of the Committee and also served through the fourth session. During the fifth session, Professor Rolf Sievert of Sweden and Dr. V. R. Khanolkar of India were elected, respectively, Chairman and Vice-Chairman of the Committee.

9. The Committee, in the course of its first session, decided to examine the matters falling within its field of competence under the following five main headings:

"(*a*) Genetics;

"(*b*) The effects of irradiation by internally absorbed isotopes and the effects of external radiation;

"(*c*) Natural radiation levels;

"(*d*) Exposures during medical procedures and occupational exposure;

"(*e*) Environmental contamination".

10. The Scientific Committee, as a working procedure, used informal *ad hoc* groups formed by specialists in the various fields. The composition of these groups fluctuated from time to time according to the specific area under examination. The method of work consisted of full and unrecorded discussions centred on a blackboard. During the meetings of these groups and in the plenary meetings of the Committee, information submitted by Governments was discussed and evaluated.

### Scientific staff

11. The Committee, at its first session, requested the Secretary-General to arrange for a number of scientists to be added temporarily to the Secretariat on a basis of rotation in order to prepare scientific data for the meetings of the Committee. Accordingly, a small scientific staff was recruited and was responsible for presenting, in a form suitable for the consideration of the Committee, the large body of information submitted by Governments.

### Co-operation with Governments, specialized agencies and individuals

12. States Members of the United Nations and members of the specialized agencies were invited to submit certain classes of information to the Committee. These reports are listed in annex I of the present report.

13. In appropriate fields, the Committee had the benefit of the valuable co-operation of the Food and Agriculture Organization of the United Nations, the United Nations Educational, Scientific and Cultural Organization, the World Health Organization, the World Meteorological Organization, the International Commission on Radiological Protection and the International Commission on Radiological Units and Measurements.

14. The Committee must also express its appreciation to the many individual scientists not directly connected with national delegations whose voluntary co-operation and good will contributed in no small measure to the preparation of the report.

### Preparation of the report

15. At the opening of its fourth session, the Committee had before it a first draft of its report to the General Assembly (A/AC.82/R.61 and addenda), prepared in accordance with the decisions taken at its third session, along with a revised version of that draft (A/AC.82/DRAFT 2 and addenda), both prepared in the Secretariat in co-operation with groups of delegates nominated by the Committee.

16. On 13 June 1958, the Committee approved the present report and decided to transmit it to the Secretary-General of the United Nations for publication and dissemination to States Members of the United Nations or members of the specialized agencies. Copies of the report were also made available to the secretariat of the Second United Nations International Conference on the Peaceful Uses of Atomic Energy.

17. This comprehensive report presents a survey of the subject based upon the information received and the conclusions reached by the Committee in the light of current scientific knowledge. It is recognized that, as knowledge in this field increases, modifications and amplifications of this report will become necessary.

# Chapter II

# GENERAL

## I. Introduction

1. The radiations to which human beings are exposed from natural and man-made sources are similar in their physical nature and in the quality of their biological effects. Radiation from both these sources must be taken into account when assessing the present and future effects upon man and his environment.

2. Although there exists a large body of information concerning the effects of irradiation, it is apparent that our knowledge is still insufficient. It is in no way comparable, for instance, to our knowledge of the physics of the radiations themselves, nor, on the biological side, to our experience with many diseases. We have some knowledge of the biological effects caused by exposure to large doses of radiation, but we know very little about the possible effects on man of intermittent small doses or of low levels of continuous irradiation. Knowledge in this area is most urgently needed, and the lack of it has been of the greatest concern to this Committee.

## II. Basic physical concepts

3. The radiations with which the Committee is concerned include X-rays, neutrons, protons, cosmic rays and the radiations ($\alpha$-, $\beta$-, $\gamma$-rays) emitted by radioactive materials. All of these radiations produce biological effects by means of the same physical process, namely energy transfer. Radiation passing through matter without energy transfer produces no effect.

4. The biological effect of a given type of radiation depends upon the energy absorbed in the tissue. For this reason, radiation dose is defined in terms of energy absorption. Whatever the type of radiation, much of the energy transferred is dissipated in ionization. Radiation comprising charged particles produces ionization directly. Other types of radiation produce ionization indirectly, by ejection of charged particles.

5. The ratio between the energy absorbed and the total ionization produced is almost independent of the kind and energy of particles producing the ionization; therefore, ionization is used as a measure of radiation exposure.

### *Types of radiation*

*Alpha rays*

6. Alpha rays are helium nuclei emitted with definite and characteristic energy by the nuclei of some radioisotopes in the process of radioactive disintegration. Because of their relatively small velocity, and because they are charged, they produce very dense ionization along with their paths, and their range or penetration in matter is consequently small. Practically none is known with a range greater than 0.1 mm in tissue.

*Beta rays*

7. Beta rays are high speed electrons emitted by the nuclei of certain radioactive isotopes. Being charged particles they produce ionization directly in matter through which they pass. They have a much greater range than alpha rays and, because of their much greater speed, they produce much less dense ionization. Few isotopes emit beta particles of maximum range greater than 2.0 cm and none of range greater than 8 cm in tissue.

*Gamma rays*

8. Gamma rays are electromagnetic radiations emitted by the nuclei of some radioactive isotopes; they have energies which are characteristic of the radioisotope by which they are emitted. Since they are not charged particles they ionize matter indirectly through ejection of high speed electrons from the material in which they are absorbed. The energy of these electrons is then dissipated by interaction with the medium. Because the attenuation of the primary gamma rays is relatively small, these electrons may be ejected at a considerable depth in tissue; each electron then dissipates its energy within a short distance (from less than a millimetre to a few centimetres depending on its energy) of its point of origin. No definite range can be given for gamma rays since they penetrate any thickness of matter but with progressively decreasing intensity.

9. Low energy gamma rays are absorbed more readily than those of high energy and for them heavy elements are more effective absorbers than those of low atomic number. For higher energies, however, the attenuation depends almost entirely on mass per unit area and is practically independent of the kind of material.

*X-rays*

10. X-rays are also electromagnetic radiations and, therefore, interact with matter and produce biological effects in the same manner as gamma rays. They differ only in the fact that the emission process is an extranuclear rather than a nuclear phenomenon. In practice, most X-rays are produced by the retardation of previously accelerated electrons in the anode of an X-ray tube. The energy of X-rays and, therefore, their penetrating power is determined by the voltage applied to the tube. The X-rays used for diagnostic medical procedures are less energetic and less penetrating than most gamma rays but it is possible to generate X-rays which are more penetrating than gamma rays from any radioactive nuclei.

*Neutrons*

11. Neutrons are normal constituents of atomic nuclei, from which they are ejected during processes such as fission. Because they are uncharged, they cannot produce ionization directly.

12. Fast neutrons lose energy mainly by collision with the nuclei of light atoms, especially those of hydrogen (protons). These nuclei recoil and, being charged, produce ions as they dissipate the energy transferred from the neutron. Because they are heavier, the recoil nuclei do not move as fast as electrons of the same energy. Therefore, they give rise to a more dense ionization than beta rays or electrons ejected during the absorption of

X-rays and gamma rays. 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.

13. Slow neutrons have no definite range either. They interact with matter mainly by nuclear reactions which result in an immediate emission of charged particles or gamma rays during the creation of isotopes, some of which are radioactive. The surrounding medium is ionized by these particles or gamma rays as well as by the delayed radiation emitted during the subsequent disintegration of the induced radioisotopes.

*Cosmic rays*

14. Cosmic rays are an extremely penetrating group of radiations that originate from heavy particles coming from extra-terrestrial sources. The primary component is absorbed in the high atmosphere, giving rise to various types of radiation, each producing ionization in its own characteristic manner.

15. Some of the principal characteristics of the above radiations are summarized in table I.

TABLE I. PRINCIPAL CHARACTERISTICS OF VARIOUS RADIATIONS

| *Radiation* | *Nature of radiation* | *Principal source* | *Typical energy* | *Penetration* |
|---|---|---|---|---|
| Alpha ($\alpha$) | High speed helium nuclei | Radioactive nuclei | A few Mev[a] | Very easily absorbed |
| Beta ($\beta$) | High speed electrons | Radioactive nuclei | A few Kev[a] to several Mev | Easily absorbed |
| Gamma ($\gamma$) | Electromagnetic radiation (photons) | Radioactive nuclei | A few Kev to several Mev | Relatively penetrating |
| X-rays | Identical with gamma | X-ray tube | A few Kev to several Mev | As for gamma rays |
| Neutrons | Uncharged particles | Nuclear fission and transmutation | Up to several Mev[b] | In general very penetrating |
| Cosmic | Mixture | Extra-terrestrial | May exceed many thousand Mev | Very penetrating |

[a] For explanation, see paragraph 17.
[b] "Thermal neutrons" have very low energies, corresponding to a velocity which is the same as that of the molecules in air of normal temperature.

*Symbols and units of measurements*

16. The quantities and units used in this report have been defined by international bodies; the current definitions are quoted in annex A. A further description is given in the following text. The *nomenclature* in this report, with a few exceptions, follows the system prepared by the International Union of Pure and Applied Physics.

*The electron-volt*

17. The energy of ionizing radiation is usually measured in electron-volt (ev) or in the multiple units of one thousand electron-volt (Kev) or one million electron-volt (Mev.). One electron-volt is the energy equal to that gained by an electron when it is accelerated through a potential difference of one volt and is equal to $1.6 \times 10^{-12}$ erg.

*Half-life of radioactive isotopes*

18. For a given radioactive isotope, the rate at which nuclei disintegrate is proportional to the number of atoms present; the fraction decaying per unit time is constant and characteristic of the particular radioactive element. It is convenient to specify this characteristic by stating the "half-life" of the radioisotope, i.e., the time in which the number of radioactive atoms will decrease to half its value. Starting with any given activity, after one half-life 50 per cent of the activity remains, after two half-lives 25 per cent remains and so on. The half-lives of different radioactive isotopes range from thousand millions of years (e.g. uranium-238) down to a small fraction of a second (e.g. radium C'). It is important to note that isotopes of very long half-lives show only a slight radioactivity per unit mass (e.g. 1 curie of uranium-238 weighs 3 tons whilst 1 curie of radium-226 weighs only 1 gram).

19. The half-lives and other characteristics of some of the radioactive isotopes with which this report will deal are given in table II.

TABLE II. PHYSICAL DATA FOR SOME RADIOACTIVE ISOTOPES

| *Isotope* | | *Types of radiation* | | *Approximate half-life*[a] |
|---|---|---|---|---|
| *Symbol* | *Name* | | | |
| $C^{14}$ | Carbon-14 | $\beta$ | | 5,600 years |
| $K^{40}$ | Potassium-40 | $\beta$ | $\gamma$ | $1.3 \times 10^9$ years |
| $Ra^{226}$[b] | Radium-226 | $\alpha$ | ($\gamma$) | 1,600 years |
| Decaying to: | | | | |
| $Rn^{222}$ | Radon (gas) | $\alpha$ | | 3.8 days |
| $Po^{218}$ | Radium A | $\alpha$ | | 3 minutes |
| $Pb^{214}$ | Radium B | $\beta$ | $\gamma$ | 27 minutes |
| $Bi^{214}$ | Radium C | $\beta$ | $\gamma$ | 20 minutes |
| $Po^{214}$ | Radium C' | $\alpha$ | | 0.00015 seconds |
| $Pb^{210}$ | Radium D | $\beta$ | $\gamma$ | 22 years |
| $Bi^{210}$ | Radium E | $\beta$ | | 5 days |
| $Po^{210}$ | Radium F (polonium) | $\alpha$ | ($\gamma$) | 140 days |
| $Sr^{90}$ | Strontium-90 | $\beta$ | | 28 years |
| Decaying to: | | | | |
| $Y^{90}$ | Yttrium-90 | $\beta$ | | 64 hours |
| $Cs^{137}$ | Caesium-137 | $\beta$ | $\gamma$ | 30 years |
| $I^{131}$ | Iodine-131 | $\beta$ | $\gamma$ | 8 days |

[a] The duration of exposure from isotopes within the body depends not only on the radioactive half-life but also on the time of retention in the body, and in some instances this is much shorter than the radioactive half-life, e.g. for Caesium-137: half-life 30 years, half period of retention 140 days.
[b] Thorium-232 and its decay products are also of interest; the details about the corresponding series of radioactive isotopes will be found in annex B.

*The activity of a radioactive sample*

20. The activity of a radioactive sample is the number of disintegrations occurring per unit time. The unit by which it may be expressed is the curie (c). One curie corresponds to $3.7 \times 10^{10}$ disintegrations per second. The denominations millicurie (mc), microcurie ($\mu$c) and micromicrocurie ($\mu\mu$c), correspond to $3.7 \times 10^{7}$, $3.7 \times 10^{4}$ and 0.037 disintegrations per second (dps), respectively. It is convenient to remember that 1$\mu\mu$c is approximately two (2.22) disintegrations per minute (dpm).

*Radiation dose*

21. The radiation *dose* in any material is the energy absorbed per unit mass of the material. Sometimes it is useful to describe exposure to radiation without reference to any actual material present. This can be done with the help of a reference substance, which is usually air because the absorbed energy can be evaluated from the measurable ionizations produced by the radiation.*

*The rad*

22. The rad is the unit of dose in the sense of absorbed energy. One rad is equal to an energy absorption of 100 ergs per gram of irradiated material at the point of interest. As defined, it is applicable to any ionizing radiation provided the energy deposited is measured (or calculated) in the material actually irradiated. The tissue dose in rads is the primary determinant of biological effect.

*The roentgen*

23. The roentgen is the unit in which exposures to X-rays or gamma rays are expressed. It is defined and measured in terms of the ionization which they produce in air under specific conditions. It is thus a unit of exposure and not of absorbed energy. As defined, it cannot be applied to radiations other than X-rays or gamma rays.

*Relative biological effectiveness (RBE)*

24. The relative biological effectiveness of the energy delivered to tissue by an ionizing radiation depends upon the type of radiation, the particular biological process and the rate and level of exposure. The RBE appears to be associated primarily with the linear energy transfer along the path of the ionizing particle. Conventionally, X-rays and gamma rays of certain energies are used as reference radiation. If, for certain processes, the RBE of alpha rays is taken to be 10, this implies that, for these processes, an alpha ray dose of one-tenth rad will produce the same degree of biological effect as an X-ray dose of one rad, even though the energy absorption is only one-tenth as great. A more detailed discussion on this subject is presented in annex A.

*The rem*

25. It is convenient to have a unit of dose biologically equivalent to the rad, i.e. taking RBE into account. This unit is the rem, defined by the relation

$$\text{Dose in rem} = \text{Dose in rad} \times \text{RBE}$$

In this report, tissue doses are generally expressed in rem. In the calculations, conventional RBE-values have been used: 1 for X-rays, gamma rays and beta rays, and 10 for alpha rays.

*Significant dose for evaluation of a specific biological risk*

26. 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.

27. In the case of genetic injury, there is evidence that the relevant tissue dose is the accumulated dose to the gonads and that the dose-effect relation is linear. In this case it is proper to weight directly the individual gonad dose instead of the possible potential effect, using as weighting factor the future number of such children to be conceived by the irradiated individual. On this basis, a *genetically significant dose* can be defined 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.

## III. Basic biological concepts

28. A living cell is a highly complex entity, all parts of which are involved in its normal functioning. Radiation may induce alterations at random in any part of this complex mechanism, and this may have harmful consequences ranging from inhibition of cell division to impaired function or cell death. *Cells* of a particular type are arranged as *tissues*, many of which form different *organs*. Some tissues are more sensitive to radiation than others; among these are tissues of the gonads, the skin, the intestines, the eye, and the blood-forming tissues present in the bone marrow, spleen, lymph nodes and elsewhere in the body.

29. The biological effects of radiations are complex because many different constituents of the intricate cellular mechanism and subsequent regulation of the whole organism are affected. The interpretation of actual damage is further complicated by interrelations of cells in the tissues, by repair processes and other regulatory reactions. There are two modes of tissue repair: recovery of the damaged cells and replacement of injured ones by others. An important feature of radiation action is damage to the recovery or repair mechanism itself, in either cells or whole organisms.

30. For practical purposes it is important to consider separately radiation injury to two categories of cells, namely, those concerned with the maintenance and integrity of the individual (such as cells in bone marrow, blood, liver or nervous system) and those concerned with the maintenance and integrity of the genetic information that is handed on from generation to generation (reproductive cells of gonads). Correspondingly, we shall speak of *somatic effects* (limited to the irradiated organism itself), and of *genetic effects* (limited to its descendants).

* The concepts introduced here as "dose" and "exposure" are more fully described by the International Commission on Radiological Units and Measurements in recommendations published in 1956, where they are referred to as "absorbed dose" and "exposure dose" respectively. See annex A.

31. Certain factors may influence the biological effects of exposure to ionizing radiation. Among the physical factors are the type of radiation (such as X-rays, alpha, beta or gamma radiation), its energy, the size of dose, its distribution in time (whether given during a short or a long period, or repeatedly), its spatial distribution (involving the whole or only part of the body) and the origin of the radiation (from outside or from within the body). Biological factors which affect the sensitivity of a tissue to radiation include its degree of oxygenation and water content, its blood supply and metabolic state, and various constitutional states of the body as a whole.

32. *External* radiation refers to radiation reaching the body from sources outside it. *Internal* radiation is that which comes from radioactive materials incorporated within the body following their ingestion, inhalation or injection. Both act in basically the same way, but internal radiation exposure is often distributed more irregularly, since radioactive materials may be concentrated mainly in certain tissues or organs, and since radiation may only penetrate for a short distance from the sites of concentration in the body.

33. When *radioactive elements* are taken up by the body, they may accumulate particularly in one tissue or organ which then becomes the most severely injured by irradiation. A *critical organ* is defined as that organ the injury of which causes the greatest damage to the body. The critical organ is usually the one which accumulates the greatest concentration of the radioactive material, but this is not always the case, since some organs are more sensitive to radiation, and some are more essential to the well-being of the body than others. The toxicity of radioactive isotopes is determined not only by the characteristics of the radiation of the nuclide. Various factors—physical (size of particles), chemical (water solubility of material, metabolic affinity of the element), ecological (balance of calcium, iodine) and physiological (mode of intake, metabolic conditions of the organism) —may affect the degree of absorption, the pattern of distribution and the metabolic fate of the radioisotopes in the body. All these factors may influence the extent of injury.

### *Somatic effects*

34. Depending upon the factors mentioned, the somatic effects of a given dose may be manifested in various ways. If a single large dose of over 600 rem of penetrating radiation is delivered to the whole human body or to a large part of it in a matter of minutes, it will cause death in a matter of days or weeks. The signs and symptoms associated with such exposures are known as the acute radiation syndrome. If, however, such a dose is delivered to a limited part of the body, as for instance to the hand, generally only a local reaction such as skin erythema will be evident. Moreover, if a dose of whole body irradiation, which would rapidly have caused death if given as a single dose, is divided into small fractions which are delivered over a period of months or years, with exposure-free intervals between them, immediate death does not occur but a pattern of chronic injury may result. This is due to the fact that the body is able, to some extent, to recover in the intervals between exposures. However, chronic exposure, despite apparent recovery, may have permanent pathological effects, and the ensuing illnesses may develop after long latent periods. Chronic irradiation may cause severe damage to the blood-forming tissues causing leukemia or hypoplastic anaemia. It may also cause fibrotic and sclerotic changes in tissues, a diminished resistance to infection, shortening of life-span and malignant tumours. Examples of the local effect of prolonged external irradiation are late skin changes (including dermatitis, atrophy and skin cancer). An example of chronic internal irradiation is the well-known case of dial painters who accidentally ingested small amounts of luminous paints containing radium, and some of whom later developed severe diseases, including tumours of bone. If some characteristic effect appears after an exposure-free interval or latent period of several months or years, it is termed a delayed effect (and leukemia or cancer may develop in this way). Among the survivors of atomic bomb explosions in Hiroshima and Nagasaki, the development of leukemia has been significantly more frequent during the years since the explosions than among a non-exposed population.

### *Genetic effects*

35. *Genes* are the entities which determine heritable characters. The genes are located at specific points—*loci* —in a certain definite sequence in threadlike structures, the *chromosomes* within the cell nucleus, whose number is characteristic of the species. Each individual inherits one set of chromosomes through the sperm from the father and another set through the egg from the mother, so that most cells of a man contain two sets of chromosomes. At formation of gametes (sperm or egg) the two sets are reduced by a special process to one complete set in which each chromosome or any given part of it may have come originally from either the mother or the father at random.

36. Both genes and chromosomes are particularly vulnerable to the effects of radiation. Therefore, exposure to radiation is expected to increase the number of random and rare heritable changes beyond that which naturally takes place in cells. These changes are known as *mutations;* they usually give rise to unfavorable genes which play a part in causing defects and diseases in man. Only the frequency of the mutational changes is altered by changed radiation exposure: the severity of the effects of any individual change is unaffected by dose.

37. The existence of a given gene is only recognizable when alternative forms of it occur which have different effects. The normal form $A$ of a gene together with some mutant for $A'$ may both be present in a population. An individual may then be characterized by any of the three combinations $AA$, $AA'$, or $A'A'$. These individuals are said to be *homozygous* for $A$, *heterozygous* for $A$ and $A'$, and *homozygous* for $A'$ respectively. $AA$ and $A'A'$ will differ; but the behaviour of $AA'$ depends upon the relation between $A$ and $A'$. If $AA'$ behaves like $AA$, $A'$ is *recessive* to $A$. If it behaves like $A'A'$, $A'$ is *dominant* to $A$. Intermediate conditions are quite usual and this relation is known as *partial dominance.*

38. The genetic constitution of an individual is derived almost equally from each of the two parents. In human populations, however, matings are influenced by a wide variety of geographic, social, economic and religious factors as well as physical and mental characteristics. Knowledge of these factors is of value for an understanding of genetic changes from generation to generation. Although the true situation is very complex, it is often a permissible approximation to regard matings as taking place at random in a human population. One consequence of this continual intermingling of genes in each generation is that the total of genes in the population really behaves in some respects as a single pool, to which mutation adds new genes, favourable and unfavourable. When a gene is recessive, so that its effects show only if

an individual receives copies of it from both parents, single copies of it in one individual are then unnoticed even although two copies may have serious consequences. Such a gene may come to be carried by many individuals through the population before an appreciable number of them are affected by having received two copies of it. By contrast, a dominant gene is able to affect individuals who have received only a single copy of it and will usually exert its effects on the more immediate descendants of the individual in whom it originated. Hence, an unfavorable dominant gene usually persists through fewer generations and spreads to a smaller fraction of the population before elimination than does a recessive gene having similar unfavourable consequences.

*Biological consequences of radiation*

39. The extent of biological effect from increased radiation is primarily determined by the quantitative relation between radiation dose and its effect. In principle, many basic types of such relation exist, but only two will be discussed here:

1. The effect is directly proportional to dose and the frequency increases linearly with increasing dose. Therefore, any dose, no matter how small, will have an effect.

2. No effect is manifested until the dose exceeds a certain value, the *threshold dose* for that effect. Therefore, doses up to this limit will have no effect.

The graphical illustration of both types is shown in figure 1.

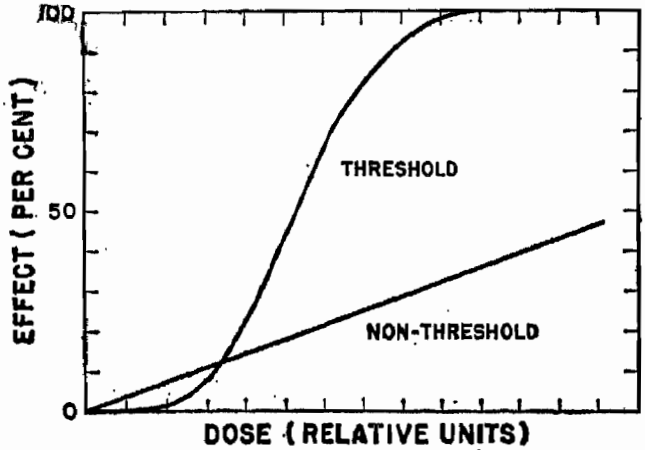



*Figure 1.* A pictorial representation of the difference between a threshold and a non-threshold situation. Dose increases to the right. Note that the non-threshold line is a straight line; it need not be. (Modified from Langham and Anderson, United Nations document A/AC.82/G/R.130, U.S.A. Congressional Hearings on Radiation, June 1957, part 2, page 1363.)

## Chapter III

# PHYSICAL DATA

### I. Introduction

1. In estimating doses to which populations are exposed, the Committee has classified the sources into three categories:

(*a*) Natural;

(*b*) Man-made (except environmental contamination);

(*c*) Environmental contamination.

The relative risks from different radiation sources, in general, increase with the radiation doses from the sources. It is therefore useful to compare the doses from various man-made sources with those from the natural sources to which the human race has always been exposed.

2. In this report, consideration has been given to those sources which are contributing to the population dose at the present time, together with some estimates of future exposure from environmental contamination. In the future, various man-made sources may increase in relative importance; the radioactive waste of atomic industry, nuclear reactor accidents and the use of isotopes in medicine, research and industry may well become problems.

### II. Dose estimates required for evaluation of biological risks

3. A quantitative estimation of the total deleterious irradiation effects in a general population must be based upon information as to the extent of the likely biological effects as estimated from assumed dose-effect relationships and also upon individual weighting factors appropriate for the deleterious consequences as discussed in chapter II, paragraphs 26 and 27.

4. Only in the case of a linear dose-effect relation with no threshold value of the dose is it relevant to add the dose contributions from various sources. This can be done in the case of genetic injury and, according to one hypothesis, also in the case of a possible induction of leukemia.

5. In order to meet the requirements of subsequent chapters which are concerned with biological consequences, it has been necessary to estimate the following doses:

(*a*) For evaluation of genetic injury: the dose to the gonads.

(*b*) For evaluation of possible induction of leukemia: the mean marrow dose (averaged overall 1,500 g of active marrow).

For most uniform exposure of the whole body, the listed gonad doses are very close to the mean whole body dose. The significance of partial exposure of the body (as in medical practice) is difficult to evaluate, but a useful index of risk seems to be the significance of each corresponding exposure of marrow as expressed by the mean marrow dose.

6. As the genetic effect of exposure is assumed to be a linear function of gonad dose, it is possible to weight the individual doses directly, the weighting factor being the future number of children to be expected by each individual subsequent to the exposure. A weighted *genetically significant dose* is accordingly defined in chapter II (paragraph 27).

7. According to one hypothesis, the induction of leukemia is also a linear function of dose. The appropriate weighting factor is not known but as a first approximation the various contributions to marrow exposure may be compared without weighting. Another hypothesis assumes a threshold for the induction of leukemia; in this case a *per capita* marrow dose has no meaning but the individual marrow doses become determining factors.

### III. Methods of measurement

8. The ultimate purpose of radiological measurements of concern to the Committee is the estimation of tissue dose from natural sources, man-made sources and environmental contamination. In some cases, however, measurements of radioactivity are also of primary concern. It is emphasized that new and improved methods are constantly being developed.

9. It is customary to classify measurements of this nature into categories relating to the method used, i.e. direct or indirect. Direct exposure measurements are those made with ionization chambers or instruments calibrated in terms of air ionization. Indirect methods are those where dose is calculated from activity measurement. The rates of exposure from medical and industrial practice and from terrestrial and cosmic radiation are sufficiently high to allow direct measurement. Exposure rates from other sources are low and the dose must usually be estimated indirectly by activity measurement and subsequent calculation.

10. A survey of the methods of measurements which have been found to be valuable in relation to the work of the Committee is given in annex E.

### IV. Natural sources of radiation

11. Man is exposed to radiations from: (*a*) external sources, namely cosmic rays and terrestrial radiations from radioactivity in the ground, the air and building construction materials, and (*b*) internal sources such as the radioisotopes potassium-40 and carbon-14 which are normal body constituents, radium and thorium deposited in bone and radon, thoron and its disintegration products in solution in blood and tissues.

#### *External natural sources*

12. The penetration of the cosmic radiation at sea level is so great that the dose rate of all organs of the human body is practically uniform and equal to the dose rate in air. This dose rate is of the order of 30 mrem per year.

13. The variation of cosmic ray intensity with altitude and geographical location is known. The altitude effect

is the more important: from sea level to 3,000 m the dose rate increases by a factor of approximately 3. At sea level the range of variation with latitude is 14 per cent; at an altitude of 4,000m it increases to 33 per cent. There are also small longitudinal and temporal variations. Cosmic ray intensity is only slightly reduced even inside massive stone buildings.

14. Radiations from the ground arise from radioactive elements in rocks and soil. The concentrations of these radioactive elements (uranium, thorium and their decay products, and potassium) vary widely with geological conditions and are generally higher in granitic rocks than in sedimentary formations or soil. Areas rich in some of these radioactive elements (e.g. monazite sand areas as in Kerala, India and Guarapari, Brazil) show exceptionally high radiation intensities[B27]. The radiations from the radioactive elements contained in some building-construction materials (masonry) often more than compensate for the shielding effect of the building, so that indoor exposures are frequently higher than those out of doors.

15. On account of the penetrating character of these radiations, the gonad, osteocyte and marrow doses may be considered to be approximately the same. Taking into account the shielding factors and time spent in buildings, it is estimated that radiations from the ground and from building-construction materials contribute in the range of 50 mrem per year to the gonad dose[B40]. This range is representative for the major part of the population in the areas for which values have been reported. In high activity areas, such as those mentioned above, the dose may range up to 830 mrem per year[B27].

16. Radon and thoron diffuse from the earth and building materials and constitute a minor external radiation source from which the gonad dose is approximately 1 mrem per year in normal circumstances. High concentrations of radon and of its decay products have been observed in ill-ventilated rooms of masonry buildings in certain areas. Under these conditions slightly enhanced, but still small, gonad doses may arise.

17. Thus, gonad, osteocyte and marrow doses from all *external* sources are usually of the order of 75 mrem per year, but may range up to 190 mrem per year with local conditions in many countries, whilst in the high activity areas they may range up to 830 mrem per year[B27].

### *Internal natural sources*

18. Some of the normal constituents of the human body are radioactive. The specific activity of potassium-40 is about $10^{-9}$ curies per gram of natural potassium; carbon-14, formed by interaction of cosmic rays with the air, has an equilibrium concentration of about $7.10^{-12}$ curies per gram of carbon, corresponding to the specific activity of the carbon of the atmospheric carbon dioxide. The specific activity is constant and therefore the dose from these radioactive isotopes is determined solely by the potassium and carbon content of the tissues. Soft tissues of the body receive a dose of about 20 mrem per year from internal potassium-40 and of 1-2 mrem per year from carbon-14. The bone (marrow excluded) contains less potassium than soft tissues, and the osteocyte dose from potassium-40 is of the order of 10 mrem per year; bone doses from carbon-14 are similar to soft tissue doses from the same isotope.

19. Soft tissues receive a dose from radon, thoron and their disintegration products taken in from the atmosphere and dissolved and retained in the tissues; the dose rate is 2 mrem per year. This rate is substantially increased in areas of high natural radioactivity and in badly ventilated buildings constructed of materials containing radioactive elements. The osteocyte dose from this source is negligible. Radium is taken up from the environment and is deposited together with calcium in bone structure. The average osteocyte dose from radium is in the range of 38 mrem per year, but it may be ten times larger in some geographical areas. With a random distribution of the radium in the bone, the average marrow dose will be 2 to 5 per cent of the osteocyte dose.

20. From the above-mentioned figures, the total soft tissue dose from natural *internal* sources is computed to be 23 mrem per year, the osteocyte dose is in the range of 50 mrem per year, dependent on the radium content of the bone, and the marrow dose is approximately 15 mrem per year.

### *Summary*

21. Estimates of doses which arise from natural sources are given in table I.

TABLE I. ANNUAL DOSES FROM NATURAL RADIATION SOURCES[a]

| Source | Annual dose | | |
|---|---|---|---|
| | Gonad dose (mrem) | Osteocyle dose (mrem) | Mean marrow dose (mrem) |
| *External* | | | |
| Cosmic rays | 28 | 28 | 28 |
| Terrestrial radiation | 47 | 47 | 47 |
| Atmospheric radiation | 2 | 2 | 2 |
| *Internal* | | | |
| K-40 | 19 | 11 | 11 |
| C-14 | 1.6 | 1.6 | 1.6 |
| Rn-Tn | 2 | — | 2 |
| Ra | — | 38 | 0.5 |
| Approximate totals | 100 | 130 | 95 |

[a] The totals in the table are for "normal" natural radiation intensities; in certain areas the values range up to ten times higher than those given.

22. Detailed considerations of natural radiation sources are to be found in annex B, including more complete data for different areas.

## V. MAN-MADE SOURCES *(except environmental contamination)*

23. At the present time radiation exposures from man-made sources (excluding environmental contamination) arise principally from:

(*a*) Medical uses of X-rays and radioactive materials,

(*b*) Industrial and research uses of X-rays and radioactive materials, and

(*c*) Other sources such as luminous dials of watches, television sets and shoe-fitting fluoroscopes.

### *Medical uses of X-rays and radioactive materials*

24. Medical uses of X-rays and radioactive materials are:

(*a*) Diagnostic uses of X-rays,

(*b*) Use of X-rays and external radioactive sources for radiotherapy, and

(*c*) Use of radioactive isotopes as internal sources for diagnosis and therapy.

This section deals only with the exposure of patients. Occupational exposure from medical uses of X-rays and radioactive materials is treated in paragraphs 34-35.

*Diagnostic uses of X-rays*

25. The diagnostic use of X-rays has been of great value in the development of medicine. The wide use of these methods in some countries and their increasing application in many others make it important to consider any risks that such radiation may entail. Estimations of the contribution to the annual genetically significant dose from diagnostic X-ray procedures have been made for some countries in which, however, the use of X-rays is extensive. In some of these countries this contribution seems to be about equal to that from natural sources. A detailed discussion on the values, which are presented in table II, is given in annex C. It should be noticed that all estimates of the genetically significant dose depend on assumptions as to the average child expectancy of various groups of patients of which little is yet known.

TABLE II. ESTIMATED LEVELS OF GONAD EXPOSURE FROM DIAGNOSTIC X-RAY PROCEDURES

| | *Annual genetically significant dose (mrem)* | |
|---|---|---|
| | *Estimated minimum* | *Probable value* |
| Denmark | 17 | |
| England and Wales | 23 | |
| France | 57 | |
| Sweden | | 38 |
| U.S.A. | 50 ± 30 | 150 ± 100 |
| | *Annual per capita gonad dose (mrem)* [a] | |
| Austria | 16–24 | |
| Japan | 10–30 | |

[a] The *per capita* gonad dose has been found to differ but little from the genetically significant dose in countries for which both have been estimated.

26. More than 80 per cent of the genetically significant dose from diagnostic X-ray exposure is contributed by six or seven procedures (those involving the region of the lower abdomen and pelvis) during which the gonads are usually in the primary field. However, these procedures constitute only about 10 per cent of all examinations.

27. For countries with an extensive use of X-rays, the average annual marrow dose of the population can be estimated to range beyond 100 mrem per person. This figure is very close to the *per capita* marrow dose from natural radiation. X-ray examinations of the gastro-intestinal tract and of the chest (including mass chest X-ray surveys) give the highest contributions to the average marrow dose. A comparison between dose-contribution is relevant only if a linear dose-effect relationship can be assumed. The average marrow dose per examination varies within the range 1-1,000 mrem for different types of examinations, and the individual doses may show a large variation around each average. This will mean the existence of some heavily exposed individuals who, in the case of a non-linear dose-effect relationship, may run a much higher risk than is indicated by the dose figures. All figures mentioned above refer to the mean dose in the whole mass of active marrow, of which only a small fraction may actually be exposed. The exposed marrow may in extreme cases receive very high doses, especially in the case of fluoroscopy where the dose-rate in the irradiated marrow may be several rem per minute.

28. The data submitted from several countries indicate that it may be possible to reduce the diagnostic exposure considerably by careful attention to techniques. Valuable precautions are described in the current recommendations of the International Commission on Radiological Protection and are collected and further elaborated in the report of the joint study group of the ICRP/ICRU (See annex C). The annual genetically significant dose that may be achieved with good practice without detriment to diagnostic information has been estimated to be 15 mrem for Sweden.

*Radiotherapy*

29. The contribution from radiotherapy in England and Wales has been estimated to be appreciably less than that from diagnostic procedures but greater than that from any other man-made contribution. In the United States, the annual genetically significant gonad dose from radiotherapy has been estimated at roughly 10 mrem. This estimate is based on what appear to be rather conservative figures for the number of treatments per year contributing to the genetically significant dose. Published data for Australia and Denmark estimate a contribution to the genetically significant dose from radiotherapy of 28 mrem per year and 1 mrem per year respectively.

30. The estimated values are not strictly comparable, since different assumptions have been made in each. In the United States estimate all treatment of malignant conditions was disregarded because:

(*a*) A high percentage of patients were above the average age of child-bearing, and

(*b*) For many, the prognosis was bad, so that the chance of subsequent parenthood was small.

In the published estimate for Australia, simplifying assumptions were made as to the area of field treated and the dose delivered in the treatment of malignant, pre-malignant and non-malignant conditions. In addition, it was assumed that a normal child expectancy existed for all surviving patients not assumed to be sterilized by the irradiation. In the Danish survey it was assumed that the patients treated for malignant conditions had one-fifth the child expectancy of normal individuals. In the summary table (table III) the range of values is quoted.

31. In considering induction of somatic injuries, the dose from some treatments, such as those of skin cancer and of various benign conditions, should be included in the population average, since prognosis is relatively good and the patients are not ruled out on the age factor. Hence, it appears that radiotherapy may give a contribution to marrow exposure of higher relative significance than the contribution to the exposure of the gonads. No estimates of the *per capita* mean marrow dose (from radiotherapy) were available to the Committee.

*Medical uses of radioactive isotopes (internal administration)*

32. The principal contributions to the population dose from the medical use of radioisotopes arise from the use of iodine-131 and phosphorus-32, which are most widely employed. While considerable quantities of gold-198 are used, the biological significance of exposure from this source is negligible since gold-198 is generally limited to palliative treatment of incurable conditions. Other radioisotopes are used in very small quantities and almost entirely for diagnostic purposes.

33. Estimates of the average gonad dose resulting from the use of iodine-131 and phosphorus-32 can be based upon information about either treatments or radioisotope shipments, the first approach being more accurate and preferable. From the report of the ICRP/ICRU

joint study group and other information available to the Committee it seems likely that the genetically significant dose is lower than 1 mrem per year, even in the countries for which the highest figures can be expected.

*Industrial and research uses of X-rays and radioactive materials*

*Occupational exposure*

34. Industrial, medical, atomic energy and research workers are subject to radiation exposure resulting from their occupation; they may also inhale or ingest radioactive material. Exposure of atomic energy workers is in all countries estimated to contribute less than 1 mrem per year to the genetically significant dose received by the population. The exposure of medical, industrial and research workers is less accurately known but probably adds at the present time less than 1 mrem to the annual genetically significant dose even in technologically advanced countries.

35. The Committee notes that systematic measurement and recording of the exposures of medical, industrial and research workers is desirable since some individual doses are likely to be relatively high.

*Other sources of radiation*

36. Watches and clocks with radioactively luminous dials give an annual genetically significant dose of about 1 mrem. X-rays from television receivers contribute less than 1 mrem. X-rays from shoe-fitting fluoroscopes contribute still less, as they expose a relatively small number of individuals, but might be an important hazard to the exposed individuals.

*Summary*

37. The doses from the principal man-made sources other than environmental contamination are summarized in table III and are appropriate for countries with an extensive use of these sources.

TABLE III. ANNUAL DOSES FROM MAN-MADE SOURCES OF RADIATION (*except environmental contamination*)[a]

| Source | Annual Dose | |
|---|---|---|
| | *Genetically significant dose (mrem)* | *Per capita mean marrow dose (mrem)* |
| *Medical (exposure of patients)* | | |
| (*a*) Diagnostic..... | 20–150 | Ranges beyond 100 |
| (*b*) Therapy..... | 1– 30 | No estimate made |
| (*c*) Internal..... | Less than 1 | Less than 10 |
| *Occupational* | Less than 2 | 1–3 |

[a] For countries having an extensive use of the radiation sources listed and reporting data to the Committee.

## VI. ENVIRONMENTAL CONTAMINATION

38. Radioactive contamination of man's environment occurs as a result of nuclear explosions and may also arise from radioactive waste disposal and accidents involving dispersion of radioactivity. At the present time the radiation doses from these last two sources are negligible, but in the future they might become appreciable.

*Radioactive fall-out*

39. Most of the radioactive isotopes which cause the environmental contamination following nuclear weapon tests are fission products. There are also some formed by neutron induction and some residual fissionable material.

*Fall-out mechanisms*

40. Fission products injected into the stratosphere constitute a reservoir from which they fall onto the whole of the earth's surface over a period of many years (stratospheric fall-out). Fission products not penetrating into the stratosphere may be transported over long distances in the troposphere by air currents but are deposited on the earth's surface by rainfall and sedimentation over a period of a few months (tropospheric fall-out). Because of the gradual deposition of fall-out from the stratosphere, most of the resulting irradiation of man arises from radioactive isotopes of long half-life such as strontium-90 and caesium-137. In contrast, the earlier deposition of tropospheric fall-out makes it necessary also to consider the doses from radioisotopes of much shorter half-life such as strontium-89, zirconium-95 and ruthenium-103 and 106, iodine-131, barium-140 and cerium-144.

41. Near the test site there is an early deposition of radioisotopes which is influenced by various meteorological and testing conditions and which may involve a special hazard to any individual in this area of immediate local fall-out.

42. Meteorological conditions and the predominant occurrence of nuclear tests in the northern hemisphere cause a non-uniform deposition of the longer-lived isotopes over the globe, as a result of which countries between 30° and 50° North experience a deposition of these about three times as great as the world-wide average. Countries in the southern hemisphere and in the tropical belt have smaller deposits with a maximum between 30° and 50° South, of the order of the world-wide average value[D18]. In some countries, tropospheric fall-out increases the deposition of the longer-lived isotopes strontium-90 by a small amount. Local meteorological and climatic factors influence the extent and mode of the deposition in a particular locality.

*Measured contamination of air and ground by strontium-90 and caesium-137*

43. Results of measurements of strontium-90 and caesium-137 concentrations in different materials are given in annex D. These show an average air concentration at ground level of strontium-90 of the order of $10^{-19}$ to $10^{-17}$ c/l in 1956-1957[D10-11]. Values for strontium-90 deposited on the ground at the middle of 1957 were about 8mc/km² in Japan, 8mc/km² in the United Kingdom, 4-21mc/km² in the United States and 3-12 mc/km² in the Soviet Union, in the northern hemisphere, and about 4mc/km² in Argentina, in the southern hemisphere. At the middle of 1957 a caesium-137 deposit of about 6mc/km² was measured in Japan and Sweden (tables XV, XVI and XVIII annex D).

*Uptake of radioisotopes*

44. Radioisotopes enter the human body by inhalation of airborne material and more particularly by ingestion following (*a*) uptake by and deposition on vegetation, (*b*) transfer through animals, (*c*) contamination of water supplies. In this respect strontium-90, caesium-137 and iodine-131 are of special importance. The particulate nature of fall-out and the occurrence of single particles with an activity higher than the average might result in the intake, by a single individual, of an amount of radioactive material exceeding that cal-

culated on the assumption of uniform distribution of the fall-out deposit. The relative importance of the various modes of intake must, however, be considered in assessing the significance of this.

*Doses from external sources*

45. For the computation of dose from fall-out deposit many factors besides the deposition of radioactive materials should be considered, such as the weathering effect on the deposit, leaching through soil and shielding by buildings. Taking into account the fall-out material deposited up to 1958 and excluding the additional radioactive material to fall from the reservoir existing at that time, gonad doses of the order of 1 to 20 mrem have been computed for a 30-year period. The wide range of these estimates is largely accounted for by regional variations. The computations have been made using a reduction factor of 10 for attenuation and shielding of buildings, and for weathering effects. Values suggested for this factor in reports submitted to the Committee range, however, from 3 to 21. It should be pointed out that the gonad dose from external gamma radiation from fall-out deposit is in most cases small compared with the gonad dose from fall-out radioisotopes taken into the body[D20-25].

*Doses from internal sources of stratospheric origin*

46. Radioactive materials entering the human body deliver a dose closely related to the time during which they are retained by the body. This means that many of the radioisotopes produced in fission do not present internal radiation hazards since they do not enter significantly into metabolic processes. Therefore, attention has been centred on radioisotopes which are potentially hazardous by reason of some or all of the following factors: (1) high fission yield, (2) fairly long physical half-life, (3) efficient transfer through the food-chain to the human diet, (4) high absorption by the body and (5) long biological retention time. Special consideration has been given to elements that concentrate in specific tissues even though they do not have all the characteristics discussed. Using these criteria, the important radioisotopes should be expected to be strontium-90 and caesium-137. Other long-lived radioisotopes are considered relatively unimportant as internal hazards as their incorporation in the body is poor. Iodine-131, although of short half-life, is given consideration because of its selective concentration in the thyroid gland.

47. In addition to fission products and neutron-induced activities, some of the residual fissionable material will also be distributed by meteorological conditions and can be hazardous since it consists of alpha-emitting bone-seekers. However, absorption by the body is so very low that there is at present no evidence of any uptake of these materials in human tissues.

*Strontium-90 in food-chains*

48. Since strontium and calcium are chemically similar, strontium-90 follows calcium through the food-chains from the environment to man and is eventually incorporated with it in bone. It has been found that, in the different steps in this chain, there is some degree of discrimination against strontium. This depends upon differences in the utilization of the two elements in various biological processes.[D34-36]

49. Computations on the transfer of strontium-90 from fall-out to human bone are complicated by the possibility that equilibrium conditions have not yet been reached throughout the chain and also that some of the first steps may be more dependent on fall-out rate than on the accumulated deposit of strontium-90. Dietary habits in different countries also vary considerably. Thus milk is by far the most important contributor of calcium to the human diet in some parts of the world, whereas, in other parts, leaf vegetables and cereals are the most important contributors. It follows that it is difficult to calculate with accuracy the transfer of strontium-90 from soil through the food-chain to human bone but information on concentrations in foods and human tissues is available from direct measurements.

*Strontium-90 in foodstuffs*

50. Concentrations of strontium-90 in various foodstuffs differ for different countries. Expressed in micromicrocuries strontium-90 per gram calcium,* the ranges of average concentrations in milk from different locations were in 1955 about 1.9 to 7.2, in 1956 1.2 to 8.8, and in 1957 2.7 to 16. In 1956, white rice in Japan contained 36 to 62 S.U. while frozen vegetables in the United States in 1956-1957 contained about 9 S.U., ranging from 1 to 29 S.U.[D48-49]

*Strontium-90 in man*

51. Mean levels of strontium-90 measured in the bones of children under the age of 5 years (excluding stillborn) were, expressed in strontium units, 1.5 (Canada, May 1956 to May 1957) 1.15 (United Kingdom, 1957), 0.67 (United States, July 1956 to June 1957), and 2.3 (USSR, second half of 1957). The range of values is typified by the interquartile values for the United Kingdom measurements, 0.7 to 1.8 S.U., while the data for the United States show an approximate gaussian distribution with a standard deviation of about 40 per cent. The age group of 0 to 5 years represents a population that spent all its life in a contaminated environment where the level of contamination of the diet was increasing. The quoted strontium-90 concentrations contribute an average dose of about 2 to 6 mrem per year to the bone cells (osteocytes) or a mean bone marrow dose of 0.7 to 2 mrem per year. A marrow cell which is almost enclosed by bone would receive a dose which may be equal to that in compact bone. The maximum marrow dose received by these cells could differ by a factor of about 5 from the quoted mean marrow levels.

52. The strontium-90 content in bone of the full-term foetus is found to be less than that in bones of children of under 5 years of age. This is typified by results from the United Kingdom where the mean level for stillborns was about 0.55 S.U. in 1957 (42 samples). The strontium-90 concentration in the latter part of the foetal life is directly correlated with the strontium-90 concentration in the mother's blood and this concentration will increase as the contamination of food increases.[D55-57]

*Caesium-137 in man*

53. The contamination of food sources by caesium-137 has been found to be rather more dependent at present on fall-out rate than upon the accumulated deposit. Caesium-137 concentrations are often expressed by the caesium-137/potassium ratio. Some evidence exists, however, that the metabolism and routes of entry into the human body of these two elements are to some degree different and that a biological meaning similar to

* 1 micromicrocurie strontium-90 per gram calcium is called 1 strontium unit, or 1 S.U.

that of the strontium-90/calcium ratios should not be implied. Because of the short biological half-life of caesium-137 (about 140 days), the level of this isotope in the human body must approach equilibrium with the environment relatively quickly.[D68-70]

54. Measurements of caesium-137 in humans in the north temperate zone showed a range of 25 to 70$\mu\mu$c per gram of potassium during 1957, corresponding to a gonad dose of about 1 mrem per year (ranging from about 0.5 to 2 mrem per year). On the assumption that the caesium concentration is the same in the marrow as in other soft tissue, the average marrow dose is computed as about 1 mrem per year.[D75-76]

*Doses from sources of tropospheric origin*

55. Fall-out from the troposphere consists mainly of short-lived isotopes. The dose contributions therefore depend to a great extent on fall-out rate rather than on total deposit. Since the mean residence time in the troposphere is relatively short there would be no further exposure from these isotopes shortly after tests were stopped.

56. Tropospheric fall-out occurs predominantly in the latitudes in which tests are conducted and the zones mostly affected are determined by the predominant weather conditions in those latitudes. Caused mainly by the distribution of test-sites, the world-wide distribution of tropospheric fall-out follows roughly the pattern of the stratospheric fall-out. The doses from tropospheric fall-out, therefore, are likely to vary with geographic location roughly in the same manner as doses from stratospheric fall-out.

*External sources*

57. The tropospheric material has an observed mean residence time of two to four weeks and although it is deposited intermittently during the year, a certain deposit of short-lived activities is built-up and maintained. The reported values indicate that a level of short-lived radioactivity maintained at about 50 to 200 mc/km$^2$. Allowing a factor of 10 for shielding and weathering, this gives annual gonad and mean bone marrow doses of the order of 0.25 to 1 mrem. Locally, even at distances of several thousand kilometres from test-sites, levels of the same order as from the natural radiation background (2 mrem/week), however, have been observed for a few days after tests.[D78]

*Internal sources*

58. The air concentration of fission products at ground level has been reported to be around $10^{-15}$ c/l during 1957. Assuming that this material has the same composition as the fall-out, the annual doses resulting from inhalation can be computed to be of the order of 0.1 mrem or less, except for a thyroid dose of about 0.6 mrem. If the material is insoluble, an annual lung dose of about 1.5 mrem may be expected.[D79]

59. Dose contributions from short-lived activities can be introduced through food-chains when the food has not been stored for a long time. Storage of food reduces the activity of short-lived isotopes, which makes it very difficult, if not impossible, to give world-wide average annual doses from tropospheric material.

60. Strontium-89/strontium-90 activity ratios in milk have been reported as fluctuating in the range 1 to 25 (Canada, Norway, United Kingdom, United States), the values largely depending on whether the cows were on pasture. The strontium-89 may thus give rise to a bone dose ranging from about 1 to 20 per cent of the dose from strontium-90. Barium-140, in the amounts that correspond to the mean residence time of the tropospheric fall-out (two to four week) gives a dose contribution that is less than 10 per cent of that from strontium-89.[D80-83]

61. Measurement of iodine-131 is of interest because of the selective concentration of iodine by the thyroid gland of man and animals. It is not possible to state a representative thyroid dose. Measurements in the United States for the period of 1955 to 1956 show that, excluding areas immediately adjacent to test-sites, the annual thyroid dose in man averaged about 5 mrem. Doses to gonads and other soft tissue from iodine-131 are negligible.[D84-90]

62. Dose contributions from short-lived activities are dependent on fall-out rate. In cases where the dependence on deposit is dominant, as for strontium-90 in the equilibrium that will eventually be reached if tests continue, contributions from short-lived activities will be negligible.

*Future doses from stratospheric fall-out*

63. Prediction of future levels of stratospheric fall-out requires information on the processes connected with the injection of long-lived radioisotopes into the stratosphere and the chain of events that occur between injection of the radioactive material and its appearance as fall-out on the ground. Available information would allow at most a short-term extrapolation.

64. The extrapolation over a short period is, however, insufficient for evaluation of the biological hazards from stratospheric fall-out. For the purpose of a biological assessment it is necessary to extend the calculation over periods much longer than those considered, and many arbitrary assumptions have to be introduced. This makes the estimated values a matter of speculation; and it is, furthermore, very difficult to give any indication as to the degree of uncertainty. Detailed discussion on the prediction of future fall-out levels for certain hypothetical conditions is given in annex D, paragraphs 94-110.

65. Table IV gives 30- and 70-year doses calculated on the basis of extrapolated values of stratospheric fall-out rate and deposit in hypothetical cases. The figures in the table include the external exposure from the deposit of stratospheric fall-out. Taking into account shielding effects of buildings and weathering effects on the deposit, external contribution from the stratospheric fall-out is expected to contribute about 20 to 40 per cent of the gonad dose.

66. It should be emphasized that the figures for doses from stratospheric fall-out are computed from population weighted world-wide average estimates of fall-out rate and deposit. Therefore, regional dose levels differing by a factor of about one-fifth to two can be expected, depending mainly upon latitude.[D18] In some areas of the world the tropospheric fall-out may tend to raise the upper limit of this range, especially in the vicinity of test sites.

67. For the calculations of future fall-out rates and deposits two assumptions are used: (*a*) the rate of fall-out of strontium-90 will remain in the future at the constant value observed for the last four years, or (*b*) the rate of injection of strontium-90 into the stratosphere will remain in the future at a value equal to the mean value for the years 1954 to 1958 inclusive. This second assumption gives a value for the fall-out rate and deposit at equilibrium about a factor of 2 higher than that calculated by using the first assumption.

TABLE IV. ESTIMATED DOSES FROM STRATOSPHERIC FALL-OUT[a]

*(Computed from population weighted world-wide average values of stratospheric fall-out rate and deposit[b])*

| | *Genetically significant dose: Maximum for any 30-year period (rem)*[D115] | | Per capita *mean marrow dose: Maximum for any 70-year period (rem)*[D122] | | | |
|---|---|---|---|---|---|---|
| | | | *Estimate for countries deriving most of dietary calcium from milk*[c] | | *Estimates for countries deriving most of dietary calcium from rice*[c] | |
| Weapon tests cease at end of 1958... | 0.010 | | 0.16 | | 0.96 | |
| | *Assumption a*[d] | *Assumption b*[d] | *Assumption a*[d] | *Assumption b*[d] | *Assumption a*[d] | *Assumption b*[d] |
| Weapon tests continue until equilibrium is reached in about a hundred years..... | 0.045 | 0.10 | 1.3 | 2.8 | 7.5 | 17 |
| | *Estimated percentages of the maximum doses for continued weapon tests* | | | | | |
| | *Assumption a*[d] | *Assumption b*[d] | *Assumption a*[d] | | *Assumption b*[d] | |
| Weapon tests cease | | | | | | |
| 1958..... | 22 | 10 | 13 | | 6 | |
| 1968..... | 45 | 33 | 24 | | 16 | |
| 1978..... | 63 | 55 | 34 | | 26 | |
| 1988..... | 72 | 62 | 42 | | 35 | |
| Weapon tests continue..... | 100 | 100 | 100 | | 100 | |

[a] The methods used for calculation of these doses are given in paragraphs 91 to 126 of annex D.

[b] Regional values may differ by a factor of about 1/5 to 2 from the estimated population weighted world-wide average values because of the latitudinal variation of fall-out rate and deposit. In some areas of the world the tropospheric fall-out may tend to raise the upper limit of this range, especially in the vicinity of test sites.

[c] The extent to which these estimates apply to populations of different dietary habits and to those living in areas of differing soil conditions is discussed in paragraph 69.

[d] Assumption *a* is that the injection rate is such as to maintain a constant fall-out rate of strontium-90 and caesium-137, whereas assumption *b* is that weapon tests equivalent in release and stratospheric injection of fission products to the whole sequence of weapon tests from the beginning of 1954 to the end of 1958 will be repeated at constant rate. This second assumption will give an equilibrium value for the fall-out rate and deposit approximately a factor of 2 higher than that calculated by using the first assumption.

68. The caesium-137 taken into the human body has been considered to be the main radiation source to the gonads and it has been assumed that the human burden of caesium-137 is a quantity dependent on fall-out rate only. The body burden of caesium-137 resulting from a certain value of fall-out rate has been found to vary by a factor of 2 owing to differences in dietary habits.

69. For the bone-marrow dose calculations, relationships between the bone content of strontium-90 and the accumulated deposit have been used. These relationships, which are discussed in detail in annex D to this report, depend on the soil characteristics and the dietary habits in the areas considered. The diet and soil characteristics used in the computations correspond to available data from the United States, the United Kingdom and from Japan for the two types of main calcium sources mentioned in the table, namely milk and rice. In actual practice populations do not subsist entirely on either milk or rice, and these calculations should, therefore, be accepted as approximations. Large local variations are possible: for example, variations by a factor of about 3 are indicated for the Japanese data, because of variations in soil characteristics. Application of these figures to other countries of apparently similar diets also implies uncertainties.[D116-121]

### *Radioactive waste*

70. Another aspect of environmental contamination is related to the disposal of radioactive wastes from atomic energy plants. This includes problems such as the ultimate disposal of fission products from spent fuel elements, the release of low-level wastes from the normal operation of reactors and chemical processing plants, and the possibility of accidents. The Committee has not given any detailed consideration to the technical aspects of these problems, but from information available it is clear that there is no general population hazard from this cause at the present time. The Committee realizes that these problems may become of importance in the future and considers that the release of radioactive wastes should be made a matter of international co-ordination and agreement.

## VII. SUMMARY AND CONCLUSIONS

71. The sources of radiation to which mankind is exposed include natural sources, medical, industrial and research uses of radiation, environmental contamination due to nuclear explosions and release of radioactive waste from atomic energy plants and miscellaneous sources such as luminous dials of watches, television sets and shoe-fitting fluoroscopes. Medical, industrial and research uses of radiation expose only a fraction of the population, whilst natural sources and environmental contamination expose the whole population to a more or less uniform level. Average doses to the population from all these sources are, however, of significance with regard to the genetic effect and possibly with regard to some somatic effects.

72. The exposure from these sources is summarized in table V, which gives the genetically significant dose and the *per capita* mean marrow dose. The genetically significant dose has been calculated for a 30-year period and the marrow dose for a 70-year period. These figures are relevant to the genetic burden and the possible induction of leukemia respectively. The contribution from occupational exposure is at present small compared to that from the other sources of radiation. Although immense quantities of radioactive materials will be produced in the future use of nuclear reactors, the exposure from this source is at present negligible and could in the future be maintained at very low levels by appropriate procedures.

73. Comments on each of the sections of table V are given in the following paragraphs, together with some qualifications regarding the applicability of the various figures. Under the appropriate headings, indications for future fields of investigation are also outlined.

### *Natural sources*

74. Exposure of the human population from natural sources is fairly uniform over the earth and a representative figure is quoted in the table. However, areas in several countries show dose levels considerably in excess of those given in the table. More data are needed concerning exceptionally large local variations of exposure from natural sources. These data can be of value in radiobiological research only if good demographic data for the population in the areas exist.

TABLE V. ESTIMATED DOSE FROM DIFFERENT RADIOACTIVE SOURCES
*(Computed from world-wide averages)*

| Source | *Genetically significant dose: Maximum for any 30-year period (rem)*[D115] | | Per capita *mean marrow dose: Maximum for any 70-year period (rem)*[D115] | | | |
|---|---|---|---|---|---|---|
| Natural sources | 3 | | 7 | | | |
| Man-made sources (except environmental contamination and occupational exposure)[a] | 0.5–5 | | Ranges beyond 7 | | | |
| Occupational exposure[b] | Less than 0.06 | | 0.1–0.2 | | | |
| Environmental contamination hypothetical cases)[c, d] | | | *Estimates for countries deriving most of dietary calcium from milk*[e] | | *Estimates for countries deriving most of dietary calcium from rice*[e] | |
| Weapon tests cease at end of 1958 | 0.010 | | 0.16 | | 0.96 | |
| | *Assumption a*[f] | *Assumption b*[f] | *Assumption a*[f] | *Assumption b*[f] | *Assumption a*[f] | *Assumption b*[f] |
| Weapon tests continue until equilibrium is reached in about a hundred years[g] | 0.060 | 0.12 | 1.3 | 2.8 | 7.5 | 17 |

| | *Estimated percentages of the maximum doses for continued weapon tests* | | | |
|---|---|---|---|---|
| | *Assumption a*[f] | *Assumption b*[f] | *Assumption a*[f] | *Assumption b*[f] |
| Weapon tests cease | | | | |
| 1958 | 17 | 9 | 13 | 6 |
| 1968 | 42 | 33 | 24 | 16 |
| 1978 | 64 | 56 | 34 | 26 |
| 1988 | 79 | 67 | 42 | 35 |
| Weapon tests continue | 100 | 100 | 100 | 100 |

[a] For countries having an extensive use of the radiation sources listed and reporting data to the Committee.

[b] Doses for certain technologically highly developed countries only.

[c] Regional values may differ by a factor of about 1/5 to 2 from the estimated population weighted world-wide average values because of the latitudinal variation of fall-out rate and deposit. In some areas of the world, the tropospheric fall-out may tend to raise the upper limit of this range, especially in the vicinity of test sites.

[d] Computed from population weighted world-wide average of stratospheric fall-out rate and deposit.

[e] The extent to which these estimates apply to populations of different dietary habits and to those living in areas of differing soil conditions is discussed in paragraph 69.

[f] Assumption *a* is that the injection rate is such as to maintain a constant fall-out rate of strontium-90 and caesium-137, whereas assumption *b* is that weapon tests equivalent in release and stratospheric injection of fission products to the whole sequence of weapon tests from the beginning of 1954 to the end of 1958 will be repeated at constant rate. This second assumption will give an equilibrium value for the fall-out rate and deposit approximately a factor of 2 higher than that calculated by using the first assumption.

[g] The values for the 30-year doses have been corrected for tropospheric fall-out in accordance with paragraph 57, using a value of 0.5 mrem/year for the period of testing.

### *Man-made sources (except environmental contamination)*

75. The doses shown under the heading "man-made sources" in the table result mainly from medical diagnostic X-ray procedures. The figures, which contain large uncertainties, refer to countries in which those procedures are now widely applied, and in these countries increasing use may be largely compensated for by improvements in technique. Although these figures are not at present representative for many countries with less extensive medical facilities, the use of X-rays in these countries can be expected to increase greatly in the next few decades. The diagnostic use of X-rays is an indispensable medical aid, and therefore a continuing exposure to mankind from this source will necessarily be incurred.

76. In addition to the diagnostic X-ray procedures, radiotherapy and the medical use of radioisotopes contribute to the population exposure in certain countries with extensive medical facilities. The *per capita* dose from radiotherapy may amount to 20 per cent of that from diagnostic X-ray procedures. However, the significance of the radiotherapeutic contribution depends on the life expectancy of the patients. The genetically significant dose from the medical use of radioisotopes is less than 1 per cent of that from diagnostic X-ray exposure.

77. As medical practice varies considerably, not only from country to country but also from hospital to hospital within the same country, it is very difficult to state the average practice within a general population. Recommendations with regard to suitable sampling procedures for estimating the genetically significant dose have been given by the ICRP/ICRU Study Group (cf. annex C).

78. It seems likely that the present exposure per examination during diagnostic procedures can be reduced considerably, without detriment to their value, by adopting methods of the type recommended by the International Commission on Radiological Protection. Future technical improvements in X-ray equipment and auxiliary devices may also result in reduced exposure per examination, if their use does not invite more extensive examinations.

79. A reduction in dose might be achieved by a further consideration by the medical profession of the circumstances in which X-ray diagnosis is appropriate. This could be facilitated by statistical information on the importance of each examination class for the reduction of any specified morbidity. Administrative co-ordination between authorities who require that certain examinations be made in the routine health surveillance of whole populations or special groups, such as school-children, students, employees, could well be improved.

80. Whilst much of the foregoing discussion relates to population exposures, it must be noted that high individual doses may be incurred during particular X-ray diagnostic procedures especially where poor techniques are used.

81. Although the occupational exposure is at present of little significance for the whole population, the dose to individuals may involve special exposure problems and should be checked by the complementary techniques of site and personal monitoring.

82. A number of sources of radiation, such as luminous watches, television sets, shoe-fitting machines, contribute to the population dose by an amount of the order of 1 per cent of the total contribution from man-made sources.

*Environmental contamination*

83. The Committee has received extensive information on the strontium-90 and caesium-137 concentrations in soil, plants, animal and human foods and in human beings. However, there are many countries from which no data have been submitted. The information so far received, whilst not sufficiently extensive to give a comprehensive world-wide picture, does enable useful conclusions to be drawn.

84. Levels of strontium-90 and caesium-137 vary with geographical location. In addition, other factors such as agricultural conditions and practices, especially of soil and water management, living and dietary habits and food technology will influence the level of these isotopes in man. Because of these factors, caution is necessary in applying data obtained in one area to an estimation of the contamination of the diet in another area.

85. There are at present no practical methods of preventing the entry of these radioisotopes into the human body once they have been released into the environment.

86. The model used in calculating the doses from environmental contamination as set out in annex D of this report is able to give valuable information for the near future, but the doses given for the 30-year and 70-year periods in tables IV and V in this chapter involve extrapolations over such an extended period that they must be considered as speculative. The figures in the table are population weighted world-wide averages. Countries between 30° and 50° North experience levels nearly a factor of 2 higher than the population weighted world-wide average, whilst countries in the southern hemisphere and those in the tropical belt experience smaller doses.

87. Adequate knowledge on the altitude and latitude distribution of fission products in the stratosphere and of injection rates is required to decrease our uncertainty in the prediction of future doses from fall-out. A better understanding of fall-out phenomena would be achieved if nations co-ordinated sampling and measurement programmes and exchanged data on methods and results. Biological sampling should be co-ordinated with fall-out sampling procedures.

88. In order to interpret information from biological sampling, it is important to consider data concerning soil conditions and pertinent agricultural procedures, such as fertilizer practices, depth of ploughing, and also food technology. The dietary habits in a given area should determine the nature and scope of the sampling programme.

89. The Committee has given initial consideration, in co-operation with UNESCO, FAO, and WHO, to the potential environmental contamination in relation to the disposal of radioactive wastes from atomic energy plants and considers that this subject should be made a matter of international co-ordination and agreement.

## Chapter IV

# FUNDAMENTAL RADIOBIOLOGY

1. The radiation effects in man, the major object of this report, are a particular case of what is known to occur in other organisms. It is generally accepted that radiation damage has its origin in individual cells, which have either been killed or impaired in function. A great deal of knowledge of fundamental importance has been obtained by the experimental study of unicellular and multicellular organisms. Despite this, we do not yet understand how radiations act on living cells: the problem is very complex and its solution requires fundamental knowledge which does not exist as yet.

### I. The sequence of events

2. The succession of events which takes place between the time of irradiation and the appearance of the recognizable effects is very intricate. The energy of the radiation dissipated in form of ionisation and excitation is "immediately" used in chemical reactions. The first step or succession of steps probably takes place in an extremely short time (which may be as short as $10^{-6}$ seconds). As many as several hundred of these primary biophysical events may occur inside one mammalian cell submitted to an irradiation of 1 rad, but these primary events may not all result in biological effects.

### II. Direct and indirect effects

3. There are two possible ways of considering the effects of radiation which are in no way mutually exclusive and may very well complement each other. The primary event may act directly on some essential molecular structures of cells *(direct effects)* or it may decompose water or common organic molecules into highly reactive radicals *(indirect effects)*. When water—the most abundant constituent of cells—is decomposed, the indirect effect is due to free hydroxyl radicals, hydrogen atoms or perhydroxyl radicals which are in turn capable of acting on the cellular constituents. The relative contribution of each of these two possible mechanisms is dependent upon the conditions of irradiation, but it is as yet unknown in detail. Both mechanisms are believed to induce rather similar changes in biological structures and they lead to the formation of long-lived organic radicals which have been detected after the irradiation of many organic compounds and of some living systems. [F1-2, F17-41, F51]

### III. Specific cellular constituents

4. Some of these primary events will have no biological effect. The alteration they produce may be reversible or they may affect one of many identical cell constituents and so be of no consequence. Some cellular functions like respiration or protein synthesis are not usually damaged immediately, because, it is believed, these activities take place in cellular structures (mitochondria or microsome) which are numerous and may also be less vulnerable. However, the factors responsible for maintaining these structures may have been impaired and delayed effects may then be observed. The secondary inhibition of respiration and of protein synthesis may lead to the inhibition of specific functions such as those involved in immunological or secretory processes.

5. On the other hand, radiation may affect cell constituents which are so specific that only one or two are likely to exist in each cell. This is the case for individual genes which express themselves in specific hereditary attributes. It is believed that they are composed of very specific desoxyribonuncleic acids (DNA)—perhaps associated with components like proteins. In a gamete (sperm or egg) there is only one gene of each kind; after fertilization the growing embryo and adult organism have two series of such units in every cell. Genes are concerned, through very complex series of biochemical processes, with the formation of cellular enzymes responsible for carrying out metabolic processes and of other constituents of the organized cellular structures. Thus, if a gene is altered (as occurs in most mutations) a whole chain of reactions may be interrupted at one link, and important cellular constituents or building blocks may fail to be formed. Of course, besides the genes there may be other vulnerable constituents but at the present time the genetic material is one of the most radiosensitive known when the consequences of its damage are observed.

6. A major characteristic of radiation damage is that it is not a single effect—many constituents of a cell are damaged more or less simultaneously and at random. It is the interplay of the activity of the remaining non-affected constituents with that of the affected ones which will determine the final outcome. This intricacy makes the problem very difficult, and an identical response in each case need not be expected.[F52-65]

7. Effects similar to the ones produced by ionizing radiation have been found to occur in cells treated with ultraviolet light or with various radiomimetic chemicals. In attempting to understand the sequence of events, studies with these agents which act often more specifically on well-defined biochemical systems are sometimes of much greater value than those of ionizing radiation.

8. The chemical constitution of most cellular structures is only very crudely known, but is of great importance for the understanding of the mechanism of the initial action of radiation. Furthermore, trace amounts of many elements such as calcium are present in chromosomes and other structures. As these may be replaced by radioactive atoms, this substitution might have consequences which are at present unsuspected. That could well be the case with strontium-90 if it replaced calcium in chromosomes.[F15-16]

### IV. Morphological damage

9. After irradiation of cells, both nucleus and cytoplasm may be found to be damaged when observed under the microscope. If chromosomes are broken, the broken ends may reconstitute normally (restitutions) or give abnormal rearrangements. Some of the latter are presumably invisible in the microscope, although the order

of genes on the chomosomes, which appears essential for their correct genetic functioning, may have been altered. Another visible sign of damage to the cell is an increase in size of both nucleus and cytoplasm. This increase is due in part to changes in permeability and osmotic relationship, and, in part, to continued synthetic activity. Furthermore, abnormal vacuoles are sometimes visible, and the particles (mitochondria) on which respiratory enzymes are organized have sometimes been found to be morphologically altered.

10. Nucleus and cytoplasm are very closely interdependent parts of the cell in normal circumstances and an alteration in either part will affect the other, as has been shown in experiments with unicellular organisms like amoeba or egg cells. It is generally believed that most genetic damage needs to be initiated inside or in the immediate neighbourhood of the gene itself. However, in some instances, chemicals can become mutagenic after irradiation.[F66-86]

## V. Biological damage to individual cells

### *Retardation of cell division*

11. Any detectable biological damage must originate in some biochemical change, but the exact sequence of events from the biochemical to the biological is still unknown. The biological damage seems to follow a constant pattern in micro-organisms, protozoa or cultures of mammalian cells. If the cells are preparing to divide, irradiation retards the process of division (mitosis). While this retardation is often associated with an inhibition of the synthesis of the genetically important DNA, instances are known where this does not necessarily occur. In these cases, other cellular structures or biochemical mechanisms which are important for cell division, may have been interfered with, but further understanding would only be possible with a fuller knowledge of normal mechanisms of mitosis. Following the retardation, cell division is resumed in a seemingly normal fashion but permanent damage has usually supervened and the cell dies after one or more division cycles.[F91-92]

### *Mutation*

12. Another frequently observed cellular alteration is mutation, which leads to the interruption of one or more important biochemical steps (such as the synthesis of an indispensable enzyme or of cellular constituent). In micro-organisms this will lead to lethal damage if the compound previously synthesized by the enzyme is not supplied to the progeny cells or if it belongs to an essential cellular component. When the cells of the germ line of multicellular organisms are irradiated, similar mutations occur which can be observed in the offspring. Somatic cells are also known to undergo mutations which may express themselves by somatic changes or damage. It takes a short time for a mutation to become established. Experimental evidence presented shows that, during this time, the process can be modified to some extent. It is believed, however, that once the process is completed, it cannot be reversed except by a new mutation (reverse mutation).[F93-96, F123-126]

### *Lethal effects*

13. Cell division is often irreversibly blocked and this may be associated with major visible chromosome damage resulting in unequal distribution of nuclear material between daughter cells. Sometimes the block in cell division only occurs after a certain number of these divisions has taken place. Chromosome damage is one known cause of delayed death of cells, but on the other hand, cytoplasmic damage might also be lethal. It is therefore impossible in most cases to establish the exact origin of cell death.[F102-104]

### *Other damage*

14. Besides mutations, delay or blocking of mitosis, or death, other effects may be observed. Exchange of ions or of organic substances between the cell and its environment, cellular movement, or the storage of chemical energy which will be used in various synthetic reactions may all be interfered with, but such effects have usually been demonstrated only after relatively high dosages of radiation. It should be stated that the available methods of analysis are still very crude and it is quite possible that many specific effects have so far remained undetected.[F97-101, F105-112]

## VI. Biological effects in tissues and in higher organisms

15. In higher organisms, all the forms of damage described for individual cells occur and these may affect both the tissues, if local damage is considered, and the organism as a whole. Our understanding of the underlying *mechanisms* is complicated by the fact that all tissues live in very close contact with each other. Furthermore, tissues are interconnected by blood and the nervous system; radiation damage to one tissue may well be intensified or compensated for by the activity of others. It is one of the objects of radiobiology to clarify these processes.

### *Cellular differentiation*

16. A cellular process which is very sensitive to radiation is that of cellular differentiation in which embryonic cells, apparently all identical during the first few division cycles, change into the fully specialized tissue cells of the adult. A relatively small number of the cells of differentiating embryos will give rise to specific organs of the adult. If some of these stem cells are killed, delayed in development or made functionally inactive, important malformations of these organs can occur.

17. Some cells remain undifferentiated during development and are present in tissues throughout adult life. Their differentiation leads to the continuous formation of blood cells or to the renewal of skin and intestinal epithelium and to the maturation of gametes. During certain stages of this differentiation these cells become more sensitive to radiation and may be killed or their differentiation may be impaired; this will produce conditions such as anaemia, leucopenia, skin and intestinal atrophy and also sterility. However, some undifferentiated cells may remain undamaged and initiate the recovery of the affected tissues. On the other hand, certain damaged cells may survive and develop into malignancies (leukemia, skin tumors, or osteosarcoma when bone is irradiated).[F113-122]

### *Latent period*

18. Somatic effects appear after a certain latent period. For the effects discussed in the previous paragraph the latent period depends on the time the cells take to differentiate and on the length of their normal life. In the case of leucopenia, anaemia or intestinal damage, the latency is usually from one to several days, whereas in the case of cataract, or of leukemia or other malignancies, it may last for many years.

*Comparative radiosensitivity in living organisms*

19. When the survival of different animal species after irradiation with the same dose is compared, it has been found that their radiosensitivity varies widely. It may take several hundred thousand rem to kill 50 per cent of individuals in a population of bacteria or protozoa but the dose necessary to kill 50 per cent of many cold-blooded vertebrates is several thousand rem and in the case of mammals it is only of a few hundred rem.

20. The variation of radiosensitivity in mammals is less marked when compared at the cellular level (as in tissue cultures). The histopathological changes in corresponding organs of species having strikingly different radiosensitivity, such as in guinea pigs and rabbits, have been found to be nearly the same. This indicates that the intervention of other mechanisms, e.g. those of neurohumoral regulations, influences the radioresistance of the whole organism.[F138-145]

*Adaptation to radiation*

21. The possibility of an acquired radioresistance of cells or of organisms has been suggested. The data now available show no acquired radioresistance of normal cells, even after a great number of heavily irradiated generations. The special case of the apparent radioresistance *in vivo* of tumours recurring after radio therapy is probably related to a change in the tissues around the tumour and to polyploidy of the tumour cells, but does not seem to be related to the selection of a more resistant genetic material in these cells. A second special case is found in the hereditary changes to radiation resistance in bacteria; these changes are now believed to be spontaneously occurring mutations which can be selected by means of irradiation rather than induced by irradiation. At present, there is no evidence of biological adaptation to ionizing radiations.[F146-151]

*Secondary damage*

22. Irradiated cells are known to give rise to unusual products which may arise either from chemical reactions during irradiation (as in the case of small amounts of peroxides) or from cellular damage (in which case enzymes may be released in abnormal concentration in the blood stream) or as the result of some abnormality in cellular metabolism. In complex organisms these products may be the cause of secondary damage far away from the site of irradiation as has been observed in a few instances; nucleic acid metabolism can be impaired in a tumour which was shielded during irradiation; and when non-irradiated thymus cells are grafted on a totally irradiated host, these thymus cells may become tumorous.[F153-158]

## VII. Biological effect on populations

23. The effects of radiation will be reflected in the individual and at the end in the population. The increase of radiation will cause an increase in the load of mutations. Although we have some knowledge of particular problems, we still do not have a satisfactory theory of the dynamic of mutations in the population and therefore it is difficult to predict the consequences of this increase in the mutation rate. Nevertheless, certain effects on the relationship between various species in biological populations cannot be excluded *a priori*.

24. Populations of living organisms commonly live in close relationship with each other and in many cases may even become interdependent. Many instances are known of specific micro-organisms living in mutually advantageous symbiosis with plants or animals. An equilibrium between mutation, adaptation and selection of these species has become established during the long process of evolution. Increased irradiation would increase the mutation rate of these species and, in the case of micro-organisms which usually divide very rapidly and are haploid cells, consequent shift in equilibrium might conceivably cause severe repercussions throughout whole populations. Consequences to humanity could be very serious, if a species with important economic implications were eliminated. So far, attention has not been given to such possible effects on populations of organisms.

## VIII. Dose-effect relationship

25. For an estimation of radiation hazards, it is of prime importance to have information on the dose-effect relationship at low doses. The data so far available point to the fact that at low dose *the amount of genetic damage is related linearly* to the increase in radiation, thus supporting the assumption that natural radiation contributes to natural mutations. This linear relationship has been found to be true for all experiments so far performed on viruses, micro-organisms, multicellular plants and animals.

These results further indicate that, as dosage is decreased, the number of individuals affected becomes smaller but the consequences to each of those affected remain the same.

A certain number of somatic effects are also related linearly to dose. For instance, the birthweight of mice born from embryos irradiated *in utero* decreases proportionately with exposure, and it is possible that the induction of leukemia in man is linearly related to the dose of radiation received.

*Threshold dose*

26. In many other instances of somatic effects no response has been so far observed below a certain dose, the "threshold dose" for that effect. One must distinguish between at least two notions of threshold. The appearance of a threshold may be explainable in physical terms in the sense that more than one primary event is needed to produce the effect; and the sigmoid dose effect curves obtained for certain types of chromosome aberrations and for the killing of mammalian cells in tissue cultures probably illustrate this phenomenon. This state of affairs, which holds for some unicellular organisms, is generally further complicated in higher organisms by the fact that different physiological conditions come into play. In mammals, for example, it may happen that before the primary effects become apparent as functional or morphological changes, some recovery processes or physiological events prevent or retard the appearance of the final biological effect. The threshold for skin erythema, for instance, is higher for a fractionated dose, because recovery is taking place between the successive irradiations.

27. The dose-effect relationship is not necessarily identical for similar effects when different species are considered. For instance, tumours can be induced in mice if they are exposed to a dose of radiation above a certain threshold. The time it takes for the tumour to appear and the longevity of the animal have to be taken into consideration and the existence of a linear relationship for similar tumours in man cannot be ruled out.

28. As a result of technical improvement and of new experimental approaches, the value of the observed

threshold has been reduced in certain instances. This is one of the reasons why maximum permissable doses have steadily decreased over the last twenty-five years, another reason being that genetic effects for which there is no threshold are now being taken into consideration and that the number of exposed people is continuously increasing.[F8-11]

*Stimulating effects*

29. In some experiments it has been claimed that low irradiation stimulates certain biological functions such as protein synthesis, increase in size or even the life span. These effects when further studied, have generally been found to be the consequence of damage done elsewhere in the cells or organisms.[F152]

## IX. Variables in radiobiological processes

### *Biological factors*

*Cell division*

30. It has been known for more than a half century that dividing cells are more sensitive (sometimes as much as one thousand times more) than resting ones. It is this radiosensitivity of dividing cells which makes radiotherapy of value in the selective destruction of some malignant tumours, in which cell division is often much more frequent than in surrounding normal tissues. This increased sensitivity of dividing cells exists usually for lethal effects, chromosome aberrations, inhibition of mitosis and mutations. The most striking exception to this phenomenon is the high sensitivity of the non-dividing lymphocytes.

*Age*

31. It has to be pointed out that very little is known about the processes involved in ageing of cells; methods of determining cellular age would be of considerable help in many radiobiological problems. However, in mice it has been found that soon after birth the radiosensitivity to killing falls progressively and then remains at a minimum until the latter part of the normal life-span, during which it increases strikingly. Birds, on the other hand, have a much more constant radiosensivitity throughout their adult life.

*Physiological conditions*

32. Dehydration usually increases the radioresistance of cells. Starvation, chronic anaemia and many other abnormal conditions may influence the susceptibility of mammals to radiation. The first two factors are believed to increase the radiosensitivity of mice; more information on this subject would be of great help in attempts to predict the sensitivity of humans living under various conditions.

*Genetic strain*

33. The sensitivity of bacteria of similar species but of different strains to killing may vary by a factor of several-fold. In higher organisms, this factor has been studied in a few cases; in mice, for example, the variation of the dose needed to produce lethal effect does not appear to vary by more than about 25-30 per cent between the most and least sensitive strains.

*Species difference*

34. Many reactions to radiation differ widely from one species to another, as can be observed by the variation of threshold values for a similar effect. It is, therefore, unwise to transpose results from experimental animals to human beings, unless there is general agreement between results throughout a wide range of organisms and preferably not before the relevant fundamental mechanisms are fully understood.[F128-135]

### *Physical and chemical factors*

*Type of radiation*

35. Radiations of various types usually produce similar biological responses, but they may differ in effectiveness: densely ionizing particles ($\alpha$ rays, neutrons which give recoil protons) have a higher efficiency in producing most forms of cellular damage than radiation ($\gamma$-, X-rays) giving lower ionic densities. Cellular damage resulting from several simultaneous ionizations within a given structure will have a higher probability of oocurring when the density of ionization is high. On the contrary, if only one ionization is needed, densely ionizing radiation will be less efficient because many ionizations will be wasted. This pattern in energy distribution in the cell may affect the final response. For example, neutrons are more effective in producing lethal effects and in decreasing the life-span of mammals. The influence of the pattern of energy distribution may also differ with the conditions of irradiation. The response to the sparsely ionizing X- and $\gamma$-rays is considerably reduced in anoxic conditions. This is not so for densely ionizing radiations. Anoxic conditions exist in the lens of the eye and this explains why neutrons produce cataract much more readily than X-rays, an unforeseen finding which was not understood until the oxygen effect for various types of radiation was studied in full detail. Our lack of understanding of many mechanisms of radiation damage should therefore call for great caution when human beings are exposed.[F4-7]

*Time distribution of dose*

36. In general, a dose which is lethal when given in a short time may produce effects which are difficult to detect when it is spread out over a lifetime. However, in some cases, the same over-all dose given in a short or a long time gives the same response; this is true for effects of the genetic material (induction of mutation) or for the formation of bacteriophage in a lysogenic bacteria.[F12-14]

*Oxygen*

37. By reducing the oxygen concentration inside cells during irradiation with X or $\gamma$ rays one may diminish by a factor of 3 to 5 the cell sensitivity to lethal effects, to chromosome damage and to some of the associated mutations as well as to some biochemical effects of radiation. The effect of oxygen is perhaps related to the formation of a perhydroxyl radical and of hydrogen peroxide, in addition to the other radicals arising from the decomposition of water. Several other hypotheses to explain the oxygen effects have been proposed and have to be kept in mind.

38. However, the presence of oxygen favours some of the cellular processes following irradiation, such as the rejoining and rearrangement of chromosome breaks which are dependent on respiration. The presence of oxygen during irradiation appears also to affect cellular functions necessary for recovery. The influence of oxygen is therefore very complex since it can affect either the primary events or the processes of recovery.

39. The effect of oxygen has so far been observed to be negligible in the case of densely ionizing radiation like alpha rays, neutrons or slow electrons.[F136-137]

*Temperature*

40. It has been shown in isolated systems (enzymes, bacteriophage) that a decrease of temperature during irradiation reduces its effect. In living organisms, a low temperature may also affect the bio-physical processes which take place during irradiation. The change of temperature may also influence the biological expression of the primary lesion or the recovery mechanism. Irradiation at low temperature may either decrease or increase genetic effects as observed by mutations or chromosome aberrations. On the other hand, when vertebrates are irradiated and kept thereafter at low temperatures, a radiation effect does not become expressed until the temperature is increased to normal levels. Nevertheless the final radiation damage is the same.

## X. Protection

41. The possibility of altering both the direct and indirect effects of radiation experimentally gives some prospect of interfering with the initial steps of radiation damage. A variety of chemical protectors have been found, but to be effective, they must be present during radiation. Among these cysteamine and AET* have been used successfully both *in vitro* and *in vivo*. It has been found possible to counteract the induction of many chemical and biochemical effects and to reduce chromosome aberrations and some mutations, as well as to increase considerably the survival of cells and tissues. Although the bulk of experiments on the survival of mammals has been done with mice and rats, successful experiments with AET have been reported on a small number of dogs and monkeys.

42. The mode of action of these chemical protectors is in no way certain and several hypotheses have been put forward: they may, as *in vitro*, act by "neutralizing" the free radicals or reducing the oxygen tension, but there is not always a correlation between the existence of an oxygen effect and the possibility of chemical protection. These agents may also protect sensitive biological sites directly by preventing radicals from attacking them or they might stabilize the sensitive biological structures. Prospects of using chemical protectors adequately in man still await the discovery of substances which are sufficiently nontoxic to be used in effective concentration.[F42-47, F150-169]

## XI. Recovery

43. Many approaches have been used to modify radiation damage after it is established. Not enough is known about the mechanisms which lead to this damage, and about natural processes of recovery, to make any rational attempt to influence them. In the case of unicellular organisms it has been found possible to alter the sequence of events with the aid of physical or chemical agents applied after irradiation. Most effects of ultra-violet radiation can be counteracted by subsequent treatment with visible light (photo-reactivation). Formation of bacteriophage in lysogenic bacteria by ultra-violet or X-rays can be greatly reduced by the action of added catalase (catalase reactivation).

44. In the case of mammals, it has been found possible to replace damaged cells by grafting normal ones to the irradiated animals. It has been clearly shown in mice that the injection of bone marrow into a lethally irradiated animal is capable of reducing the mortality: the injected cells substitute for the ones killed by irradiation. The practical applicability to human beings of bone marrow grafts depends on an understanding of the immunological defence mechanisms by which mammals destroy any foreign tissue grafted upon them. Intensive fundamental and applied research is needed.

45. It is possible to combine the effects of chemical protectors and of recovery factors. When this is done for mice, they have a still better chance of surviving than if either treatment is applied independently. However, even when chemical protectors and recovery factors are applied simultaneously, considerable cellular damage may persist and it frequently becomes expressed as a tumour at a later stage.[F173-187]

## XII. Conclusions

46. In this chapter an attempt has been made to point out the fundamental problems of radiobiology, their present status and their relevance to the practical human hazards of today.

47. In order to estimate the hazards to human beings, it is necessary to take into account the cumulative effects of radiation in each individual, although the average hazard often seems statistically very small. An understanding of the basic mechanisms by which the damage is produced may be the only way of making any rational assessment of the damage produced at very low doses. While the physical events are more or less understood on the basis of our knowledge of modern physics or physical chemistry, the unknowns on the biological side are still enormous. The need for fundamental research is therefore very great. The only way of meeting this challenge is by the training of scientists in the different disciplines that biological research demands.

48. The lack of fundamental knowledge of normal cell structure and function is in our opinion the major factor limiting progress in radiobiology. Further research is urgently needed in general biology taken in its widest possible sense.

49. The major problems on which radiobiological research is needed include:

(*a*) The nature of the primary damage to cellular structures and the pathways of expression of this damage.

(*b*) The dose-effect relationships at low dosages.

(*c*) The mechanisms of chemical protection and recovery.

Other fields whose importance is still undetermined may become soon of very great interest, as e.g. the mode of action of radionuclides at the cellular level (paragraph 8).

50. Despite the benefits brought to mankind by the proper use of ionizing radiations in medicine, the evidence points to the fact that these radiations are harmful and that their effects are frequently cumulative. Even very small doses may occasionally have highly deleterious biological consequences. It is also known that radiosensitivity tends to increase with the degree of complexity of the organisms. In addition to these established facts, problems no less compelling have arisen (paragraphs 8, 23) and it is possible that they have not yet received sufficient attention. These problems will have to be reckoned with before one can obtain a completely accurate estimate of radiation hazards. In the light of these considerations there is an imperative need for keeping the radiation level as low as feasible.

* S-2-aminoethylisothiuronium Br. HBr. Recently it was found that a re-arrangement occurs in organism to 2-mercaptoethylguanidine HBr (see F 163).

## Chapter V

# SOMATIC EFFECTS OF RADIATION

1. The effects of ionizing radiations on man and animals have been observed for many years. These observations have shown that all mammalian cells are vulnerable to this type of injury; they have also demonstrated that tissues and people can, to a very large extent, recover from radiation injury even after severe damage. The clinical manifestations of radiation injury are the end-result of the biophysical effects and of the biochemical reactions through which radiations produce effects on the molecular and cellular level and of a variety of local and systemic physiological and regulatory factors which determine the course and eventual outcome of any injury to the human body. In analysing the action of radiation on the body, it is necessary to consider the physical factors of exposure as well as the relevant biological factors.

### I. Physical factors

2. The principal physical factor determining the biological effect of ionizing radiation is the *dose*, defined in chapter II. If the dose is expressed in rem, the influence of the type of radiation (linear energy transfer) is taken into account. The dose of radiation absorbed in all organs must be known. Furthermore, since there may be important differences between the doses absorbed in various organs or even locally within a single organ, the distribution of dose is an important consideration.

3. In the case of external sources of radiation, such differences may result from the following factors: the radiation beam may be directed at only one part of the body (e.g. the hand). The radiation beam may be attenuated as it passes through the body (e.g. X-rays) or may not even penetrate below the surface (e.g. alpha particles). The radiation (e.g. X-rays) may be absorbed quite differently by tissues of different chemical composition (bone, muscle).

4. The distribution in time of the radiation exposure must also be considered. The same dose may be received: (*a*) quickly, in one exposure (e.g. 10 minutes); (*b*) slowly and continuously over an extended period (e.g. 5 years); or (*c*) fractionally (e.g. 1 single dose each year for 10 years). Extending the over-all exposure time as in (*b*) and (*c*) greatly reduces the amount of somatic damage with the exception of those changes where a linear dose-effect relationship may apply. Factors of importance in determining the duration of exposure from a radioactive isotope and its daughter products are their physical half-lives, the type and energy of the radiations emitted, the time of retention and the rate of excretion from the body.

5. In the case of radioactive isotopes that enter the body, the dose distribution is determined by the capacity of the various organs to absorb the isotope from the blood. Certain isotopes such as sodium remain in the fluids of the body and thus travel through the whole body. Other isotopes are taken rapidly from the blood by a particular organ, as in the case of iodine concentration in the thyroid gland, or strontium in bone. In such instances, the dose of radiation absorbed is largely confined to certain organs. The ability of an organ to absorb a specific isotope from the blood depends on its stage of development and varies from time to time with changes in its metabolic state. For instance, in the early stages of human development, the precursors of bone do not selectively absorb strontium. Later on, however, during bone growth, strontium is rapidly absorbed. Still later, when growth has ceased, the rate of uptake decreases.

#### *Concept of sensitivity*

6. Originally, investigators were struck by the rapid and dramatic morphological changes which they observed in the blood-forming organs, the skin, the intestines and the gonads, and therefore classified these organs as "radiosensitive". The greater doses required to produce equally obvious changes in the blood vessels, the lens and nervous system led to an intermediate classification for these tissues or organs. Finally, muscles and connective tissues were classified as "radio-resistant".

7. In the light of our present knowledge, such a simple classification is no longer adequate, and in some respects may be misleading. There are several major factors that enter into the estimation of sensitivity. In general, the estimate will depend on the nature and functional or metabolic state of the biological system under investigation. More specifically, and perhaps more importantly, however, it will also depend on the particular part of the system investigated and on the sensitivity of the methods employed for this purpose. Thus, an organ examined with the microscope will appear to be more sensitive than when examined with the naked eye. Similiarly, an organ examined with the most refined physiological techniques may prove to be much more sensitive than when examined by classical morphological methods. It is apparent that as our method of observation changes, the observed sensitivity of the biological system will also change.

#### *Relation between dose and effect*

8. For the scientific study of radiation effects it is necessary to know quantitatively the relation between magnitude or frequency of *biological effects* and *radiation dose*, i.e. the dose-effect relationship. Various relations are theoretically possible; two general types will be mentioned here. First, the effect may be direct proportion to the dose. Thus any dose, no matter how small, will have some effect, although after a small dose the somatic effect may be minute. Secondly, there may be a threshold dose below which no effect occurs. In the case of mice of a typical strain, for example, there is a threshold dose of about 400 rem (whole-body exposure to X-rays) below which practically no acute deaths occur. Above this threshold, the number of deaths increases rapidly with the dose, reaching 100 per cent within two weeks after exposure to twice this dose. It may be assumed that intermediate relations exist, represented by a curved line, showing extremely little effect

at low dose, thus indicating an "apparent" threshold.

9. All studies of the dose-effect relationship are complicated by the unavoidable presence of natural radiations. In man, the annual dose from natural radiations is about 100 mrem. It is assumed that a certain amount of genetic damage (some natural mutations) in man is caused by these radiations. It is conceivable that analogous changes may occur in somatic cells and that such changes, being cumulative with age, may have adverse influences. However, there is at present no evidence for such an assumption. It is conceivable that noxious agents, such as carcinogenic compounds, bacteria, parasites and virsuses, in our environment may potentiate the effects of radiations.

10. The interpretation of the dose-effect relationship following multiple exposures is more complex than in the case of a single exposure; such an interpretation must take into account a variety of biological factors, recovery and sensitization, for instance. These factors, which are variable, may act separately or in conjunction with each other. The injury may build up in simple proportion to the exposure or it may not increase because the tissues are able to recover before the next exposure occurs. However, repeated exposures would act to diminish the physiologic reserve of the irradiated tissue, and eventually a state can be reached in which repair no longer balances injury. Moreover, previously irradiated organisms may show modifications in radiosensitivity. However, such modifications have not been sufficiently studied.

11. Although a characteristic dose-effect curve may be associated with each somatic effect, the curve will be subject to certain variations which stem from constitutional differences in the populations of animals or human beings. Other factors which have an influence on radiation reactions are sex and age. For certain effects, infants and children react more quickly and with greater severity than adults. During senescence, resistance to radiation declines. Even within groups of individuals homogeneous in age and sex, individual variations occur as a result of differences in genetic constitution and individual history.

## II. General pathology

12. Analysis of the biological action of radiations on multicellular organisms has shown that the sequence of events generally begins with the local damage at the place of the primary biophysical event. Such damage usually involves cellular and extracellular structures of diverse origin and function, and it may range from the almost imperceptible to the very gross. The former may appear as a transitory change, such as an alteration in the permeability of a membrane or an interruption in the secretory activity of a cell, whereas in the latter case the injury will be quite apparent, as in the case of a radiation burn, for instance.

13. Injury, no matter what its cause, brings into play a number of well-known co-ordinated physiological events that are concerned with defence and repair and with maintenance of the integrity of the organism as a whole. Radiation injury follows this universal biological law of reaction to injury, although radiations can modify these reactions to some extent. It is clear that, without repair, we could not use radiations in the treatment of malignant diseases.

14. It is important to remember that radiations do not produce effects that are specific or novel in character. This is true of the morphological changes as well as of the functional responses. Many of the former can be produced by a number of other agents and some of the transient functional responses to low levels of radiation have been compared to the non-specific alterations associated with the stress-syndrome which can also be elicited by a variety of agents.

15. Radiation injuries have no pathognomonic features which distinguish them from other injuries, but with experience and with a history of radiation exposure, it is possible to recognize patterns of changes which are fairly distinctive. Just as mutations produced by irradiation do not differ in kind from those which occur spontaneously, in the same way, exposure of somatic cells to ionizing radiations has not created new types of diseases. What has been observed is that the incidence of certain types of diseases has been increased by such exposures.

16. It has been observed that, after acute lethal or sublethal irradiation, mammals become susceptible to infection and, indeed, often die because their natural defence mechanisms have been impaired. These mechanisms are complex, but they are chiefly dependent on three main functions: (*a*) natural barriers to invading organisms; (*b*) cellular defence-mechanisms (phagocytosis), and (*c*) humoral-defence mechanisms (antibodies). All three of these functions may be severely affected by a large single exposure, but the extent of impairment from small doses is not known.

17. Disturbances of immunological mechanisms can be produced by external and internal radiation. In the latter case, disturbances may occur when the cells of the reticulo-endothelial system have incorporated radioactive material. This may inhibit the immunological functions of the cells.

18. Exposure to ionizing radiation can lead to the formation of pathologic metabolic products in the tissues, as is known to occur in some other types of injury, e.g., thermal burns. It is possible that these products may play a part in the origin of a number of secondary radiation effects. There is some evidence for the presence of certain toxic products in blood coming from irradiated organs of experimental animals and in the lymph withdrawn from the thoracic duct of these animals. The chemical nature of these substances, normally bound and inactive within the cell, is not known as yet, but some of them are histamine-like substances.

19. Certain types of radiation injury require months or years to make their appearance. This is true whether or not acute manifestations of injury were observed at the time of exposure. Delayed injuries of this type are frequently the result of metabolic and nutritional disturbances in irradiated organs. When the blood supply of the organ has also been impaired, the disturbances are increased and lead to marked diminution in function accompanied by heightened liability to injury and to tumour formation. Such changes are readily observed in the skin and can occur in any organ that has received a sufficiently high dose, either in one brief exposure or over an extended period of time.

## III. Special pathology

20. Clinical observations on large numbers of human beings and numerous studies on a great variety of experimental animals have provided much valuable information on many types of radiation injury in various organs. In general, these lesions are the result of relatively large doses of the order of 100 r. and greater, delivered to

small parts of the body, but the effects of small doses have also been extensively studied.

*The blood-forming organs*

21. The tissues producing the formed elements of the blood (red cells, white cells and platelets) are widely distributed throughout the body; they are found principally in the bone marrow, the lymph nodes, the spleen, the thymus (in children) and in the foetal liver. The widespread distribution of these tissues makes it very difficult to irradiate any part of the body without exposing part of this system.

22. The majority of the cells composing the blood-forming organs are known to react promptly and to relatively small single doses of radiation. Of the white cells, the lymphocytes are the most sensitive and their response as measured in the circulating blood is a most sensitive indicator of whole-body exposure to radiation in man. Under special conditions of clinical investigation, a temporary drop in lymphocytes has been reported after a single dose of 250 mrem. After repeated doses of a few roentgens, changes in the morphology of lymphocytes (bilobed) have been reported to be more readily detected than a mere reduction in number. It has been established that the blood-forming organs of children are more sensitive than those of adults.

23. Chronic or repeated exposures at low dose levels will impair production of white cells and red cells, but this impairment may not become apparent or detectable for some years. For these reasons, blood examinations are not as sensitive or as reliable a diagnostic procedure as was previously thought. Radiologists and others who, in the past, have been exposed almost daily for many years to relatively low levels of radiation have shown reduced numbers of white cells (leucopenia) and of red cells (anaemia). Among the delayed effects of radiation exposure of the blood-forming organs, leukemia is the most serious condition. An increased incidence of the disease has been reported among the following five groups of people exposed to radiations: (1) radiologists; (2) atomic bomb survivors of Hiroshima and Nagasaki; (3) patients with severe arthritis of the spine who were treated with X-rays for this condition; (4) children who had been treated with X-rays in infancy to reduce the size of the thymus gland; and (5) a group of children who were exposed when still *in utero* during diagnostic X-ray examinations of the mother. In two of these five groups, it has been possible to make estimates of the degree of exposure and to relate them to the incidence of leukemia. These data are discussed in detail in appendix G. Finally, it must be mentioned that leukemia can also be induced in certain species of experimental animals by exposure to radiations. Laboratory mice, which are especially susceptible to one particular type of leukemia, have been intensively studied.

*Skin*

24. Of all the organs in the human body, the skin is the most frequently exposed, and it probably has been the most frequently damaged, as all external radiations must pass through it before reaching other structures. Since the discovery of X-rays, therefore, skin changes have been very prominent and they have been very carefully analysed. In fact, for a long time, skin reactions (erythema) served as a quantitative measure of radiation dose in man.

25. Until relatively recently, reactions in the skin have been a severe limiting factor in radiation therapy of deep-seated cancers, and most of our knowledge concerning the effects on the skin has been obtained from observations of the results of therapeutic irradiation with X-rays. Diagnostic procedures rarely lead to observable changes and then only in the case of prolonged or repeated exposures. Contamination of the skin with radioactive material can also produce severe lesions in the skin if the radiation dose is sufficiently great, as has been observed among Japanese fishermen and inhabitants of the Marshall Islands exposed to immediate and local fall-out in 1954.

26. Depending on the size of the field irradiated and on the dose absorbed, changes can be observed ranging from transient erythema, changes in pigmentation, and temporary loss of hair to severe necrosis and ulceration. Among the early radiologists, chronic radiation dermatitis of the hands and face was a common condition, and cancer often occurred in the damaged skin. This was the form of radiation-induced tumour first to be described in man.

*Gastro-intestinal tract*

27. The gastro-intestinal tract is relatively easily affected by radiations, and radiologists have learned to exercise particular care when administering radiation to the abdomen. Changes can range from interference with physiological functions such as intestinal mobility and secretion of digestive juices to denudation and ulceration of the mucosal lining. Relatively large doses of radiation can cause transient and even permanent depression or cessation of acid and pepsin secretion in the stomach, for instance. Ulcerations produced by radiation may lead to local infection and bacteriaemia. These are often produced by bacteria that normally live in the intact intestinal tract without causing harm. Injury by irradiation can thus adversely affect the delicate balance that exists in nature between host and parasite. Denudation may also result in intractable loss of body fluid through the impaired intestinal mucosa. The dose levels required to produce these serious effects have a high threshold. This type of injury to the small and large intestines plays an important and often crucial role in the outcome of the acute radiation syndrome which will be described later.

28. The passage of ingested radioactive materials through the intestinal tract might produce similar injury, especially when such material is insoluble and when it remains for prolonged periods in certain portions of the intestinal tract where for physiological reasons it moves slowly and in concentrated form, as it would do in the colon. No such injury has been described in human beings, but experiments with animals have shown that such lesions can be produced by feeding very large amounts of insoluble radioactive materials.

*Nervous system*

29. In the past, when morphological criteria were used almost exclusively for the classification of organs according to their radiosensitivity, the central and peripheral nervous system were regarded as belonging to the more resistant organs. While it is still generally true that considerable doses are required to produce morphological alterations in nervous tissue, it has become apparent in recent years that functional changes can be elicited with much smaller and often very low doses and that such changes may be of great significance.

30. Among these changes one may mention: decrease in excitability, the induction of an imbalance between

the processes of excitation and inhibition, and changes in conditioned reflexes. Modifications of the electro-encephalogram have been described at very low doses. Changes of a transitory character are seen in cases of whole-body exposure to doses of several tens of roentgens. Irradiation of animals with 300 to 400 r produces changes in the electro-encephalogram of about one week's duration. In cases of exposure to 800-900 r, changes start immediately after irradiation and persist up to the time of death.

*Bone*

31. Many lesions of bone have been described in human beings and experimental animals following exposure to radiations from external and internal sources. Damage has ranged from temporary inhibitions of bone growth in children and young animals with relatively small doses (of the order of 100 r) to bone necrosis and fractures following exposure in radiotherapy to doses greater than 1000 r. It is important to emphasize that the growing bones of children and young animals are much more vulnerable than those of mature and older individuals. Skeletal development in childhood can be arrested temporarily by moderate doses. The majority of the bone abnormalities reported has resulted either from large doses used in radiotherapy or from deposits of radioactive materials such as radium and mesothorium in bone. With both types of exposure, malignant tumours have been observed to develop either in bone itself or in structures adjacent to bone. Bone-seeking radioactive materials such as radio-strontium are at present incorporated at greater concentrations in the growing bones of children than in the bones of adults. Such deposition is likely to occur in the areas of most active bone growth (epiphyses). Studies of bones following single or multiple doses of radio-strontium in experimental animals have shown that severe lesions and tumours are most likely to arise in these particular areas.

*Gonads*

32. The ovaries and testes are more sensitive than many other organs to damage by radiation. Temporary changes in fertility can be produced, in either sex, by single exposures (30 r in the male and 300 r in the female) or through the cumulative effects of repeated exposures of a few roentgens. Eggs and sperm during development are more susceptible to damage than when mature. The minimal sterilizing dose is less for men than for women. Functional changes in the gonads as a result of exposure to small doses can be observed more readily in women by irregularities or temporary suppression of ovulation and menstruation. Temporary sterility as evidenced by suppression of menstruation may last from a month to a year or so, depending on the dose.

33. In the mouse, chronic irradiation with multiple doses is more effective in producing abnormalities such as changes in the oestrus cycle than is a single exposure. Under chronic irradiation with gamma rays and fast neutrons, fertility of male mice is affected earlier than female fertility; these changes preceded other deviations from normal. Neutrons are more effective in producing changes in the gonads than X or gamma rays. Various types of benign and malignant tumours have been observed in the ovaries of mice following single and repeated exposures to external irradiation. Such tumours are the result not only of the local action of the radiations on the ovaries but also of hormonal disturbances created in the animal as a whole.

*Vascular system*

34. Functional and morphological abnormalities in blood and lymphatic vessels have been observed in many irradiated organs, ranging from transient changes in permeability to necrosis and rupture with haemorrhage into the extra-vascular spaces. Changes in the vascular and lymphatic system play an important part in the pathogenesis of many acute and delayed types of radiation damage, as for example in the skin. Erythema of the skin is primarily due to changes in blood vessels, and chronic skin lesions are usually accompanied by prominent vascular abnormalities such as dilated or completely obliterated blood and lymphatic channels. Lesions in blood vessels are likely to produce impairment of arterial and venous blood flow through the affected parts of an organ. Thus they can cause secondary metabolic changes due to diminished blood supply.

*Eyes*

35. Acute conjunctivitis and keratitis have been observed following exposure with relatively large doses of a few hundred r. The sensitivity of the retina can be used as a detecting procedure of the effect of radiation upon the human body. However, apart from the retina, perhaps the lens has proved to be the most sensitive part of the eye. Lens opacities (cataracts) have been reported to occur following whole-body and partial body irradiation in man and in experimental animals. Cataracts are a characteristically late effect of radiation. In man, the minimal single dose required for cataract production is estimated to be near 200 rad of X and gamma rays. By a single exposure to radiations from atomic bomb explosions, cataract cases have been reported to be one of the late effects. Neutrons are more effective in inducing cataracts, and several such instances have been observed among physicists in recent years. Cataracts have also been observed in experimental animals (dogs) several years after the administration of radio-strontium.

*Lungs*

36. When heavily irradiated, the lungs show slowly developing, progressive changes which have been known as radiation pneumonitis. The rich vascular system of the lungs is susceptible to radiation injury, and delayed changes have been observed in blood vessels. Fibrosis and cancer of the lung have been described in miners of radioactive ores, but many other factors have undoubtedly played an important part in the production of these diseases. However, radiation from radon and its decay products deposited in the lungs of miners undoubtedly augmented the effects of other noxious agents. Radiation pneumonitis and cancer of the lung have been produced in experimental animals by inhalation of radioactive materials such as plutonium and cerium.

*Endocrine organs*

37. Functional disturbances of organs with internal secretion have not received as much attention as those of other organs. However, the role of the adrenal cortex in the "alarm-reaction" and in the "stress-syndrome" has been investigated with regard to injury by radiation, and it has been established that radiation can produce certain non-specific effects which are mediated through the adrenal gland (lymphopenia, for instance) and that they are identical with those produced by other "stress" agents. This emphasizes the non-specific character of some effects of radiation. Effects of this type can be obtained with a few hundred roentgens of X-rays, and it is possible that other endocrine processes also con-

cerned with regulatory functions in the body can likewise be affected by such doses. These are matters which require much further investigation.

38. Of all the glands with internal secretion, the thyroid gland is the one that has been studied most thoroughly in man, especially in connexion with radioactive iodine, which is selectively concentrated in this organ. The effects of radiation from radioactive iodine upon the thyroid gland in hyperthyroidism have been of great benefit in the treatment of this disease. Corollary studies have also thrown much light on the early functional effects that radiation may have on this organ and on the morphological alterations that follow later, including the complete destruction of the gland. Endocrinological studies have demonstrated that it is relatively easy to disturb certain sensitive hormonal equilibria existing in the body.

*Embryonic development*

39. Radiation has long been known to be harmful to embryos. Malformations have been observed in children who had been exposed to X-rays or other ionizing radiations while they were developing in the uterus. Our knowledge of these effects is based on what happens after accidental exposure of human embryos coupled with extensive experiments with laboratory mammals. In rats and mice, 200 r of conventional X-rays (250 kv) given to the pregnant mother will selectively destroy specific primitive cells in the embryo at certain stages; this will interfere with subsequent developmental processes. The kind of malformation which results depends upon the phase of embryological development going on at the time of irradiation. In the laboratory it is possible to produce virtually at will a whole series of malformations of the nervous system, skeleton, eye and other organs by properly timing the radiation. In general, a critical period exists for the induction of any particular malformation.

40. The dose of radiation is also an important determinant because some developmental processes are more sensitive than others to disturbances produced by radiation. After low doses (25 to 50 r) only certain abnormalities may occur at given stages, whereas 400 r is so damaging that the embryo usually becames extremely malformed or it may even be killed at once. In general, the malformative processes that result from radiation of developing mammals can be explained by embryologic principles worked out for other vertebrates.

41. Although human data on the results of exposure of embryo and foetus are meagre and fragmentary, there are sufficient experimental quantitative data to provide a guide for avoiding clinical hazards. The lowest dose of conventional X-rays (250 kv) that will produce visible destruction of embryonal cells in such animals is 30 r and doses of 25 r are capable of causing deviations of skeletal development in mice with certain predisposing genetic backgrounds. In laboratory mammals some of the grossest malformations follow radiation given in the earlier somite stages, or period of early organogenesis but some tissues continue to be highly susceptible to radiation injury throughout intra-uterine life and into the newborn period. For example, the retina of the eye and the brain are particularly vulnerable to malformation. If one makes inferences about man from the results of experimental work on animals in an attempt to assess the risk to the foetus, it can be stated that parts of the human brain are probably susceptible to considerable injury until the last months of gestation and that loss of single developing neurons is possible well into early infant life. Among the children who were exposed *in utero* to radiations from atomic bombs, some cases of microcephaly with mental retardation have been observed.

42. It has been demonstrated in experimental animals that soluble radioactive materials when ingested by the mother can be transferred through the placenta to the embryo and growing foetus. Radio-strontium and other substances which may pass through the placental barrier can become fixed in the skeleton or in other organs and produce damage. In the very early stages of embryogenesis, radiation exposure of this type can involve all cells of the growing embryo and resemble whole-body exposure, whereas in later stages of development it will resemble partial body exposure through fixation of material in specific organs.

*Whole body irradiation: single dose*

*Acute radiation syndrome*

43. Clinical studies on people injured by exposure to nuclear radiations from explosions of nuclear weapons and from similar exposures in laboratory accidents have added much to our knowledge of the acute and subacute effects of whole-body radiation in human beings in and below the lethal range. The median lethal dose for man is considered to be approximately 300-500 rem. This dose will produce an acute illness, fatal within thirty to sixty days to 50 per cent of the people thus exposed. A few additional people will die after this period. The following is a synopsis of the most important clinical symptoms and of the course of the illness following such an exposure.

44. The earliest symptoms are nausea and vomiting and sometimes diarrhoea; these may appear within an hour after exposure and can last as long as two days. They are accompanied by a feeling of great prostration and fatigue, by hyper-excitability of reflexes and other symptoms attributable to disturbances of the somatic and autonomic nervous system. This first phase, after an exposure to about 400 rem, is followed by a period of subjective well-being, although tissue-damage progresses. Characteristic changes in the white blood cells begin very early; usually they are already present on the first day. An early and rapid fall occurs in the lymphocytes. The granulocytes, after a transient initial increase, also rapidly fall below normal levels. In the fatally injured, all types of white blood cells continue to decrease to extremely low levels. A similar, though less severe and somewhat delayed, fall will be seen in the red blood cells, causing progressive anaemia. There is a tendency to bleeding. This is due to a reduction in the number of platelets, as well as to an increased permeability of blood vessels. Anaemia and leucopenia may be severe at death.

45. At the height of the illness, usually during the second and third week, the fully developed radiation syndrome is characterized by a sustained high fever and extreme exhaustion; there is loss of weight, reddening of the skin (erythema) and loss of hair and there are haemorrhages in the skin, and ulceration of the mouth, throat and intestines. Loss of protective function of the mucosa of the mouth and intestinal tract combined with severe impairment of white blood cell production and of other immunological functions make irradiated individuals susceptible to infections from bacteria normally residing in the individual and usually harmless. Infections of this kind have frequently been the cause of death.

46. It is apparent that initial injury leads to complex chains of events involving practically all organs of the body and may seriously interfere with the balanced in-

terplay between them (homeostasis). Apart from cellular damage, general reactions of the vascular and nervous systems, marked alterations in fluid and electrolyte balance and other metabolic changes play an important and often decisive role in the pathogenesis of this illness.

47. Survivors of injury of this magnitude recover slowly and require a prolonged period of convalescence. Disturbances in the blood-forming organs and in the gonads are the last to disappear and some of the changes in the bone marrow and in the circulating white cells may persist for many months. The patterns of recovery from massive radiation injury of this kind clearly demonstrate that radiation, in addition to producing damage, temporarily inhibits the mechanisms of repair. Interference with reaction to injury is an important factor and its significance may be equal to that of the primary sensitivity of cells.

48. When the dose of a single whole-body exposure is reduced, illness of the type described above is correspondingly less severe and fewer symptoms are observed. It has been suggested that, with a dose of 100 rem, not more than 15 per cent of those exposed would be affected and that illness would be of short duration and comparatively mild. At low dose levels (between 25 and 50 rem) significant findings may be restricted almost entirely to the blood; these will be difficult to detect without special methods.

*Possible delayed effects*

49. It is a peculiar and striking characteristic of radiation injury that although apparent recovery occurs among surviviors after exposure to a large single dose of about 400 rem, certain delayed effects may be observed in the years following exposure and recovery. Late changes have now been observed in survivors of a large dose of radiation to the whole body and they include the following: loss of hair, changes in texture and pigmentation of hair, cataracts, impaired spermiogenesis, anaemia and leucopenia and leukemia. It has been said that there is also, in man, a non-specific increase in the mortality rate (shortening of the normal life-span through diseases other than leukemia) but there is as yet no definite evidence for this from studies of atomic bomb survivors in Japan or of comparable groups.

50. Whole-body irradiation may, by randomly producing non-specific tissue changes, adversely influence all those disorders which commonly affect human beings and which ordinarily increase with age.

*Shortening of the life span*

51. All the major delayed effects discussed above will tend to diminish the average life-span. In addition, radiation may have the effect of accelerating the sequence of changes which constitute the "normal" process of ageing. Experiments on animals have demonstrated that whole-body exposure to doses that cause no early deaths and relatively few acute symptoms can, nevertheless, shorten the average life-span, and it is possible that the same may be true for man, although specific human evidence of this point is difficult to obtain. Observations in the United States on radiologists and others using X-rays, during the past twenty years or so, have thus far established an increased incidence of leukemia in this population, and have suggested further that there may be an increased total rate from other "non-specific" causes. Preliminary results of a survey of radiologists in the United Kingdom, however, show no evidence of shortening of life-span in this group as compared with other medical groups and control populations. The data from man and from laboratory experimentation relating to shortening and lengthening of the life-span are dealt with in annex G.

*Cancer*

52. Within a decade following the discovery of X-rays it became apparent that exposure to radiation carried with it the risk of malignant disease. The first evidence was that of cancer of the skin developing in severe radiation lesions of persons exposed occupationally or in the course of treatment. It has since been found that radiations of various types, external and internal, have induced or help to induce tumours in the blood-forming organs (leukemia), the skin and subcutaneous tissue, the skeleton (sarcoma of bone in radium poisoning), the lung (cancer of the lung in miners of radioactive ores), the thyroid and liver, for instance. Parallel experiments with animals have emphasized the general susceptibility of most tissues of the higher species to cancer induced by radiation.

53. In common with ultra violet rays and with a great variety of chemical agents known to produce cancer, exposure to ionizing radiation is followed by a long induction period before the appearances of malignant growths. In man, the induction period for cancer is often of ten to twenty years duration and it may be even longer. For leukemia the induction period appears to be shorter, and the disease more commonly develops between five and ten years after a single irradiation. It is impossible to estimate the induction time of tumours which occur "spontaneously" in man since their causes are unknown; but the common increase in cancer incidence during later life may indicate that long induction periods are characteristic for human tumours.

54. This induction period is characterized by general tissue changes as outlined earlier, such as destruction of cells followed by compensatory proliferation of new cells and deterioration in the nourishment of tissue due to defects in its blood supply. In the course of these changes, a general derangement occurs in the architecture of the affected tissue. Although the majority of radiation-induced tumours have originated in tissues so altered, the reasons for the increased frequency of cancer in such situations are unknown. Clinical experience suggests that malignant tumours are an infrequent and not an invariable or inevitable result of severe radiation exposure.

55. In certain cases, it has been shown that tumour induction occurs through the mediation of specific physiological or endocrine responses of the whole organism, rather than by specific radiation action on the cell. Such mechanisms are responsible for the induction by irradiation of tumours of the ovary and pituitary in mice. As another example, it has been shown that unirradiated thymic cells introduced into an irradiated host may become the origin of malignant tumours. Such indirect physiological mechanisms have not been demonstrated in man, but it is possible that they exist.

56. Clinical and experimental evidence show that where the total body is irradiated, leukemia is the most probable end-result among the various forms of malignant disease. Leukemia has been the predominant finding among the groups of radiologists studied. Although the relatively soft X-rays to which these men were presumably largely exposed produce more ionization in some calcium-rich areas than in the soft tissues, no increase in bone tumour incidence has been noted.

57. When the skeleton is selectively irradiated by radioelements such as radium, an increase in bone tumours is a prominent result. This is borne out by clinical studies of many persons who, twenty-five to thirty-five years ago, accidentally ingested radium in the process of painting watch dials or received it orally or by injection during inappropriate medical treatment. Cases are recorded in which tumours have arisen in patients who, after twenty or more years, retained between one-half and one microcurie of radium in the whole skeleton, implying an original intake of about one hundred times that amount; this delivered a total average dose to bones of about 2000 rads. Since most of this radiation was delivered by alpha particles, the average dose in rems would be considerably higher. However, some patients with a total radium burden of more than 10 microcuries after more than twenty years have not developed tumours although such individuals invariably show a sequence of destructive and proliferative changes in bone similar to those observed at the sites of origin of malignant tumours induced by radiation.

58. From experiments with animals it is clear that other radioelements which are deposited in the skeleton, e.g. plutonium, strontium-89 and -90 and various rare earth elements can likewise produce bone tumours and other tissue changes which have been observed in radium poisoning in man. While no such cases are recorded in human beings, this may be attributed to the fact that there have been no comparable human exposures to these radioelements. Experimental data suggest that bone tumour incidence can adequately be approximated on the basis of the dose in rems to the osteocytes. Experiments with mice suggest that ten microcuries of strontium-90 in the skeleton are equivalent in carcinogenic effect to not more than one microcurie of radium. In the one series of animal experiments which was designed to determine the dose-effect relationship for radiostrontium and bone tumour, the relationship appeared to be sigmoid; however, there is as yet no critical discrimination between interpretations in terms of a sigmoid, a linear, or a strictly threshold relationship.

59. Since tumours induced by radiations in man and various animals have arisen almost exclusively in damaged tissue, and since experiments have shown that there are levels of radiation below which no increase in the normal "biological background" of tumour incidence can be detected, it has been believed that there is a minimum (threshold) dose of radiation causing the induction of tumours. Such thresholds vary from organ to organ and with the age of the organism. Owing to limitations in experimental methods, including the lapse of time before tumours appear after application of cancer-inducing agents and owing to the "biological background" of spontaneous tumours, and the physical background radiation, the possibility remains that there may not be a true threshold. The situation would then be analogous to that obtaining in the case of genetic changes.

60. In accordance with the latter concept, it has been suggested that the tumour may have its origin through a mutational change in a single somatic cell; or alternatively, that the somatic mutation may be one of the events leading to tumour development. In its simplest form, the somatic mutation theory would postulate that each increment of radiation above the natural background would carry with it a proportional probability of tumour development (linear response). An upper estimate of the effect of radiation in causing tumours of bone can be obtained by the following consideration. If it were assumed that 10 per cent of all primary bone tumours were attributable to a natural radiation level of 9 rem per 70-year human life-time, and if it were assumed further that the natural frequency of these tumours is between 5 and 10 cases per million individuals per year, and that the increment from added radiation is a linear function of the response and that there is no threshold, then the increment from an addition of one rem per 70 years would be one-ninetieth of the natural incidence. Thus, in 70 years to an assumed 350 to 700 cases per million of population, an additional 4-8 cases would be added. This may be taken as the worst case; if a threshold exists for the induction of bone tumours which is higher than the assumed total radiation, then the increment would be zero. More complex mechanisms of cancer formation would be expected to lead to intermediate values.

61. In attempting similar predictions in the case of leukemia, it also seems reasonable to assume that not all leukemia is due to natural radiation, since there are other known causes in the environment and since human observations at high irradiation doses indicate a lower slope to the dose-incidence curve. Assuming that the increased incidence per rem would be 1.5 per 1 million per year for the rest of the lives of the exposed individuals, and considering the two limiting mechanisms as discussed in the preceding paragraph, we can derive the number of cases added to the natural incidence by 1 rem per 70 years (for a population of mean age 35) as 1.5 x 35, or 52 induced cases per million persons per 70 years (that is about 150,000 cases per 70 years in a world population of 3 thousand million), in the upper limiting case, and zero in the lower limiting case. The upper value would represent an increment to the natural leukemia incidence which is estimated at 1,400 to 3,500 per million per 70 years (or within the limits of four and ten million in the total population of the world). These are theoretical computations, and it is difficult to estimate the relative importance of radiation and other environmental factors in tumour induction in man.

## IV. Summary and conclusions

62. A large body of knowledge has accumulated during the last sixty years on the somatic effects of ionizing radiations on man and animals. This knowledge has come from numerous observations on human beings and from extensive experimentation with laboratory animals. In both cases, the effects of external and internal radiation have been studied and, although many of these effects are far from being understood in all details, our knowledge is sufficient to provide a general picture of the events that occur after human beings and animals have been exposed to ionizing radiations of all kinds. In general, the effects following exposure to relatively large doses are well known, whereas the effects of small doses are not understood nearly as well.

63. All types of ionizing radiations produce similar biological effects; these are usually not distinguishable from other pathological conditions. Some radiations, such as neutrons and alpha rays, are more efficient in producing certain types of somatic effects. Physical factors of exposure such as dose, dose rates and dose distribution are as important in determining the nature and extent of the biological effects as are the age and sex of the individual exposed and the part of the body that has suffered exposure. Radioactive isotopes produce harmful effects in those organs in which they are selectively retained. The extent of these effects depends on the physical characteristics of the isotopes, such as the half-life, and the type and energy of the radiations

emitted, as well as on the time of retention in a particular organ and the sensitivity of that particular organ to radiation injury. Absorption of measurable quantities of radioactive materials in human beings and animals has been demonstrated in recent years. Strontium-90, having a half-life of 28 years and being deposited selectively in bone, may be cited as an example to which particular attention must be given.

64. Exposure to relatively large doses of external or internal irradiation produces a variety of characteristic and well-known somatic effects which may occur either immediately or with a delay of a few days to several years. Certain organs, such as the blood-forming organs, the skin and the gonads, are particularly vulnerable to injury by ionizing radiations. Many of the acute effects, such as erythema of the skin and radiation sickness following whole-body exposure, have characteristic threshold doses. Similar thresholds exist for acute blood and bone disorders following ingestion of large amounts of radium and other radioactive materials.

65. The tissues of the embryo and foetus are among the most sensitive to radiation. Malformations and other pathological conditions have been observed following exposure of pregnant women to accidental and therapeutic irradiation and to diagnostic procedures, e.g. pelvimetry. Experimental work has demonstrated that radioactive materials, such as strontium and other soluble radionuclides circulating in the blood of the mother, can be absorbed and deposited in foetal organs such as the skeleton, where they may produce lesions.

66. As the dose of radiation is reduced below the amounts giving rise to acute functional or morphological alterations, the reactions of the organism become more difficult to detect immediately and the effects may be progressively delayed in time. Thresholds are not easily revealed under these conditions of exposure; in fact, for some of the most delayed phenomena, it is uncertain whether they exist.

67. It is a very characteristic feature of radiation injury that delayed reactions may occur many months or years following exposure. The morphological and functional alterations which occur during the long periods of latency are poorly understood. It has been shown that even after such periods acute manifestations of somatic effects may develop. Among the late effects, leukemia, bone cancer and other malignant changes are worthy of mention. It has been demonstrated that whole-body exposure can shorten the average life span of experimental animals, and it is possible that the same may be true for man.

68. Small doses of radiation given repeatedly can have a cumulative effect in those cases in which the processes of recovery and compensation are limited. It is not known whether sensitization occurs. The existence of adaptation in the broad biological sense of the term has not been proven.

69. In view of the present tendency of the levels of ionizing radiations to increase gradually, as a result of various influences, and on account of the life span of man, it is felt that along with measurements of these levels there should be continuing research on all aspects of the somatic effects of radiation. To ensure a thorough examination of all relevant factors, the Committee points out the importance of:

(*a*) Demographic studies of populations living in areas that differ in natural radiation levels with reference to effects perhaps attributable to these levels or to other environmental variables which might produce similar effects;

(*b*) Systematic studies, on a wide scale, of groups of persons who have received radiation for medical purposes;

(*c*) Continued and expanded experimental work on a wide range of experimental organisms regarding the late somatic effects of small amounts of external and internal radiation with particular emphasis on dose-effect relationships;

(*d*) The development of methods to serve as sensitive indicators of damage produced by exposure to small amounts of radiation;

(*e*) Expanded clinical and experimental studies on the nature of cancer and leukemia in connexion with radiation exposure, and on the basic cellular biological problems which may have bearing upon this;

(*f*) Increased opportunities for exchange of experience among experts engaged in all of these fields of research.

70. It can be anticipated that research in all of these fields will greatly benefit mankind. This will come about not only through a better understanding of the effects of ionizing radiations, but also through increased knowledge of malignant diseases and of the ageing process. At the present time, due to the fact that threshold doses for the delayed somatic effects of radiation are not exactly known, it must be recognized that the exposure of human populations to increasing levels of ionizing radiations may cause considerable and widespread somatic damage.

# Chapter VI
# GENETIC EFFECTS OF RADIATION

1. The inherited characteristics of man distinguish him from other species and in part determine the nature of each one of us. They have been accumulated over many generations. Experimental work on many organisms has shown that ionizing radiation can cause mutations, which are permanent, and for the most part deleterious, changes in the inherited characters. It therefore cannot be doubted that exposure of the germ cells of human beings to such radiations will occasionally cause similar changes and so, over many generations, affect individual descendants in populations yet unborn and never themselves exposed.

2. While some hazards are implicit in almost all technological advances, it must be remembered that inherited changes are an inescapable consequence of the irradiation of human populations, and that they affect at random persons who can seldom, if ever, be individually identified. They therefore pose ethical and legal problems which should be of special concern to Governments. This chapter is concerned both with mutation, especially in man, and with the consequences that can be expected from an increase in this process brought about by small general increases in the radiation exposure of human populations. Certain technical terms employed have already been described (chapter II, paragraphs 35-38).

## I. MUTATION

### *General*

3. Some facts about mutation have been so widely confirmed by experiments in other organisms that one can have every confidence in applying them to mutation in man as well:

(*a*) Mutations, once completed, are irreparable. The altered or mutant genes can be changed only by further mutational processes.

(*b*) Mutations arise at random in this sense: they are not brought about by that particular aspect of the environment toward which the mutant organism will subsequently show an altered response.

(*c*) The great majority of observed effects of mutations are harmful. The combinations of genes naturally present in the individuals of a species have been selected during very many generations; any random change has, therefore, little chance to be of immediate benefit.

4. Mutations may be roughly classified according to whether they are structural changes involving whole regions of the chromosomes, or whether they are so-called point mutations which apparently involve only single genes.[H2] The main problem for man is the effect of irradiation upon the cells of the germ-line from which eggs and sperm are later produced. In experimental studies of animals, gross chromosomal changes are more rarely observed among offspring conceived long after such irradiations than are point mutations: they are also comparatively rare at low doses. Hence, the mutations which are transmitted to future generations are principally the apparent gene mutations—point mutations and those minor re-arrangements and losses that behave like them.[H2] The effects of these small changes range from trivial variation or slight detriment to disturbances having serious effects on reproduction or even survival.

### *Natural mutations*

5. By natural mutations are meant those which result from conditions beyond our control in normal life, such as natural sources of radiation, thermal agitation and chemical processes within cells. Experimental studies of natural mutations in a wide range of organisms from the unicellular forms to the higher plants, insects and mammals, have indicated that mutation at any one specific gene locus is a very rare event.[H28] There is, however, a considerable variation in rates of mutation between various loci as well as between various organisms.[H24-28] The estimates of frequencies of appearance of new mutant genes for the mouse and for the fruit fly *Drosophila* mostly range between $10^{-5}$ and $10^{-6}$ per locus per tested gamete but, because natural mutation is a rare event, they are subject to large sampling errors and perhaps to some bias in respect of the group for which estimates are available. Frequencies as low as $10^{-9}$ per locus per cell have been observed in bacteria. In man, test matings cannot be employed to associate a given mutation with a specific locus and special methods, either direct or indirect, must be used to analyze the available material.

6. The direct method[H30] is restricted to the study of mutations to dominant genes, that is, to genes which are manifested in heterozygotes, and in a modified form to the study of mutations of genes located upon the chromosomes which determine sex. It is based upon direct counts of the number of sporadic and inherited cases of the condition under investigation. For single clinical entities the estimated frequencies of appearance of new dominant mutant genes mostly range between $4 \times 10^{-6}$ and $40 \times 10^{-6}$ per gamete. These values are supported by calculations using the indirect approach. It must, however, be remembered that a single clinical entity may be affected by mutation of any one of many genes.

7. The mutation rates for clinical entities due to recessive genes cannot be estimated by direct counting, but can nonetheless be calculated by an indirect method.[H31] This is based upon the hypothesis that there is in the population under study a genetic equilibrium at which as many new forms of genes are produced by mutations as are eliminated by subsequent failures of reproduction. An attempt is then made to estimate this last number. However, a possible slight advantage or disadvantage in heterozygotes may grossly affect the figures, which for this and other reasons are very uncertain indeed.[H32] To improve the accuracy of the estimates more information is needed about such selective pressures.

### *Radiation-induced mutations*

8. All the kinds of ionizing radiations which have been tested experimentally upon living organisms are able to induce mutations which are transmissible to the progeny, if energy is absorbed in the cells of the germ line.

9. It is of basic importance for any discussion of the genetic effects of radiation to establish the relationship between frequency of induced mutation and dose, and especially whether this relationship is linear at the lower dose levels. The Committee emphasizes that there is at present no known threshold of radiation exposure below which genetic damage does not occur. The experimental foundation for a linear dose relationship is fairly well established at moderate doses but is increasingly meagre at lower doses, terminating in one experiment upon *Drosophila* sperm at 25 rad.[H10] Experiments already planned or under way in the United Kingdom and in the United States will together test linearity over the range of doses from 37.5 to 600 rad for spermatogonial irradiation of the mouse.[H11] However, the range from 5 rad to 25 rad is of primary concern in discussing human hazards. If methods can be found in any organism to test linearity in the above range of doses, especially for gonial irradiation, this test should be carried out. In the meantime, it is prudent to assume at least as much hazard as is implied by a linear relation between mutation and gonad dose, as has been done in the present report.

10. In organisms other than man it has been confirmed that the mutational effect of a given dose is independent of its rate of delivery over a wide range. Moreover, it has been shown that there is no recovery from mutational damage with time in the mouse for periods up to two years after irradiation. The range of times investigated experimentally does not extend nearly as far as the breeding period of some thirty years involved in the chronic irradiation of human populations. Nevertheless, in the absence of evidence to the contrary, the Committee accepts the conclusion that the mutational effects of small doses of radiation delivered to the cells of the human germ line over long periods of time are cumulative. Hence, any irradiation of whole populations must be considered as having genetic consequences.

11. In a number of organisms there is good reason to believe that the radiation-induced mutational event is not completed at the moment of irradiation, but through subsequent physiological processes which may occupy some tens of minutes or even a period of hours. Aside from possible prevention beforehand, the opportunity to effect repair may therefore exist for a limited period after irradiation.[H12-13] The Committee considers that investigations directed towards the understanding and the possible eventual establishment of such opportunities should be actively pursued and supported.

12. The balance of evidence at present available suggests that mutations induced by ionizing radiations are in general similar in kind and effect to those of natural origin.[H16] In the present report it has therefore been assumed that this is so. Nevertheless, the Committee recognizes that further research is needed before we can be sure that radiation-induced mutations are not sometimes different qualitatively from those of spontaneous origin, and possibly more severe in their effects.[H17,18]

13. It will be seen below that, in order to estimate the hazards which arise from the irradiation of human populations, it is convenient to speak of the dose which would produce in a generation as many additional mutations as already occur naturally, called the "doubling dose".[H62] Particularly in view of the current acceptance of a linear relationship between dose and frequency of induced mutation, the Committee accepts the validity and practical usefulness of the concept of a representative doubling dose; that is, it accepts that a mean value properly averaged over a large class of human genes, in so far as it can be estimated, can be taken as a representative figure for the large classes of genes which together determine broad categories of damage in populations.[H62]

14. Any estimate in man of induced mutation rates of individual genes requires extremely difficult studies of very large numbers.[H46-58] In fact, completed surveys of the progeny of irradiated parents have failed to demonstate unequivocal changes, or increases in any clinical entities investigated.[H50-51] This very failure provides some reason to suppose that the representative doubling dose for human genes does not lie below 10 rad.[H71] However, in these surveys, small changes are rather consistently observed to occur[H50-51] in the directions expected to result from increased mutation rates. Taken together, these observed marginal changes do seem to establish the occurrence of phenomena expected to result from increased mutation: moreover, it seems somewhat unlikely that they would have been observed if the representative doubling dose for human genes exceeded 100 rad. The Committee therefore accepts as reasonably probable that the representative doubling dose for human genes lies in the range 10 to 100 rad, but for purposes of calculation the geometric mean (about 30 rad) is a convenient figure.[H73] The representative doubling dose for human gene mutations cannot in any event lie below about 3 rad, the magnitude of the genetically significant dose delivered in most areas by natural sources of radiation.[H72]

15. Any further narrowing of the limits upon the quantitative relations between dose and mutation in man, here expressed through the representative doubling dose, can come only from comparative surveys of the offspring of special irradiated and control groups. The phenomenon which comes closest to being established is a shift in the sex ratio at birth among the progeny of irradiated parents.[H50] To clarify this phenomenon and its interpretation, experiments on animals, especially mammals, are urgently needed in parallel with the continuation and extension of surveys relevant to radiation-induced genetic injury to man.

16. There is another approach to expressing the overall quantitative relation between radiation exposure and induced mutation in man. It is to ask the question: what total number of mutations is produced by a given exposure of a set of human genes to radiation? Because no direct observations of radiation-induced mutations in man have been made, an answer to this question can only be estimated by the very uncertain procedure of analogy with other species.[H74]

## II. Estimates of the effects of irradiation

17. It would be desirable to estimate the genetic effects of exposure to radiation in terms of "social consequences". However, such consequences are so diverse in their effects on the individual, on his family and on the community as to be impossible to express numerically. It is possible, however, to measure a number of components, the most satisfactory of which is, at present, the number of people more or less seriously affected by hereditary defects. An alternative measure, more directly related to the total mutation rate, can be expressed in terms of reductions in the capacities of individuals to survive and reproduce.[H82]

18. Even complete knowledge of the dose-mutation relations in man would not suffice to make useful estimates of the social consequences (in the sense of the preceding paragraph) resulting from a given exposure

of a population to radiation. Indeed, such estimates cannot be made with any given degree of completeness before the science of human genetics is equally complete. In the present state of knowledge, the Committee has chosen to approach the problem by inquiring successively as to: (*a*) the magnitude of the social consequences now laid upon human populations by unfavourable genes; (*b*) the proportion of this due to continually occurring gene mutation; and (*c*) the increase in gene mutation rates, expressed as a fraction of the natural rates, that can be expected from a given addition to the natural radiation exposure. Under certain assumptions these quantities may be multiplied together to yield a measure of the social burden resulting from a given population exposure.[H83] These assumptions are:[H85]

(i) That the part of the present genetic social burden due to recurrent mutation is related to the present natural rate of occurrence of mutations, through a balance between production and elimination of unfavourable mutant genes. In fact, the current rate of elimination of such genes must, through their present number and distribution, be related in a complex manner to the history of mutation and elimination in the population.

(ii) That the future environment will be sufficiently similar to the present one for the manifestation of the mutation to be generally the same then as now; in particular, that the relationship between the social consequences and the elimination of the mutant gene will not be significantly affected.

(iii) That the gene mutations brought about by irradiation are qualitatively the same as those of natural origin.

The Committee considers that assumptions (i) and (ii) are reasonable and accepts (iii) as an approximation.

## III. The social burden conferred upon populations by the presence of unfavourable genes, and the effects of increased exposure to radiation

19. One of the tasks of human genetics is to extend our knowledge of the part played by genetic factors in health and disease. This task is largely achieved by highly specialized examinations of affected individuals and their families and by studies of the children of closely related parents, of twins, and of whole populations. All research in this wide field is highly relevant to the problems discussed in the present report.

### *Genetic morbidity due to specific traits*[H88-94]

20. It is estimated that about 4 per cent of liveborn infants suffer or will suffer from detectable genetic traits of importance. However, it is only under certain conditions that the relationship between changes in mutation rate and changes in trait frequencies can be predicted. Specifically, it must be known that the trait frequency is largely determined by a balance between mutation and selection against the trait concerned: in general, this condition can be satisfied only for traits determined by simple genetic mechanisms, and usually by single mutant genes. In the liveborn, the total frequency of traits thought to satisfy both these criteria is probably not more than 1 per cent of all live births, including some traits whose effects are small.[H90] Most of the mutant genes concerned are dominant, although some are recessive.

21. In addition to these traits, there is a considerable number, affecting about 1 per cent of all live births,[H90] genetically determined by mechanisms which are by no means clear. In some, the environment of the embryo in the uterus appears to be of importance in determining whether they are expressed and there is some evidence to suggest that many genes modifying the process in a complex manner are involved. The cleft palate syndromes constitute a good example of this class. Such traits are concentrated in families, but seldom to any extent explicable by genetic theory based upon any simple mechanism.

22. The remaining 2 per cent fall into two groups of unequal size.[H90] Those of the smaller group do appear in families in the proportions to be expected from a simple theory of recessive gene transmission, but the over-all frequency of appearance, taken in association with extreme negative selection due to the severity of the traits, is too high to be explained entirely by a balance between mutation and selection—that is, unless mutation rates are postulated which are many times greater than those estimated either for dominant mutations in man or for genes studied experimentally in animals. An excellent example is fibrocystic disease of the pancreas. It may be noted here that many estimates of mutation rates to recessive genes would be very high if they were to be calculated on the assumption of a balance between mutation and selection against the traits concerned. Those of the larger group are illnesses, individually common and severe, which have been attributed by some to simple mutants modified in some way in their expression, but for which the extent and manner of genetic influence is uncertain and hard to determine. The best examples of this class are diabetes mellitus and schizophrenia. If the observed high frequencies of such traits are assumed to be due to a balance of mutation with selection, it is necessary to postulate mutation rates which seem quite unreasonably high; this is true especially if some degree of expression of the trait is common in heterozygotes.

23. Only in respect of the strictly limited category of traits first mentioned above (those determined by single genes), is it possible to predict with any assurance the effect of a given increment in the mutation rate.[H92] For all the other traits mentioned, any increment in mutation would eventually be reflected in some equal or lesser increment of trait frequency.[H92] Thus, a category of traits affecting some 1 per cent of all live births would be expected eventually to increase in direct proportion with any change in mutation rate maintained over sufficiently long periods. The remaining classes of traits discussed above, affecting some 3 per cent of all live births, would also be expected to increase but this increase would be less than proportional to the change in mutation rate, although the precise extent of it cannot at present be estimated. A permanent doubling of the mutation rate might therefore result eventually in an increase in the present 4 per cent of live births affected by something more than 1 per cent and less than 4 per cent; that is, the proportion affected would rise to between 5 per cent and 8 per cent.

24. The total number of individuals who will ultimately be affected by a given small increase of the mutation rate during just one generation is also calculable: it is equal to the extra number who would be affected in every generation under conditions of equilibrium with a mutation rate permanently increased to the same extent. However, the affected individuals making up this total number would be distributed in an unknown manner over many generations subsequent to that in which the temporary increase of mutation rate occurred.

25. These considerations do not take into account the effects of mutation on the so-called "biometrical" char-

acters considered in paragraph 27 and the succeeding paragraphs; moreover, they disregard the existence of a larger class of mutations to genes with relatively small effects known to occur in experimentally irradiated organisms. Such mutant genes, having individually less adverse effects upon survival and reproduction, would be expected to spread to more members of a population than those considered here, and might indeed constitute the major element in the over-all social consequences of a prolonged increase in mutation rate.

26. On the preceding basis, a simple calculation of the numbers of affected individuals can be made[H92] for a steady population of 1 million persons per generation and for each rad of continuous genetically significant exposure per generation. After reaching equilibrium (i.e. after many generations), the number of individual defects attributable to this one rad per generation would probably lie between 100 and 4,000 in each generation of a million persons, i.e. an increase in the number of affected persons of between 0.01 per cent and 0.40 per cent of the population. If the one rad dose were applied only once, to a single generation, a total number of individuals with defects between 100 and 4,000 would be expected, but they would occur spread out in an unknown manner over many subsequent generations. Much of the genetic damage occasioned by mutation takes a considerable time to appear in the form of affected individuals. If it is supposed that the world's population will be stabilized at $5 \times 10^9$ in the interim before current mutation is so expressed, and that the world population below the mean age of breeding is then about $2.5 \times 10^9$, the preceding figures become respectively 250,000 and 10 million in each generation after equilibrium is reached, and 250,000 and 10 million total, but spread out in an unknown manner over a long period subsequent to the irradiation. These calculations would apply to each rad from any source of irradiation affecting the whole population of the earth.

### *Biometrical characters*[H95-103]

27. Some human characteristics show a type of genetically controlled variation somewhat different from the all-or-none control by specific genes so far considered in this report. These characters can generally be measured in quantitative terms, and are therefore termed *biometrical*. They are determined by genes just like those previously discussed except that their effects are so small, or related to each other and to the environment in such a complex manner, that the effects of individual genes cannot be distinguished, and can only be studied collectively by statistical methods. Consequently, little is known experimentally of their mutations or other behaviour. Yet they are known to exert considerable effects on such important characters as life-span, birthweight, stature and intelligence. Both the average value and the extent of variations of such characters in a population may be influenced by its genetic constitution; and changes in both must be considered in relation to reproductive fitness as well as to their social consequences.

28. There are two questions of basic knowledge that are largely unanswered: (*a*) the extent to which the population average is determined by recurrent mutation rather than solely by a balance between selective forces,[H99-100] and (*b*) the fraction of the genetic component of variability that is due to recurrent mutation.[H97-98] The possibility cannot be excluded that for some characters the mutation rate is the primary factor in determining the average and the variability of the population. On the other hand, since influences such as environmental changes and possible over-all survival and reproductive advantage of heterozygotes may be decisive, the mutation rate may be comparatively unimportant. It must be borne in mind that a rather small number of genes, each maintained at a high frequency by a balance between different selective forces, may well have as large an influence on the mean and variability of the population as would a much larger number of genes each maintained at a lower frequency by a balance between recurrent mutation and selection.

### *Intelligence*[H102]

29. Intelligence is the character of greatest human concern. It is a biometrical character in so far as it is measured by the standard intelligence quotient. An increased mutation rate among the genes ordinarily determining the genetic variability of the intelligence quotient would tend to increase that variability. This would theoretically lead to an increase in the numbers of persons with high and with low intelligence quotients, although not necessarily equally. At the same time, by analogy with genes whose effects are large enough to be individually detectable and which are commonly found to interfere in a destructive manner with the biological structures or mechanisms primarily affected by them, it would be expected that new mutations would, in general, be such as to diminish the average intelligence quotient. Thus the most probable effect of an increased mutation rate would be to lower the average intelligence quotient, although there is not sufficient experimental basis for any judgement as to the amount of any such lowering.

### *Life span*[H103]

30. Correlations between relatives and studies of twins strongly suggest a considerable degree of genetic control over the life-span in man, so that mutation would be expected to have some effect upon it. A shortening of the life-span has been observed in the immediate offspring of male mice irradiated with fast neutrons. It is imperative that these studies be continued and extended, for until human data are available we must rely on results from experiments on animals. However, man and mouse are sufficiently different for quantitative extrapolation between the two species to be particularly uncertain. By analogy with the results on mice, a decrease in life-span in subsequent generations would be expected following an increase in mutation rate, but the amount of any such decrease is very uncertain. It should be understood that some of the factors that reduce life-span are the specific genetic diseases and abnormalities discussed earlier.

### *General fertility*[H82, 104]

31. With appropriate corrections for changes in population size, each unfavourable gene that arises by mutation in a population will be balanced by the elimination in a subsequent generation of a copy descended from it; otherwise the frequency of the mutant gene in the population would increase cumulatively. The means by which these eliminations are brought about is the reduced effective fertility of individuals. This can be thought of as a reduction in the chance that individuals, starting at the time of fertilization of the egg, will complete normal reproductive cycles. Thus, in a population in genetic equilibrium—that is, one in which the appearance of unfavourable genes by mutation is exactly balanced by elimination—the total of reductions in fertility could be estimated to a first approximation if all unfavourable mutations could be detected and counted.

32. Many calculations have been made concerning the

possibility of general reduced fertility as a consequence of increased mutation rate. In the light of these, the Committee considers that the human race appears to have sufficient reserve capacity for breeding to make the possibility of its slow extinction by reduced fertility of genetic origin due to doubling of the normal mutation rate by any mutagenic agent seem very remote.[H105]

### *Pool of unfavourable recessive genes*[H106-109]

33. Although not directly related to the social burden caused by mutation, the attempt to measure the total of unfavourable recessive genes per individual in the population is of great interest.[H106] This can be done, because matings occur between related individuals, such as cousins. There is a predictable chance that the offspring of such a mating will receive two identical copies of the same gene from a common ancestor, one copy through the mother and one through the father. If the gene has a visible effect and is recessive, it will show up in these homozygous progeny more often than in the population at large. In this way, it has been estimated that each individual in the general poulation carries on the average about one or at most three unfavourable recessive genes of a kind giving rise, when homozygous, to some specific detectable clinical entity.[H107]

34. It is also possible to estimate the over-all effect of unfavourable recessive genes by examining the vital statistics of cousin marriages. Although the available data are somewhat limited and inconsistent, it appears that the average individual may well contain a number of unfavourable recessive genes having a total effect equivalent to that of 3 to 5 genes, each of which would, if homozygous, cause failure to survive to maturity.[H107] Comparison of these two estimates, the specific and the general, can in principle give some indication of the proportion of the total unfavourable effect of recessive genes upon reproduction and survival that is mediated through specific clinical entities detectable at the present time. Because the specific conditions studied have an effect less extreme than total failure to reproduce, this proportion may perhaps lie in the neighbourhood of one-third or one-tenth.[H107]

## SUMMARY

### *Conclusions*

35. It is accepted that radiation-induced mutations are, in general, harmful and increase in direct proportion to the genetically significant exposure, even at very low dose levels; and that a dose of between 10 and 100 rads per generation would probably be required to double the natural mutation rate in human populations. About 4 per cent of all births are affected with hereditary disorders, some one-quarter of which appear to be at least largely determined by single gene differences. On this basis, an increase in the mutation rate would eventually result in a directly proportional increase in a part of this 4 per cent, amounting to more than one quarter but less than the whole of it. In addition, there would be some changes in other hereditary characteristics of a less sharply defined nature, but the probable extent of these and their importance cannot be assessed at the present time. The Committee concludes from the foregoing genetic facts that exposures to ionizing radiation should be reduced wherever possible, and that medical and industrial procedures tending to increase radiation levels to which human populations might be exposed should be carefully weighed as to such benefits or hazards as each may have.

### *Areas of uncertainty*

36. The chief uncertainties associated with an attempt to assess the consequences of a given increase in radiation centre around the following:

(*a*) The dose required to double the mutation rate, is, for the present, believed to be reliable only within a tenfold range.

(*b*) Any assessment of the present extent of hereditary defects in the population simply in terms of affected people is admittedly an incomplete measure of "social consequences", which can in any case vary from country to country with the social environment.

(*c*) The proportion of the hereditary defects which is maintained by recurrent mutation is not at all certain. In the absence of adequate and appropriate observations on the workings of selection pressures in man, present opinions have had to be based on essentially crude criteria.

(*d*) The possible extent to which irradiation would affect human biometrical characters, their range and mode of variation, is at present largely a matter of speculation.

(*e*) The effect of a future environment on the magnitude of the "social burden" is not known. Improvements in social, medical, and biological procedures which can be brought to bear on human populations might lessen the effects of some of the deleterious changes. However, such influences could also operate in the opposite direction. Therefore, we cannot predict how future changes in environment will interact with any hereditary alterations so as to influence the general and the individual states of health in future human populations.

### *Indications for research*

37. Although much is known, quantitative estimates of the mutational consequences of genetically significant irradiation of human populations remain subject to grave limitations, especially in the areas just outlined. These limitations underlie several of the recommendations for genetical research made by a study group of the World Health Organization in a report submitted to this Committee and now published. The Committee draws the attention of the General Assembly to these recommendations, and, in particular, to the following areas of research:

(*a*) Studies of children whose parents have received substantial radiation exposure, together with investigations of natural mutation rates in man;

(*b*) Studies of the reproductive patterns both of diverse human populations and of carriers of detrimental genes;

(*c*) Studies relevant to the genetics of biometrical characters in man, such as intelligence or life-span, and of balanced selective systems in general;

(*d*) Any other studies which shed light on induced or natural mutation rates in man or in cells of human tissues;

(*e*) Studies on the production by ionizing radiation, especially at low doses, of mutations and related events in a variety of materials but particularly in the cells of mammals;

(*f*) Studies of the effects of irradiation on whole populations;

(*g*) Studies of the mutation event itself, including the time and manner in which the mutational process can be influenced;

(*h*) Comparative studies of the mutations which occur naturally and those which are induced by different ionizing radiations.

38. Certain measures would expedite the needed research on human populations: extended support of the existing research institutes for human genetics, to make possible the undertaking of long-term research programmes, development of new research centres as competent specialists become available, and collaboration with human geneticists by agencies dealing with vital statistics, public health, and demography with a view to making their data more accessible and suitable for genetic analyses. The lines of research pursued must, however, cover a very wide range; experimentation on a variety of plants and animals is essential and is complementary to work on man.

# Chapter VII
# SUMMARY AND CONCLUSIONS

1. In estimating the possible hazards of ionizing radiation, it is clearly necessary to know both the levels of such radiation received by man and his environment from various sources, and the present and future effects likely to be produced thereby. It is of particular importance to assess the effects of radioactive fall-out from nuclear weapons, since this source of general environmental contamination is of recent origin, has been of uncertain significance, and has led to concern in the minds of many people. All sources of radiation must, however, be reviewed for a complete evaluation of the situation.

2. The Committee, aware of the complexity of this task, knows that our present information about radiation levels and effects is inadequate for an accurate evaluation of all hazards, and that many of the estimates will necessarily be approximate or tentative.

3. The physical characteristics of ionizing radiation, and the amounts of human exposures to it, are at present more accurately known than its biological consequences, especially where small doses and dose rates are concerned. In the present chapter, therefore, we review first the amounts of radiation received by man, both in regard to the exposure of individuals and of whole populations, and in respect to present and possible future levels. We then attempt to estimate the biological effects of varying amounts of radiation of different types, and to evaluate the hazard resulting from certain sources of particular significance.

4. The relevant physical data refer to the world's population as a whole, as well as to individuals and groups of people receiving relatively higher exposures because of their occupation or place of living. These exposures may involve the whole body uniformly, or may be greater for certain organs or tissues, as when radioactive material is selectively concentrated in them.

5. Tissues of the embryo, of the bone and bone marrow, and of the gonads are of particular importance. Irradiation of the embryo (and of the foetus) may lead to abnormalities of development or may prove fatal. Irradiation of bone marrow and of bone may give rise to leukemia and to bone tumours, and these tissues are subjected to higher doses than other tissues of the body by radioactive materials such as strontium-90 and radium which become concentrated in bone. Irradiation of the gonads is able to bring about changes in the hereditary material; and these may be transmitted to subsequent generations if the irradiation is received before or during the years of reproductive activity.

6. As with any scientific assessment, the conclusions of this report must be subject to revision in the light of advancing knowledge; and the Committee hopes that the report itself, after submission to the General Assembly, will assist this advance by stimulating critical discussion amongst scientists. In view of the complex nature of the subject, individual sentences or assessments may easily be misunderstood unless related to the context of the report as a whole.

## I. Levels of radiation

7. Table I summarizes our estimates of the average amounts of radiation likely to be received by populations during specified periods, and gives the basis for a comparison between the amounts received from natural and artificial sources. The method of calculation is described in chapter III, the averaging periods of 30 and 70 years being used as relevant respectively to transmissible genetic changes and to somatic injury during the lifetime of an individual. The estimates for medical examinations and occupational exposures are based upon the present situation in certain countries with developed facilities, rather than on a forecasted world average. The values quoted for various hypothetical future circumstances are not intended as predictions, but are calculations based on assumptions discussed in chapter III, and the values and ranges are subject to all the uncertainties outlined there.

### *Radiation from natural sources*

8. The radiation received by man from natural sources varies somewhat from place to place according to the local radioactivity of the earth's surface; and that of only occasional populated areas exceeds the average by a factor of 10. Studies on populations living in these areas are of extreme interest for the development of our knowledge on the effects of small doses of radiation. The contribution from cosmic rays differs at different altitudes and geomagnetic latitudes. That from the normal radioactive potassium and carbon content of the body is about the same in different people, but the radiation due to radium, thorium and their decay products varies considerably. The radioactivity of the masonry used for some types of dwelling may appreciably increase the radiation exposure of the occupants. The variations in levels of irradiation from natural sources are discussed in chapter III; the magnitude of these variations, as well as of the average level, is informative in making comparisons with exposures due to artificial sources. Harmful effects attributable to radiation from natural sources are not known with any certainty, but it seems likely that some genetic, and possibly some somatic, injury is caused in this way.

### *Exposure due to medical procedures*

9. It is useful to estimate this exposure, appropriately averaged over whole populations, since the genetic, and perhaps some somatic, effects of these procedures will depend upon this average value. In the countries with extensive medical facilities where its magnitude has been estimated, the radiation given for medical purposes makes the largest artificial contribution to the irradiation of the population, but no data are available for countries with fewer such facilities. The reported values of genetically significant doses are of the same order as the doses from natural sources. Among medical procedures, the contribution from diagnostic X-ray examinations greatly exceeds that from radiotherapy and radioisotope applications, the latter making only a small contribution; and

TABLE I. ESTIMATED DOSE FROM DIFFERENT RADIOACTIVE SOURCES
*(Computed from world-wide averages)*

| *Source* | *Genetically significant dose Maximum for any 30-year period (rem)*[D115] | | Per capita *mean marrow dose Maximum for any 70-year period (rem)*[D122] | | | |
|---|---|---|---|---|---|---|
| Natural sources | 3 | | 7 | | | |
| Man-made sources (except environmental contamination and occupational exposure)[a] | 0.5–5 | | Ranges beyond 7 | | | |
| Occupational exposure[b] | Less than 0.06 | | 0.1–0.2 | | | |
| Environmental contamination (hypothetical cases)[c, d] | | | *Estimates for countries deriving most of dietary calcium from milk*[e] | | *Estimates for countries deriving most of dietary calcium from rice*[e] | |
| Weapon tests cease at end of 1958 | 0.010 | | 0.16 | | 0.96 | |
| | *Assumption a*[f] | *Assumption b*[f] | *Assumption a*[f] | *Assumption b*[f] | *Assumption a*[f] | *Assumption b*[f] |
| Weapon tests continue until equilibrium is reached in about a hundred years[g] | 0.060 | 0.12 | 1.3 | 2.8 | 7.5 | 17 |
| | *Estimated percentages of the maximum doses for continued weapon tests* | | | | | |
| | *Assumption a*[f] | *Assumption b*[f] | *Assumption a*[f] | | *Assumption b*[f] | |
| Weapon tests cease | | | | | | |
| 1958 | 17 | 9 | 13 | | 6 | |
| 1968 | 42 | 33 | 24 | | 16 | |
| 1978 | 64 | 56 | 34 | | 26 | |
| 1988 | 79 | 67 | 42 | | 35 | |
| Weapon tests continue | 100 | 100 | 100 | | 100 | |

[a] For countries having an extensive use of the radiation sources listed and reporting data to the Committee.

[b] Doses for certain technologically highly developed countries only.

[c] Computed from population weighted world-wide average of stratospheric fall-out rate and deposit.

[d] Regional values may differ by a factor of about ⅓ to 2 from the estimated population weighted world-wide average values because of the latitudinal variation of fall-out rate and deposit. In some areas of the world the tropospheric fall-out may tend to raise the upper limit of this range, especially in the vicinity of test sites.

[e] The extent to which these estimates apply to populations of different dietary habits and to those living in areas of differing soil conditions is discussed in paragraph 69 of chapter III.

[f] Assumption *a* is that the injection rate is such as to maintain a constant fall-out rate of strontium-90 and caesium-137, whereas assumption *b* is that weapon tests equivalent in release and stratospheric injection of fission products to the whole sequence of weapon tests from the beginning of 1954 to the end of 1958 will be repeated at constant rate. This second assumption will give an equilibrium value for the fall-out rate and deposit approximately a factor of 2 higher than that calculated by using the first assumption.

[g] The values for the 30-year doses have been corrected for tropospheric fall-out in accordance with paragraph 57 of chapter III, using a value of 0.5 mrem/year for the period of testing.

80 to 90 per cent of the total diagnostic dose to the gonads is due to relatively few types of examination of the abdomen and pelvis.

10. Most of these values are preliminary estimates, and further investigations are needed, for which procedures have been suggested by the International Commissions on Radiological Protection and on Radiological Units and Measurements in a report prepared at the request of this Committee and submitted to it in document A/AC.82/G/R.117.

11. The significant dose to bone and bone marrow from medical procedures has been less closely studied than the genetically significant dose, although it may be of importance if bone tumours or leukemia are induced by radiation at low dose levels. Although individual marrow exposures vary very widely, the average is unlikely to differ greatly from that received by the marrow from all natural sources.

12. The contribution made by medical procedures to the radiation exposure of populations has only lately been estimated and has increased very rapidly in some countries in recent years, so that it is difficult to evaluate such genetic and somatic effects as are associated with an increasing employment of radiological procedures in medicine. No information is yet available for prediction of the future trend of medical exposures. It is expected that improvements in equipment and techniques may considerably reduce individual exposures, but the ever-expanding use of X-rays may well increase the world population dose. Precautions of the type described by the International Commissions on Radiological Protection and on Radiological Units and Measurements should make possible such reduction of exposure to radiation as is without detriment to the medical value of these procedures.

### *Occupational exposure*

13. At present, the exposure to ionizing radiation received occupationally forms only a small contribution to the total irradiation of the population as a whole, amounting to about 2 per cent of that from natural sources in countries in which occupational exposure is probably largest. With an increasing use of nuclear reactors, of radioactive materials and probably of medical and industrial radiological procedures, this is clearly a figure which should be kept under close review. Although this source does not appear likely to make a substantial contribution to the total radiation exposure of populations in the immediate future, the occupational exposure of some individuals may represent a large fraction of their total radiation exposure.

14. Since 1928, the International Commission on Radiological Protection has recommended "maximum permissible doses" for those who are occupationally exposed to radiation, and has proposed appropriate methods of measurement. Their present recommendations, which have recently been reviewed in the light of progress in radiobiological knowledge and which propose reductions in dose levels, may not be final but are at present widely accepted as a sound basis for the protection of those exposed occupationally to ionizing radiation.

*Radioactive wastes*

15. The discharge of radioactive waste in countries with nuclear reactors has not led to appreciable radiation exposure of populations, and only small proportions of the wastes produced need to be discharged. The likely future extension in the use of such reactors, however, and the possibility of accidental releases of fission products, clearly require that this subject be kept under review. It is important that work should be actively continued on methods of minimizing environmental contamination from these causes.

*Radiation from fall-out*

16. Fall-out from nuclear weapon tests causes radiation exposure in several ways (chapter III). Exposure of the world population results from the slow fall-out of fission products which have been distributed in the stratosphere. Exposures also result from any fall-out from the radioactive "cloud" which passes through the troposphere without having reached the higher stratosphere, and from the fall-out which may occur in areas adjacent to weapon tests or within some thousand kilometres of them.

17. We also consider the ways in which fall-out material causes irradiation to different parts of the body, to people on different diets or under different agricultural conditions, and to people of different ages; and the change in the amounts of radiation that would result from altered or unaltered rates of injection of radioactive materials into the stratosphere.

*Fall-out adjacent to tests*

18. The early fall-out of radioactive materials near to the sites of nuclear explosions, which is influenced by various meteorological and testing conditions, may cause high radiation exposure to individuals within these areas. The amount of such radiation exposures varies very greatly with the weapon tested, with the height of firing, with the distance from the point of explosion, with the direction of winds at various altitudes and with the chance occurrence of rainfall through radioactive material in the early hours after the test. Therefore, at present, these doses cannot in general be calculated. Under very special conditions, high radiation exposure and deleterious effects have been reported, as in the cases of the Marshall Islanders and the crew of a Japanese fishing vessel. Not enough information is available as to the general circumstances in which such local deposition may occur, and the extent and duration of the exposures liable to be involved.

*Fall-out from the troposphere*

19. Radioactive materials injected into the atmosphere below the tropopause (at about 14 km) are brought down to the earth's surface by rainfall and sedimentation. This process takes a few months during which they are carried several times around the world. This tropospheric fall-out consists of a mixture of radioactive materials, most of which are short-lived isotopes. At the present time, the tropospheric fall-out is deposited intermittently during the year and a certain deposit of short-lived activities is built up and maintained. When appropriate factors for shielding and weathering effects are included, the gonad and average marrow dose from this deposit, as an external source, is calculated to be about 0.5 mrem per year.

20. Transient increases of the doses from tropospheric fall-out have been observed in limited areas shortly after weapon tests. These transient increases may give rise for a few days to dose rates of the order of those from natural sources.

21. The radioisotopes of tropospheric fall-out may be taken up into the body by inhalation and ingestion. Since the radioisotopes of principal concern are short-lived, storage of the contaminated food products reduces the dose which they contribute. The gonad dose over the whole population from inhaled and ingested tropospheric material is negligible as compared with the contribution from this material as an external source. The average bone marrow dose from internal sources is about 0.2 mrem per year.

22. Increases in radioactivity of the thyroid gland have been found during periods of several weeks or a few months following weapon tests. In human thyroids a dose from iodine-131 of about 5 mrem per year has been estimated for 1955-1956 in the United States excluding areas immediately adjacent to weapon test sites. Doses of this order are unlikely to cause detectable damage or functional change in the gland.

23. Irradiation of bone may result from incorporation of intermediate and short-lived fission products. Although these materials do not cause prolonged irradiation, they may become selectively concentrated into those areas of bone in which active growth is taking place at the time, and so cause more intense radiation locally than if the same amounts of these materials were distributed throughout the whole skeleton.

24. The Committee has insufficient information on local variations and temporary increases of tropospheric fall-out in populated areas at different distances from weapon test sites, and emphasizes the lack of further data which would permit evaluation of the biological significance of this source of environmental contamination.

*World-wide fall-out from the stratosphere*

25. Radioactive materials injected into the stratosphere, especially by high-yield nuclear explosions, constitute a reservoir from which they fall onto the whole of the earth's surface for many years. The rate of fall-out varies with latitude and is greater in the northern hemisphere, where most of the tests are carried out. Within any given small area, fall-out rate may also vary with local meteorological conditions. The figures given in table I are computed from world-wide average deposits from stratospheric fall-out. The radiation due to stratospheric fall-out from weapons exploded so far will contribute a 30-year gonad dose of 10 mrem, and a 70-year *per capita* mean marrow dose of 160 mrem and 96 mrem for two populations deriving most of their dietary calcium from milk and rice respectively.

26. Owing to the relatively gradual fall-out from the stratosphere, most of the subsequent radiation is due to two radioactive isotopes of slow decay, other fissio

products already having largely undergone decay. These two radioactive isotopes are caesium-137 and strontium-90. The physical properties and chemical behaviour of the two differ.

27. Caesium-137 is responsible for most of the gonad radiation from fall-out noted in table I. When it is taken into the body, it becomes distributed more or less evenly throughout the tissues, causing uniform irradiation of the whole body; and when present in the surroundings, its penetrating gamma radiations cause a similarly uniform irradiation of tissues.

28. Strontium-90, on the other hand, is not a gamma-emitter and does not contribute significantly to the irradiation of any part of the body from without. However, on being taken into the body, it becomes incorporated in bone because of its chemical similarity to the normal bone-forming element calcium. This similarity with calcium and selective concentration in bone raises problems which do not occur with caesium-137.

29. The average concentration of strontium-90 in the bones of children, in whom new bone is continuously being formed, is higher than in adults whose bones were largely formed before the environment, and consequently the food supply, became contaminated with strontium-90. The highest concentrations of strontium-90 in bone have in fact been observed in children from a few months to five years old. The bone marrow exposures from fall-out given in table I are due to the strontium-90 content of bone and refer to the concentrations estimated for children of these ages. The corresponding exposures of bone cells from fall-out are, on the average, about three times the values for bone marrow. Marrow cells almost enclosed by bone would receive doses similar to those in compact bone. The maximum marrow dose could differ by a factor of about 5 from the average level.

30. The radiostrontium concentration in bone is also affected by dietary habit and by the ratio of the amounts of strontium-90 to calcium in the diet. At present this ratio differs in various dietary constituents; it is higher in brown rice than in white, somewhat higher in many vegetables than in milk products, higher in rain-water than in river water, and lower in sea fish than in fresh-water fish.

31. Agricultural conditions may also affect the content of strontium-90 in the diet, since the available calcium of the soil will, within certain limits, influence the ratio of strontium-90 to calcium in crops derived from the soil. The distribution of soils which are highly deficient in calcium and their utilization require further study. More work is also needed to understand the distribution of strontium-90 in the soil, its chemical availability to plants and uptake through their roots, its behaviour under ploughing and the leaching of it from soil by the action of water, since the figures in table I for future strontium-90 levels in bone are calculated on the assumption that this material will not be leached from soil, and this assumption may lead to unduly high values.

32. Bone marrow exposures from fall-out are given in table I for two conditions: one based on observations in the United States of America and the United Kingdom, where milk is the main source both of dietary calcium and of strontium-90, and where soil calcium contents are commonly high; and the other based upon data from Japan where milk products are much less used and where rice and other vegetable products form the main source of dietary calcium and strontium-90, and where low calcium soils are frequent. These two estimates demonstrate the present range of known dietary contaminations. They will be used in an attempt to estimate the hazard of radiation from fall-out in paragraph 57 below, when the nature and frequency of the biological effects of radiation have been considered.

33. It is evident that the radiation exposures from fall-out which are most likely to be of significance are:

(*a*) Those from short-lived fission products and radioactive material due to local or tropospheric fall-out;

(*b*) Those of the gonads and other organs from caesium-137 due to stratospheric fall-out;

(*c*) Those of bone and adjacent tissue from strontium-90 which also comes largely from the stratosphere. The relative importance of these contributions varies from region to region.

## II. Biological effects of radiation

34. The biological effects of ionizing radiation are exhibited in different ways according to whether isolated cells, tissues, organs or organisms are examined. In passing from unicellular to higher organisms, the primary physicochemical consequences of radiation become increasingly influenced by secondary effects due to the reactions of the organism to the primary events. Detailed knowledge of these reactions is needed for a full understanding of the results and mode of action of radiation. The following paragraphs deal first with the cellular effects of radiation; then with the somatic effects on the irradiated individual and with the genetic effects on his progeny.

35. The effects of ionizing radiations on living matter are extremely complicated, and their exact mechanisms are still largely unknown. The initial disturbance is associated with ionization (and excitation) of molecules which lead to alterations in their properties. Many functions of the cell are thus affected by radiation, and, although some specific effects may be caused by one or a few events in the cell, many are probably the combined result of numerous such events.

36. The minimum doses causing certain detectable biological effects differ very much in different organisms, but for most mammals they are of about the same magnitude, so that the results of experiments on such animals can, as a first approximation, be applied to man. The sensitivity of different tissues to radiation varies considerably, however. Our knowledge of the biological effects of low radiation levels is meagre because of experimental difficulties and the lengthy observations necessary to obtain results in this field. At present, opinions as to the possible effects of low radiation levels must be based only on extrapolations from experience with high doses and dose rates.

### *Effects of radiations on man*

37. Man may prove to be unusually vulnerable to ionizing radiations, including continuous exposure at low levels, on account of his known sensitivity to radiation, his long life, and the long interval between conception and the end of the period of reproduction.

38. Embryonic cells are especially sensitive to radiation, and some evidence suggests that exposure of the foetus to small doses of radiation may result in leukemia during childhood. Irradiation of pregnant mammals has shown that doses exceeding 25 rem to the foetus during

certain stages of its development can cause abnormalities in some organs. Some embryonic cells (neuroblasts) of certain species cultivated *in vitro* respond to doses as small as 1 rad. If these results should be applicable to man and since they relate to the development of the brain, the opinion seems justified that even a very small dose to the human foetus may involve some risk of injurious effects if received during a critical period of pregnancy. Radiostrontium must be expected to enter foetal bone when calcification starts in the second trimester of pregnancy, and so cause irradiation of the adjacent developing nervous system and hypophysis with exposures ranging up to that occurring in the bone. The uptake of radiostrontium in foetal bone tissue is, however, at present very small, contributing less radiation than 1 per cent of that due to natural sources; but if the present rate of test explosions is continued, it will rise ultimately to some 10 per cent of that due to natural sources.

39. Children are regarded as being more sensitive to radiation than adults, although there is little direct evidence on this subject, except for an indication that cancer of the thyroid may result from doses of a few hundred rad which do not induce this change in adults.

40. In human adults it is difficult to detect the effect of a single exposure to less than 25 to 50 rem, or of continuing exposure to levels below 100 times the natural levels. The first sign of radiation damage to the blood-forming tissues seems to be a drop in the number of lymphocytes and platelets and the appearance of abnormalities such as bilobed lymphocytes.

41. Rapid but transient disturbances have been observed in mammals after exposure to a single dose of 25 to 200 mrem. Appropriate biochemical and physiological techniques have, however, only recently been applied to the study of irradiated organisms, and have not yet given a clear picture of what happens to organisms irradiated with small doses or dose rates. Too few mammalian species have hitherto been studied in this respect, and there is a clear need to widen this basis, from which inferences can be drawn concerning man.

42. Processes of repair play an important role in the final outcome of radiation damage. They are one cause of the existence of a threshold dose (or dose rate) characterized by the fact that this dose or greater ones produce a particular biological effect which does not appear when the dose is less than the threshold. In the latter case, physicochemical events have occurred, but recovery processes have prevented the final appearance of the biological damage. Threshold doses are found for some somatic effects, such as erythema of skin. Other forms of radiation damage to cells, tissues or organisms, however, appear to be cumulative; for instance, mutational damage, once established, is not repaired.

43. Damaged cells or tissues may be eliminated and replaced by regenerated normal cells, this process being most active in embryos and young animals and in certain tissues of the adult. The affected cells may also re-establish apparently normal biochemical functions. During the process of regeneration of tissues damaged by radiation, malignant tumours may be induced.

44. The power of repair differs considerably in different organisms and types of cells, and varies to a high degree with the physiological conditions. No chemical treatment has yet been discovered which will induce or accelerate recovery from radiation damage in man. The grafting of blood-forming tissue has so far been successful only in small mammals irradiated with a lethal dose to the whole body, and no attempt to apply this treatment to irradiated man has yet been reported.

45. Prevention of the effects of radiation is rendered more difficult, and complete protection against it impossible, because changes which already occur during the irradiation lead to later damage. The discovery of chemical protectors, although important theoretically, has not yet yielded methods which appreciably reduce radiation damage in man. At present, effective protection from external radiation sources can only be achieved by adequate shielding or by keeping at a safe distance from the source. Much work is in progress on the effect of certain (chelating) agents in discharging from the body radioisotopes incorporated there, and so diminishing exposure to internal irradiation.

46. Morphologically recognizable damage may be induced by total or partial, continuous or intermittent irradiations much in excess of the currently accepted "maximum permissible levels" of occupational exposure. Such damage includes leucopenia, anemia and leukemia. Other pathological conditions such as cataract, carcinoma of the thyroid, and bone sarcoma are known to have resulted from partial body irradiations, but with rather high doses involving hundreds or even thousands of rem given to these organs.

47. The shortening of the life-span in small rodents exposed to large doses has suggested the possibility that certain degenerative processes may be aggravated by continued exposure to low radiation levels. Such a shortening has also been inferred from an analysis of the published death rates of United States radiologists compared with those of certain other groups of medical men. However, studies in the United Kingdom have failed to demonstrate such an effect.

48. Present uncertainty about the effects of low dose levels makes it imperative that as much relevant information as possible be collected about groups of persons chronically exposed at these levels and for whom adequate control groups exist, for instance, certain populations in areas of high natural radiation and workers in uranium mines.

49. Exposure of gonads to even the smallest doses of ionizing radiations can give rise to mutant genes which accumulate, are transmissible to the progeny and are considered to be, in general, harmful to the human race. As the persons who will be affected will belong to future generations, it is important to minimize undue exposures of populations to such radiation and so to safeguard the well-being of those who are still unborn.

50. The present assumption of the strictly cumulative effect of radiation in inducing mutations in man is based upon some theoretical considerations and a limited amount of experimental data obtained by exposure of experimental organisms to relatively high dose levels. This assumption underlies all present assessments of the mutational consequences of irradiation. Therefore, extension of the experimental data to the lowest practicable dose levels is needed.

51. The knowledge that man's actions can impair his genetic inheritance, and the cumulative effect of ionizing radiation in causing such impairment, clearly emphasize the responsibilities of the present generation, particularly in view of the social consequences laid on human populations by unfavourable genes.

52. Besides increasing the incidence of easily discernible disorders, many of them serious but each comparatively rare, increased mutation may affect certain universal and important "biometrical" characters such as intelligence or life-span. In this way, it is possible that continued small genetically significant exposures of a population may affect, not only a correspondingly small number of individuals seriously, but also most of its members to a correspondingly small extent. While less easy to detect, this second kind of effect on a population could also be serious. Unfortunately, the great majority of the genes affecting the "biometrical" characters are not individually detectable and so can only be studied collectively and with difficulty. In consequence, far less is known about them than about genes responsible for individually detectable changes and very little indeed about their response to irradiation, even in the best-studied experimental organisms. Hence it is impossible, at the present time, to estimate with any assurance the effect upon biometrical characters of any given level of irradiation of human populations. Much further research throughout this field is therefore needed.

53. The Committee emphasizes the urgent necessity for well-planned investigations which may lead to a better understanding of the mechanism of mutation and the eventual possibility of controlling this process. More information is needed on the effect of radiation in inducing mutations in man. Indeed, even the dose required to double the normal mutation rate in man is not known with any accuracy. There is also need for a much closer co-operation between geneticists and demographers in elucidating the nature of the complex process of human selection. Many important subjects of relevant genetical research have been reviewed by a study group of the World Health Organization in their report "Effects of Radiation upon Human Heredity", document A/AC.82/G/R.58.

## III. General conclusions

54. The exposure of mankind to ionizing radiation at present arises mainly from natural sources, from medical and industrial procedures, and from environmental contamination due to nuclear explosions. The industrial, research and medical applications expose only part of the population while natural sources and environmental sources expose the whole population. The artificial sources to which man is exposed during his work in industry and in scientific research are of value in science and technology. Their use is controllable, and exposures can be reduced by perfecting protection and safety techniques. All applications of X-rays and radioactive isotopes used in medicine for diagnostic purposes and for radiation therapy are for the benefit of mankind and can be controlled. Radioactive contamination of the environment resulting from explosions of nuclear weapons constitutes a growing increment to world-wide radiation levels. This involves new and largely unknown hazards to present and future populations; these hazards, by their very nature, are beyond the control of the exposed persons. The Committee concludes that all steps designed to minimize irradiation of human populations will act to the benefit of human health. Such steps include the avoidance of unnecessary exposure resulting from medical, industrial and other procedures for peaceful uses on the one hand and the cessation of contamination of the environment by explosions of nuclear weapons on the other. The Committee is aware that considerations involving effective control of all these sources of radiation involve national and international decisions which lie outside the scope of its work.*†

55. Certain general conclusions emerge clearly from the foregoing part of this report:

(*a*) Even the smallest amounts of radiation are liable to cause deleterious genetic, and perhaps also somatic, effects.

---

*The USSR submitted a draft proposal for paragraph 54 which, as amended by Czechoslovakia with the agreement of the USSR, read as follows:

"The scientific information received by the Committee indicates that the genetic effects of radiation must be considered reactions for which there is no threshold. This means that any increase in the exposure of the human organism to radiation will lead to an increase in the incidence of hereditary diseases. According to one body of scientific opinion, malignant neoplasms and also leukemias are diseases the incidence of which may increase as the level of radiation rises. These data, together with the fact that there is very little likelihood that the human organism can adapt itself to conditions of increased environmental radiation, indicate that any increase in the radiation dose above the natural radiation level must be considered undesirable for mankind. Efforts should accordingly be made to improve the physical basis and the technique of the medical use of radiation by formulating more precise indications for the use of radiation and by eliminating adverse side effects. It is also essential to develop, on the basis of broad international co-operation among scientists, research on the improvement of protection and safety techniques in atomic industry and in science and technology. The physical and biological data presented in the report make it plain that efforts should be made to eliminate the uncontrolled source of radiation, i.e., to end experimental nuclear and thermonuclear explosions, and enable the Committee to draw the conclusion that there should be an immediate cessation of test explosions of nuclear weapons."

This proposal was rejected by the following roll-call vote:

*In favour:* Czechoslovakia, Union of Soviet Socialist Republics, United Arab Republic.

*Against:* Argentina, Australia, Brazil, Canada, France, Japan, Mexico, Sweden, United Kingdom of Great Britain and Northern Ireland, United States of America.

*Abstaining:* Belgium *(Chairman)*, India.

The above text expresses the dissenting view of Czechoslovakia, the United Arab Republic and the USSR to the wording of paragraph 54, which was approved by a majority of the Committee.

†India also submitted a draft proposal for paragraph 54 which, with amendments accepted by India, read as follows:

"The exposure of mankind to ionizing radiation at present arises mainly from natural sources, from medical and industrial procedures, and from environmental contamination due to nuclear explosions. The industrial, research and medical applications expose only part of the population while natural sources and environmental sources expose the whole population. The artificial sources to which man is exposed during his work in industry and in scientific research are of value in science and technology. Their use is controllable, and exposures can be reduced by perfecting protection and safety techniques. All applications of X-rays and radioactive isotopes used in medicine for diagnostic purposes and for radiation therapy are for the benefit of mankind and can be controlled. Radioactive contamination of the environment resulting from explosions of nuclear weapons constitutes a growing increment to world-wide radiation levels. This involves new and largely unknown hazards to present and future populations; these hazards, by their very nature, are beyond the control of the exposed persons. The physical and biological data contained in the report lead to the conclusion that it is undesirable to allow any general rise in the level of world-wide contamination because of its harmful effects and that any activity which produces such a rise should be avoided. Nuclear tests are the main source at present which produce such a rise."

This proposal was rejected by the following roll-call vote:

*In favour:* Brazil, France, India, Japan, United States of America.

*Against:* Argentina, Australia, Mexico, Sweden, United Kingdom of Great Britain and Northern Ireland.

*Abstaining:* Belgium *(Chairman)*, Canada, Czechoslovakia, Union of Soviet Socialist Republics, United Arab Republic.

(*b*) Both natural radiation and radiation from fall-out involve the whole world population to a greater or lesser extent, whereas only a fraction of the population receive medical or occupational exposure. However, the irradiation of any groups of people, before and during the reproductive age, will contribute genetic effects to whole populations in so far as the gonads are exposed.

(*c*) Because of the delay with which the somatic effects of radiation may appear, and with which its genetic effects may be manifested, the full extent of the damage is not immediately apparent. It is, therefore, important to consider the speed with which levels of exposure could be altered by human action.

It is clear that medical and occupational exposure, and the testing of nuclear weapons, can be influenced by human action, and that natural radiation and the fall-out of radioactive material already injected into the stratosphere, cannot.

56. Present knowledge concerning long-term effects and their correlation with the amounts of radiation received does not permit us to evaluate with any precision the possible consequence to man of exposure to low radiation levels. Many effects of irradiation are delayed; often they cannot be distinguished from effects of other agents; many will only develop once a threshold dose has been exceeded; some may be cumulative and others not; and individuals in large populations, or particular groups such as children and foetuses may have special sensitivity. These facts render it very difficult to accumulate reliable information about the correlation between small doses and their effects either in individuals or in large populations. Even a slow rise in the environmental radioactivity in the world, whether from weapon tests or any other sources, might eventually cause appreciable damage to large populations before it could be definitely identified as due to irradiation. Appearance and elimination of adverse genetic effects would be very slow; and, as the radioactive contamination accumulated, it might so act as to increase the likelihood of somatic injury in individuals due to the additional exposure. Such a situation requires that mankind proceed with great caution in view of a possible underestimation. At the same time, the possibility cannot be excluded that our present estimates exaggerate the hazards of chronic exposure to low levels of radiation. Only further intensive research can establish the true position.**

57. Any present attempt to evaluate the effects of sources of radiation to which the world population is exposed can produce only tentative estimates with wide margins of uncertainty. Estimates are given in chapter III for the radiation exposure of populations from such sources, and in chapters V and VI for the likely somatic and genetic effects of given exposures. On the basis of these, the Committee has tried to evaluate the possible effect of natural and of fall-out radiation in causing leukemia, tumours of bone and major genetic defects (table II) since these are conditions which may possibly be induced by irradiation at low dose levels. The methods of calculation, and the main sources of uncertainty in these estimates, are described in chapters III, V and VI, where factors of correction are also given for the different estimates corresponding to differences in the assumptions on which the calculations are based. It will be evident that the estimates indicate only the order of magnitude of the frequency with which effects may be produced, and that our ignorance as to whether thresholds exist for the induction of leukemia or bone tumours by radiation cause the greatest uncertainty in the estimates.

*Indications for research*

58. This report presents evidence both of the increasing levels of radiation exposure, and of our uncertainties as to the nature and extent of the effects of radiation on man, particularly when received at low dose rates over long periods. It is most important, therefore, that scientific research and the collection of information on the effects of radiation should be actively continued and developed so that the uncertainties in all branches of radiobiology are reduced or removed.

** The maximum permissible levels of exposure and maximum permissible body burdens of radioactive isotopes recommended in 1954–1955 by the International Commission on Radiological Protection as applying in the case of *occupational* exposure must not be misinterpreted to apply in the case of exposure of *whole populations.*

TABLE II. ESTIMATES OF CERTAIN POSSIBLE ANNUAL CONSEQUENCES OF RADIATION RECEIVED BY WORLD POPULATION FROM CERTAIN SOURCES

| *Consequence* | *World population assumed (in millions)* | *Natural occurrence assumed per year* | *Source of radiation* | | |
|---|---|---|---|---|---|
| | | | *Natural radiation* | *Fall-out from weapon tests* | |
| | | | | *Tests stopping in 1958* | *In equilibrium after prolonged continuation of tests* |
| *Leukemia* | | | | | |
| If threshold 0 rem | 3,000 | 150,000 | 15,000 | 400 to 2000[a] | — |
| | 5,000 | 250,000 | 25,000 | — | 5,000 to 60,000 |
| If threshold 400 rem | 3,000 | 150,000 | 0[b] | 0[c] | — |
| | 5,000 | 250,000 | 0[b] | — | 0[d] |
| *Major Genetic Defects*[e] | 5,000 | 700,000 to 3,000,000 | 25,000 to 1,000,000 | [f] | 500 to 40,000 |

[a] Maximum rate during peak period. An estimated total of less than 25,000 to 150,000 would ultimately occur.

[b] Unless individual bone marrow dose exceeds mean value by a factor of 60.

[c] Unless individual bone marrow dose exceeds mean value by a factor of 80 to 500.

[d] Unless individual bone marrow dose exceeds mean value by a factor of 5 to 60.

[e] Conditions which are at least a serious handicap to those affected, as listed in table XI of annex H.

[f] A total of 2,500 to 100,000 would occur over subsequent years.

NOTES.—The methods of estimating incidences of leukemia and major genetic defects are described in annex D, paras. 127 to 130.

The quantitative evaluation of an increase in incidence of primary bone tumour attributable to radiation presents great difficulties. If it were assumed that 5 to 10 cases per million normally occurred per year, and that 10 per cent of these were induced by natural radiation the following figures could be calculated from the 70-year osteocyte doses if a non-threshold hypothesis were assumed:

For tests stopping in 1958 and world population 3,000 million, 70 to 900 per year (as the maximum rate).

In equilibrium after prolonged continuation of tests and world population 5,000 million, 1,000 to 25,000 per year (as the continuing rate).

If a threshold of 400 rem were assumed, the incidences would be zero unless individual osteocyte doses exceeded the mean value by a factor of 80 to 500 in the case of tests stopping in 1958 and by a factor of 5 to 60 in equilibrium after prolonged continuation of tests.

59. Our knowledge of radiation and of its hazards is not however static; although still limited, it has been expanding rapidly. In recent years, considerable and sometimes spectacular advances have been made in our understanding of many of these matters. In the light of general scientific experience, the Committee confidently expects that continuing research on an increasing scale will furnish the knowledge urgently needed to master those risks which we know to be associated with the development and scope of the uses of nuclear energy for the welfare of mankind.

*Indications for research into radiation levels*

60. The doses received by both individuals and whole populations from various sources are not yet adequately known. Consequently,

(*a*) The range of tissue dose rates due to natural radioactivity, particularly in heavily populated areas with adequate demographic records, as well as the variations in content of natural radioactive substances in human beings need further examination;

(*b*) Fuller information is required as to the exposure of various populations to radiation during industrial procedures and during medical procedures, especially in so far as this involves children or foetuses and exposure of the bone marrow or gonads. It would be valuable if these further investigations could provide (i) a more representative estimate for some countries already studied, (ii) a fuller study of the dosage associated with the varied extent of medical facilities in different countries, (iii) clearer estimates of the radiation given to different tissues, including bone, (iv) the contribution from radiotherapy and (v) a continuing study of future developments and of changes in the medical radiation exposure;

(*c*) More extensive research is required on the fate of industrial radioactive effluents of various types and on the prevention of radiation exposures of populations from this source;

(*d*) Many factors which determine the distribution of local, tropospheric and stratospheric fall-out from experimental nuclear explosions require further investigation. In particular, more evidence is required on the behaviour of fission products in the stratosphere. Collation of information is needed to determine the pattern and extent of global fall-out on land and oceans. Far more extensive information is needed as to the mechanisms whereby fission products, particularly strontium-90 and caesium-137, reach food-chains and enter the human body, as well as the concentration of those materials in human tissues, particularly under the conditions where this is likely to be greatest.

*Indications for research into biological effects*

61. Information concerning the biological effects of irradiation of man is derived from experimental biology, and from clinical observations and statistical surveys.

(*a*) All advance in radiobiology depends upon progress in general cellular biology, and requires intensive study of the fields concerned.

(*b*) Fundamental biological knowledge is required for our understanding and control of the way in which radiation influences cells and their hereditary material, and how it brings about carcinogenesis. Further studies of these phenomena are needed, and form the only satisfactory basis for measures which could be adopted to prevent or cure the harmful effects of radiation.

(*c*) To identify any occasional harmful effects of low doses and dose rates requires systematic and long-term observation and the recording of relevant facts, especially concerning the frequency of certain somatic disorders and the genetic structure of populations. It is a task to which this Committee urgently draws the attention of demographers and medical statisticians, especially in regard to possible correlation of certain diseases with high natural or artificial radiation exposure.

*Training for research*

62. The advance of research in all these fields depends upon appropriate training of scientific workers.

# ANNEXES

## Annex A

# DEFINITIONS OF QUANTITIES, UNITS AND SYMBOLS

1. The 1956 report of the International Commission on Radiological Units and Measurements[1] gives the following definitions of quantities and units used in radiological physics.*

"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 of unit cross-sectional area centred at that place.

"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 radioactive material, evaluated according to its radioactivity, is the *curie* (c). One curie is a quantity of a radioactive nuclide in which the number of disintegrations per second is $3.700 \times 10^{10}$.

"1.14 *Specific gamma-ray emission* (specific gamma-ray output) of a radioactive 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/$\mu$).

"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 cm$^2$/mg)."

2. The RBE symbol is described in the I.C.R.U. report, in the following way:

"2.1 *RBE* (relative biological effectiveness) is used to compare the effectiveness of absorbed dose of radiation delivered in different ways. It has been commonly represented by the symbol $\eta$. It signifies that m rads delivered by a particular irradiation procedure produces a biological response identical with that produced by m$\eta$ rads delivered by a different procedure.

The statement that 'the RBE of $\alpha$ radiation relative to $\gamma$ radiation is 10' signifies that m rads of $\alpha$ radiation produces a particular biological response in the same degree as 10m rads of $\gamma$ radiation. This statement may be further summarized as $\eta \frac{\alpha}{\gamma} = 10$.

The concept of RBE has a limited usefulness because the biological effectiveness of any radiation depends on many factors. Thus the RBE of two radiations cannot in general be expressed by a single factor but varies with many subsidiary factors, such as the type and degree of biological damage (and hence with the absorbed dose), the absorbed dose rate, the fractionation, the oxygen tension, the pH, and the temperature.

"2.2 *RBE dose* is equal numerically to the product of the dose in rads and an agreed conventional value of the RBE with respect to a particular form of radiation effect. The standard of comparison is X- or gamma radiation having a LET in water of 3 kev/$\mu$ delivered at a rate of about 10 rad/min.

"2.3 The unit of RBE is the *rem*. It has the same inherent looseness as the RBE and in addition assumes conventional and not necessarily measured

---

* 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; $^{14}C$ or $C^{14}$; 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 (1955) 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.

NOTE: Throughout this report and its annexes cross-refercenes are denoted by a letter followed by a number : the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

values of RBE. It is therefore recommended that its use be restricted to statements relating to radiation protection. For example the statement might be made:

The permissible weekly whole body RBE dose is 0.3 rem regardless of the type of radiation to which a person is exposed.

Should occasion arise when results have been evaluated with other than agreed conventional values of RBE, the values used should be clearly stated.

In the case of mixed radiations the 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 $= \Sigma$ [(absorbed dose in rads) x RBE]."

## Reference

1. International Commission on Radiological Units and Measurements (ICRU): Report of the ICRU, 1956. U.S. National Bureau of Standards, Handbook 62, Washington 1957.

# Annex B
# RADIATION FROM NATURAL SOURCES

TABLE OF CONTENTS


| | Paragraph |
|---|---|
| I. COSMIC RAYS | 2-7 |
| Absorption in air | 3-4 |
| Variations | 5-6 |
| Variations with altitude | 7 |
| II. PROPERTIES OF NATURAL RADIOACTIVE ISOTOPES | 8-9 |
| III. NATURAL RADIOACTIVE ISOTOPES IN THE ENVIRONMENT | |
| Uranium and thorium | 10-11 |
| Radium | 12 |
| Radon | 13 |
| Thoron | 14 |
| Particle-borne radioisotopes in the atmosphere | 15 |
| Potassium | 16 |
| Carbon-14 | 17 |
| Tritium | 18 |
| IV. IRRADIATION FROM EXTERNAL SOURCES | |
| Calculated values for gamma-ray intensities | 19 |
| Measured total outdoor radiation | 20 |
| External irradiation in buildings | 21-22 |
| Special areas | 23-24 |
| Summary of irradiation by external sources | 25 |
| Gonad and bone doses | 26-27 |
| V. INTERNAL RADIOACTIVE SOURCES | |
| Radioactive substances in the body | 28 |
| Carbon-14 | 29 |
| Potassium-40 | 30-31 |
| Radium | 32 |
| Particulate air-borne activity | 33 |
| VI. IRRADIATION FROM INTERNAL SOURCES | 34-39 |
| Conclusion | 40 |
| References | |


1. A distinguishing characteristic of irradiation by natural sources is that the entire population of the world is exposed to it and that it remains relatively constant in time, while varying from place to place with local geological conditions. The various natural sources include:

(*a*) External sources of extra-terrestrial origin (cosmic rays) and external sources of terrestrial origin, i.e. the radioactive isotopes present in the crust of the earth and in air.

(*b*) Internal sources, i.e. the radioisotopes $K^{40}$ and $C^{14}$ which exist as a small percentage of these elements and are normal constituents of the body, and other isotopes such as $Ra^{226}$, $Th^{232}$ and their decay products that are taken up from the environment.

## I. COSMIC RAYS

2. The primary component of cosmic rays is the radiation incident upon the top of the atmosphere of the earth. It is composed of 79 per cent (in number) of protons, 20 per cent of alpha particles, 0.78 per cent of C, N, O nuclei and 0.22 per cent of nuclei with $Z > 10$.[1]* The energy of the primary particles is very high and values up to $10^{19}$ eV have been reported.

### *Absorption in air*

3. The primary particles lose energy in their passage through matter by ionization, radiation, and nuclear interactions and thus produce new groups of rays. This secondary radiation, still very energetic, is composed of electrons, photons, neutrons and mesons. The composition of the radiation changes with altitude.

---

*NOTE: Throughout this report and its annexes cross-references are denoted by a letter followed by a number: the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

4. The radiation at sea level is composed of mesons (~80 per cent) which constitute the secondary hard component, electrons (~20 per cent), which constitute the secondary soft component, and some primary protons (~0.05 per cent)[2]. The average mass absorption coefficient of the soft component at sea level has been reported to be $8.5 \times 10^{-3}$ cm²/g (E. Regener, quoted by Hess[3]).

### *Variations*

5. The intensity of cosmic rays increases very strongly with altitude in consequence of decreased atmospheric absorption, and increases with increasing geomagnetic latitude in consequence of the effect of the earth's magnetic field. The latitude effect is confined to latitudes between 0° and approximately 55° (apparently at all altitudes). Small, short-lived changes of intensity in time are produced by solar flares (up to 12 per cent)[4,5]. Temperature changes in the upper layers of the atmosphere, local increases in pressure, air fronts and other factors also produce negligible temporary variations in intensity, but they are not significant from the point of view of the external irradiation of the organism.

6. Different authors give different values for cosmic ray intensities at sea level (table I) even at comparable latitudes. There are indications[6,7] that the most reliable figure for the intensity at the middle latitudes (~50°) and at sea level is 1.9 – 1.96 ion-pairs/cm³·sec, which gives a soft tissue and gonad dose of ≈ 28 mrad/year.

TABLE I. INTENSITY OF COSMIC RAYS AND DOSES TO THE SOFT TISSUES AND GONADS IN VARIOUS REGIONS NEAR SEA LEVEL

| *Place of observation* | *Geomagnetic latitude in degrees* | *Ionization in ion pairs per cm³·sec* | *Dose to the soft tissues and gonads in mrad/year* | *Ref.* |
|---|---|---|---|---|
| Great Britain... | 55° N | 1.92 | 28 | 8 |
| United States... | 41° N | 1.96 | 29 | 6 |
| Austria[a]..... | 48° N | 1.9 | 28 | 9 |
| France..... | 49° N | 1.66 (Hard 1.15, Soft 0.51) | 24 | 10 |
| Japan..... | 25° N | 2.35 (Hard 1.76, Soft 0.59) | 34 | 11 |
| Argentina[a]..... | 23° 15′ S | 1.4 | 20 | 12 |
| | 52° 42′ S | 1.9 | 28 | |

[a] Measured by counters.

### *Variation with altitude*

7. The ionization in ion pairs/cm³·sec and corresponding dose rates in air at NTP are given in table II for certain locations. The table shows that an increase in altitude from 0 m to 3,000 m gives an approximately threefold increase in intensity, while the latitude variation even at 3,000 m is only 50 per cent. Neher's data for sea level intensity, on which table II is based, are 30 per cent higher than those of other observers. Therefore, the values given in this table may be considered as upper limits.

TABLE II.[13] COSMIC RAY INTENSITIES AND DOSE RATES

| *Altitude m* | *Intensity ion pairs/cm³·sec* | | *Dose rate mrad/year* | |
|---|---|---|---|---|
| | *At 50° latitude* | *Near Equator* | *At 50° latitude* | *Near Equator* |
| 0..... | 2.8 | 2.4 | 41 | 35 |
| 1500..... | 4.5 | 3.0 | 66 | 44 |
| 3050..... | 8.8 | 6.1 | 128 | 89 |
| 4580..... | 18 | 12 | 263 | 175 |
| 6100..... | 34 | 23 | 500 | 340 |

## II. PROPERTIES OF NATURAL RADIOACTIVE ISOTOPES

8. Naturally occurring radioactive isotopes such as $H^3$, $C^{14}$, $K^{40}$, $Rb^{87}$, $Th^{232}$ and $U^{238}$ and the decay products of the last two isotopes are widely distributed in rocks and soils and in the air. Physical characteristics of some isotopes are given in tables IIIa and IIIb. The data given in these tables may be found in many textbooks, but they are included here because they illustrate the relative importance of different radioactive elements and are used in calculations later on. The dose rate for an element at given concentration is determined from decay, yield and energy of its radiation. Shielding factors are assessed in the light of the penetrating power of the radiation. The relative contribution of the decay products of radium and thorium to total doses can be calculated, and the deviation from the theoretical equilibrium concentration of the decay products of radium in bones, caused by partial diffusion of radon, can be taken into account.

9. Some of the isotopes listed in the tables viz. $K^{40}$, $Th^{232}$, $U^{238}$, have half-lives comparable to the geological age of the earth, estimated at $4 \times 10^9$ years, and for this reason are still present in nature. Other isotopes, in spite of their short half-lives, are also present today, because they are decay products of long-lived isotopes like $Ra^{226}$, or because they are produced from atmospheric nuclei by cosmic rays, like $C^{14}$ and $H^3$.

## III. NATURAL RADIOACTIVE ISOTOPES IN THE ENVIRONMENT

### *Uranium and Thorium*

10. Naturally radioactive elements are widely distributed over the earth's surface. Thorium-bearing minerals are found in the United States (Rocky Mountains area and the Carolinas), in India (Kerala coast), in Brazil (coastal region of Espirito Santo), on Taiwan and in other parts of the world. Uranium has been found in large quantities in the United States (in brown coal deposits, petroleum beds, and the phosphatic rocks of Florida), the Belgian Congo, Ontario and Saskatchewan in Canada, Fergana in the USSR, Czechoslovakia and South Africa and other areas. For fuller information on the distribution of uranium aid thorium, see Kerr.[15]

11. Radioactive elements are more commonly associated with certain types of rock than with others. Acid igneous rocks are richer in them than basalts. Shales, in particular, which contain organic substances, are more highly radioactive than other sedimentary rocks (table IV). Potassium, thorium and radium show a tendency to concentrate in rocks with a high silicon content (table V). Tables IV, V and VI contain data on concentrations of radioactive elements in rocks.

TABLE IIIa. DATA ON PARTICLE RADIATION FROM CERTAIN NATURALLY OCCURRING RADIOACTIVE ISOTOPES

| Isotope | | Radiation | Number per disintegration | Energy (Mev) | Radioactive half-life | |
|---|---|---|---|---|---|---|
| Symbol | Name | | | | | |
| $H^3$ | Tritium | $\beta$ | 1 | 0.018 | 12.26 | years |
| $C^{14}$ | Carbon-14 | $\beta$ | 1 | 0.155 | 5,600 | years |
| $K^{40}$ | Potassium-40 | $\beta$ | 0.9 | 1.3 | $1.3 \times 10^9$ | years |
| $Ra^{226}$ | Radium | $\alpha$ | 1 | 4.78 | 1,600 | years |
| $Ra^{222}$ | Radon | $\alpha$ | 1 | 5.49 | 3.825 | days |
| $Po^{218}$ | Radium A | $\alpha$ | 1 | 6.00 | 3.05 | min |
| $Pb^{214}$ | Radium B | $\beta$ | 1 | 0.7 | 26.8 | min |
| $Bi^{214}$ | Radium C | $\beta$ | 1 | 3.15 | 19.7 | min |
| $Po^{214}$ | Radium C′ | $\alpha$ | 1 | 7.68 | $1.5 \cdot 10^{-4}$ | sec |
| $Pb^{210}$ | Radium D | $\beta$ | 1 | 0.027 | 22 | years |
| $Bi^{210}$ | Radium E | $\beta$ | 1 | 1.17 | 5.0 | days |
| $Po^{210}$ | Polonium | $\alpha$ | 1 | 5.30 | 138 | days |
| $Th^{232}$ | Thorium | $\alpha$ | 1 | 3.98 | $1.39 \cdot 10^{10}$ | years |
| $Ra^{228}$ | Mesothorium I | $\beta$ | 1 | 0.05 | 6.7 | years |
| $Ac^{228}$ | Mesothorium II | $\beta$ | 1 | 0.4–2.2 | 6.1 | hours |
| $Th^{228}$ | Radiothorium | $\alpha$ | 1 | 5.4 | 1.9 | years |
| $Ra^{224}$ | Thorium X | $\alpha$ | 1 | 5.6 | 3.64 | days |
| $Rn^{220}$ | Thoron | $\alpha$ | 1 | 6.28 | 54.5 | sec |
| $Po^{216}$ | Thorium A | $\alpha$ | 1 | 6.77 | 0.158 | sec |
| $Pb^{212}$ | Thorium B | $\beta$ | 0.86 | 0.34 | 10.6 | hours |
| | | $\beta$ | 0.14 | 0.58 | | |
| $Bi^{212}$ | Thorium C | $\alpha$ | 0.337 | 6.05 | 60.5 | min |
| | | $\beta$ | 0.663 | 2.25 | | |
| $Po^{212}$ | Thorium C′ | $\alpha$ | 0.663 | 8.78 | $3.10^{-7}$ | sec |
| $Tl^{208}$ | Thorium C″ | $\beta$ | 0.337 | 1.79 | 3.1 | min |

TABLE IIIb. DATA ON GAMMA RADIATION FROM NATURAL RADIOISOTOPES[17]

| Isotope | | Energy E Mev | Number of quanta per primary disintegration n |
|---|---|---|---|
| Symbol | Name | | |
| $K^{40}$ | Potassium-40 | 1.5 | 0.11 |
| $Pb^{214}$ | Radium B | 0.241 | 0.106 |
| | | 0.294 | 0.240 |
| | | 0.350 | 0.435 |
| $Bi^{214}$ | Radium C | 0.609 | 0.359 |
| | | 0.769 | 0.078 |
| | | 0.934 | 0.038 |
| | | 1.120 | 0.273 |
| | | 1.238 | 0.099 |
| | | 1.378 | 0.116 |
| | | 1.509 | 0.039 |
| | | 1.764 | 0.220 |
| | | 1.848 | 0.023 |
| | | 2.204 | 0.070 |
| | | 2.432 | 0.025 |
| $Ac^{228}$ | Mesothorium II | 0.336 | 0.0884 |
| | | 0.410 | 0.0394 |
| | | 0.458 | 0.0295 |
| | | 0.907 | 0.246 |
| | | 0.964 | 0.197 |
| | | 1.587 | 0.118 |
| | | 1.64 | 0.197 |
| $Pb^{212}$ | Thorium B | 0.087 | 0.305 |
| | | 0.238 | 0.330 |
| | | 0.300 | 0.344 |
| $Bi^{212}$ | Thorium C | 0.721 | 0.046 |
| | | 0.81 | 0.104 |
| | | 1.03 | 0.039 |
| | | 1.34 | 0.026 |
| | | 1.61 | 0.046 |
| | | 1.81 | 0.046 |
| | | 2.20 | 0.013 |
| $Tl^{208}$ | Thorium C′′ | 0.277 | 0.030 |
| | | 0.510 | 0.073 |
| | | 0.58 | 0.265 |
| | | 0.859 | 0.053 |
| | | 2.62 | 0.337 |

TABLE IV. RADIUM, THORIUM AND POTASSIUM CONTENTS IN VARIOUS ROCKS[16]

| *Type of rock* | $Ra^{226}$, g/g x $10^{12}$ | $Th^{232}$, g/g x $10^{6}$ | $K^{39}$, g/g x $10^{2}$ |
|---|---|---|---|
| *Igneous rocks:* | | | |
| Mean value[18] | 1.3 | 12 | 2.6 |
| *Granites:* | | | 3.5 |
| North America, Greenland | 1.6±0.1 | 8.1 | |
| Finland | 4.7±0.4 | 28±2.4 | |
| Alps | 4.4±0.7 | 33±5 | |
| *Basalts:* | | | 1.3 |
| North America, Greenland | 0.96±0.7 | 9.8±0.8 | |
| Great Britain, Germany, France and Hungary | 1.3 ±0.1 | 8.8±1.0 | |
| *Sedimentary rocks:* | | | |
| Sandstone | approx. 0.3 | | |
| Limestone | up to 1.5 (1[17]) | 1 | 0.1–0.5 (0.3[17]) |
| Alum shales in Sweden | up to 120 (60[17]) | 0.6–1.2 (1.5[17]) | 3.5[17] |

TABLE V. RADIUM, THORIUM AND POTASSIUM CONTENTS IN SILICEOUS ROCKS[19]

| *Type of rock* | $Ra^{226}$, g/g x $10^{12}$ | $Th^{232}$, g/g x $10^{6}$ | $K^{39}$, g/g x $10^{2}$ |
|---|---|---|---|
| *Igneous rocks:* | | | |
| Acid rocks >65% $SiO_2$ Granites | 3.1 | 20 | 3.4 |
| Young granites (Max. level) | 6.5 | 59 | 5.1 |
| ...(Granodiorite) | 2.7 | 18 | 2.5 |
| Intermediate rocks 65–55% $SiO_2$ ...(Diorite) | 1.4 | 6 | 1.7 |
| Basic rocks <55% $SiO_2$ ...(Gabbro) | 0.87 | 5.1 | 0.7 |
| *Ultrabasic rocks:* ...(Peridotite) | 0.52 | 3.3 | 0.8 |

TABLE VI. AVERAGE RADIUM, URANIUM, THORIUM AND POTASSIUM CONTENTS IN VARIOUS ROCKS[18]

| *Type of rock* | $Ra^{226}$, g/g x $10^{12}$ | $U^{238}$, g/g x $10^{6}$ | $Th^{232}$, g/g x $10^{6}$ | $K$, g/g x $10^{2}$ |
|---|---|---|---|---|
| Igneous | 1.3 | 4.0 | 12 | 2.6 |
| *Sedimentary rocks:* | | | | |
| Sandstones | 0.71 | 1.2 | 6 | 1.1 |
| Shales | 1.08 | 1.2 | 10 | 2.7 |
| Limestones | 0.42 | 1.3 | 1.3 | 0.27 |

## *Radium*

12. The radium concentration in rocks has been found to vary between $10^{-11}$ and $10^{-13}$ gram of radium per gram of rock.[20] The average radium content in the soil is estimated at 2 x $10^{-12}$ gram of radium per gram of soil;[22] the radium concentration in the soil in various parts of the United States has been found by measurement[23] to vary between 0.9 and 8.0 x $10^{-13}$ gram of radium per gram of soil. Tables IV to VI show radium concentrations in various minerals. The radioactivity of fresh surface water is sometimes due to radon in higher concentration than that corresponding to the radium contration, and it should be noticed that many old data on natural radioactivity of water refer to radon and not radium concentration. The natural radioactivity of drinking water is in most cases mainly due to $Ra^{226}$. The radium content of water sources is determined by the extent to which the water is enriched by the leaching of rocks. Water containing calcium, barium and stable strontium is particularly likely to be enriched with radium. This is one of the reasons for the wide variations in the radium content of water. The concentration varies between wide limits and characteristic values are given in table VII.

TABLE VII. CONCENTRATION OF RADIUM IN WATER

| *Origin* | *Concentration* g/cm³ | *Ref.* |
|---|---|---|
| *Ocean* | 0.7–7 x $10^{-17}$ | 23 |
| *Rivers in U.S.A.* | | |
| Average | 7 x $10^{-17}$ | 23 |
| Mississippi | 1–3 x $10^{-15}$ | |
| *Public water supplies* | | |
| Sweden (tap water) | 2–10 x $10^{-16}$ | 24 |
| U.S.A. (tap water) | | |
| Average for 41 towns | 0.42 x $10^{-16}$ | 25 |
| Maximum (Joliet, Ill.) | 7 x $10^{-15}$ | 23 |
| USSR mean value (fresh water) | 10 x $10^{-16}$ | 26 |
| Austria, Bad Gastein (tap water) | 6.2 x $10^{-16}$ | 27 |
| Germany, Frankfurt-am-Main (tap water) | 1.4–3.1 x $10^{-16}$ | 27 |
| *Springs in special areas* | | |
| Boulder, Col., U.S.A. | 3 x $10^{-10}$ | 23 |
| Hot Springs, Japan | 7 x $10^{-10}$ | 23 |
| Jáchymov (Joachimstal), Czechoslovakia | 5 x $10^{-10}$ | 28 |
| Bad Gastein, Austria | 1 x $10^{-10}$ | 29 |
| France | 0.3 x 1.4 x $10^{-13}$ | 30 |

Some measurements of the $Ra^{226}$ content in foodstuffs are given in table VIII.

TABLE VIII. $Ra^{226}$ CONTENTS IN FOODSTUFFS[27]

| *Food* | *Ra content in g per g of food x* $10^{13}$ |
|---|---|
| Wheat | 20–26 |
| Potatoes | 67–125 |
| Milk | 0.0575/millilitre |
| Meat | 8.0 |

### *Radon*

13. $Rn^{222}$, an isotope of the gaseous element radon and a decay product of $Ra^{226}$ in the uranium series, accumulates in the soil in areas where uranium-bearing minerals are present, and diffuses into the air. The average radon concentration in the soil is of the order of $10^{-12}$ curie/gram[31]. The rate of injection into the atmosphere is approximately $4.3 \times 10^{-10}$ curies per hour per square metre of the surface (in the neighbourhood of Leningrad, USSR[26]). Seasonal changes occur in the rate of injection. The radon content of the air at ground level depends to a considerable extent on meteorological conditions. The average "equivalent" concentration of radon with its decay products in the air is approximately $1—3 \times 10^{-13}$ c/l (see table XIa). In areas with higher radioactivity (granite and other areas) the radon content may be higher than the concentrations given above by several factors of ten.

### *Thoron*

14. Thoron ($Rn^{220}$) another isotope of radon is a decay product of $Th^{232}$ and also diffuses from the ground into the air. As for radon, the concentration in air depends to a considerable extent upon meteorological conditions. The average concentration in air is approximately $0.5 \times 10^{-13}$ c/l (see table XIa) but in areas with higher radioactivity it may be higher by several factors of ten.

### *Particle-borne radioisotopes in the atmosphere*

15. In addition to radon and thoron, the atmosphere contains their solid decay products, mainly Ra B, Ra C and Th B, which attach themselves to small particles and thus constitute the natural particulate air-borne activity. The distribution of the aerosol-borne activity according to particle size is shown in table IX[17]. The particulate activity can be collected by special filters or by electrostatic precipitation. Long-lived material that remains after the decay of Th B (10.6 h half-life) constitutes only a very minor part of the total activity. Concentrations vary widely with local and meteorological factors. Extensive reference to data on radon equivalent content in both indoors and outdoors air is given by Hultqvist,[17] and a summary of some typical values has been given by Lowder and Solon[28] (see also table XIa). The particle-borne radioactivity is relevant to internal irradiation resulting from *inhalation,* since the particles, *but not the gases,* accumulate in the respiratory tract.

TABLE IX.[17] DISTRIBUTION OF RADIOACTIVITY ACCORDING TO PARTICLE DIAMETER

| *Diameter of particles in microns* | *Radioactivity in percentage* |
|---|---|
| <0.005 | 5 |
| 0.005–0.015 | 25 |
| 0.015–0.025 | 50 |
| 0.025–0.035 | 10 |
| >0.035 | 10 |

### *Potassium*

16. Potassium is relatively abundant in nature. Its radioactive isotope $K^{40}$ constitutes 0.0119 per cent of the total amount of potassium and contributes 32 $\beta$-dps per g K and 3.4$\gamma$-dps per g K. The potassium content of various rocks has been given in tables IV-VI. The potassium concentration in the soil varies between $10^{-3}$ and $3 \times 10^{-2}$ g of potassium per g of soil. The radioactivity of ocean water is mainly due to $K^{40}$ with a concentration of $3—5 \times 10^{-13}$ c/cm$^3$.

### *Carbon-14*

17. The carbon isotope $C^{14}$ is formed in the atmosphere as a result of nuclear reactions between cosmic rays and atmospheric nuclei. All the carbonaceous substances taking part in carbon exchange with the atmosphere have a constant equilibrium concentration of $C^{14}$ equal to $7.21 \times 10^{-12}$ c per g of carbon,[37] corresponding to a distintegration rate of 0.27 dps per g of carbon. Rocks in which such exchange cannot take place have a lower specific activity of $C^{14}$, depending on their geological age. Ancient carbonaceous rocks (marble and others) of geological age greater than the half-life of carbon[14] do not as a rule contain this isotope. Observation has shown, however, that the concentration of $C^{14}$ in nature has been increasing recently owing to contributions from a new source, namely, the explosion of nuclear weapons.[38,21]

### *Tritium*

18. Tritium ($H^3$) has always been present in nature since it is formed in the atmosphere by the action of cosmic rays. The total quantity of tritium is at an equilibrium level equal to the rate of formation multiplied by the mean radioactive lifetime. The aqueous component of the cells of the human body probably has a tritium concentration equal to the one observed in foodstuffs and drinking water. The natural atomic concentration of tritium in the hydrogen of river water[39] is $5 \times 10^{-18}$. Such a tritium concentration may be calculated to result in a dose rate of $1.8 \times 10^{-8}$ mrad/year to soft tissues.

## IV. IRRADIATION FROM EXTERNAL SOURCES

### *Calculated values for gamma-ray intensities*

19. The gamma radiation over rocks and soils containing known amounts of radioactive materials was first calculated by Hess.[40] Later, Hultqvist[17] calculated characteristic radiation values for minerals with the concentrations of radioactive materials given in table IV. Hultqvist developed simple numerical expressions for the gamma-ray dose, corrected for the scattered radiation. If his formulae are used to estimate the contribution to the dose rate (D, rad/year) from various concentrations of radioactive materials in the ground (s, g per g), the following expressions are obtained:

$$\left.\begin{aligned} D_{Ra} &= 18.4 \times 10^{12} \times s_{Ra} \\ D_U &= 6.4 \times 10^{6} \times s_U \\ D_{Th} &= 3.1 \times 10^{6} \times s_{Th} \\ D_K &= 13.3 \times 10^{2} \times s_K \end{aligned}\right\} \quad \ldots\ldots\ldots (1)$$

Dose rates calculated from Hultqvist's equations (1) using the data of table VI are given in table X.

TABLE X. DOSE RATES OF EXTERNAL GAMMA IRRADIATION FROM THE ELEMENTS Ra, U, Th AND K CONTAINED IN ROCKS

| *Type of rock* | *Dose rate in mrad/year[a] from* | | | |
|---|---|---|---|---|
| | $Ra^{226}$ | $U^{238}$ | $Th^{232}$ | $K^{40}$ |
| Igneous rocks | 24 | 25.8 | 36.8 | 34.6 |
| *Sedimentary rocks:* | | | | |
| Sandstones | 13 | 7.7 | 18.4 | 14.6 |
| Shales | 20 | 7.7 | 30.6 | 36 |
| Limestones | 7.7 | 8.4 | 4 | 3.6 |

[a] Calculated from equations (1) and the data in table VI.

TABLE XI. DOSE RATES OF EXTERNAL GAMMA IRRADIATION OUT OF DOORS IN VARIOUS COUNTRIES

| Country | Dose rate mrad/year | Comment | Ref. |
|---|---|---|---|
| Great Britain.... | 48 | | 41 |
| France..... | 45–90 | | 10 |
| | 180–350 | Granites and shales | |
| United States[a]... | 50–160 | For 19 inhabited localities | 34 |
| Austria..... | 58 | | 35 |
| Sweden[a]..... | 85 | Stockholm street | 36 |
| | 60–120 | Igneous rocks | |
| | 50 | Clay | |

[a] Values obtained by subtraction of 28 mrad/year for cosmic rays.

TABLE XIa. CONCENTRATIONS OF RADON AND THORON IN EQUILIBRIUM WITH THEIR DECAY PRODUCTS PRESENT IN THE AIR IN VARIOUS REGIONS AND CORRESPONDING CALCULATED DOSES

| Place of observation | Average concentration in $c/l \times 10^{12}$ | | Dose in mrad/year | | Ref. |
|---|---|---|---|---|---|
| | Rn | Tn | Rn | Tn | |
| Czechoslovakia.... | 8.0 | | 11 | | 28 |
| Great Britain..... | 3.0 | | 4.3 | | 32 |
| Japan..... | 1–2.5 | | 1.4–3.5 | | 11 |
| France..... | 2.0 | 0.6 | 2.8 | 0.8 | 34 |
| Austria..... | 1–3 | | 1.4–4.3 | | 35 |
| Sweden..... | 1.0 | | 1.4 | | 36 |
| USSR..... | 1.0 | 0.5 | 1.4 | 0.7 | 26 |

### *Measured total outdoor radiation*

20. Total gamma ray and cosmic ray intensities have been measured by various authors using ionization chambers. The experimental dose rates are given in table XI and may be compared with calculated values. Where necessary, gamma ray figures in table XI have been obtained by subtracting an average value of 28 mrad/year for cosmic rays.

TABLE XII. DOSE RATES OF EXTERNAL GAMMA IRRADIATION IN SWEDISH BUILDINGS[17, 14]

| Building material (Outer walls) | Mean dose rate, in mrad/year[a] | | |
|---|---|---|---|
| | Centre of room | Highest reading | Lowest reading |
| Wood..... | 49 | 57 | 48 |
| Brick..... | 104 | 112 | 99 |
| Light-weight concrete..... (containing alum shale) | 172 | 202 | 158 |

[a] Using table VI of ref. 17 and excluding cosmic rays (1.9 ion-pairs/cm$^3$·sec).

TABLE XIII. DOSE RATES OF EXTERNAL GAMMA IRRADIATION INSIDE BUILDINGS IN GREAT BRITAIN[41]

| Type of Building | Sites measured | Dose rate, mrad/year | |
|---|---|---|---|
| | | Local gamma rays | Mean |
| 1. All granite | (a) Aberdeen, Laboratory..... | 107 | |
| | (b) Aberdeen, bell tower..... | 99 | 102 |
| | (c) Aberdeen, entrance hall.... | 101 | |
| 2. Concrete or brick | (a) Aberdeen, rooms on various floors..... | 73 | |
| | (b) Leeds, rooms in hospital building..... | 81 | 78 |
| | (c) Leeds, single storey laboratory..... | 80 | |
| | (d) Leeds, various rooms in house | 77 | |

TABLE XIV. DOSE RATE OF EXTERNAL GAMMA IRRADIATION INSIDE BUILDINGS IN AUSTRIA[35]

| Type of building | Dose rate, mrad/year |
|---|---|
| Wooden house..... | 54–64 |
| All granite..... | 85–128 |
| Brick (brick or concrete)..... | 75–86 |

### *External irradiation in buildings*

21. External irradiation by gamma rays is greater inside buildings of brick, concrete, shales and other materials than out of doors because of the radioactive elements contained in these materials. Some increase in the dose may be produced by the accumulation of radon or thoron as a result of poor ventilation in the buildings. On the other hand, the buildings reduce the dose of external irradiation by absorbing the radiation from sources outside the buildings. Tables XII, XIII and XIV indicate the dose rates of external gamma irradiation inside buildings, table XV the dose rate from radon and thoron present in the air in buildings (*without ventilation*).

TABLE XV. DOSE RATE OF EXTERNAL GAMMA IRRADIATION FROM Rn AND Tn PRESENT IN THE AIR IN SWEDISH BUILDINGS

| Material (outer walls) | Average concentration in $c/l \times 10^{12}$ | | Dose rate, mrad/year[a] | |
|---|---|---|---|---|
| | Rn | Tn | Rn | Tn |
| Wood..... | 0.527 | 0.0276 | 7.5 | 0.4 |
| Brick..... | 0.909 | 0.091 | 13 | 1.3 |
| Light-weight concrete (containing alum shale) | 1.86 | 0.0959 | 26.4 | 1.35 |

[a] Table XV of ref. 17 was used, the calculation being made according to equation (2).

22. The gamma radiation from radioactive material in the air can be calculated by Hultqvist's relations[17]

$$\left.\begin{aligned} D_{Rn} &= 14.2\times10^{12}\times C_{Rn} \text{ mrad/year} \\ D_{Tn} &= 14.0\times10^{12}\times C_{Tn} \text{ mrad/year} \end{aligned}\right\} \quad \ldots\ldots (2)$$

where C is the concentration of radon and thoron in curies per litre of air. Values corresponding to the concentrations of columns 2 and 3 of table XIa are given in columns 4 and 5.

### *Special areas*

23. Much higher values of the external radiation have been found in some areas where the thorium content in the soil is particularly high.

24. The region of Kerala (India), which is approximately 100 km$^2$ in area (about 200 km long and several hundred metres wide) has a population of about 100,000. The available measurements[43] have been made in ten villages of the intensity of the radiation *inside buildings* of three types constructed of various materials typical of the region. The basic materials are brick and cement (A), clay (B) and wood (C). The results of the measurements and corresponding calculated doses are given in tables XVII and XVIIa. The mean value of the individual dose is 1,300 mrad/year, calculated from the equation

$$D = \frac{\sum_r P_r X_r}{\sum_r P_r}$$

where $P_r$ is the population in village r and $X_r$ is the mean value of the dose in village r.

TABLE XVI. EXTERNAL IRRADIATION IN SPECIAL AREAS

| Geology | Location | Area | Population | External irradiation mrad/year | Ref. |
|---|---|---|---|---|---|
| Monazite sand alluvial deposits | Brazil States of Rio de Janeiro and Espirito Santo (Outdoor) | Sequence of intermittent coastal strips each several km long and several hundred metres wide | 50,000 | Average 500 peak values 1,000 | 42 |
| Mineralized volcanic intrusives | Brazil States of Minas Gerais and Goias (Outdoor) | Approximately 6 km² in a dozen scattered places | Pasture land, scattered farms, 1 village with 350 inhabitants | Average 1,600 peak values 12,000 | 42 |

TABLE XVII. DOSES OF EXTERNAL GAMMA IRRADIATION INSIDE BUILDINGS AT TEN INHABITED LOCALITIES IN THE KERALA REGION (INDIA)[43]

| Name of village | Area of village in 1,000 sq. metres | No. of population (in thousands) | Type of house | No. of houses | Mean dose rate mrad/year |
|---|---|---|---|---|---|
| 1. Kadiapattam..... | 83 | 6 | B, C | 17 | 2,814 |
| 2. Manavalakuruchi.. | 660 | 11 | A, B, C | 36 | 2,164 |
| 3. Muttam..... | 208 | 6 | A, B, C | 21 | 736 |
| 4. Midalam..... | 370 | 10 | A, C | 40 | 1,573 |
| 5. Vilingem..... | 540 | 10 | A, B, C | 22 | 131 |
| 6. Karamanal..... | 41.5 | 2 | A, B, C | 19 | 1,283 |
| 7. Kavalem..... | 8.3 | 1 | C | 1 | 814 |
| 8. Kullatoor..... | 54 | 2 | A, B | 10 | 370 |
| 9. Vettoor..... | 29 | 3 | B | 10 | 527 |
| 10. Varkala..... | 41.5 | 1 | A | 12 | 1,376 |
| | | 52 | | 193 | |

TABLE XVIIa. DOSES OF EXTERNAL GAMMA-IRRADIATION INSIDE BUILDINGS OF VARIOUS TYPES IN THE KERALA REGION (INDIA)[43]

| | Type of house and building material | No. of houses | Percentage of total number of houses in the region | Dose, mrad/year | |
|---|---|---|---|---|---|
| | | | | Maximum value | Minimum value |
| Type A. | Brick..... Cement..... | 73 | 15 | 2,890 | 66 |
| Type B. | Clay..... | 62 | 60 | 3,150 | 105 |
| Type C. | Wood..... Bamboo..... Palm..... | 52 | 25 | 3,950 | 145 |

TABLE XVIII. MEAN VALUES OF DOSES OF EXTERNAL IRRADIATION FROM VARIOUS SOURCES OF RADIATION

| Source of radiation | Dose rate, mrad/year | | |
|---|---|---|---|
| | Mean value | Extreme values | |
| 1. Cosmic rays..... | 28 | 20–34 | Table I |
| *Ordinary regions:* | | | |
| 2. Gamma rays over rocks..... | 73 | 25–120 | Table X |
| 3. Gamma rays out of doors..... | 70 | 48–160 | Table XI |
| 4. Gamma rays from aerial sources... | 3 | 1.4–11 | Table XIa |
| *Active regions:* | | | |
| 5. Gamma rays, granitic regions in France..... | 265 | 180–350 | Table XI |
| 6. Gamma rays, monazite region, Kerala in India..... | 1,270[a] | 131–2,814 | Table XVII |

[a] By subtraction of cosmic ray dose of 28 mrad/year from total.

*Summary of irradiation by external sources*

25. An approximate estimate of the level of external irradiation from natural sources can be made from the above material. The measured doses out-of-doors in various regions give a mean dose equal to 70 mrad/year (excluding highly radioactive regions). On the other hand, a value for the mean dose over rocks of 73 mrad/year may be derived by calculation from the mean concentrations of radioactive elements in the most widely distributed rocks (Table X). Thus in normal regions the mean dose can be estimated at approximately 70 mrad/year. Summary data on external irradiation are given in Table XVIII, column 3 of which indicates mean doses, column 4 the spread of typical values, and column 5 of the reference to the data used in estimating the mean level of irradiation.

*Gonad and bone doses*

26. In calculating the doses to the gonads and bones from external gamma irradiation, a coefficient (shielding factor) must be introduced to allow for the partial absorption of gamma radiation by outer tissues. Spiers[32] gives the following estimates for the gonads:

TABLE XIX. GONADAL SHIELDING FACTOR FOR GAMMA RAYS IN THREE POSITIONS: HORIZONTAL, SITTING AND STANDING

| Position | Shielding factor | | | |
|---|---|---|---|---|
| | Female | Average | Male | Average |
| Horizontal | 0.52 | | 0.67 | |
| Sitting | 0.58 | 0.56 | 0.70 | 0.70 |
| Standing | 0.59 | | 0.72 | |

Mean factor for both sexes: 0.63

The mean shielding factor in the case of bones will also be taken here to be 0.63.

27. Estimated aggregate values can now be given for the gonad and bone doses from natural sources of radiation—cosmic rays and radioactive elements. The populations are subdivided into three groups according to level of irradiation: people living in normal regions—*i.e.* regions where the level of irradiation is not more than 100 mrad/year; population groups living in active regions with a higher level of irradiation, up to 500 mrad/year; and lastly, persons living in regions with a high level of irradiation—over 500 mrad/year. Such a division is artificial, but is useful in considering the biological effects of irradiation.

TABLE XX. MEAN DOSE TO GONADS AND BONES FROM NATURAL EXTERNAL SOURCES IN NORMAL REGIONS AND MORE ACTIVE REGIONS

| Region | Population in millions | Aggregate mean dose mrem/year[a] |
|---|---|---|
| 1. Normal regions | 2,500 | 75 |
| 2. Granitic regions in France | 7 | 190 |
| 3. Monazite region, Kerala in India | 0.1 | 830 |
| 4. Monazite region Brazil | 0.05 | 315 |

[a] Using a shielding factor of 0.63 for $\gamma$-rays and a dose rate of 28 mrem/year due to cosmic rays.

## V. INTERNAL RADIOACTIVE SOURCES

*Radioactive substances in the body*

28. The radioactive isotopes $C^{14}$ and $K^{40}$ are normal constituents of the human body. $Ra^{226}$ is taken up from food and water and is present with its decay products in the body. Radioactive material from the atmosphere enters the respiratory tract by inhalation and some airborne particulate material is retained.

*Carbon-14*

29. The total carbon content of the body is approximately 18 per cent or 12.6 kg for a total body weight of 70 kg. Therefore, the amount of $C^{14}$ for a total body weight of 70 kg is of the order of 0.1 mc.

*Potassium-40*

30. The total potassium content of the body has been given as 0.185 per cent or 130 g by Sievert,[44] as the average value of a series of observations by several authors. While individual values range between 0.12 and 0.35 per cent, the majority of results group together rather closely around the average value given above.

31. The concentration of radioactive potassium in various organs, according to Forbes and Lewis,[45] is given in table XXI.

TABLE XXI. POTASSIUM CONTENT OF VARIOUS ORGANS OF MAN[45]

| Organ | Percentage of total body weight | Concentration in percent |
|---|---|---|
| Skin | 6.5 | 0.16 |
| Skeleton | 13.4 | 0.11 |
| Tibia | 1.4 | 0.05 |
| Muscles | 39.6 | 0.31 |
| Nervous system | 2.1 | 0.30 |
| Liver | 2.3 | 0.23 |
| Heart | 0.6 | 0.19 |
| Lungs | 2.2 | 0.27 |
| Kidneys | 0.4 | 0.23 |
| G.I. tract | 1.5 | 0.14 |
| Adipose tissue | 21.4 | 0.06 |
| Remainder | 6.4 | 0.18 |
| Total body weight: 73 kg | | 0.2 |

*Radium*

32. Radium, like calcium, is selectively incorporated in bone. As the amount of radium daily ingested in food has been estimated[46] to be around $1.6 \times 10^{-12}$ g, the uptake through drinking water is significant only if the radium concentration in the water is at least $10^{-15}$ g $Ra^{226}/cm^3$. Consumption of such water may result in an increased body burden of radium, but, as the concentration is normally lower, the body content of radium is believed to depend in most cases on the radium content of the food. The following figures have been reported for the total radium content in the human body: $1.6 \times 10^{-10}$ g[47], $3.3 \times 10^{-10}$ g[27], and $0.4—3.7 \times 10^{-10}$ g[48]. Muth[27] (table XXII) has recently published values of radium concentrations in different tissues which seem to indicate that a substantial proportion of the radium burden is located in soft tissues. These values have not yet been confirmed in other laboratories.

TABLE XXII. RADIUM CONTENT IN VARIOUS TISSUES[27]

| Tissue | Number of samples | Ra content per g of untreated tissue | | |
|---|---|---|---|---|
| | | Minimum value | Mean value | Maximum value |
| Bones | 6 | 4.9 | 9.7 | 16 |
| Lungs | 4 | 1.6 | 2.3 | 3.5 |
| Liver | 4 | 0.4 | 3.4 | 11 |
| Spleen | 3 | 1.8 | 4.6 | 7.4 |
| Muscles | 2 | | 1.4 | |
| Testicles | 28 | | 0.6 | |

*Particulate air-borne activity*

33. Because the disintegration products of radon and thoron are present in the air attached to the particles of aerosols, the amount of radioactive air-borne material retained in the respiratory tract depends upon the filtering properties of this tract for particles of different sizes. Figure 1 shows some characteristic average retention values for particles of different sizes taken from a graph given by Hultqvist (ref. 17, p. 46). Virtually all the activity is concentrated in particles of no more than 0.04 microns in diameter and up to about 70 per cent of such particles will be retained in the lungs according to the graph.

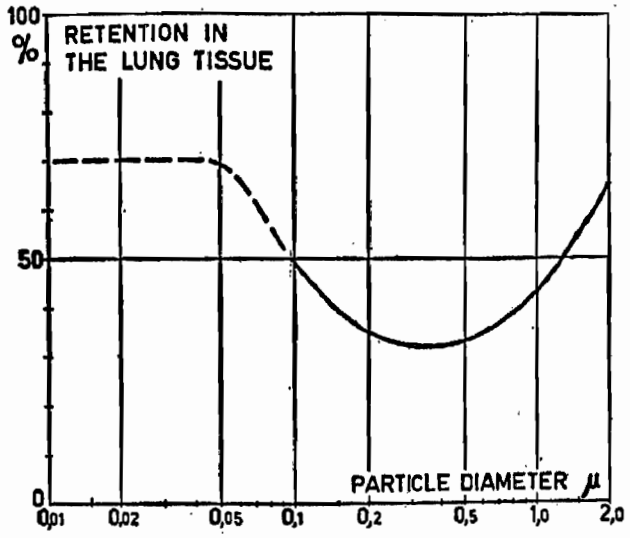



*Figure 1* Approximate "median curve" for the alveolar retention. The broken line refers to that magnitude range for which no experimental investigations are available. (Reproduced from Hultqvist, ref. 17, page 46.)

## VI. Irradiation from internal sources

34. The dose rates from potassium and carbon are approximately uniform over the body and are calculated from the known concentration of these elements and the specific energies of their radiations. Calculated dose rates are given in table XXIII, using the following parameters:

$K^{40}$: energy of quanta E $\gamma$ = 1.5 Mev, 0.1 quantum per disintegration, average energy of $\beta$ particles $\overline{E\beta}$ = 0.6 Mev, 50 per cent of the energy of the gamma quanta is absorbed by the tissues;

$C^{14}$: average energy of $\beta$ particles $\overline{E\beta}$ = 0.067 Mev.

35. In calculating the doses of irradiation from radium taken up into the organism, only the alpha-particle energy is taken into account as a rule, and all the radium is assumed to be in the bones. Figures published recently[27] (table XXII) present a rather different picture of the distribution of radium in the organism, but this has not yet been confirmed by other researchers. The local distribution of radium in bone tissue is of considerable importance in estimating osteocyte doses[49,50] and it is generally studied by radioautography but at the level of the natural concentration of radium in the bones, this method does not yield reliable results: the data published on radium distribution have been obtained with relatively large concentrations of radium. The question therefore arises whether a similar picture of radium distribution in bone tissue would be obtained with small concentrations. There is as yet no satisfactory answer to this question and it is accordingly assumed here that when radium is present in natural concentrations in non-active regions, its distribution in bone tissue is uniform.

36. As the range of alpha-particles in the tissues is approximately of the same order as the diameter of the cavities in bone tissue, the relationship between alpha-particle range and cavity size must be taken into account in calculating the dose. According to Spiers[49] this may be reduced to introducing into the equation for calculating the dose a geometric factor having different values for bones of differing structure. Spiers (*op. cit*) expresses the equation for calculating the bone dose in the case of alpha particles from radium in the bones in the following form (in which 50 per cent of the energy is assumed to come from disintegration products):

$$D = 1.78 \times 10^{11}\ \overline{F} m \text{ mrad/year}$$

where $\overline{F}$ is the mean geometric factor, m the radium content in the bones in grams of radium per gram of bone.

37. For a body burden of $10^{-10}$ g $Ra^{226}$, which is average for normal (non-active) regions, the numerical value of the osteocyte dose is then

$$D = 38 \text{ mrem/year}$$

where $\overline{F}$ = 1.48, using an RBE = 10. The mean dose to the bone marrow is largely due to the $\beta$ activity of the radium decay products, and may be estimated to be approximately 0.5 mrem/year

$$D\beta = 0.5 \text{ mrem/year}$$

38. The dose of irradiation by radon and thoron and their distintegration products is considerably greater (as compared with external irradiation) if these substances are taken up into the organism with inhaled air. In this case the lungs are the critical organ. Assuming, in accordance with the data given above, that 60 per cent of the aerosol particles carrying the radioactivity of the disintegration products of Rn and Tn are retained in the tissues and that the volume of the lungs is 3,000 $cm^3$ and their weight 800 g, the numerical value of the lung dose can be calculated, according to Hultqvist,[14,17] from the following equations:

$$\left.\begin{aligned} D_{Rn} &= 5.0 \times 10^{14}\ C_{Rn} \text{ mrem/year} \\ D_{Tn} &= 66.5 \times 10^{14}\ C_{Tn} \text{ mrem/year} \end{aligned}\right\} \quad \ldots\ldots\ldots (3)$$

TABLE XXIII. RADIOACTIVITY OF THE BODY AND TISSUE DOSES FROM $K_{40}$ AND $C^{14}$ (*standard man, 70 kg*)

| *Element* | *Weight in percentage* | *Weight in g* | *Radiation* | *Activity in curies x $10^8$* | *Gonad dose, mrad/year* | *Osteocyte dose mrad/year* |
|---|---|---|---|---|---|---|
| K..... | 0.20 | 140 | | | | |
| $K^{40}$..... | $2.38 \cdot 10^{-5}$ | $1.66 \cdot 10^{-2}$ | $\beta$ | 10.4 | 16.5 | 9.0[a] |
| | | | $\gamma$ | 1.15 | 2.3 | 2.3 |
| C..... | 18.0 | 12,600 | | | | |
| $C^{14}$..... | $2.8 \cdot 10^{-11}$ | $1.96 \cdot 10^{-8}$ | $\beta$ | 9.0 | 1.6 | 1.6 |

[a] Using the potassium content in the bones according to Table XXI.

(*based on measurements carried out in Sweden*)

| Outer wall librium | Concentration of Rn in c/l x $10^{12}$: Assuming equilibrium | Concentration of Rn in c/l x $10^{12}$: With ventilation $10^{-3}$ sec | Concentration of Tn in c/l x $10^{12}$: Assuming equilibrium | Concentration of Tn in c/l x $10^{12}$: With ventilation $10^{-3}$ sec | Dose in mrem/year: Rn: In equilibrium | Rn: With ventilation | Tn: In equilibrium | Tn: With ventilation |
|---|---|---|---|---|---|---|---|---|
| Wood | 0.527 | 0.537 | 0.0278 | 0.136 | 263 | 73 | 185 | 52 |
| Brick | 0.909 | 0.913 | 0.0910 | 0.450 | 453 | 128 | 605 | 173 |
| Light weight concrete (contain. alum shale) | 1.86 | 1.86 | 0.0959 | 0.461 | 930 | 262 | 640 | 178 |

where C is the radon or thoron concentration in curies/litre, and radioactive equilibrium is assumed. In another case—that of ventilated buildings, where the air in the building is renewed every seventeen minutes, i.e. $10^{-3}$ of the air is renewed per second—Hultqvist obtained the following equations:

$$\left.\begin{aligned} D_{Rn} &= 1.4 \times 10^{14}\ C_{Rn}\ \text{mrem/year} \\ D_{Tn} &= 3.85 \times 10^{14}\ C_{Tn}\ \text{mrem/year} \end{aligned}\right\} \quad \ldots\ldots\ldots (4)$$

where C is the radon or thoron concentration in curies/litre. The results of measurements carried out in three types of buildings in Sweden are given in table XXIV; the doses were calculated from equations (3) and (4).

39. Aggregate figures for internal irradiation give the following dose rates: gonads 20 mrem/year and osteocytes 50 mrem/year.

## Conclusion

40. Since the data given in the text relate to individual inhabited regions and are naturally far from complete, it may be asked whether they can be considered representative for the whole population of the world. As far as the level of irradiation from sources such as cosmic rays and radioactive elements that are constituents of the body (potassium and carbon) is concerned, the answer is in the affirmative. In the case of other sources of external and internal irradiation present in the soil, water and air are capable of being taken up into the organism, the level of irradiation depends on the geological features of the region concerned and therefore varies considerably from one place to another. In this case, only a very approximate estimate of the mean level of irradiation is possible. The results of such an approximation are given in table XXV.

Table XXV. Doses of external and internal irradiation from natural sources of radiation

| Irradiation | Dose mrem/year: To gonads and other soft tissues[a] | To bones | Comment |
|---|---|---|---|
| *External irradiation:* | | | |
| Cosmic rays | 28 | 28 | At sea level |
| Gamma rays out-of-doors | 47 | 47 | |
| *Internal irradiation:* | | | |
| $K^{40}$ | 19 | 11 | |
| $C^{14}$ | 1.6 | 1.6 | |
| $Ra^{226}$ | ? | 38 | |
| Total irradiation from all sources | 95 | 125 | At sea level |

[a] Including bone marrow since the contribution from Ra in bone does not exceed about 0.5 mrem per year.

## References


1. Rossi, B., High energy particles, Prentice Hall, New York, p. 520 (1952).
2. Rossi, B., High energy particles, Prentice Hall, New York, p. 8 (1952).
3. Hess, V. F. and Vancour, R. P., J. Atm. Terrest. Phys. 1, 13 (1950), UN document A/AC.82/G/R.102, Radiological Data, submitted by Austria.
4. Wilson, J. A. (Editor), Progress in cosmic physics, Amsterdam, (1952).
5. UN document A/AC.82/G/R.15, Information submitted by Sweden, (1956).
6. Hess, V. F. and O'Donnell, C. A., Journal of geophysical research, 56, No. 4, p. 557 (1951).
7. Hess, V. F., Arch. Met. Geophys. Biol. A, 3, pp. 56-63 (1950).
8. UN document A/AC.82/G/R.2, Information submitted by the United Kingdom, (1956).
9. UN document A/AC.82/G/R.102, Information submitted by Austria, (1957).
10. UN document A/AC.82/G/R.179, Information submitted by France, (1958).
11. UN document A/AC.82/G/R.70, Information submitted by Japan, (1957).
12. UN document A/AC.82/G/R.81, Information submitted by Argentina, (1957).
13. Libby, W. F., Science, 122, 57 (1955).
14. Hultqvist, B., in UN document A/AC.82/G/R.15. Also published in Kungl. Svenska Vetenskapsakademiens Handlingar, Vol. 6, Ser. 4, No. 3 (1956).
15. Kerr, P. F., International Conference on Peaceful Uses of Atomic Energy, Geneva, 6, 5-59 (1955).
16. Faul, H. (Editor), Nuclear geology, New York, (1954).
17. Hultqvist, B., Kungl. Svenska Vetenskapsakademiens Handlingar, Vol. 6, Ser. 4, No. 3 (1956).
18. Rankama, K. and Sahama, T. C., Geochemistry, University of Chicago Press (1950).
19. Hikschfelder, J. O., Magee, J. L. and Hull, M. H., Phys. Rev. 73, 852 (1948); Holmes, A., Radioactivität und geologie. Verhandl. Naturforsch. Ges., Basel, XLI, pp. 136-185 (1930).
20. Kaye, G. and Laby, T. H., Phys. and Chem. Constants, Longmans Green Co., N.Y., (1948).
21. Leipunsky, O. I., Atomic Energy, 12 Vol. III, p. 530, (1957).
22. Cowan, F. P., Everyday radiation, Physics Today 5, No. 1010 (1952).
23. UN document A/AC.82/G/R.55, Lowder, W. M., and Solon, L. R., Background radiation, p. 13.

24. UN document A/AC.82/G/R.15, Sievert, R. M., Measurements of low-level radioactivity, particularly the γ radiation from living subjects, (1956).
25. UN document A/AC.82/G/R.95, Lough, S. Allan, Deputy Director, The radium content of soil, water, food and humans. Reported values, (1957).
26. UN document A/AC.82/G/R.39, Information submitted by the USSR, Content of natural radioactive substances in the atmosphere and in water in the territory of the USSR, (1956).
27. Muth, H., Schramb, A., Aurand, K., and Mantue, H. J., Brit. J. Radiobiology, Suppl. No. 7 (1957).
28. UN document A/AC.82/G/R.17, Information submitted by Czechoslovakia.
29. UN document A/AC.82/G/R.19, Information submitted by Austria.
30. Fritsch, A., Puiset, I. and Coursajet, J., J. Radiol. Electr. et Med. Nucléaire (in press).
31. Eisenbud, M. and Harley, J., Science 117, 141 (1953).
32. UN document A/AC.82/G/R.2, Information submitted by the United Kingdom, The hazards to men of nuclear and allied radiations.
33. UN document A/AC.82/G/R.70, Information submitted by Japan, Radiological data in Japan.
34. Solon, L. K., Lowder, W. M., Zila, A. V., Devine, H. D., Blatz, M. and Eisenbud, M., External environmental radiation in U.S.A., U.S.A.E.C. Health and Safety Laboratory, N.Y. (1958).
35. UN document A/AC.82/G/R.102, Information submitted by Austria, Radiological data.
36. Sievert, R. M. and Hultqvist, B., Variations in natural γ radiation in Sweden. Acta Radiogica, Vol. 37, F. 3-4 (1952).
37. Anderson, E. C. and Libby, W. F., Phys. Rev., 81, 64 (1951).
38. Rafter, T. A. and Fergusson, G. J., N.Z.J. Science and Tech. B38, 871 (1957).
39. Anderson, E. C., Ann. Rev. of Nucl. Science, 2, 63, (1953).
40. Hess, V. F., in Ergebnisse der Kosmischen Physik, Vol. II, 95-149, Akademische Verlagsgesellschaft, Leipzig, (1934). Cf. R. Muhleisen: Atmosphärische Elektrizität. Handbuck der Physik, Vol. 48 (1957).
41. Spiers, F. W. and Griffith, H. D., Brit. J. Radiol. N.S. 29, 175 (1956).
42. UN document A/AC.82/G/R.34. Roser, R. X. and Cullen, T. L., Intensity levels of natural radioactivity in selected areas in Brazil.
43. UN document A/AC.82/G/R.166 (1958). Bharatwal, D. S. and Vaze, G. H., Measurements on the radiation fields in the monazite areas of Kerala in India.
44. Sievert, R. M., Intern. Conf. Peaceful Uses of Atomic Energy, Geneva 13, 187 (1956) and UN document A/AC.82/G/R.15 (1956).
45. Forbes, G. B. and Lewis, A. M., J. Chem. Invest. 35, No. 6 (1956).
46. Hursh, J. B., *The natural radioactivity of man*, Proc. Bio-assay and Anal. Chem. Meeting, National Lead Co., Ohio, October 6-7, (1955), pp. 110-123.
47. Hursh, J. B. and Gates, A. A., Nucleonics, 7, No. 1, 46 (1950).
48. Stehney, A. F. and Lucas, H. F., International Conference on the Peaceful Uses of Atomic Energy, Geneva 11, 49 (1956).
49. Spiers, F. W., The Brit. J. of Radiology, Vol. XXVI, No. 306 (1953).
50. UN document A/AC.82/G/R.14, Hindmarsh, M., Lamerton, L. F., Owen, M., Spiers, F. W., Vaughan, J., The relative hazards of $Sr^{90}$ and $Ra^{226}$.

# Annex C

# MAN-MADE SOURCES

## (Other than environmental contamination)

TABLE OF CONTENTS


*Paragraph*

I. INTRODUCTION ..... 1

II. MEDICAL USES OF X-RAYS AND RADIOACTIVE MATERIALS ..... 2

The genetically significant dose ..... 6
Calculations ..... 6
Statistical data ..... 18

Exposure of the bone marrow ..... 27

Diagnostic uses of X-rays ..... 33
Estimates of the genetically significant dose ..... 34
Estimates of bone marrow dose ..... 41
Accuracy of estimates ..... 54
Reduction of gonadal dose ..... 60

Radiotherapy ..... 67
Genetically significant dose ..... 67
Bone marrow dose ..... 68

Internally administered radioisotopes ..... 69

III. INDUSTRIAL AND RESEARCH USES OF X-RAYS AND RADIOACTIVE MATERIALS

Occupational exposure ..... 72
Medical workers ..... 73
Atomic energy workers ..... 77
Industrial and research workers ..... 80
Summary ..... 82

IV. OTHER MAN-MADE SOURCES OF RADIATION ..... 84

APPENDICES I-X:

DATA FOR EVALUATION OF THE GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

I. Australia
II. Austria
III. Denmark
IV. England and Wales
V. France
VI. Japan
VII. New Zealand
VIII. Norway
IX. Sweden
X. United States of America

APPENDIX XI:

DATA ON DIAGNOSTIC X-RAY EXPOSURE: GONAD DOSE FOR EXAMINATION FOR THE MOST IMPORTANT EXPOSURE CLASSES

REFERENCES

## I. Introduction

1. The various estimates of genetically significant dose which have been available to the Committee are discussed in this annex, and some preliminary estimates of mean marrow doses are also given. The presentation follows, as far as possible, the scheme given in chapter III.

## II. Medical uses of X-rays and radioactive materials

2. Medical uses of X-rays and radioactive materials are responsible for the largest man-made exposures of many populations at the present time, the doses possibly ranging up to more than 100 per cent of the dose due to natural sources in some of the countries for which estimates have been made.

3. The medical exposure is mainly an exposure of patients undergoing diagnostic examinations or radiation therapy. It is also an occupational exposure, from which, however, the dose to the population as a whole is comparatively very small. This occupational exposure is treated separately in paragraphs 72-83.

4. In view of the importance of the medical exposure, the Committee invited the International Commission on Radiological Protection (ICRP) and the International Commission on Radiological Units and Measurements (ICRU)

"(*a*) To consider and discuss the question of how to arrive at reliable data indicating the doses to different parts of the body (particularly the gonads) received by individuals and, in the aggregate, by large population groups due to medical uses of ionizing radiations and

"(*b*) To examine what recording system, if any, is at present feasible for the determination of the relevant dose values."

The two Commissions formed a joint study group to consider and prepare a report[1] for the Committee on these problems.* The following is the summary of their report.**

*"1. Preliminary considerations*

"(*a*) The principal objective has been to recommend methods for the evaluation of the genetically significant annual gonad dose, $G_m$, which arises from medical uses of ionizing radiation.

"(*b*) It is assumed that the magnitude of the significant gonad dose due to natural background may be taken as a standard of reference and that 25 per cent of this dose is the greatest absolute accuracy which need be aimed at for an initial determination.

"(*c*) While not always yielding values strictly in terms of $G_m$ as defined in paragraph 4 (of the ICRP/U Study Group report), the preliminary surveys which have already been conducted have yielded values of $G_m$ of the order of 100 mrad (probable value) and 50 mrad (minimum value) for the U.S.A. and of the order of 20-40 mrad (minimum values) for Denmark, Sweden and the United Kingdom (England and Wales).

"(*d*) These surveys show at present that diagnosis makes a much larger contribution than therapy, and that some 85 per cent of the diagnostic dose arises from 6 or 7 types of examination, constituting only about 10 per cent of all examinations of the types listed.†

"(*e*) It follows that, as regards dosimetry, those 6 or 7 types call for special consideration in future surveys.

*"2. Recommendations*

"(*a*) It is recommended that the basic studies be continued and extended, making use of suitable ionization dosemeters in order to obtain data that may be used in the preparation of standard tables which give the average gonad dose in mrad corresponding to each type of diagnostic and therapeutic use of ionizing radiation. Special attention should be paid to the six or seven types of diagnostic examinations which account for 85 per cent of the gonad dose.

"(*b*) It is recommended that in all countries the analysis of film records, together with the results of 2 (a) above, be used as a first approximation to $G_m$. If the dose so calculated exceeds a few per cent of natural background, a detailed analysis is recommended.

"(*c*) It is recommended that where required, the more detailed analysis should be obtained by means of a sampling programme, operated through personal contact between trained surveyors and both medical institutions and radiation practitioners, and that data obtained from this sampling programme should be used for the determination of $G_m$.

"(*d*) It is recommended that prior to initiating the main sampling programme (referred to in 2 (c) above), a number of presurveys should be conducted in order to obtain information useful in planning and conducting the programme.

"(*e*) It is recommended that in preparation for the main sampling programme, careful planning and instructional programmes should be initiated by a properly selected group of medical physicists, health physicists, radiologists, statisticians, biometricians, and surveyors. Appropriate dosemeters should be made available to the surveyors who should be instructed in their use.

"(f) It is suggested that surveys will result in improved practices with a consequent reduction in exposure. This is likely to be a most important consequence of all surveys, and specific suggestions are made for the reduction of gonad dose due to diagnostic procedures.

* Note: Throughout this report and its annexes cross-references are denoted by a letter followed by a number: the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

** The references to pages in the Joint Study Group report have been omitted here.

† The list referred to here excludes dental examinations and mass miniature radiography.

*"3. Not recommended*

"The systematic recording and registration of the radiation received by every member of the population is not recommended."

5. The ICRP/ICRU Joint Study Group was mainly concerned with how the genetically significant dose should be assessed. This problem is discussed in further detail in this report. As the scheme of computation is common for all types of exposure, it is presented separately, before the various classes of exposure are discussed.

*The genetically significant dose*

*Calculations*

6. A general definition of genetically significant dose has been given in chapter II. 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*

$$D = \frac{\sum_j \sum_k (N_{jk}^{(F)}\ w_{jk}^{(F)}\ d_{jk}^{(F)} + N_{jk}^{(M)}\ w_{jk}^{(M)}\ d_{jk}^{(M)})}{\sum_k (N_k^{(F)}\ w_k^{(F)} + N_k^{(M)}\ w_k^{(M)})} \qquad (1)$$

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.

7. For the practical work, Equation (1) can be simplified considerably, the first step being to replace the denominator by $w \cdot N$, where

$$w = \frac{N^{(F)}}{N} \cdot w^{(F)} + \frac{N^{(M)}}{N} \cdot w^{(M)} \qquad (2)$$

and

$$w^* = \frac{1}{N^*} \sum_k w_k^*\ N_k^* \qquad (3)$$

In the last expression, * denotes the sex. N is the tota 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.

8. As equation (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.

9. 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

$$w_a^* = \sum_{t=a}^{\infty} c_t^* \cdot \Delta t \cdot P_a^*(t) \qquad (4)$$

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,
$\Delta t$ = number of years included in age-group t,
$P_a^*(t)$ = probability of an individual of age a to reach age (group) t.

10. 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.

11. $W^* = w_{a \to o}^*$ 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.

12. The female and the male contribution to the genetically significant dose can both be written

$$D^* = \frac{1}{wN} \sum_j \sum_k N_{jk}^*\ w_{jk}^*\ d_{jk}^* \qquad (5)$$

13. If the gonad dose due to an examination of type j is nearly uniform for all age-classes k, then

$$d_{jk}^* = d_j^* \qquad (6)$$

approximately for all k, and Equation (5) reduces to

$$D^* = \frac{1}{wN} \sum_j d_j^* \sum_k N_{jk}^*\ w_{jk}^* \qquad (7)$$

or

$$D_j^* = d_j^* \cdot \frac{1}{wN} \sum_k N_{jk}^*\ w_{jk}^*$$

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

$$\boxed{D_j^* = d_j^* \cdot \frac{N_j^*}{N} \cdot \frac{w_j^*}{w}} \qquad (8)$$

which is the expression that has been used for presentation of the data in most of appendices I–X.

14. The necessary information to make it possible to calculate $D_j^*$ by help of Equation (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,

* The degree of approximation involved in the use of equation (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.

(*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.

15. 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.

16. 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,

$$w_j^* = \frac{\sum_k w_{jk}^* N_{jk}^*}{N_j^*} \approx \frac{\sum_k w_k^* N_{jk}^*}{N_j^*} \qquad (9)$$

where $w^*$ can be taken from Equation (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.

17. In the case where the age-distribution in an examination class is not known, a yet more simplified assumption must 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 Equation (3) that

$$w^* = \frac{n^*}{N^*} \cdot W^* \qquad (10)$$

which is also, indirectly, a definition of the "mean age of child-bearing". Equation (8) reduces approximately to

$$D_j^* = \frac{n_j^*}{n} \cdot d_j = \frac{N}{n} \cdot \frac{n_j^*}{N} \cdot d_j \qquad (11)$$

*Statistical data*

18. The scheme of calculation presented in paragraphs 6-17 is the one that has been followed by the Committee in evaluating reported data on gonad exposure. The difficulty of applying any standardized method of calculation to a large amount of heterogeneous information from various countries confirms the importance of carefully planning any survey of exposure levels which is to yield a statistically useful result.

19. Appropriate measures should be taken to determine more accurately the frequency of each type of examination or treatment. The data available at the present time are particularly scarce or unreliable with regard to the following:

(*a*) Diagnostic examinations by non-radiologists (by radiographic and fluoroscopic methods but particularly by the latter) in countries where these constitute an appreciable part of the total radiological practice.

(*b*) X-ray treatment.

(*c*) Diagnostic and therapeutic uses of internally-administered radioisotopes.

In collecting these data, examinations and treatments should be classified by

(i) radiological type;

(ii) anatomical part;

(iii) age and sex of patient;

(iv) disease (for therapy and radioisotopes, at least).

For (i), (ii) and (iii), the classifications recommended by the ICRP/ICRU Study Group[1] should be used.

20. The classification of examinations suggested by the ICRP/ICRU Joint Study Group[1] has been slightly rearranged, for the purposes of this report, to comprise

1. Hip and femur (upper third)
2. Femur (middle and lower third)
3. Pelvic region
4. Lumbosacral
5. Lumbar spine
6. Dorsal spine
7. Urography (descending [intravenous] pyelography)
8. Retrograde (ascending) pyelography
9. Urethrocystography (bladder examinations, cystography, urethrography)
10. Pelvimetry
11. Hysterosalpingography
12. Obstetrical abdomen
13. Abdomen (pancreas, spleen, liver, pneumoperitoneum, general examinations of the urinary tract)
14. Lower gastrointestinal tract (small intestine, appendix, colon, "barium enema")
15. Upper gastrointestinal tract (pharynx, oesophagus, stomach, "barium swallow and meal")
16. Gall bladder (cholecystography)
17. Chest (heart, cardiac angiography, aorta, respiratory system, lungs)
18. Thorax (sternum, ribs, shoulder, clavicle)
19. Upper limb (hand, forearm, upper arm)
20. Lower leg and foot
21. Head (skull, cervical spine)
22. Dental
23. Mass miniature radiography (photofluoroscopy)

21. For countries where a large part of the radiological work is done in private offices, much of it perhaps by non-radiologists, it is very difficult to determine the total number of examinations per year, and still more difficult to establish the number of examinations of each type or the age and sex distribution of the patients examined. Film consumption provides some check on total volume of radiography, but none at all on fluoroscopy. Under these circumstances it appears that a rather carefully organized survey along the lines suggested by the ICRP/ICRU Study Group is required to obtain the necessary data. It is important to specify whether a total number of examinations, or a figure for film consumption in a country, in fact includes all practices. Special care should be given the presentation of dental and mass chest examinations.

22. For countries where the major part of the diagnostic radiology is controlled by governmental institutions and a high percentage of the examinations is carried out in hospitals, it is probable that the total number of procedures is known fairly accurately and

that sampling of representative hospitals is satisfactory for determining the number of examinations of each type carried out.

23. All information on the number of films, views taken, size of fields and radiographic factors used for an "average" examination are helpful for calculation of dose in the absence of measurements, or as a check on measured values. Measurements performed by specialists give, however, more reliable results than any calculations.

24. The gonad dose per examination should be determined more carefully for those exposure classes in which the doses are expected to have the greatest genetic significance. The dose should be investigated in a manner that permits the assessments of an average for a whole population. The doses received by children require particular attention since few data are available. In any estimates of genetically significant doses, at least children and adults should be treated separately and, when the inaccuracy in other factors has been reduced sufficiently, it may be desirable to classify adults on the basis of size as well.

25. Foetal exposure has a special genetic significance because of the comparatively high relative child-expectancy, which in the case of the foetus becomes W/w (stillborns neglected).

26. The difference between the mean child-expectancy of each class of patients and the mean child-expectancy of the same age and sex group in the population should be determined with regard to its correlation with:

(*a*) type of diagnostic examination;

(*b*) disease treated and type of treatment.

The correlation with type of diagnostic examination may prove to be small but there is at present no evidence. In therapy, the dependence on disease treated is obvious but must be determined quantitatively to permit accurate estimation of the genetically significant dose.

*Exposure of the bone marrow*

27. According to one hypothesis, the possible radiation induction of leukemia is a linear function of dose. The same dose to different individuals will probably entail different degrees of risk for the subsequent occurrence of the disease, depending upon the age at the time of exposure and other unknown factors. As the appropriate weighting procedure is not known, the various contributions to marrow exposure must, at present, be compared without weighting, and the *per capita* dose in a population is taken as approximately determining the total number of cases of leukemia to be expected during the years following a certain exposure.

28. For the linear dose-effect relationship the relevant dose is assumed to be the mean marrow dose, averaged over the whole mass of active marrow (ca. 1,500 g in an adult). The active marrow is taken to be distributed approximately as follows:

| | |
|---|---|
| Spinal column | 40 per cent |
| Ribs and sternum | 25 " " |
| Pelvis | 15 " " |
| Skull | 10 " " |
| Other (e.g. in extremities, etc.) | 10 " " |

Infants and children have a wide distribution of active marrow throughout the skeleton, making estimates of the mean dose difficult, especially as the distribution is dependent on age.

29. According to another hypothesis, there is a threshold dose for the induction of leukemia; in this case a *per capita* marrow dose has no relevance but the individual marrow doses become the determining factors. As the relevant dose may then well be the maximum dose to the marrow, wherever it occurs, the mean dose will not give a measure of the possible risk.

30. As the evaluation of the significance of a marrow exposure may involve the number of "years-at-risk", the mean life-expectancy of each class of patients should be studied.

31. More extensive measurements of the marrow dose resulting from diagnostic and therapeutic procedures should be made.

32. The weight and distribution of active marrow at different ages should be determined.

*Diagnostic uses of X-rays*

33. It has been estimated that 75 to 90 per cent of the total dose from medical uses of ionizing radiations results from the diagnostic uses of X-rays.[1]

*Estimates of the genetically significant dose*

34. It should be noticed that almost all estimates of the genetically significant dose from diagnostic exposure have been made under the assumption that the child-expectancy of the patients is not influenced by the nature of the condition for which they were examined. This assumption has not yet been supported by any evidence.

35. The Committee has considered data on gonad exposure from diagnostic X-ray procedures in Australia,[2] Austria,[3] Denmark,[4] England and Wales,[5] France,[6] Japan,[7] Norway,[8] Sweden[9] and U.S.A.[10] Some authors have reported all data needed for an estimate of the genetically significant dose (with the exception stated in paragraph 34), while others have given less complete information. Because of the different procedures of estimates and because of the difference in diagnostic practice, the data are not strictly comparable. However, as far as practicable the material is presented in this report according to the same uniform scheme, following the procedure given in paragraphs 6-26.

36. The material from the various countries is presented separately in appendices 1-10, as it has been found difficult to make a step by step comparison of the data. So far as possible the anatomical classification of examinations recommended by the ICRP/ICRU Study Group[1] has been used. When the original report differs from this classification, the authors' own terms have been used, within quotation marks, following the number of the most closely related standard class. For uniformity of presentation, the data are recorded in terms of equation (8).

37. The procedure by which $D_j$ was estimated for each country is indicated in the introduction to each set of tables. Values of $d_j$ for some of the more important examinations are collected in appendix XI.

38. The most obvious feature of the detailed results has already been pointed out by the ICRP/ICRU Study Group[1] and by others, namely that about 85 per cent of the genetically significant dose results from six or seven anatomical types of examinations (those in the region of the lower abdomen and pelvis), during which the gonads are usually in the primary beam, although these constitute less than 10 per cent of the total number of examinations.

39. Data from countries for which it has been possible to calculate both the *per capita* gonad dose and the genetically significant dose indicate that, at present, these doses are almost the same. This is, of course, a mere coincidence and is true only for the *total* of all contributions. The *relative* contribution from the various exposure classes is quite different in the two cases. For example, while both the annual *per capita* gonad dose and the annual genetically significant dose in the British minimum estimate (see appendix IV) are 23 mrem, the corresponding contributions for an examination of a group with a low child-expectancy such as "female bladder", are 0.26 and 0.08 mrem, and the contributions from a high child-expectancy group such as "foetal exposure in pelvimetry" are 1.4 and 3.4 mrem respectively.

40. Some of the available data have been collected in table I, which gives a comparison of the frequency of examinations and the level of exposure in various countries. The *per capita* number of radiographic examinations reported by Martin in Australia is unusually high and is the main source for the high estimate of the genetically significant dose in this country.

TABLE I. DATA ON GONAD EXPOSURE FROM DIAGNOSTIC X-RAY PROCEDURES IN VARIOUS COUNTRIES

| Country | Year of study | Population at time of study ($N$) | Population under mean age of child bearing ($n$) | Mean child expectancy ($w$) | Expected number of children after birth ($W$) | Relative child expectancy after birth ($W/w$) | Annual number of examinations per capita of total population: •R Radiography (except dental & mass survey) | •F Fluoroscopy | •M Mass surveys | •D Dental | Consumption of X-ray films—Annual number per capita ($f$) | Annual genetically significant dose ($D_1$) (mrem) | $\frac{D_1}{(\bullet R+\bullet F)}$ (mrem) | $D_1/f$ (mrem) | Per capita dose (mrem) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Australia | 1955-1957 | 9,500,000 | | | | | 0.48 | —[a] | 0.19 | no data | | 160 (28[d]) | 330 (58[d]) | | 150 (28[d]) |
| Austria | 1955-1957 | 6,974,000 | 3,095,000 | | | 2.25 | 0.067 | 0.31 | 0.0075 | no data | | | | | 16-24 |
| Denmark | 1956-1957 | 4,450,000 | (1,610,000) | 0.92 | 2.54 | 2.76 | 0.23 | —[a] | 0.23 | no data | 1.0 | 17[d] | 75[d] | 17[d] | 25[d] |
| England & Wales | 1955 | 44,440,000 | (18,700,000) | 0.93 | 2.20 | 2.36 | 0.30 | —[a] | 0.076 | 0.021 | | 23[d] | 75[d] | | 23[d] |
| France | 1957 | 42,000,000 | 19,000,000 | | | 2.21 | 0.15 | 0.62[c] | 0.50[c] | no data | 0.86 | 57[d] | 75[d] | 65[d] | 57[d] |
| Japan | 1956 | 90,000,000 | 58,000,000 | | | 1.55 | 0.28 | 0.04 | 0.26 | no data | | | | | 10-30 |
| New Zealand | 1957 | 2,221,000 | (1,160,000) | 1.71 | 3.28 | 1.92 | 0.34 | —[a] | 0.09 | 0.24 | | | | | |
| Norway | 1956 | 3,400,000 | | | | | | | 0.15 | | 1.1 | | | | |
| Sweden | 1955 | 7,178,000 | (2,980,000) | 0.91 | 2.19 | 2.41 | 0.31 | —[a] | 0.14 | (0.3[b]) | 1.0 | 38 | 115 | 36 | |
| U.S.A. | 1955-1956 | 162,000,000 | 81,700,000 | | | 1.98 | 0.25 | 0.08 | 0.13 | 0.4 (1.2[b]) | 0.68 | 141 (50[d]) | 430 (150[d]) | 210 (75[d]) | 170 |

[a] Fluoroscopy is generally performed only in connexion with radiography.

[b] Number of films.

[c] 26,000,000 fluoroscopic examinations per year in France include 19,000,000 mass surveys on the population under age 30. In addition, 2,000,000 photofluoroscopic examinations are performed annually, so the total number of mass survey examinations is likely to exceed 21,000,000 per year.

[d] Minimum estimate.

*Estimates of bone marrow dose*

41. The reports on the dose resulting from the treatment of *Ankylosing Spondylitis* provide the best basis at present for evaluation of a possible risk for radiation-induced leukemia.[11] A discussion on the interpretation of this material is given in chapter V. It should be noticed that some references to marrow dose in literature refer to the mean *spinal* marrow dose instead of the average over the whole mass of active marrow. The latter dose is only about 40 per cent of the mean dose in the spine marrow if other marrow than the spinal has not been exposed.

42. Few measurements of the dose resulting from *diagnostic* X-ray exposure of the bone marrow have been published. The annual mean marrow dose from diagnostic X-ray exposure in Australia has been estimated to be about 100 mrem *per capita*.[12] An attempt has been made here to make another estimate based upon a good current practice and an average frequency of examinations in the same countries which have reported data on gonad exposure.

43. A representative number of examinations of each type $N_j$, has accordingly been taken from the data on the genetically significant dose, and the mean marrow dose, averaged over the whole active marrow dose, has been calculated from available information on number of films per examination, size of films, skin dose per film, percentage depth dose, etc. Since the estimate at best is only a very preliminary one, it has been considered justifiable to make several simplifying assumptions.

44. All estimates have been based on "standard man" as defined by the ICRP.[13] It has been assumed that the total weight of active marrow is 1,500 grams and that it is distributed as follows: spinal column, 40 per cent; ribs and sternum, 25 per cent; pelvis, 15 per cent; skull, 10 per cent; other, 10 per cent. No estimates for children have been attempted; this would be more difficult because of the wide distribution of active marrow throughout the skeleton of a child and the dependence of this distribution on age.

45. The number of films per examination have been determined from manuals of radiology[14,15] and from published reports on radiographic techniques. The number of films assumed per examination range from one to five (including spot films), depending on the anatomical part; the average is 2.6 as compared with an average of 3 assumed by Laughlin and Pullman.[10] In most cases, Webster and Merrill's[16] values of skin dose have been used. These are considerably lower than many of the published values (e.g. Ritter, Warren and Pendergrass[17]) but are not as low as those of Ardran and Crooks.[18] They are probably fairly representative of the best present-day radiological practice but may be appreciably lower than the skin doses in average practice.

46. The half-value layer of the incident radiation has been assumed to be 3.0 mm of aluminium in all cases, corresponding to an effective voltage of 33.6 kV. The position of the marrow for each view has been determined from "A Cross-Section Anatomy" by Eycleshymer and Schoemaker[19] and the amount of marrow included in the field estimated from reproductions of typical radiographs as found in manuals of radiographic

techniques.[15,16] The percentage depth dose at the level of the marrow has been determined in each case from depth dose tables published by Johns, Epp and Fedoruk,[20] their values being corrected for differences in focus-skin distance and for shielding of marrow by the surrounding bone. The absorption coefficient assumed for bone is not too important since, for the quality of radiation used, the reduction in dose due to bone shielding is probably less than 20 per cent in every case. No correction has been made for the fact that the marrow is located in a trabecular bone structure since it has been estimated[21] that the increase in marrow dose due to proximity of bone is not more than 5 to 15 per cent for radiation of diagnostic quality.

47. The product of the skin dose, the corrected percentage depth dose and the fraction of active marrow assumed to be in the field gives the contribution to the mean marrow dose for each location of marrow. Calculation of dose by this method gives values somewhat lower than measurements of marrow dose reported by Jones and Ellis[21] but are not in serious disagreement. The calulated doses are in good agreement with some preliminary measurements by Laughlin *et al.*[22] of the dose received by the marrow of the vertebral column during a photofluorographic chest examination.

48. The estimates of mean marrow dose from fluoroscopic procedures are much more uncertain than those from radiography. Skin dose rates of 5 r per minute and 10 r per minute have been assumed for radiologists and non-radiologists respectively, and the total time of fluoroscopy taken to be two to five minutes depending on examination. For a country, such as the United States, where the number of examinations by non-radiologists is high, the annual contribution from these examinations to the *per capita* mean marrow dose can be estimated to be between 10 and 20 mrem. In the examinations made by radiologists the fluoroscopic contribution to the *per capita* mean marrow dose is less important although the individual dose from this practice in extreme cases may be very high.

49. From the mean marrow dose, calculated under the simplified assumptions specified above, a *per capita* marrow dose from each type of examination has been estimated, assuming an average frequency of each examination fairly representative for countries such as the United Kingdom, the United States and Sweden. The breakdown of the total by type of examination is given in table II.

50. It is apparent from the table that the highest contribution to the *per capita* mean marrow dose comes from examinations of the gastro-intestinal tract and that mass chest X-ray surveys are of relatively much greater importance here than they are in the case of genetically significant dose. The sum of the contributions in the table is approximately 45 mrem/year and after allowance for the contribution from fluoroscopy, the *per capita* mean marrow dose might be of the order of 50-100 mrem per year, somewhat lower than the Australian estimate[12] and current British estimates[68].

51. The mean marrow dose per examination in mass chest X-ray procedures has been measured by several investigators, who report doses between 70 and 120 mrem

TABLE II. ANNUAL PER CAPITA MEAN MARROW DOSE FROM DIAGNOSTIC X-RAY EXPOSURE (EXCLUDING FLUOROSCOPY)

(Figures based upon an assumed average practice, cf. text)

| *No.* | *Examination* | *Views* | *Mean marrow dose (mrem)* | *No. exam. per 1,000 of total pop.* | *Annual per capita marrow dose (mrem)* |
|---|---|---|---|---|---|
| 1. | Lower femur | 1 AP + 1 LAT | 5 | 5 | 0.025 |
| 2. | Hip and femur | 1 AP + 1 LAT | 30 | 5 | 0.15 |
| 3. | Pelvis | 1 AP | 20 | 5 | 0.1 |
| 4. | Lumbo-sacral | 1 AP + 1 LAT + 2 OBL | 300 | 5 | 1.5 |
| 5. | Lumbar spine | 1 AP + 2 LAT | 400 | 5 | 2.0 |
| 6. | Dorsal spine | 1 AP + 1 LAT + 1 OBL | 400 | 5 | 2.0 |
| 7. | Intrav. pyelography | 5 AP | 200 | 5 | 1.0 |
| 8. | Retrog. pyelography | 2 AP | 100 | 2 | 0.2 |
| 9. | Urethrocystography | 1 AP + 1 LAT + 2 OBL | 300 | 1 | 0.3 |
| 10. | Pelvimetry | 1 AP + 1 outlet + 2 LAT | 800 | 0.5 | 0.4 |
| 11. | Salpingography | 3 AP | 100 | 0.2 | 0.02 |
| 12. | Abdomen (obstetrical) | 1 AP | 100 | 0.5 | 0.05 |
| 13. | Abdomen | 1 AP | 50 | 5 | 0.25 |
| 14. | Lower G.I. | 2 AP + 3 PA | 700 | 10 | 7.0 |
| 15. | Upper G.I. | 1 AP + 2 PA + 1 LAT | 500 | 20 | 10 |
| 16. | Cholecystography | 4 PA | 400 | 5 | 2.0 |
| 17. | Chest | 1 PA + 1 LAT | 40 | 80 | 3.2 |
| 18. | (*a*) Ribs and sternum | 1 PA + 1 LAT | 200 | 2 | 0.4 |
| | (*b*) Shoulder | 1 PA + 1 LAT | 20 | 5 | 0.1 |
| 19. | Arm | 1 | 2 | 30 | 0.06 |
| 20. | Foot | 1 | 2 | 30 | 0.06 |
| 21. | (*a*) Skull | 1 AP + 1 PA + 2 LAT | 50 | 30 | 1.5 |
| | (*b*) Cervical spine | 1 AP + 1 PA + 2 LAT | 50 | 5 | 0.25 |
| 22. | Dental | 1 | 20 | 100 | 2.0[a] |
| 23. | Mass min.[b] | 1 PA | 100 | 100 | 10 |

[a] American practice including about 400 examinations per year per 1,000 of total population gives a mean marrow dose of 8 mrem *per capita* and year. British practice involves only 20 examinations per year per 1,000 of total population, which corresponds to less than 0.4 mrem *per capita* and year. The assumptions on location of active marrow make estimates for skull exposure very uncertain.

[b] See discussion in text, paragraphs 51–52.

for good practice, with examinations involving only a postero-anterior view.[12,22,23,63] In some countries lateral views are taken in addition to the postero-anterior view.[28] Although the doses reported per examination might be considered as low estimates for the current practice, there are indications that it may be possible to reduce this exposure considerably in the future.

52. The relatively high *per capita* mean marrow dose from mass chest X-ray examinations is due to the high frequency of this examination. Assuming 10 per cent of the population examined each year the annual *per capita* mean marrow dose from this type of examination would be 10 mrem; however, certain regions report as high frequency as one examination *per capita* per year which would result in the ten-fold *per capita* dose.

53. In countries where fluoroscopy has not been replaced by photofluoroscopy for mass surveys,[6] the annual *per capita* mean marrow dose probably results to a high degree from these surveys and may considerably exceed 100 mrem.

*Accuracy of estimates*

54. The Committee is in agreement with the suggestion of the ICRP/ICRU Study Group[1] that since the accuracy in estimating the annual genetically significant dose to a "normal" population due to natural sources is about ± 25 mrem, the same absolute accuracy is satisfactory for a first estimate, at least, of the genetically significant dose due to medical sources. This means an accuracy of ± 25 per cent for e.g. the United States and about ± 100 per cent for countries such as Denmark and Sweden. It is stated by Osborn and Smith[5] that the estimate for the United Kingdom may be out by a factor of 2 to 10 and there is a factor of nearly 3 between the minimum and probable doses estimated for the United States.[10] It is evident that the accuracy desired for even a first estimate has not yet been obtained: the eventual objective should be to reduce the absolute uncertainty of the estimate well below that of the background dose.

55. It is convenient to discuss the inaccuracies in the estimates which have been made of the genetically significant dose in terms of equation (8). As pointed out in paragraphs 21-22, the total number of examinations is not very accurately known in countries where a large part of the radiological work is done in private offices and even by non-radiologists.

56. Estimation of the factor $w_j/w$ in equation (8) depends, as has already been said, on two considerations: (*a*) the age and sex distribution of patients receiving each type of examination and (*b*) the difference between the child-bearing expectancies of class jk and class k as a whole. There does not appear to be any evidence on the latter point. However, for most types of diagnostic examination $w_{jk}$ may not differ greatly from $w_k$. Further, it is only for the six or seven examinations which make the largest contributions that a difference between $w_{jk}$ and $w_k$ can affect appreciably the estimate of genetically significant dose.

57. The determination of the distribution of the total number of examinations on various exposure classes and on age and sex groups must be made by sampling procedures. This is difficult to carry out satisfactorily unless a high percentage of the examinations are made out at a relatively small number of hospitals.

58. The same difficulty is related to the estimate of a representative average gonad dose per examination. As the gonad dose per examination varies from hospital to hospital it is very difficult to give an average with a good accuracy. This is probably the main source of uncertainty to the calculated genetically significant dose and the *per capita* mean marrow dose. Values of the gonad dose per examination as measured in various countries are collected by type of examination in appendix XI.

59. Another source of uncertainty in the *per capita* mean marrow dose is the scant information on the distribution of active marrow.

*Reduction of gonadal dose*

60. From an international point of view, the most serious criticism is the fact that to date, estimates are available for only six or seven countries. Fortunately, the have been made for some of the countries in which medical exposures may be expected to be highest.

61. It has been demonstrated[1,9,13,16,18,22,24-26,61] that gonad doses can be reduced very decidedly by improved techniques (e.g., by a factor of 50 to 100) for some examinations of males. The greatest attention must be paid, of course, to the six or seven examinations which contribute the largest significant doses. Methods have been pointed out by the ICRP.[1,18]

62. The following is quoted from the report of the ICRP/ICRU Joint Study Group:[1]

"1. *Current Recommendations*

"*Equipment for fluoroscopy*

"The fixed total filter equivalent value should be at least 2 mm aluminium, and should be based on the value obtained at the highest voltage of the X-ray apparatus.

"The use of a timer to measure the fluoroscopy time is recommended.

"*Procedure for fluoroscopy*

"Before a fluoroscopic examination is begun, the eyes must be sufficiently dark-adapted. In order to work with the lowest possible dose-rate, the adaptation period should be at least 10 minutes. A smaller time may be used if there has been preliminary adaptation using red goggles.

"*Equipment for radiography*

"A total filter of at least 2 mm aluminium should be used.

"An automatic switch should be incorporated.

"*Other types of diagnostic work*

"*Dental radiography*

"Fluoroscopy is strongly deprecated.

"*Mobile diagnostic equipment*

"All transportable equipment should be provided with cones or with other restricting devices so that the smallest anode skin distance is normally at least 30 cm (12 in.).

"It should be noted that damage has occurred to workers and patients from contact radiography.

"At least 1.5 mm aluminium equivalent should be provided as a fixed total filter.

"Fluoroscopy should be used only if the equipment meets the requirements recommended for fluoroscopic equipment.

"*Protection of patients*

"*General rules*

"By X-ray protection of the patient it is meant that the radiation exposure of the patient should be reduced as much as is compatible with successful diag-

nostic investigation or therapeutic treatment. In the case of non-malignant diseases, therapeutic treatment shall be employed with caution. In all therapeutic and diagnostic exposures, the integral dose should be kept as low as possible in order to protect the patient as much as possible from the radiation. Moreover, for this purpose, the tube-current, or the mAs value, and the number of examinations should be kept to a minimum. An automatic timer should indicate the length of the diagnostic or therapeutic exposure. In all diagnostic investigations, the beam that strikes the patient should have a cross-section no larger than is essential for the investigation. This is of particular importance in fluoroscopy. In all irradiations the gonads should be protected as much as possible by collimation of the beam or by protective screens. In the case of children, it is important, in view of the little known action of radiation on growing tissues, to be cautious about repeating diagnostic examinations and to avoid too frequent systematic examinations of the whole of the body.

*"Exposure in diagnostic examinations*

"For ease and clarity in the consideration of exposures received in diagnostic work, it is recommended that tables be set up giving doses for radiography and fluoroscopy of lung, stomach, intestines, etc. Integral dose should also be taken into account as it gives a much clearer picture of the true exposure. Special attention should be given to the possible hazards to pneumothorax patients who, as a result of the many screenings after each inflation, may receive large doses. The screenings should be replaced in part by radiographs.

*"Radiation certificate*

"In view of the continually increasing medical and technical use of ionizing radiation, it is desirable to accumulate information regarding the doses received both by individuals and by the population as a whole. As far as the individual is concerned, the information could be obtained by the introduction of a certificate in which are recorded details of all radiation exposure (medical and occupational) received through life. Probably it is impracticable to introduce such a certificate at present, but it is recommended that all radiologists and dentists keep records of the doses given, and the field sizes and radiation qualities used, in all diagnostic procedures. (It is presumed that such records are already available in the case of therapeutic procedures.)

"2. *Recommendations regarding the following items are under consideration*

"(*a*) The provision of specially designed protective devices for the gonads of patients.

"(*b*) Additional recommendations regarding minimum film-focus distances.

"(*c*) Increasing the protective requirements for diagnostic and therapeutic tube housings.

"(*d*) Improvements in beam collimation.

"(*e*) The provision of permanent filters of at least 2 mm Al equivalent on all diagnostic X-ray tubes.

"(*f*) The advantages of using high voltage techniques for diagnostic work.

"(*g*) The provision of exposure counters on all diagnostic equipment.

"(*h*) The use of image intensifiers to reduce the dose to the patient, and consequently to the operator, rather than as a means of permitting more extensive and prolonged fluoroscopy than hitherto."

63. It is improbable that there will be great improvement in accuracy of estimation of gonad doses until the range of actual doses is reduced appreciably by conscientious adherence to procedures as have been recommended by the ICRP. In this connexion it is probable that the "feedback" suggested by the ICRP/ICRU Study Group is already operating, i.e., the attention to estimation of the genetically significant dose is already reducing the dose.

64. Reduction of gonad dose may also be obtained in the future by means of improved radiological equipment and supplies, e.g., faster films, faster screens, etc. The advantage to be gained by increased use of image amplifiers has already been pointed out by the ICRP/ICRU.[1]

65. Finally, reduction in gonad dose can be achieved by a reconsideration by the medical profession of the circumstances under which X-ray diagnosis is appropriate. This could be facilitated by statistical information on the significance of each examination class for the reduction of any specified morbidity. When medical decision has been taken, administrative co-ordination should be improved between authorities who require that certain examinations be made in the routine health surveillance of whole populations or special groups such as school-children, students, employees, immigrants.

66. The tables in appendix XI point to the possibility of carrying out some examinations at much lower gonad exposure levels than are likely to be obtained in the average case at present. The annual genetically significant dose that may be achievable without detriment to diagnostic information has been estimated to be less than 30 mrem for Australia[2] and 15 mrem for Sweden.[9]

### *Radiotherapy*

*Genetically significant dose*

67. S. H. Clark[37] has estimated the genetically significant dose due to radiotherapy in the United States as about 10 mrem per year. This figure, quoted by Laughlin and Pullman,[10] is based on the assumption that treatment of malignant conditions are not genetically significant. It may hence be an under-estimate. For Australia, Martin[2,36] reports an estimate of the contribution to the genetically significant dose from radiotherapy as 28 mrem per year, assuming a normal child-expectancy of all surviving patients that were not assumed to be sterilized by the irradiation. Survey by Purser and Quist[38] yields an estimate of 1 mrem *per capita* gonad dose per year in Denmark. In the Danish survey it was found that 22 per cent of the genetically significant dose resulted from treatment of malignant conditions, assuming that the patients treated for malignancies have one-fifth the child-expectancy of normal individuals.

*Bone marrow dose*

68. It does not appear possible to estimate with any certainty even the order of magnitude of the *per capita* mean marrow dose, due to radiotherapy, from the data at present available to the Committee.

### *Internally administered radioisotopes*

69. The principal contributions to the population dose from the medical use of radioisotopes arise from the use of $I^{131}$ and $P^{32}$ which are most widely employed. While considerable quantities of $Au^{198}$ are used, the biological significance of exposure from this course is negligible

since $Au^{198}$ is generally limited to palliative treatment of incurable conditions. Other radioisotopes are used in very small quantities and almost entirely for diagnostic purposes.

70. Estimates of the *per capita* gonad dose resulting from the use of $I^{131}$ and $P^{32}$ can be based upon information about either treatments or radioisotope shipments, the first approach being more accurate and preferable.[37,39,40] From the report of the ICRP/ICRU Joint Study Group[1] and other information available to the Committee,[39,40] it seems likely that the genetically significant dose is lower than 1 mrem per year, even in the countries for which the highest figures can be expected.

71. Some experience on the effects of ingesting radioactive substances relates to the early period when the hazard was not realized. The work with radioactive luminous materials was early recognized as hazardous if not properly conducted,[41] but radioactive contrast media such as Thorotrast were being used occasionally in X-ray diagnostic work until a few years ago. The high retention of the radioactive material in the liver and the spleen resulted in rather high exposure, with dose-rates of the order of 0.3 rem per day during periods of years.[42,43]

## III. Industrial and research uses of X-rays and radioactive materials

### *Occupational exposure*

72. The exposure from industrial and research uses of X-rays and radioactive materials is mainly an occupational one. The extent to which non-occupationally exposed individuals are exposed depends upon the degree of environmental contamination. The latter problem is treated in annex D.

### *Medical workers*

73. The countries reporting on the number of persons in medical radiological work[3,7,10,44–46] have presented figures ranging from 0.17—0.69 per 1,000 of the total population. However, in many cases it is not clear what has been meant by "medical worker".

74. The following table shows the extent of X-ray work in New Zealand[45] and Sweden[47] and gives an idea of the relative number of various installations in countries with extensive medical facilities.

Table III. Number of X-ray installations

| Type of installation | New Zealand, 1957: Number of plants per 1,000 of total population | Sweden, 1955: Number of plants per 1,000 of total population | Sweden, 1955: Number of exposed workers per 1,000 of total population |
|---|---|---|---|
| Diagnostic | 0.14 | 0.15 | 0.46 |
| Therapy | 0.02 | 0.01 | 0.03 |
| Dental | 0.24 | 0.40 | 0.93 |
| Chiropractors and naturopathic | 0.02 | — | — |
| Total medical | 0.42 | 0.56 | 1.42 |
| Shoefitting | 0.03 | — | — |
| Veterinary | 0.01 | 0.004 | 0.01 |
| Industrial | 0.003 | 0.02 | 0.06 |
| Research and educational | 0.01 | 0.03 | 0.02 |

75. The age-distribution of the workers is usually such that about 50 per cent are under the mean age of child-bearing.[3,7,46] Hence, the genetically significant dose is approximately equal to the *per capita* dose. Average annual doses ranging from 500 - 5,000 mrem have been reported to the Committee as resulting from occupational medical exposure,[3,7,44–46] but this exposure does not refer to all installations shown in table III. For example, the exposure of dentists or their assistants is usually very small,[47] and most radiotherapy with X-rays can be carried out under conditions ensuring good protection of the personnel.[48] Annual average doses of up to 5,000 mrem refer to less than 0.2 persons per 1,000 of the total population and result therefore in a *per capita* dose of less than 1 mrem per year, mostly from X-ray diagnostic work.[48,49]

76. Medical radioisotope work is usually performed with little exposure of the personnel.[48] An important exception is the work with implantation of radium applicators and needles where the personnel may at present be exposed to considerably more than 100 mrem per week.[50,66,67] This exposure, however, involves only a very small group of people.

### *Atomic energy workers*

77. More complete and more accurate data are available for this group than for any other occupationally exposed group, since in countries in which atomic energy establishments are operated, monitoring procedures have been set up to cover exposed personnel.

78. The contribution from exposure of atomic energy workers to the genetically significant dose to the population is about 0.1 mrem per year or less in countries for which it has been estimated.[44,46,51,52] However, since the number of atomic energy workers is expected to increase in the near future, this figure may increase in proportion.

79. The figures in table IV have been taken from a report of the United States Atomic Energy Commission.[51]

Table IV. Exposure of atomic energy personnel in the United States of America

(a) *Exposure of A.E.C. contractor personnel to penetrating radiation (1955)*

| Annual dose (mrem) | Number of workers | Percentage |
|---|---|---|
| 0– 1,000 | 56,708 | 94.2 |
| 1,000– 5,000 | 3,157 | 5.2 |
| 5,000–10,000 | 285 | 0.5 |
| 10,000–15,000 | 41 | <0.1 |
| >15,000 | 3 | <0.01 |
| | 60,194 | 100.0 |

(b) *Highest accumulated yearly doses to individual A.E.C. contractor employees during routine operations (accidents excluded)*

| Year | Highest dose (rem) | Average of 10 highest doses (rem) |
|---|---|---|
| 1947 | 23.5 | 5.2 |
| 1948 | 20.3 | 4.2 |
| 1949 | 13.6 | 2.6 |
| 1950 | 9.0 | 2.2 |
| 1951 | 7.1 | 1.8 |
| 1952 | 15.7 | 2.9 |
| 1953 | 12.9 | 3.4 |
| 1954 | 27.8 | 3.9 |
| 1955 | 17.9 | 4.1 |

*Industrial and research workers*

80. The information on exposure of industrial and research workers is less complete than the information on exposure of the other occupational groups.[3,44-46,48,53] As is evident from the relation between the number of persons and number of plants in table III, the concept "research worker" is not well defined. If the exposure is assumed to be equal to that in the group of medical workers, the contribution to the population dose is lower, because of the smaller number of workers. Industrial γ-radiography is one of the main sources of exposure of this group.[48]

81. A special occupational problem is the exposure of workers in mining and milling radioactive materials such as uranium.[48,54] If not properly conducted, this work may involve considerable hazard to the workers.

*Summary*

82. From the information surveyed above, it appears that the contribution from occupational exposure to the genetically significant dose is less than 2 mrem per year for most countries. Despite the fact that this contribution is relatively small and the corresponding contribution to doses significant for somatic injury is also small, the exposure of radiation workers merits special attention for two reasons: (*a*) there will be a considerable increase in the near future in the number of atomic energy employees in many countries, and (*b*) individual exposures may be high even though the contribution to the mean dose of the population is small.

83. Methods for reducing the occupational exposure have been pointed out by ICRP[18] and ILO.[55]

### IV. Other man-made sources of radiation

84. Watches and clocks with radioactive luminous dials give an annual genetically significant dose of about 1 mrem.[46,56] X-rays from television receivers contribute less than 1 mrem.[46] X-rays from shoe-fitting fluoroscopes contribute still less, as they normally expose a relatively small number of individuals.[45,46,57] (However, they might be an important hazard to the exposed individuals, see reference 64.)

## Appendices

## DATA FOR EVALUATION OF THE GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

### Appendix I

### AUSTRALIA

The data on gonad exposure in Australia have been taken from papers by Martin[2,36]. The author has rearranged his material for the purpose of this report. Martin's estimate of the annual genetically significant dose is unusually high. This is mainly due to the high *per capita* number of examinations, which the author has assumed to be 60 per cent higher than the number for England and Wales (cf. paragraph 40).

(*See Appendix I. Table I on page 71.*)

## Data for evaluation of the genetically significant dose from diagnostic X-ray exposure

Appendix I. Table I.

Australia

| No. | Examination | Females | | | | | | | | | | Males | | | | | | | | | | TOTAL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | <30 | | | 30–44 | | | >44 | | | | <30 | | | 30–44 | | | 44> | | | | |
| | | $d_j^*$ (mrem) | 1,000 $N_{jk}^*/N$ | $w_{jk}^*/w$ | $D_{jk}^*$ (mrem) | 1,000 $N_{jk}^*/N$ | $w_{jk}^*/w$ | $D_{jk}^*$ (mrem) | 1,000 $N_{jk}^*/N$ | $w_{jk}^*/w$ | $D_{jk}^*$ (mrem) | $d_j^*$ (mrem) | 1,000 $N_{jk}^*/N$ | $w_{jk}^*/w$ | $D_{jk}^*$ (mrem) | 1,000 $N_{jk}^*/N$ | $w_{jk}^*/w$ | $D_{jk}^*$ (mrem) | 1,000 $N_{jk}^*/N$ | $w_{jk}^*/w$ | $D_{jk}^*$ (mrem) | $D_j$ (mrem) | Per cent |
| 1. | "Hips" | 440 | 1.94 | 3.05 | 2.61 | 1.34 | 0.25 | 0.15 | 3.48 | 0.003 | 0.0046 | 880 | 1.97 | 2.76 | 4.8 | 1.24 | 0.58 | 0.63 | 2.42 | 0.003 | 0.0061 | 8.2 | 10.8 |
| 2. | | | | | | | | | | | | | | | | | | | | | | | |
| 3. | "Pelvis" | 800 | 1.7 | " | 4.15 | 1.17 | " | 0.235 | 3.04 | " | 0.0007 | 1,080 | 1.9 | " | 5.66 | 1.19 | " | 0.749 | 2.34 | " | 0.007 | 10.8 | 14.2 |
| 4. | "L. S. J." | 1,025 | 2.06 | " | 6.45 | 1.42 | " | 0.364 | 3.68 | " | 0.0113 | 81 | 3.28 | " | 0.734 | 2.06 | " | 0.097 | 4.03 | " | 0.001 | 7.7 | 10.1 |
| 5. | | | | | | | | | | | | | | | | | | | | | | | |
| 6. | "D. Vert" | 124 | 1.27 | " | 4.82 | 0.87 | " | 0.27 | 2.27 | " | 0.0084 | 17.2 | 1.75 | " | 0.083 | 1.1 | " | 0.011 | 2.15 | " | 0.0001 | 5.2 | 6.8 |
| 7. | "I. V. P." | 1,360 | 1.4 | " | 5.83 | 0.96 | " | 0.328 | 2.5 | " | 0.0102 | 590 | 1.68 | " | 2.73 | 1.05 | " | 0.36 | 2.06 | " | 0.0037 | 9.3 | 12.2 |
| 8. | "Ret. Pyel." | 800 | 0.3 | " | 0.73 | 0.21 | " | 0.042 | 0.54 | " | 0.0013 | 700 | 0.29 | " | 0.56 | 0.18 | " | 0.073 | 0.35 | " | 0.0007 | 1.4 | 1.8 |
| 9. | "Bladder" | 210 | 0.18 | " | 0.115 | 0.12 | " | 0.0063 | 0.32 | " | 0.0002 | 240 | 0.44 | " | 0.29 | 0.28 | " | 0.0383 | 0.54 | " | 0.0004 | 0.45 | 0.6 |
| 10. | | | | | | | | | | | | | | | | | | | | | | | |
| 11. | "Salpine" | 25,000 | 0.12 | " | 9.15 | 0.08 | " | 0.5 | 0.21 | " | 0.016 | — | — | — | — | — | — | — | — | — | — | 9.7 | 12.7 |
| 12. | | | | | | | | | | | | | | | | | | | | | | | |
| 13. | "Ur. tract" | 203 | 2.9 | " | 1.795 | 2 | " | 0.101 | 5.19 | " | 0.00315 | 110 | 4.01 | 2.76 | 1.22 | 2 52 | 0.58 | 0.161 | 4.93 | 0.003 | 0.0016 | | |
| | "Kidney" | 60 | 0.12 | " | 0.0021 | 0.08 | " | 0.0001 | 0.21 | " | — | 3.7 | 0.15 | " | 0.0014 | 0.09 | " | 0.0002 | 0.18 | " | — | | |
| | "Liver" | 20 | 0.06 | " | 0.0037 | 0.4 | " | 0.0002 | 0.11 | " | — | 2.0 | 0.07 | " | 0.0003 | 0.04 | " | 0.0001 | 0.09 | " | — | 3.3 | 4.3 |
| 14. | "Intest. Tract" | 520 | 1.45 | " | 2.3 | 1 | " | 0.13 | 2.6 | " | 0.0041 | 130 | 1.82 | " | 0.651 | 1.14 | " | 0.086 | 2.24 | " | 0.0009 | 3.2 | 4.2 |
| 15. | "Stomach" | 360 | 3.27 | " | 3.59 | 2.26 | " | 0.203 | 5.85 | " | 0.0063 | 470 | 6.05 | " | 7.84 | 3.8 | " | 1.04 | 7.43 | " | 0.010 | 12.7 | 16.7 |
| 16. | "Gall Bladder" | 70 | 2.78 | " | 0.591 | 1.92 | " | 0.0335 | 4.97 | " | 0.001 | 2.7 | 1.39 | " | 0.0105 | 0.87 | " | 0.0014 | 1.71 | " | — | 4.0 | 5.2 |
| | "Cholecyst." | 378 | 2.76 | " | 3.17 | 1.9 | " | 0.179 | 4.94 | " | 0.0056 | 13.5 | 1.01 | " | 0.0375 | 0.64 | " | 0.005 | 1.24 | " | — | | |
| 17. | "Chest" | 2.4 | 17.6 | " | 0.1285 | 12.1 | " | 0.0073 | 31.4 | " | 0.0023 | 0.4 | 15.2 | " | 0.0168 | 9.55 | " | 0.0022 | 18.7 | " | — | 0.2 | 0.2 |
| 18. | "Ribs" | 3.8 | 0.49 | " | 0.0055 | 0.34 | " | 0.0003 | 0.88 | " | — | 0.7 | 0.37 | " | 0.0008 | 0.23 | " | 0.0001 | 0.45 | " | — | | |
| | "Shoulder" | 3.4 | 0.91 | " | 0.0095 | 0.63 | " | 0.0005 | 1.63 | " | — | 0.7 | 1.75 | " | 0.0033 | 1.1 | " | 0.0005 | 2.15 | " | — | 0.02 | 0.03 |
| 19. | "Extrem." | 1.0 | 10.6 | " | 0.0324 | 7.3 | " | 0.0018 | 19 | " | — | 2.1 | 19.6 | " | 0.113 | 12.3 | " | 0.015 | 24.1 | " | 0.0002 | 0.2 | 0.2 |
| 20. | | | | | | | | | | | | | | | | | | | | | | | |
| 21. | "Skulls, etc." | 1.0 | 7.5 | " | 0.0229 | 5.4 | " | 0.0013 | 13.4 | " | 0.0004 | 0.2 | 9.2 | " | 0.005 | 5.77 | " | 0.007 | 11.3 | " | 0.0001 | 0.05 | 0.06 |
| | "C. Vert." | 1.2 | 1.03 | " | 0.0037 | 0.71 | " | 0.0002 | 1.84 | " | — | 1.5 | 1.09 | " | 0.0044 | 0.68 | " | 0.0006 | 1.34 | " | — | | |
| 22. | | | | | | | | | | | | | | | | | | | | | | | |
| 23. | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | 100 |

| | | | |
|---|---|---|---|
| Sub-total: | Adult examinations | 76 | 47 |
| | Children | 46 | 28.4 |
| | Foetus | 22.6 | 14.0 |
| | Fluoroscopy | 17 | 10.5 |
| | Mass surveys | 0.2 | 0.1 |
| | Total | 162 | 100.0 |

## APPENDIX II
## AUSTRIA

The data submitted by Austria[3] do not permit a presentation according to Equation (8). The following information is given:

| *Type of examination* | *1,000 $N_j/N$* | *$d_j$ (mrem)* Females | Males |
|---|---|---|---|
| (A) *Radiography:* | | | |
| Pelvis, hips, lumbar spine | 6 | 40–240 (AP) 20–80 (Lat) | 6–24 (AP) 8–30 (Lat) |
| Abdomen, colon, genito-urinary | 7.5 | 6,000 | 12,000 |
| Pelvimetry, obstetrics | 0.75 | 200 (AP) 1,000 (Lat) | — |
| Other classic techniques | 52 | 60 | 40 |
| Tomography | 0.15 | 2 | 2 |
| Other special techniques | 0.75 | — | — |
| Dental | not known | 10–100 | 10–100 |
| Mass surveys | 7.5 | 2 | 1 |
| (B) *Fluoroscopy:* | | | |
| Mass surveys | negligible | — | — |
| Other examinations | 310 | not known | not known |

From the above data, the *per capita* gonad dose from diagnostic X-ray exposure is estimated to be 16-25 mrem per year.

## APPENDIX III
## DENMARK

### *The primary material*

1. The following estimate of the genetically significant dose from diagnostic X-ray procedures in Denmark is based upon data published by Hammer-Jacobsen.[4] The author assumes the annual number of examinations in Denmark to be 1,000,000 plus 1,000,000 mass chest photofluoroscopies. The data are assumed to be representative for 1956 (the dose-measurements were made during September 1956-February 1957).

2. The examinations cover the total practice with radiography and fluoroscopy combined. However, the distribution of examinations with respect to type and sex is as observed in one hospital in which about 5 per cent of the total number of examinations are performed.

3. The author estimates a *per capita* dose of 26 mrem from the above data, but considers that this may be a minimum estimate.

4. No data on foetal exposure are given. The author estimates the foetal contribution to the total *per capita* dose in proportion to the relation foetal/female contribution given by Osborn and Smith.[5]

### *Presentation of the material for this report*

5. The Danish data include values for $N_j$ and $d_j$ in all cases needed for an estimate of $D_j$.

6. No values for $w_j/w$ are given. The values for $w_j/w$ presented in the table for England and Wales have been used as substitutes in the first approximation. This gives female and male contributions of 5 and 8 mrem to the genetically significant dose, as compared to the author's *per capita* doses of 7 and 15 mrem respectively.

7. If the foetal contribution is taken in proportion to the female contribution and the ratio 72.2 per cent from the British report is used, the foetal value will be 4 mrem. This seems, however, to be a low value, as a back calculation by help of the known value of $w_j/w$ for the foetus, implies a foetal dose of, e.g., less than 500 mrem per examination from pelvimetry, whereas other countries report values ranging from 2,500-4,500 mrem.

DATA FOR EVALUATION OF THE GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

APPENDIX III. TABLE I. DENMARK

| *No.* | *Type of examination* | *Females* $1{,}000\ N_j/N$ | $d_j$ *mrem* | $w_j/w$ | $D_j$ *mrem* | *Males* $1{,}000\ N_j/N$ | $d_j$ *mrem* | $w_j/w$ | $D_j$ *mrem* | *Totals* $D_j$ *mrem* | $D_j$ *per cent* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Hip and femur | 2.5 | 54 | 0.7 | 0.09 | 2.2 | 911 | 1.1 | 2.20 | 2.29 | 13.4 |
| 2. | "Knee and crus" | 4.7 | 0.6 | 0.7 | 0.00 | 4.3 | 3.25 | 1.1 | 0.02 | 0.02 | 0.1 |
| 3. | Pelvic region | 0.7 | 195 | 0.9 | 0.13 | 2.5 | 527 | 0.6 | 0.79 | 0.92 | 5.4 |
| 4. 5. | Lumbar spine | 3.4 | 206 | 0.6 | 0.42 | 4.3 | 97 | 0.8 | 0.33 | 0.75 | 4.4 |
| 6. | Dorsal spine | 1.1 | 14 | 0.7 | 0.01 | 2.2 | 20 | 0.8 | 0.04 | 0.05 | 0.3 |
| 7. | Intraven. pyelography | 4.3 | 525 | 0.8 | 1.81 | 4.3 | 948 | 0.5 | 2.04 | 3.85 | 22.5 |
| 8. | Retrograde pyelography | 0.4 | 1,060 | 0.8 | 0.34 | 0.9 | 2,400 | 0.5 | 1.08 | 1.42 | 8.3 |
| 9. | "Urethrocystography" | 0.0 | 430 | — | 0.00 | 0.4 | 3,450[a] | 0.5 | 0.69 | 0.69 | 4.0 |
| | "Cystogr. dur. micturition" | 0.4 | 406 | 0.3 | 0.04 | 0.4 | 4,720 | 0.23 | 0.43 | 0.45 | 2.6 |
| 10. | Pelvimetry | 2.2 | 764 | 0.9 | 1.51 | — | — | — | — | 1.51 | 8.8 |
| 11. | Hysterosalpingography | 0.9 | 183 | 1.1 | 0.18 | — | — | — | — | 0.18 | 1.1 |
| 12. | Obstetrical abdomen | 2.0 | 177 | 1.8 | 0.64 | — | — | — | — | 0.64 | 3.7 |
| 13. | "Abdomen, A. P., urin." | 0.4 | 79 | 0.6 | 0.02 | 0.4 | 567 | 0.6 | 0.14 | 0.16 | 0.9 |
| 14. | "Barium enema" | 4.3 | 19 | 0.2 | 0.02 | 4.3 | 37 | 0.4 | 0.06 | 0.08 | 0.5 |
| 15. | "Barium swallow and meal" | 7.2 | 8.4 | 0.4 | 0.02 | 7.4 | 19 | 0.04 | 0.06 | 0.08 | 0.5 |
| 16. | "Gall bladder" | 4.0 | 14.5 | 0.2 | 0.01 | 2.0 | 1.7 | 0.3 | 0.00 | 0.01 | 0.1 |
| 17. | "Chest" | 36.0 | 0.07 | 1.3 | 0.00 | 34.6 | 0.33 | 1.3 | 0.01 | 0.01 | 0.1 |
| | "Chest, special" | 3.8 | 5.0 | 0.5 | 0.01 | 4.5 | 34 | 0.8 | 0.12 | 0.13 | 0.8 |
| 18. | "Shoulder" | 2.0 | 0.03 | 0.7 | 0.00 | 2.2 | 0.20 | 0.9 | 0.00 | 0.00 | 0.0 |
| | "Ribs and sternum" | 0.2 | 0.15 | 0.4 | 0.00 | 0.4 | 0.45 | 0.7 | 0.00 | 0.00 | 0.0 |
| 19. | "Arm and hand" | 5.8 | 0.05 | 1.1 | 0.00 | 9.4 | 0.24 | 1.5 | 0.00 | 0.00 | 0.0 |
| 20. | "Foot" | 2.9 | 0.6 | 1.0 | 0.00 | 4.7 | 3.25 | 1.2 | 0.02 | 0.02 | 0.1 |
| 21. | "Head" | 14.8 | 0.2 | 1.5 | 0.00 | 17.5 | 0.8 | 1.6 | 0.02 | 0.02 | 0.1 |
| | "Teeth" | 1.3 | 0.8 | 1.0 | 0.00 | 1.8 | 4.4 | 0.9 | 0.01 | 0.01 | 0.1 |
| | "Cervical spine" | 4.0 | 0.17 | 0.5 | 0.00 | 3.8 | 1.6 | 1.1 | 0.01 | 0.01 | 0.1 |
| 22. | Dental | — | — | 0.5 | 0.00 | — | — | 0.4 | — | 0.00 | 0.0 |
| 23. | Mass min. radiography | 110 | 0.15 | 1.3 | 0.02 | 110 | 0.25 | 0.9 | 0.02 | 0.04 | 0.2 |
| | SUB-TOTALS | — | — | — | 5.25 | — | — | — | 8.09 | 13.3 | — |
| | Allowance for foetal exposure, assumed to be 72.2% of female contribution | | | | | | | | | 3.8 | 22.4 |
| | | | | | | | | | TOTAL | 17 | 100 |

[a] The dose 3,450 mrem for males in item 9 is an average of dose measurements from 7 male adults urethrography + 1 boy urethrography + 2 male adults cystography.

## APPENDIX IV

## ENGLAND AND WALES

### *The primary material*

1. The Committee has not received material upon which it can base an estimate of the probable genetically significant dose for England and Wales. It is, however, possible to give a lower limit under certain assumptions. The primary figures (for radiography and fluoroscopy combined) have been taken from a report by Osborn and Smith (1956).[5] These authors have used values for the gonad dose per examination published by Stanford and Vance (1956).[58] They computed the product $N_j^* w_j^* d_j^*$ using the following statistics:

(*a*) The total number of diagnostic examinations per year based on official figures.

(*b*) The distribution of examination with respect to type, age and sex in what was believed to be a representative sample of hospitals.

(*c*) The child-expectancy derived from official statistics and assumed not to be influenced by the nature of the condition for which the patient was examined (except in the case of hysterosalpingography).

2. An extensive British survey of the diagnostic exposure in the United Kingdom is at present being made,[59] but no data are available for this report.

### *Presentation of the material for this report**

3. After division by wN the values reported by Osborn and Smith may be taken as approximate lower limits of the contributions to the genetically significant dose for England and Wales. The values of $w_j/w$ for each examination class have been calculated from the known values of $N_j/N$, $d_j$ and the approximation of $D_j$, and should depend only upon the age-distribution within the class following the assumption under 1. (*c*) above.

* These calculations are based on available figures which in some cases have been "rounded off" in publication. The results are therefore approximate and, although adequate for the present purpose, are less accurate than could be derived from calculations based on the original data.

NUMBER OF EXAMINATIONS PER 1,000 OF TOTAL POPULATION
(1000 $N_j^*/N$)

APPENDIX IV. TABLE I. ENGLAND AND WALES

| *Exam. No.* | *Females (all ages)* | *Males (all ages)* | *Foetal gonads* |
|---|---|---|---|
| 1. | | | |
| 2. "Hip and femur" | 5.6 | 5.6 | 0.03 |
| 3. Pelvis | 2.8 | 2.8 | 0.09 |
| 4. | | | |
| 5. "Lumbar spine" | 5.6 | 5.6 | 0.10 |
| 6. "Thoracic spine" | 2.4 | 2.0 | 0.04 |
| 7. | | | |
| 8. "Pyelography" | 2.4 | 2.8 | 0.07 |
| 9. "Bladder" | 0.4 | 0.4 | 0.014 |
| 10. Pelvimetry | 0.58 | — | 0.58 |
| 11. Salpingography | 0.14 | — | — |
| 12. | | | |
| 13. "Abdomen with obstetric" | 4.4[a] | 2.4 | 2.15[b] |
| 14. "Barium enema" | 2.8 | 2.0 | 0.02 |
| 15. "Barium swallow and meal" | 6.4 | 10.4 | 0.11 |
| 16. Cholecystography | 1.6 | 0.8 | 0.02 |
| 17. Chest | 50[c] + 3.2[d] | 47[c] + 1.6[d] | 1.2[c] + 0.24[d] |
| 18. "Ribs and sternum + shoulder" | 0.4 + 2.4 | 1.6 + 3.2 | 0.00 + 0.00 |
| 19. Arm | 17.1 | 19.1 | 0.20 |
| 20. Lower leg | 15.6 | 20.0 | 0.17 |
| 21. "Head + cervical spine" | 13.6 + 2.8 | 15.4 + 1.6 | 0.25 + 0.00 |
| 22. Dental | 11.9 + 1.2[e] | 7.2 + 0.8[e] | 0.14 |
| 23. Mass surveys | 30.2 | 46 | |
| 24. Others | 0.8 | 16.3 | |

[a] Including 1.94 obstetrical.
[b] Including allowance for possible pregnancy in non-obstetric abdominal examinations.
[c] Large film.
[d] Special film.
[e] Teeth exam. at hospitals.

$(w_j^*/w)$

APPENDIX IV. TABLE II. ENGLAND AND WALES

| *Exam. No.* | *Females (all ages)* | *Males (all ages)* | *Foetal gonads* |
|---|---|---|---|
| 1. | | | |
| 2. "Hip and femur" | 0.75 | 1.13 | 2.36 |
| 3. Pelvis | 0.93 | 0.56 | " |
| 4. | | | |
| 5. "Lumbar spine" | 0.63 | 0.83 | " |
| 6. "Thoracic spine" | 0.67 | 0.80 | " |
| 7. | | | |
| 8. "Pyelography" | 0.81 | 0.53 | " |
| 9. "Bladder" | 0.30 | 0.23 | " |
| 10. Pelvimetry | 0.94 | — | " |
| 11. Salpingography | 1.07 | — | — |
| 12. | | | |
| 13. "Abdomen with obstetric" | 1.08 | 1.54 | 2.36 |
| 14. "Barium enema" | 0.22 | 0.58 | " |
| 15. "Barium swallow and meal" | 0.40 | 0.43 | " |
| 16. Cholecystography | 0.16 | 0.28 | " |
| 17. Chest | 1.3/0.50 | 1.3/0.85 | " |
| 18. "Ribs and sternum + shoulder" | 0.38/0.67 | 0.74/0.88 | " |
| 19. Arm | 1.1 | 1.5 | " |
| 20. Lower Leg | 0.98 | 1.2 | " |
| 21. "Head + cervical spine" | 1.5/0.52 | 1.6/1.1 | " |
| 22. Dental | 0.53/1.0 | 0.37/0.87 | " |
| 23. Mass surveys | 1.32 | 0.88 | " |
| 24. Others | | | |

(See footnotes to table I).

GONAD DOSE PER EXAMINATION

($d_j^*$ in mrad or mrem)

APPENDIX IV. TABLE III. ENGLAND AND WALES

| *Exam. No.* | *Females (all ages)* | *Males (all ages)* | *Foetal gonads* |
|---|---|---|---|
| 1. | | | |
| 2. "Hip and femur" | 195 | 660 | 744 |
| 3. Pelvis | 195 | 1,020 | 744 |
| 4. | | | |
| 5. "Lumbar spine" | 663 | 120 | 663 |
| 6. "Thoracic spine" | 14 | 20 | 14 |
| 7. | | | |
| 8. "Pyelography" | 1,200 | 452 | 2,990 |
| 9. "Bladder" | 642 | 260 | 2,430 |
| 10. Pelvimetry | 1,190 | — | 2,490 |
| 11. Salpingography | 1,580 | — | — |
| 12. | | | |
| 13. "Abdomen with obstetric" | 186 | 64 | 539 |
| 14. "Barium enema" | 18.6 | 37 | 18.6 |
| 15. "Barium swallow and meal" | 8.4 | 18.6 | 8.4 |
| 16. Cholecystography | 14.5 | 1.7 | 14.5 |
| 17. Chest | 0.065/5.0 | 0.33/34 | 0.065/5.0 |
| 18. "Ribs and sternum + shoulder" | 0.15 /0.03 | 0.45/ 0.20 | 0.15 /0.03 |
| 19. Arm | 0.05 | 0.24 | 0.05 |
| 20. Lower leg | 0.56 | 3.3 | 0.56 |
| 21. "Head + cervical spine" | 0.2 /0.17 | 0.74/ 1.6 | 0.2 /0.17 |
| 22. Dental | 0.74 | 4.4 | 0.74 |
| 23. Mass surveys | 0.14 | 0.23 | 0.14 |
| 24. Others | | | |

(See footnotes to table I).

ANNUAL GENETICALLY SIGNIFICANT DOSE

($D_j^*$ in mrem)

APPENDIX IV. TABLE IV. ENGLAND AND WALES

| Exam. No. | | Females (all ages) | Males (all ages) | Foetal | Total | Per cent of total |
|---|---|---|---|---|---|---|
| 1. | | | | | | |
| 2. | "Hip and femur" | 0.82 | 4.18 | 0.05 | 5.05 | 21.8 |
| 3. | Pelvis | 0.51 | 1.60 | 0.16 | 2.27 | 9.8 |
| 4. | | | | | | |
| 5. | "Lumbar spine" | 2.34 | 0.56 | 0.16 | 3.06 | 13.2 |
| 6. | "Thoracic spine" | 0.02 | 0.03 | 0.00 | 0.05 | 0.2 |
| 7. | | | | | | |
| 8. | "Pyelography" | 2.33 | 0.67 | 0.49 | 3.49 | 15.0 |
| 9. | "Bladder" | 0.08 | 0.02 | 0.08 | 0.18 | 0.8 |
| 10. | Pelvimetry | 0.65 | — | 3.47 | 4.06 | 17.5 |
| 11. | Salpingography | 0.24 | — | — | 0.24 | 1.0 |
| 12. | | | | | | |
| 13. | "Abdomen with obstetric" | 0.88 | 0.24 | 2.73 | 3.85 | 16.6 |
| 14. | "Barium enema" | 0.01 | 0.04 | 0.00 | 0.05 | 0.2 |
| 15. | "Barium swallow and meal" | 0.02 | 0.08 | 0.00 | 0.10 | 0.4 |
| 16. | Cholecystography | 0.00 | 0.00 | 0.00 | 0.00 | 0.0 |
| 17. | Chest | 0.01 | 0.07 | 0.00 | 0.08 | 0.3 |
| 18. | "Ribs and sternum – shoulder" | 0.00 | 0.00 | 0.00 | 0.00 | 0.0 |
| 19. | Arm | 0.00 | 0.07 | 0.00 | 0.07 | 0.3 |
| 20. | Lower leg | 0.01 | 0.08 | 0.00 | 0.09 | 0.4 |
| 21. | "Head + cervical spine" | 0.01 | 0.02 | 0.00 | 0.03 | 0.1 |
| 22. | Dental | 0.00 | 0.01 | 0.00 | 0.01 | 0.0 |
| 23. | Mass surveys | 0.01 | 0.01 | 0.00 | 0.02 | 0.1 |
| 24. | Others | 0.01 | 0.44 | 0.00 | 0.45 | 1.9 |
| | TOTAL | 8.0 | 8.1 | 7.1 | 23.2 | 100 |

## APPENDIX V

## FRANCE

### *The primary material*

1. The estimate presented here is based upon data submitted by Reboul and Istin.[6] The authors assume the annual number of *radiographic* examinations in France to be 5,000,000 plus 1,300,000 examinations of employees and militaries. The distribution on various types of examinations is studied on 18,889 cases. The data are assumed to be representative for 1957.

2. The authors point out that the foetal exposure due to pelvimetry and obstetrical examinations is lower in France than in other countries, due to the low frequency of these examinations.

3. 28,000,000 *fluoroscopies* are performed annually, 19,000,000 of which are examinations of patients under age 30, mostly in mass chest examinations. There are only 2,000,000 *photofluoroscopies* per year. The gonad dose from photofluoroscopy has been estimated by Turpin, Dupire, Jammet and Lejeune.[60]

4. The authors consider their values to be minimum estimates.

### *Presentation of the material for this report*

5. The French data include values of $N_j$ for the whole material, and the corresponding values of $d_j$ in most cases. Where the dose is not reported, an average dose, likely to be representative, has been used. These values are indicated with an asterisk in the table.

6. Values for the relative child expectancy ($w_j/w$) cannot be derived from the French data. However, an approximate figure can be calculated from the information on the fraction of patients under age 30, for each type of examination. The approximate figures differ little from the values of $w_j/w$ presented in the table for England and Wales. Therefore, the British values may be regarded as fairly representative also for the French material, and they have accordingly been used in the calculations.

7. The contribution from radiography, 27 mrem, is most likely a very low estimate. An interesting feature of the French material is the remarkably high contribution of *fluoroscopy used in mass survey examinations.* Because of the uncertainty with regard to average viewing time and other factors determining the dose per examination, the total value 57 mrem must be considered uncertain by at least a factor of two.

DATA FOR EVALUATION OF THE GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

A. ANNUAL CONTRIBUTION FROM 5,000,000 RADIOGRAPHIC EXAMINATIONS

(foetal exposure excluded)

APPENDIX V. TABLE I. FRANCE

| No. | Examinations involving radiography | Females: 1000 $N_i/N$ | Females: $d_i$ mrem | Females: $w_i/w$ | Females: $D_i^{(F)}$ mrem | Males: 1000 $N_i/N$ | Males: $d_i$ mrem | Males: $w_i/w$ | Males: $D_i^{(M)}$ mrem | Total: $D_i$ mrem | Total: Per cent |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | | | | | | | | | | | |
| 2. | "Membres inf. 1/3 sup." | 1.59 | 150 | 0.7 | 0.17 | 2.18 | 1,200 | 1.1 | 2.88 | 3.05 | 11.3 |
| 3. | "Bassin" (items 10 and 12 excluded) | 3.30 | 1,200 | 0.9 | 3.56 | 3.13 | 1,500 | 0.6 | 2.82 | 6.38 | 23.7 |
| 4. | "Colonnes lombaires" | 2.43 | 750 | 0.6 | 1.09 | 2.79 | 130 | 0.8 | 0.29 | 1.38 | 5.1 |
| 5. | | | | | | | | | | | |
| 6. | "Colonnes dorsales" | 1.70 | 20 | 0.7 | 0.02 | 2.13 | 6 | 0.8 | 0.01 | 0.03 | 0.1 |
| 7. | "Urographies" | 1.38 | 2,100 | 0.5 | 1.45 | 1.54 | 380 | 0.4 | 0.23 | 1.68 | 6.2 |
| 8. | "Urètho-Cysto" (not incl. item 11) | 0.25 | 1,200 | 0.5 | 0.15 | 0.30 | 2,000 | 0.4 | 0.24 | 0.39 | 1.4 |
| 9. | | | | | | | | | | | |
| 10. | "Pelvimetries" | 0.038 | 1,200* | 0.9 | 0.04 | — | — | — | — | 0.04 | 0.1 |
| 11. | "Hysterographies" | 0.46 | 1,700* | 1.1 | 0.86 | — | — | — | — | 0.86 | 3.2 |
| 12. | "Grossesses" | 0.26 | 1,600* | 1.8 | 0.75 | — | — | — | — | 0.75 | 2.8 |
| 13. | "Pneumo et retropneumoperitoines" | 0.043 | 300 | 0.6 | 0.01 | 0.074 | 160 | 0.6 | 0.01 | 0.02 | 0.1 |
| | "Splenoportographies" | 0.046 | 70 | | 0.00 | 0.111 | 32 | | 0.00 | 0.00 | 0.0 |
| 14. | "Grèle" | 0.28 | 250* | 0.2 | 0.01 | 0.21 | 75* | 0.4 | 0.01 | 0.02 | 0.1 |
| | "Lavement" | 2.28 | 220 | | 0.10 | 1.65 | 140 | | 0.09 | 0.19 | 0.7 |
| 15. | "Oesophages" | 0.51 | 6* | 0.4 | 0.00 | 0.87 | 6* | 0.4 | 0.00 | 0.00 | 0.0 |
| | "Estomacs" | 3.17 | 190 | | 0.24 | 4.95 | 60 | | 0.12 | 0.36 | 1.3 |
| 16. | "Vesicules" | 1.97 | 40 | 0.2 | 0.02 | 1.20 | 28 | 0.3 | 0.10 | 0.12 | 0.4 |
| 17. | "Poumons" | 20.7 | 9 | 1.3 | 0.24 | 28.9 | 13 | 1.3 | 0.49 | 0.73 | 2.7 |
| | "Lipiodols" | 0.042 | 250* | 0.5 | 0.01 | 0.13 | 320 | 0.8 | 0.03 | 0.04 | 0.1 |
| | "Arteriographie" | 0.12 | 250* | 0.5 | 0.02 | 0.24 | 320* | 0.8 | 0.06 | 0.08 | 0.3 |
| | "Tomographies" | 1.07 | 1,900 | 0.5 | 1.02 | 2.93 | 1,500 | 0.8 | 3.52 | 4.54 | 16.9 |
| 18. | "Membres sup. 1/2 sup." | 1.50 | 0.9* | 0.7 | 0.00 | 1.85 | 0.4* | 0.9 | 0.00 | 0.00 | 0.0 |
| 19/20. | "Membres sup./inf. 1/2 inf." | 1.93 | 0.4* | 1.1 | 0.00 | 3.74 | 0.4* | 1.5 | 0.00 | 0.00 | 0.0 |
| | "Extrémites osseuses" | 2.41 | 0.3* | 1.0 | 0.00 | 3.79 | 0.3* | 1.2 | 0.00 | 0.00 | 0.0 |
| 21. | "Crânes" | 2.57 | 4 | 1.5 | 0.02 | 4.37 | 4 | 1.6 | 0.03 | 0.05 | 0.2 |
| | "Col. cervicales" | 0.94 | 15 | 0.5 | 0.01 | 0.95 | 15 | 1.1 | 0.02 | 0.03 | 0.1 |
| 22. | — | | | | 0.00 | | | | 0.00 | 0.00 | 0.0 |
| 23. | "Radiophotographies" | 240 | 0.3 | 1.3 | 0.09 | 240 | 0.3 | 0.9 | 0.06 | 0.15 | 0.6 |
| | TOTALS | | | | 10.32 | | | | 10.74 | 20.9 | 77.4 |

B. ADDITIONAL CONTRIBUTION FROM 1,300,000 RADIOGRAPHIC EXAMINATIONS OF EMPLOYEES AND MILITARIES

| | | |
|---|---|---|
| Contribution estimated in proportion to number of examinations, photofluoroscopy excluded | 5.2 | 19.3 |

C. ALLOWANCE FOR FOETAL EXPOSURE

Estimate from British values in proportion to the frequency of examinations

| | | U.K.: $D_i$ (mrem) | U.K.: 1000 $N_i/N$ | France: 1000 $N_i/N$ | | |
|---|---|---|---|---|---|---|
| 10. | "Pelvimetries" | 3.47 | 0.58 | 0.038 | 0.2 | 0.7 |
| 12. | "Grossesses" | 2.73 | 1.94 | 0.26 | 0.4 | 1.5 |
| | | | | TOTAL RADIOGRAPHY: | 27 | 100 |

D. CONTRIBUTION FROM FLUOROSCOPY

19,000,000 examinations under age 30, with an average gonad dose of 30 mrem per exam. (mostly mass surveys)

| | | 1000 $N_i/N$ | $d_i$ (mrem) | $w_i/w$ | |
|---|---|---|---|---|---|
| 23. | "Examens systématiques" | 452 | 30 | 2.21 | 30 |
| | | | | TOTAL DIAGNOSTIC: | 57 |

## APPENDIX VI

## JAPAN

The data submitted by Japan[7] do not permit a presentation according to Equation (8). The following information is given:

| *Type of examination* | *1000 $N_j/N$* | *$d_j$ (mrem)* |
|---|---|---|
| (A) *Radiography:* | | |
| Chest, large film | 109 | 0.06–0.5 |
| Chest, tomography | 57 | 1–3 |
| Abdomen | 68 | 100 |
| Mass surveys | 260 | 0.05–0.4 |
| Others | 46 | 1 |
| (B) *Fluoroscopy:* | | |
| Chest | 18 | 1.6–12.7 |
| Abdomen | 22 | 200–1000 |

From the above data, the *per capita* gonad dose from diagnostic X-ray exposure is estimated to be 10 - 30 mrem per year.

## APPENDIX VII

## NEW ZEALAND

1. No exposure data have been submitted from New Zealand, but it has been reported that an extensive survey of diagnostic exposure has been initiated. New Zealand has full records of all diagnostic X-ray plants in the country and a system of medical services that permits a quantitative assessment of virtually all diagnostic X-ray work done.

2. Data on the number of examinations have been reported[45] to the Committee and are presented in table I in the main text of annex C. A characteristic feature is the high annual number of dental examinations (0.24 *per capita*). 95 per cent of these are made on school children between the ages of 12 and 16.

3. The frequency of mass miniature chest examination (with an annual number of 0.09 *per capita*) is reported together with the information that 23 per cent of all notified cases of pulmonary tuberculosis are discovered by mass X-ray surveys, with a case yield of about 1.8 per 1,000 examinations.

## APPENDIX VIII

## NORWAY

The data submitted by Norway[8] do not permit any estimate of the genetically significant dose. Gonad doses have been measured by Koren and Maudal;[65] their annual consumption of X-ray films is 1.1 *per capita*, the values are included in the tables in appendix XI. As the contribution from diagnostic X-ray procedures to the genetically significant dose is likely to be high enough to warrant more detailed analysis, which is reported to be planned.

## APPENDIX IX

## SWEDEN

### *The primary material*

1. The estimate of the genetically significant dose from diagnostic X-ray procedures in Sweden is based upon a report by Larsson.[9] The data are representative for 1955.

2. Dose measurements were performed on 1,957 patients in 17 X-ray departments. Of the patients, 394 were children. The age-distribution in the various types of examinations is based upon a material of 39,315 examinations.

3. The total number of examinations for 1955 was found to be 1,910,000. The annual increase during the period 1945-1954 was 15.5 per cent. The number of mass miniature radiographs during 1955 was estimated at 1,000,000.

4. In addition to the actually occurring doses, the author presents "possible" values found after simple measures to reduce the gonad exposure. If the indications for pelvimetry and obstetric examinations are made more restrictive, the achievable annual genetically significant dose that would result is estimated to be 15 mrem instead of the value of 38 mrem found for 1955.

### *Presentation of the material for this report*

5. In the original paper the genetically significant dose was calculated for each sex as an average dose per productive gamete. The sum of these doses was taken to express the radiation burden to the zygote. The figures in the following table have been recalculated by the author to conform with the presentation in this report.

## APPENDIX X

## UNITED STATES OF AMERICA

### *The primary material*

1. The estimate of the genetically significant dose for the United States of America is based upon a survey of literature up to about the middle of 1956, reported by Laughlin and Pullman[10]. In the report, which is only preliminary, the authors have computed the *probable* annual gonad dose per person up to age 30 years. They also give a *minimum* estimate.

2. The most characteristic feature of these data is that the surveyors have listed radiography and fluoroscopy separately and, in the case of fluoroscopy, also separated radiologists' examinations from those of non-radiologists.

3. The primary material of the Laughlin-Pullman report is shown in the tables I to VI, with regard to the estimate of the *probable* dose. The probable *per capita* gonad dose up to age 30 is found to be about 140 $\pm$ 100 mrem. The minimum estimate is 50 $\pm$ 30 mrem.

### *Presentation of the material for this report*

4. As nothing is known about the actual child-expectancy of patients undergoing X-ray examinations, the first approximation has been to assume that it is not influenced by the nature of the condition for which the patient was examined. The value of $w_j/w$ for each examination class would then depend only upon the age-distribution within the class. With this assumption, the annual gonad dose per person up to age 30 years may be taken as an approximate figure for the annual genetically significant dose. $w_j/w$ has been calculated from the known values of $N_j/N$, $d_j$ and this approximation of $D_j$. It has been necessary to assume that the dose per examination is the same for the two age-groups "12-29 years" and "over 12". Tables VII to XVI give the final presentation of the material.

## DATA FOR EVALUATION OF THE GENETICALLY SIGNIFICANT DOSE FROM DIAGNOSTIC X-RAY EXPOSURE

### APPENDIX IX. TABLE I. SWEDEN

| No. | Type of examination | Female adults | | | | Female children | | | | Male adults | | | | Male children | | | | Foetus | | | | Subtotal (mrem) | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1,000 $N_i^*/N$ | $w_i^*/w$ | $d_i^*$ (mrem) | $D_i^*$ (mrem) | 1,000 $N_i^*/N$ | $w_i^*/w$ | $d_i^*$ (mrem) | $D_i^*$ (mrem) | 1,000 $N_i^*/N$ | $w_i^*/w$ | $d_i^*$ (mrem) | $D_i^*$ (mrem) | 1,000 $N_i^*/N$ | $w_i^*/w$ | $d_i^*$ (mrem) | $D_i^*$ (mrem) | 1,000 $N_i^*/N$ | $w_i^*/w$ | $d_i^*$ (mrem) | $D_i^*$ (mrem) | $D_i^{(F)}$ (mrem) | $D_i^{(M)}$ (mrem) | $D_i^{(Fet)}$ (mrem) | $D_i$ (mrem) | Per cent |
| 1. | "Hip" | 4.3 | 0.10 | 260 | 0.11 | 0.12 | 2.47 | 460 | 0.14 | 2.5 | 0.68 | 1090 | 1.85 | 0.091 | 2.35 | 1600 | 0.34 | • | 2.41 | 260 | 0.01 | 0.25 | 2.19 | 0.01 | 2.45 | 6.5 |
| 2. | "Femur" | 0.84 | 0.71 | 35 | 0.021 | 0.040 | " | 6.1 | 0.0006 | 1.7 | 0.89 | 830 | 1.25 | 0.066 | " | 960 | 0.15 | • | " | 35 | 0.006 | 0.022 | 1.40 | 0.006 | 1.43 | 3.8 |
| 3. | Pelvic region | 3.8 | 0.25 | 200 | 0.19 | 0.30 | " | 280 | 0.21 | 3.6 | 0.41 | 870 | 1.29 | 0.45 | " | 1330 | 1.41 | ◦ | " | 200 | 0.03 | 0.40 | 2.70 | 0.03 | 3.13 | 8.3 |
| 4. 5. | "Lumbar and sacral spine" | 6.8 | 0.31 | 490 | 1.05 | 0.22 | " | 580 | 0.31 | 8.7 | 0.49 | 940 | 4.00 | 0.43 | " | 2270 | 2.30 | • | " | 490 | 0.14 | 1.36 | 6.30 | 0.14 | 7.80 | 20.6 |
| 6. | "Thoracic spine" | 2.6 | 0.28 | 6.2 | 0.0046 | 0.026 | " | | | 3.2 | 0.93 | 3.3 | 0.01 | <0.0082 | " | | | • | " | 6.2 | <0.001 | 0.0046 | 0.01 | <0.001 | 0.015 | <0.1 |
| 7. 8. | "Intravenous urography" | 3.6 | 0.42 | 925 | 1.40 | 0.22 | " | 445 (910) [d] | 0.37 | 5.2 | 0.45 | 1240 | 2.91 | 0.10 | " | 930 (3880) [d] | 0.57 | • | " | 925 | 0.16 | 1.77 | 3.48 | 0.16 | 5.41 | 14.3 |
| 9. | Urethrocystography | 0.20 | 0.28 | 1940 | 0.11 | 0.011 | " | 1240 | 0.034 | 0.93 | 0.30 | 3700 | 1.05 | 0.035 | " | 6370 | 0.52 | ◦ | " | 1940 | 0.016 | 0.14 | 1.57 | 0.016 | 1.73 | 4.6 |
| 10. | Pelvimetry | 0.59 | 0.44[a] | 1080 | 0.28 | <0.0006 | " | | | — | — | — | — | — | — | — | — | 0.59 | " | 4500 | 6.4 | 0.28 | — | 6.4 | 6.68 | 17.6 |
| 11. | Hysterosalpingography | 1.2 | 0.36[b] | 2600 | 1.12 | 0.0036 | " | | | — | — | — | — | — | — | — | — | — | — | — | — | 1.12 | — | — | 1.12 | 3.0 |
| 12. | Obstetrical abdomen | 0.59 | 0.44[a] | 265 | 0.064 | <0.0006 | " | | | — | — | — | — | — | — | — | — | 0.59 | 2.41 | 910 | 1.3 | 0.064 | — | 1.2 | 1.26 | 3.3 |
| 13. | "Abdomen survey" | 2.4 | 0.30 | 1150 | 0.84 | 0.030 | " | | 0.085 | 2.5 | 0.49 | 1360 | 1.65 | 0.040 | 2.35 | | 0.13 | • | " | 1150 | 0.11 | 0.93 | 1.78 | 0.11 | 2.82 | 7.4 |
| 14. | "Colon" | 4.8 | 0.20 | 1520 | 1.43 | 0.16 | " | | 0.60 | 3.9 | 0.27 | 310 | 0.32 | 0.17 | " | 600 | 0.24 | • | " | 1520 | 0.21 | 2.03 | 0.56 | 0.21 | 2.80 | 7.4 |
| 15. | "Stomach" | 17.1 | 0.27 | 29 | 0.13 | 0.17 | " | 105 | 0.044 | 12.8 | 0.48 | 14 | 0.086 | 0.065 | " | 75 | 0.011 | • | " | 29 | 0.02 | 0.17 | 0.097 | 0.02 | 0.29 | 0.8 |
| 16. | Cholecystography | 8.5 | 0.35 | 16.8 | 0.050 | 0.017 | " | | 0.0007 | 3.5 | 0.50 | 6.3 | 0.011 | <0.0035 | " | | <0.0001 | ◦ | " | 16.8 | 0.007 | 0.051 | 0.011 | 0.007 | 0.07 | 0.2 |
| 17. 18. | "Chest" | 41.6 | 0.37 | 4.1 | 0.063 | 2.2 | " | 2.4 | 0.013 | 33.8 | 0.61 | 1.8 | 0.037 | 1.8 | " | 1.0 | 0.0042 | • | " | 4.1 | 0.005 | 0.076 | 0.041 | 0.005 | 0.12 | 0.3 |
| 19. 20. 21. | "Lower leg, skull, fore and upper arm, hand, foot" | 39.6 | 0.41 | 0.5 | 0.008 | 4.4 | " | <0.5 | <0.0054 | 52.8 | 0.53 | 1 | 0.028 | 5.9 | " | <1 | <0.014 | • | " | 0.5 | 0.0015 | <0.013 | <0.042 | 0.0015 | 0.06 | 0.2 |
| 22. | Dental | 128 | 0.41 | ≪1 | ≪0.052 | 27 | " | ≪1 | ≪0.067 | 124 | 0.53 | <1 | <0.066 | 28 | " | <1 | <0.066 | ◦ | " | ≪1 | ≪0.10 | ≪0.12 | <0.13 | ≪0.10 | 0.35 | 0.9 |
| 23. | Mass miniature (photofluoroscopy) | 58.2 | 0.44 | 1.8 | 0.046 | 12.1 | " | 3.6 | 0.11 | 56.1 | 0.59 | 0.76 | 0.025 | 12.6 | " | 1.6 | 0.046 | • | " | 1.8 | 0.093 | 0.16 | 0.071 | 0.093 | 0.32 | 0.8 |
| | TOTALS | | | | 7.0 | | | | 2.0 | | | | 14.6 | | | | 5.8 | | | | 8.5 | 9.0 | 20.4 | 8.5 | 37.9 | 100 |

[a] A correction of the normal age-specific child-expectancy has been made here.
[b] Every three women are expected to have a child subsequently.
[c] In all cases of foetal exposure except pelvimetry and obstetrical abdomen, the foetal contribution has been derived from the assumption that 5.6 per cent of the women in fertile ages were pregnant.
[d] Including two radiographs over the trigone.

## Number of female examinations under age 30 per 1000 of total population
## ($1000n_j^{(F)}/N$)

### Appendix X. Table I.

USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | 12–29 | 0–11 | 12–29 | 0–11 | 12–29 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 2.54[a] 0.40[b] | 2.81[c] | | | 0.35[h] | 0.50[i] |
| 7. 8. | "Pyelography" | | 1.11 | 0.043[f] | 0.90[f] | 0.30[f] | 0.28[f] |
| 9. | "Urinary tract" | | 0.71 | | | | |
| 10. | Pelvimetry | — | 2.26 | | | | |
| 11. | Salpingography | — | 0.08 | | | | |
| 12. | Abdomen (obstetrical) | — | 0.62 | | | | |
| 13. 14. | "Abdomen and colon" | (1.0) | 3.26 | 0.86 | 1.80 | 0.38 | 0.48 |
| 15. | Stomach and upper G.I. | (1.0) | 3.53 | 1.04 | 2.16 | 0.25 | 0.60 |
| 16. | "Gall bladder" | | 0.81 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (3.6) | 9.5 | 0.22[g] | 0.45[g] | (0.60) | 1.44 |
| 18. 19. 20. | "Skeleton—extremities and chest" | (2.8) | 3.26 | | | (0.20) | 0.48 |
| 21. | Head | (2.0) | 2.17 | | | (0.13) | 0.24 |
| 22. | Dental | 35[d,e] | 275[d] | | | | |
| 23. | Mass surveys | (all ages (0–29): | 20.4 | | | | |

[a] Pelvis and hips.
[b] Lumbar spine.
[c] Including 0.09 from chiropractors.
[d] Each film counted as one examination.
[e] Children under 10 years.
[f] Genito-urinary region.
[g] Heart.
[h] Including 1/3 of all examinations of age-group under 2 years.
[i] Including 0.10 from chiropractors.

(*Figures in brackets have been derived by an arbitrary split of a figure for a larger group of examination-classes.*)

## Female gonad dose per examination
## ($d_j^{(F)}$ in mrem)

### Appendix X. Table II.

USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | 12–29 | 0–11 | 12–29 | 0–11 | 12–29 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 500[a] 1,300[a] | 1,000[b] | | | 1,000[a] | 3,000[b] |
| 7. 8. | "Pyelography" | | 1,200 | 1,000[a] | 3,000[a] | 1,000[a] | 3,000[a] |
| 9. | "Urinary tract" | | 1,000 | | | | |
| 10. | Pelvimetry | — | 2,500 | | | | |
| 11. | Salpingography | — | 10,000 | | | | |
| 12. | Abdomen (obstetrical) | — | 260 | | | | |
| 13. 14. | "Abdomen and colon" | (550) | 500 | 1,500 | 1,500 | 1,000 | 1,500 |
| 15. | Stomach and upper G.I. | (350) | 300 | 750 | 750 | 500 | 350 |
| 16. | "Gall bladder" | | 200 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (60) | 0.3 | 15[a] | 15[a] | (30) | 10 |
| 18. 19. 20. | "Skeleton—extremities and chest" | (60) | 0.5 | | | (30) | 5 |
| 21. | Head | (60) | 0.2 | | | (30) | 5 |
| 22. | Dental | 4[a] | 2[a] | | | | |
| 23. | Mass surveys | (all ages 0–29): | 3 | | | | |

[a] See footnotes to table I.
[b] The dose from chiropractors has been assumed to be 1000 mrem/exam.

## Annual female gonad dose per person under age 30

$$(1.98 \times \frac{n^{(F)}}{N} \times d_j^{(F)} \text{ in mrem})$$

Appendix X. Table III. USA

| Exam. No. | | Radiography: Radiologists and non-radiologists 0–11 | Radiography: Radiologists and non-radiologists 12–29 | Fluoroscopy: Radiologists 0–11 | Fluoroscopy: Radiologists 12–29 | Fluoroscopy: Non-radiologists 0–11 | Fluoroscopy: Non-radiologists 12–29 |
|---|---|---|---|---|---|---|---|
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 2.5[a] | 5.6[b] | | | 0.7[a] | 2.6[b] |
| | | 1.0 | | | | | |
| 7. 8. | "Pyelography" | | 2.6 | 0.1[a] | 0.5[a] | 0.6[a] | 1.7[a] |
| 9. | "Urinary tract" | | 1.4 | | | | |
| 10. | Pelvimetry | — | 11.2 | | | | |
| 11. | Salpingography | — | 1.6 | | | | |
| 12. | Abdomen (obstetrical) | — | 0.3 | | | | |
| 13. 14. | "Abdomen and colon" | (1.1) | 3.2 | 2.6 | 5.3 | 0.8 | 1.4 |
| 15. | Stomach and upper G.I. | (0.7) | 2.1 | 1.5 | 3.2 | 0.2 | 0.4 |
| 16. | "Gall bladder" | | 0.3 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (0.4) | 0.01 | 0.01[a] | 0.01[a] | (0.04) | 0.03 |
| 18. 19. 20. | "Skeleton—extremities and chest" | (0.03) | 0.00 | | | (0.01) | 0.00 |
| 21. | Head | (0.02) | 0.00 | | | (0.01) | 0.00 |
| 22. | Dental | 0.3[a] | 1.1[a] | | | | |
| 23. | Mass surveys | (all ages 0–29): | 0.1 | | | | |
| | Total | 6.5 | 29.5 | 4 | 9 | 2.5 | 6 |

[a] See footnotes to table I.

[b] Including 0.2 from chiropractors.

## Number of male examinations under age 30, per 1,000 of total population

$$(1{,}000\ n_j^M/N)$$

Appendix X. Table IV USA

| Exam. No. | | Radiography: Radiologists and non-radiologists 0–11 | Radiography: Radiologists and non-radiologists 12–29 | Fluoroscopy: Radiologists 0–11 | Fluoroscopy: Radiologists 12–29 | Fluoroscopy: Non-radiologists 0–11 | Fluoroscopy: Non-radiologists 12–29 |
|---|---|---|---|---|---|---|---|
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 2.85[a] | 3.11[c] | | | 0.40[b] | 0.55[i] |
| | | 0.45[b] | | | | | |
| 7. 8. | "Pyelography" | | 1.24 | 0.05[f] | 0.10[f] | 0.34[f] | 0.31[f] |
| 9. | "Urinary tract" | | 0.79 | | | | |
| 10. | Pelvimetry | — | — | | | | |
| 11. | Salpingography | — | — | | | | |
| 12. | Abdomen (obstetrical) | — | — | | | | |
| 13. 14. | "Abdomen and colon" | (1.1) | 3.63 | 0.99 | 2.02 | 0.44 | 0.53 |
| 15. | Stomach and upper G.I. | (1.1) | 3.93 | 1.19 | 2.43 | 0.29 | 0.67 |
| 16. | "Gall bladder" | | 0.91 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (4.1) | 10.6 | 0.25[g] | 0.51[g] | (0.69) | 1.60 |
| 18. 19. 20. | "Skeleton—extremities and chest" | (3.2) | 3.63 | | | (0.23) | 0.53 |
| 21. | Head | (2.2) | 2.42 | | | (0.15) | 0.36 |
| 22. | Dental | 33[d,e] | 172[d] | | | | |
| 23. | Mass surveys | (all ages 0–29): | 16.7 | | | | |

[a] Pelvis and hips.
[b] Lumbar spine.
[c] Including 0.09 from chiropractors.
[d] Each film counted as one exam.
[e] Children under 10 years.
[f] Genito-urinary region.
[g] Heart.
[h] Including 1/3 of all exams. of age-group under 2 years.
[i] Including 0.11 from chiropractors.

*(Figures in brackets have been derived by an arbitrary split of a figure for a larger group of examination classes.)*

## Male gonad dose per examination
($d_j$ in mrem)

### Appendix X. Table V

USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | 12–29 | 0–11 | 12–29 | 0–11 | 12–29 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 1,100[a] / 2,000[a] | 2,000[b] | | | 2,000[a] | 6,000[a] |
| 7. 8. | "Pyelography" | | 2,000 | 2,000[a] | 6,000[a] | 2,000[a] | 6,000[a] |
| 9. | "Urinary tract" | | 300 | | | | |
| 10. | Pelvimetry | — | — | | | | |
| 11. | Salpingography | — | — | | | | |
| 12. | Abdomen (obstetrical) | — | — | | | | |
| 13. 14. | "Abdomen and colon" | (750) | 200 | 750 | 750 | 2,000 | 750 |
| 15. | Stomach and upper G.I. | (750) | 200 | 500 | 500 | 600 | 500 |
| 16. | "Gall bladder" | | 10 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (120) | 1.2 | 20[a] | 20[a] | (40) | 10 |
| 18. 19. 20. | "Skeleton—extremities and chest" | (120) | 1.0 | | | (40) | 5 |
| 21. | Head | (120) | 0.6 | | | (40) | 5 |
| 22. | Dental | 12[a] | 8[a] | | | | |
| 23. | Mass surveys | (all ages 0–29): | 1 | | | | |

[a] See footnotes to table I.

[b] The dose from chiropractors has been assumed to be 2,000 mrem/exam.

## Annual male gonad dose per person under age 30
($1.98 \times \frac{n_j^{(M)}}{N} \times d_j^M$ in mrem)

### Appendix X. Table VI.

USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | 12–29 | 0–11 | 12–29 | 0–11 | 12–29 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 6.2[a] / 1.8 | 12[b] | | | 1.6[a] | 5.7[b] |
| 7. 8. | "Pyelography" | | 4.9 | 0.2[a] | 1.2[a] | 1.3[a] | 3.7[b] |
| 9. | "Urinary tract" | | 0.5 | | | | |
| 10. | Pelvimetry | — | — | | | | |
| 11. | Salpingography | — | — | | | | |
| 12. | Abdomen (obstetrical) | — | — | | | | |
| 13. 14. | "Abdomen and colon" | (1.6) | 1.4 | 1.5 | 3.0 | 1.7 | 0.8 |
| 15. | Stomach and upper G.I. | (1.6) | 1.6 | 1.2 | 2.4 | 0.3 | 0.7 |
| 16. | "Gall bladder" | | 0.02 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (1.0) | 0.03 | 0.01[a] | 0.02[a] | (0.05) | 0.03 |
| 18. 19. 20. | "Skeleton—extremities and chest" | (0.8) | 0.01 | | | (0.02) | 0.00 |
| 21. | Head | (0.5) | 0.003 | | | (0.01) | 0.00 |
| 22. | Dental | 0.8[a] | 2.7[a] | | | | |
| 23. | Mass surveys | (all ages 0–29): | 0.03 | | | | |
| | Total | 14.5 | 23 | 3 | 6.5 | 5 | 11 |

[a] See footnotes to table I.

[b] Including 0.4 from chiropractors.

NUMBER OF FEMALE EXAMINATIONS PER 1000 OF TOTAL POPULATION
$(1{,}000.N_j^{(F)}/N)$

APPENDIX X. TABLE VII.

| Exam. No. | | Radiography | | Fluoroscopy | | |
|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiol |
| | | 0–11 | Over 12 | 0–11 | Over 12 | 0–11 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 2.54 / 0.40 | 9.7 | | | 0.35 |
| 7. 8. | "Pyelography" | | 4.6 | 0.043 | 0.28 | 0.30 |
| 9. | "Urinary tract" | | 2.9 | | | |
| 10. | Pelvimetry | — | 2.26 | | | |
| 11. | Salpingography | — | 0.16 | | | |
| 12. | Abdomen (obstetrical) | — | 0.75 | | | |
| 13. 14. | "Abdomen and colon" | (1.0) | 12.4 | 0.86 | 6.1 | 0.38 |
| 15. | Stomach and upper G.I. | (1.0) | 13.1 | 1.04 | 7.3 | 0.25 |
| 16. | "Gall bladder" | | 2.9 | | | |
| 17. | Chest (lungs, heart, oesophagus) | (3.6) | 35.9 | 0.22 | 1.5 | (0.60) |
| 18. 19. 20. | "Skeleton—extremities and chest" | (2.8) | 6.3 | | | (0.20) |
| 21. | Head | (2.0) | 9.1 | | | (0.13) |
| 22. | Dental | 35 | 515 | | | |
| 23. | Mass surveys | (All ages) | 61 | | | |

FEMALE GONAD DOSE PER EXAMINATION
($d_j^{(F)}$ in mrem)

APPENDIX X. TABLE VIII.

| Exam. No. | | Radiography | | Fluoroscopy | | |
|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radio |
| | | 0–11 | Over 12[a] | 0–11 | Over 12[a] | 0–11 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 500 / 1,300 | 1,000 | | | 1,000 |
| 7. 8. | "Pyelography" | — | 1,200 | 1,000 | 3,000 | 1,000 |
| 9. | "Urinary tract" | — | 1,000 | | | |
| 10. | Pelvimetry | — | 2,500 | | | |
| 11. | Salpingography | — | 10,000 | | | |
| 12. | Abdomen (obstetrical) | — | 260 | | | |
| 13. 14. | "Abdomen and colon" | (550) | 500 | 1,500 | 1,500 | 1,000 |
| 15. | Stomach and upper G. I. | (350) | 300 | 750 | 750 | 500 |
| 16. | "Gall bladder" | | 200 | | | |
| 17. | Chest (lungs, heart, oesophagus) | (60) | 0.3 | 15 | 15 | (30) |
| 18. 19. 20. | "Skeleton—extremities and chest" | (60) | 0.5 | | | (30) |
| 21. | Head | (60) | 0.2 | | | (30) |
| 22. | Dental | 4 | 2 | | | |
| 23. | Mass surveys | (All ages) | 3 | | | |

[a] It has been assumed that the dose in the age-group over 12 years is the same as in the age-group 12–29.

[b] Weighted average including chiropractors' contribu

## Relative female child expectancy
## $(w_j^{(F)}/w)$[a]

Appendix X. Table IX. USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | Over 12 | 0–11 | Over 12 | 0–11 | Over 12 |
| 1. | "Skeleton—pelvic region" | 1.98 | 0.58 | | | 1.98 | 0.59 |
| 2. | | | | | | | |
| 3. | | | | | | | |
| 4. | | | | | | | |
| 5. | | 1.98 | | | | | |
| 6. | | | | | | | |
| 7. | "Pyelography" | | 0.48 | 1.98 | 0.64 | 1.98 | 0.49 |
| 8. | | | | | | | |
| 9. | "Urinary tract" | | 0.48 | | | | |
| 10. | Pelvimetry | — | 2.0 | | | | |
| 11. | Salpingography | — | 1.0 | | | | |
| 12. | Abdomen (obstetrical) | — | 1.69 | | | | |
| 13. | "Abdomen and colon" | 1.98 | 0.52 | 1.98 | 0.58 | 1.98 | 0.38 |
| 14. | | | | | | | |
| 15. | Stomach and upper G. I. | 1.98 | 0.53 | 1.98 | 0.59 | 1.98 | 0.43 |
| 16. | "Gall bladder" | | 0.55 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | 1.98 | 0.6 | 1.98 | 0.6 | 1.98 | 0.5 |
| 18. | "Skeleton—extremities and chest" | 1.98 | 0.6 | | | 1.98 | 0.5 |
| 19. | | | | | | | |
| 20. | | | | | | | |
| 21. | Head | 1.98 | 0.6 | | | 1.98 | 0.5 |
| 22. | Dental | 1.98 | 1.1 | | | | |
| 23. | Mass surveys | (All ages): | 0.7 | | | | |

[a] Figures back-calculated from tables II, III and VII.

## Female contribution to the annual genetically significant dose
## $(D_j^{(F)}$ in mrem)[a]

Appendix X. Table X. USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | Over 12 | 0–11 | Over 12 | 0–11 | Over 12 |
| 1. | "Skeleton—pelvic region" | 2.5 | 5.6 | | | 0.7 | 2.6 |
| 2. | | | | | | | |
| 3. | | | | | | | |
| 4. | | | | | | | |
| 5. | | 1.0 | | | | | |
| 6. | | | | | | | |
| 7. | "Pyelography" | | 2.6 | 0.1 | 0.5 | 0.6 | 1.7 |
| 8. | | | | | | | |
| 9. | "Urinary tract" | | 1.4 | | | | |
| 10. | Pelvimetry | — | 11.2 | | | | |
| 11. | Salpingography | — | 1.6 | | | | |
| 12. | Abdomen (obstetrical) | — | 0.3 | | | | |
| 13. | "Abdomen and colon" | (1.1) | 3.2 | 2.6 | 5.3 | 0.8 | 1.4 |
| 14. | | | | | | | |
| 15. | Stomach and upper G. I. | (0.7) | 2.1 | 1.5 | 3.2 | 0.2 | 0.4 |
| 16. | "Gall bladder" | | 0.3 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (0.4) | 0.01 | 0.01 | 0.01 | (0.04) | 0.03 |
| 18. | "Skeleton—extremities and chest" | (0.3) | 0.00 | | | (0.01) | 0.00 |
| 19. | | | | | | | |
| 20. | | | | | | | |
| 21. | Head | (0.2) | 0.00 | | | (0.01) | 0.00 |
| 22. | Dental | 0.3 | 1.1 | | | | |
| 23. | Mass surveys | (All ages): | 0.1 | | | | |
| | Total | 6.5 | 29.5 | 4 | 9 | 2.5 | 6 |

[a] Figures identical with those in table III.

## Number of male examinations per 1000 of total population
## ($1{,}000.N_j^{(M)}/N$)

### Appendix X. Table XI. USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | Over 12 | 0–11 | Over 12 | 0–11 | Over 12 |
| 1. | | | | | | | |
| 2. | | 2.85 | | | | | |
| 3. | "Skeleton—pelvic region" | | 11.0 | | | 0.40 | 1.91 |
| 4. | | | | | | | |
| 5. | | 0.45 | | | | | |
| 6. | | | | | | | |
| 7. | "Pyelography" | | 5.2 | 0.05 | 0.32 | 0.34 | 1.27 |
| 8. | | | | | | | |
| 9. | "Urinary tract" | | 3.2 | | | | |
| 10. | Pelvimetry | — | — | | | | |
| 11. | Salpingography | — | — | | | | |
| 12. | Abdomen (obstetrical) | — | — | | | | |
| 13. | "Abdomen and colon" | (1.1) | 13.9 | 0.99 | 6.9 | 0.44 | 2.79 |
| 14. | | | | | | | |
| 15. | Stomach and upper G. I. | (1.1) | 14.7 | 1.19 | 8.2 | 0.29 | 3.17 |
| 16. | "Gall bladder" | | 3.2 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (4.1) | 40.5 | 0.25 | 1.7 | (0.69) | 7.6 |
| 18. | | | | | | | |
| 19. | "Skeleton—extremities and chest" | (3.2) | 7.0 | | | (0.23) | 2.1 |
| 20. | | | | | | | |
| 21. | Head | (2.2) | 10.3 | | | (0.15) | 1.7 |
| 22. | Dental | 33 | 580 | | | | |
| 23. | Mass surveys | (All ages): | 69 | | | | |

## Male gonad dose per examination
## ($d_j^{(M)}$ in mrem)

### Appendix X. Table XII. USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | Over 12[a] | 0–11 | Over 12[a] | 0–11 | Over 12[a] |
| 1. | | | | | | | |
| 2. | | 1,100 | | | | | |
| 3. | "Skeleton—pelvic region" | | 2,000 | | | 2,000 | 5,200[b] |
| 4. | | | | | | | |
| 5. | | 2,000 | | | | | |
| 6. | | | | | | | |
| 7. | "Pyelography" | | 2,000 | 2,000 | 6,000 | 2,000 | 6,000 |
| 8. | | | | | | | |
| 9. | "Urinary tract" | | 300 | | | | |
| 10. | Pelvimetry | — | — | | | | |
| 11. | Salpingography | — | — | | | | |
| 12. | Abdomen (obstetrical) | — | — | | | | |
| 13. | "Abdomen and colon" | (750) | 200 | 750 | 750 | 2,000 | 750 |
| 14. | | | | | | | |
| 15. | Stomach and upper G. I. | (750) | 200 | 500 | 500 | 600 | 500 |
| 16. | "Gall bladder" | | 10 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (120) | 1.2 | 20 | 20 | (40) | 10 |
| 18. | | | | | | | |
| 19. | "Skeleton—extremities and chest" | (120) | 1.0 | | | (40) | 5 |
| 20. | | | | | | | |
| 21. | Head | (120) | 0.6 | | | (40) | 5 |
| 22. | Dental | 12 | 8 | | | | |
| 23. | Mass surveys | (All ages): | 1 | | | | |

[a] It has been assumed that the dose in the age-group over 12 years is the same as in the age-group 12–29.

[b] Weighted average including chiropractors' contributions.

## Relative male child expectancy
## $(w_j^{(M)}/w)$[a]

Appendix X. Table XIII. USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | Over 12 | 0–11 | Over 12 | 0–11 | Over 12 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 1.98 | 0.55 | | | 1.98 | 0.57 |
| 7. 8. | "Pyelography" | 1.98 | 0.47 | 1.98 | 0.62 | 1.98 | 0.48 |
| 9. | "Urinary tract" | | 0.5 | | | | |
| 10. | Pelvimetry | — | — | | | | |
| 11. | Salpingography | — | — | | | | |
| 12. | Abdomen (obstetrical) | — | — | | | | |
| 13. 14. | "Abdomen and colon" | 1.98 | 0.50 | 1.98 | 0.58 | 1.98 | 0.4 |
| 15. | Stomach and upper G. I. | 1.98 | 0.54 | 1.98 | 0.59 | 1.98 | 0.4 |
| 16. | "Gall bladder" | | 0.6 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | 1.98 | 0.6 | 1.98 | 0.6 | 1.98 | 0.4 |
| 18. 19. 20. | "Skeleton—extremities and chest" | 1.98 | 1 | | | 1.98 | 0.4 |
| 21. | Head | 1.98 | 0.6 | | | 1.98 | 0.4 |
| 22. | Dental | 1.98 | 0.6 | | | | |
| 23. | Mass surveys | (All ages) | 0.7 | | | | |

[a] Figures back-calculated from tables V, VI and XI.

## Male contribution to the annual genetically significant dose
## $(D_j^{(M)}$ in mrem)[a]

Appendix X. Table XIV. USA

| Exam. No. | | Radiography | | Fluoroscopy | | | |
|---|---|---|---|---|---|---|---|
| | | Radiologists and non-radiologists | | Radiologists | | Non-radiologists | |
| | | 0–11 | Over 12 | 0–11 | Over 12 | 0–11 | Over 12 |
| 1. 2. 3. 4. 5. 6. | "Skeleton—pelvic region" | 6.2 | 12 | | | 1.6 | 5.7 |
| 7. 8. | "Pyelography" | 1.8 | 4.9 | 0.2 | 1.2 | 1.3 | 3.7 |
| 9. | "Urinary tract" | | 0.5 | | | | |
| 10. | Pelvimetry | — | — | | | | |
| 11. | Salpingography | — | — | | | | |
| 12. | Abdomen (obstetrical) | — | — | | | | |
| 13. 14. | "Abdomen and colon" | (1.6) | 1.4 | 1.5 | 3.0 | 1.7 | 0.8 |
| 15. | Stomach and upper G. I. | (1.6) | 1.6 | 1.2 | 2.4 | 0.3 | 0.7 |
| 16. | "Gall bladder" | | 0.02 | | | | |
| 17. | Chest (lungs, heart, oesophagus) | (1.0) | 0.03 | 0.01 | 0.02 | (0.05) | 0.03 |
| 18. 19. 20. | "Skeleton—extremities and chest" | (0.8) | 0.01 | | | (0.02) | 0.01 |
| 21. | Head | (0.5) | 0.00 | | | (0.01) | 0.00 |
| 22. | Dental | 0.8 | 2.7 | | | | |
| 23. | Mass surveys | (All ages) | 0.03 | | | | |
| | Total | 14.5 | 23 | 3 | 6.5 | 5 | 11 |

[a] Figures identical with those in table VI.

FOETAL EXPOSURE

APPENDIX X. TABLE XV. USA

| Exam. No. | | $d_j$ mrem | $n_j/N = N_j/N$ x1,000 | $w_j/w$ (back-calculated) | $D_j$ mrem[a] |
|---|---|---|---|---|---|
| 1. | "Skeleton—pelvic region" | | | | |
| 2. | | | | | |
| 3. | | | | | |
| 4. | | | | | |
| 5. | | | | | |
| 6. | | | | | |
| 7. | "Pyelography" | | | | |
| 8. | | | | | |
| 9. | "Urinary tract" | | | | |
| 10. | Pelvimetry | 4,000 | 2.53 | 1.98 | 20.0 |
| 11. | Salpingography | | | | |
| 12. | Abdomen (obstetrical) | 400 | 0.88 | 1.98 | 0.7 |
| 13. | "Abdomen and colon" | | | | |
| 14. | | | | | |
| 15. | Stomach and upper G.I. | | | | |
| 16. | "Gall bladder" | | | | |
| 17. | Chest (lungs, heart, oesophagus) | 0.3 | 10.5 | 1.98 | 0.01 |
| 18. | "Skeleton—extremities and chest" | | | | |
| 19. | | | | | |
| 20. | | | | | |
| 21. | Head | | | | |
| 22. | Dental | | | | |
| 23. | Mass surveys | | | | |
| 24. | Others | | | | |
| | TOTAL | | | | 20.7 |

[a] 1/0.67 of the figures given by Laughlin and Pullman.

GENETICALLY SIGNIFICANT DOSE ($D_j$ IN MREM); SUMMARY TABLE

APPENDIX X. TABLE XVI. USA

| Exam. No. | | Children | Female adults | Male adults | Foetal | Total | Per cent |
|---|---|---|---|---|---|---|---|
| 1. | "Skeleton—pelvic region" | 13.8 | 8.2 | 17.7 | | 39.7 | 28 |
| 2. | | | | | | | |
| 3. | | | | | | | |
| 4. | | | | | | | |
| 5. | | | | | | | |
| 6. | | | | | | | |
| 7. | "Pyelography" | 2.2 | 4.8 | 9.8 | | 16.8 | 12 |
| 8. | | | | | | | |
| 9. | "Urinary tract" | | 1.4 | 0.5 | | 1.9 | 1.3 |
| 10. | Pelvimetry | — | 11.2 | — | 20.0 | 31.2 | 22 |
| 11. | Salpingography | — | 1.6 | — | | 1.6 | 1.1 |
| 12. | Abdomen (obstetrical) | — | 0.3 | — | | 0.3 | 0.2 |
| 13. | "Abdomen and colon" | 9.3 | 9.9 | 5.2 | 0.7 | 25.1 | 18 |
| 14. | | | | | | | |
| 15. | Stomach and upper G.I. | 5.5 | 5.7 | 4.7 | | 15.9 | 11 |
| 16. | "Gall bladder" | | 0.3 | 0.0 | | 0.3 | 0.2 |
| 17. | Chest (lungs, heart, oesophagus) | 1.5 | 0.1 | 0.1 | 0.0 | 1.7 | 1.2 |
| 18. | "Skeleton—extremities and chest" | 1.1 | 0.0 | 0.0 | | 1.1 | 0.8 |
| 19. | | | | | | | |
| 20. | | | | | | | |
| 21. | Head | 0.7 | 0.0 | 0.0 | | 0.7 | 0.5 |
| 22. | Dental | 1.1 | 1.1 | 2.7 | | 4.9 | 3.5 |
| 23. | Mass surveys | [a] | 0.1 | 0.0 | | 0.1 | 0.1 |
| | TOTAL | 35.2 | 44.7 | 40.7 | 20.7 | 141 | 100 |

[a] Included in adult figures.

## DATA ON DIAGNOSTIC X-RAY EXPOSURE: GONAD DOSE PER EXAMINATION FOR THE MOST IMPORTANT EXPOSURE CLASSES

### APPENDIX XI

The tables I to XIV have been taken from the report of the ICRP/ICRU Joint Study Group. They show estimates of various authors of the gonad doses due to given types of examinations. The wide variations probably result from different techniques rather than from uncertainty in measurements. Hence the lower values indicate what levels may be achieved with good practice. Further details and references are given in the ICRP/ICRU Study Group report.

TABLE I. HIPS

| *Reference* | *Technical data* | *Measurements made on* | *Remarks* | *Gonad dose per examination (mrad)* | |
|---|---|---|---|---|---|
| | | | | *Male* | *Female* |
| Hammer-Jacobsen (1957) Denmark[4] | 62–64 kv, 400–450 mAs FFD = 100 cm 2 films per examination | Patients: 12 male 9 female | | 567 (20–3600) | 53 (30–100) |
| Larsson Sweden[9] | 60–70 kv, 200–500 mAs 3 films per examination | Patients: 19 male 18 female | | 1150 (100–2600) | 205 (75–450) |
| | | | Years: | | |
| Laughlin and Pullman (1957) U.S.A.[10] | | | 0– 2 | 480 | 270 |
| | | | 2– 7 | 840 | 420 |
| | | | 7–12 | 2100 | 900 |
| | | | 12–30 | 650–2000 | 600–1000 |
| Stanford and Vance (1955) U.S.A.[58] | 68 kv, 200 mAs FFD = 90 cm | Patients | | 710 | 210 |

TABLE II. FEMUR

| *Reference* | *Technical data* | *Measurements made on* | *Remarks* | *Gonad dose per examination (mrad)* | |
|---|---|---|---|---|---|
| | | | | *Male* | *Female* |
| Hammer-Jacobsen (1957) Denmark[4] | 58–60 kv, 250 mAs FFD = 100 cm 2 films per examination | Patients: 7 male 4 female | | 1393 (50–3500) | 63 (20–100) |
| Koren and Maudal Norway[65] | 62 kv, 250 mAs FFD = 100 cm 2 films per examination | Phantom | | 73 | 9·6 |
| Larsson Sweden[9] | 50–78 kv, 80 mAs | Patients: 6 male 2 female | | 65–650 | 50 |
| | | | Years: | | |
| Laughlin and Pullman (1957) U.S.A.[10] | | | 12–30 | 1650 | 300 |

TABLE III. PELVIS

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per film (mrad) | | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|---|---|
| | | | | Male | Female | Male | Female |
| Hammer-Jacobsen (1957) Denmark[4] | 60–63 kv, 200–360 mAs<br>FFD = 100 cm<br>1–2 films per examination | Patients:<br>7 male<br>1 female | | | | 567<br>(50–2500) | 70 |
| Koren and Maudal Norway[65] | 70 kv. 250 mAs<br>FFD = 100 cm | Phantom | | 3580 | 96 | 3580 | 96 |
| Larsson Sweden[9] | 59–64 kv, 500 mAs<br>FFD = 100 cm<br>1 film per examination | Patients:<br>16 male<br>20 female | | | | 1010<br>(50–2800) | 190<br>(100–300) |
| Laughlin and Pullman (1957) U.S.A.[10] | | | Years:<br>0– 2<br>2– 7<br>7–12<br>12–30 | | | 480<br>840<br>2100<br>1650–2000 | 270<br>420<br>900<br>600–1000 |
| Stanford and Vance (1955) U.K.[58] | 65 kv, 100 mAs<br>FFD = 90 cm | Patients | AP | 1100 | 210 | 1100 | 210 |
| Ardran and Crooks (1957) U.K.[25] | 65 kv, 100 mAs<br>FFD = 90 cm,<br>no extra filter | | Normal technique | 2000 | | | |
| | 65 kv, 100 mAs<br>FFD = 90 cm,<br>3mm Al-filter | | | 670 | | | |
| | 75 kv, 80 mAs<br>FFD = 110 cm,<br>3 mm Al-filter. | | 'AERE'† technique | 480 | 80* | | |
| | The same, but testes covered with lead | | | 20 | | | |

* Measurement made on phantom.
† Atomic Energy Research Establishment.

TABLE IV. LUMBAR SPINE

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per film (mrad) | | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|---|---|
| | | | | Male | Female | Male | Female |
| Hammer-Jacobsen (1957) Denmark[4] | 65–84 kv, 1250 mAs FFD = 100 cm 3 films per examination | Patients: 22 male 22 female | | | | 104 (10-400) | 222 (20–600) |
| Koren and Maudal Norway[65] | 68kv, 310 mAs FFD = 100 cm | Phantom | AP | 4.5 | 60 | 4.5 | 60 |
| | 75 kv, 500 mAs FFD = 90 cm | | Lat. | 6 | 91 | 6 | 91 |
| Larsson Sweden[9] | 65–70 kv, 500 mAs FFD = 90–100 cm 4 films per examination | Patients: 12 male 7 female | Lumbar spine and lumbo-sacral region | | | 375 (68–1180) | 680 (490–860) |
| Laughlin and Pullman (1957) U.S.A.[10] | | | Years: 0– 2 2– 7 7–12 | | | 2700 2400 900 | 900 1050 2190 |
| Stanford and Vance (1955) U.K.[58] | 68 kv, 200 mAs FFD = 90 cm | Patients | AP | 24 | 227 | 24 | 227 |
| | 72 kv, 500 mAs FFD = 90 cm | | Lat. | 26·6 | 86 | 26·6 | 86 |
| | 120 kv, 20 mAs FFD = 90 cm | | AP | 6 | 40 | 6 | 40 |
| | 120 kv, 60 mAs FFD = 90 cm | | Lat. | 7 | 16 | 7 | 16 |
| Ardran and Crooks (1957) UK[25] | 68 kv, 200 mAs FFD = 90 cm, no extra filter | | Normal technique | 24 | | | |
| | 68 kv, 200 mAs FFD = 90 cm, 3 mm Al-filter | | | 6·0 | | | |
| | 75 kv, 80 mAs FFD = 110 cm 3 mm Al-filter | | 'AERE'† technique | 1·0 | 95* | | |
| | The same, but testes covered with lead | | | 0·5 | | | |

* Measurement made on phantom.
† Atomic Energy Research Establishment.

TABLE V. INTRAVENOUS PYELOGRAPHY

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per film (mrad) | | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|---|---|
| | | | | Male | Female | Male | Female |
| Hammer-Jacobsen (1957) Denmark[4] | 61–65 kv, 3300–4300 mAs<br>FFD = 130–143 cm<br>6 films per examination | Patients:<br>50 male<br>50 female | Adults<br>Adults | | | 1383<br>(100–4000)<br>† | 424<br>(50–4000) |
| | 65–73 kv, 650–1700 mAs<br>FFD = 130–143 cm<br>6 films per examination | Patients:<br>14 male<br>8 female | Childen under 15 years | | | 654<br>(100–1600) | 706<br>(100–3800) |
| LeFebvre and Serra (1957) France | 10 films<br>12 films<br>16 films | Patients | Children:<br>3 months<br>3 years<br>6 years | 50<br>84<br>95 | 30<br>56<br>87 | 500<br>1008<br>1520 | 300<br>678<br>1384 |
| Larsson Sweden[9] | 66–120 kv, 95 mAs<br>12–26 films per examination | Patients:<br>25 male<br>17 female | Hospital 1 | | | 790<br>(141–2160) | 1820<br>(935–2680) |
| | 55 kv, 250–270 mAs<br>5–11 films per examination | Patients:<br>10 male | Hospital 2 | | | 1300<br>(22*–2500) | |
| Laughlin and Pullman (1957) U.S.A.[10] | | | 12–30 years Pyelography | | | 100–2000 | 200–1200 |
| Stanford and Vance (1955) U.K.[68] | 72 kv, 100 mAs<br>FFD = 90 cm<br>6 films per examination | Patients | | | | 486 | 1290 |
| Ardran and Crooks (1957) U.K.[25] | 75 kv, 80 mAs<br>FFD = 110 cm<br>3 mm Al added | Male:<br>patients<br>Female:<br>phantom | | 0·5* | 95 | | |

* With lead rubber over the scrotum.
† Doses reduced to 1–3% by shielding of scrotum.

TABLE VI. RETROGRADE PYELOGRAPHY

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| Hammer-Jacobsen (1957) Denmark[4] | 63–67 kv, 4000 mAs<br>FFD=130—143 cm<br>7 films per examination | Patients:<br>8 male<br>9 female | | 2580<br>(700–3800) | 1136<br>(200–4000) |
| Laughlin and Pullman (1957) U.S.A.[10] | | | 12–30 years Pyelography | 100–2000 | 200–1200 |

TABLE VII. URETHROCYSTOGRAPHY

| *Reference* | *Technical data* | *Measurements made on* | *Remarks* | *Gonad dose per examination (mrad)* | |
|---|---|---|---|---|---|
| | | | | *Male* | *Female* |
| Hammer-Jacobsen (1957) Denmark[4] | 71 kv, 3285 mAs<br>FFD = 137 cm<br>6 films per examination | Patients:<br>7 male | Urethrography | 4209<br>(2700–8400) | |
| | 63–87 kv,<br>2000–2850 mAs<br>FFD = 100–130 cm<br>5 films per examination | Patients:<br>2 male<br>2 female | Cystography | 5261<br>(3500–7000) | 460<br>(350–560) |
| | 102–109 kv,<br>357–476 mAs<br>FFD = 90 cm<br>9 films per examination | Patients:<br>9 male<br>9 female | Urethrocystography during micturition<br>Adults | 7841<br>(2400–17200) | 669<br>(200–1500) |
| | 79–86 kv,<br>256–341 mAs<br>FFD = 90 cm<br>8 films per examination | Patients:<br>6 male<br>5 female | Under 15 | 2314<br>(200–4700) | 205<br>(120–330) |
| Koren and Maudal Norway[65] | 75 kv, 200 mAs<br>100 kv, 500 mAs<br>FFD = 60 cm<br>1+4 films per examination | Phantom | AP<br>Lat. | | 210<br>104<br>} 314 |
| Larsson Sweden[9] | 80–100 kv | Patients:<br>26 male<br>16 female | Hospital 1 | 4100<br>(1000–11000) | 1000<br>(550–1650) |
| | 100–200 mAs<br>5–15 films per examination | Patients:<br>5 male | Hospital 2 | 760<br>(320–1240) | |
| Laughlin and Pullman (1957) U.S.A.[10] | Radiography | | Years:<br>12–30 | 100–300 | 200–1000 |
| | Fluoroscopy | | Years:<br>0–12<br>12–30 | 500–2000<br>500–6000 | 500–1000<br>500–3000 |

## Table VIII. Pelvimetry

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per film (mrad) female | Gonad dose per examination (mrad) female |
|---|---|---|---|---|---|
| Hammer-Jacobsen (1957) Denmark[4] | 81–85 kv, 1354 mAs FFD = 100 cm 2–3 films per examination | 15 patients | AP+Lat. | | 738 (400–1400) |
| | 84–92 kv, 1250 mAs FFD = 97 cm 3–4 films per examination | 4 patients | Stereoscopic AP+Lat. | | 906 (650–1300) |
| Koren and Maudal Norway[65] | 78 kv, 310 mAs FFD = 100 cm | Phantom | AP | 86 | 86 |
| | 85 kv, 500 mAs FFD = 90 cm | | Lat. | 76 | 76 |
| Larsson Sweden[9] | 2 films: 90 kv 640 mAs 1 film: 90 kv 95 mAs FFD = 90–100 cm | 12 patients | 3 different projections | | 1500 (760–2500) |
| Laughlin and Pullman (1957) U.S.A.[10] | | | | | 700–2500 |
| Stanford and Vance (1955) U.K.[66] | 120 kv, 100 mAs 120 kv, 50 mAs FFD = 90 cm | Patients | AP Lat. | 240 840 | |

## Table IX. Salpingography

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per examination (mrad) Female |
|---|---|---|---|---|
| Hammer-Jacobsen (1957) Denmark[4] | 69 kv, 1259 mAs FFD = 100 cm 2–7 films per examination | 7 patients | | 197 (140–270) |
| Larsson Sweden[9] | 65–90 kv, 120–150 mAs 6–11 films per examination | 32 patients | | 2650 (1100–6700) |
| Laughlin and Pullman (1957) U.S.A.[10] | | | | 600–1000 |

## Table X. Abdomen

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| Hammer-Jacobsen (1957) Denmark[4] | 63–70 kv, 600 mAs FFD = 100–143 cm 1 film per examination | Patients: 5 male 4 female | AP | 610 (40–1800) | 85 (40–100) |
| | 71 kv, 750 mAs FFD = 100 cm 1–2 films per examination | Patients: 21 female | Obstetric | | 90 (60–600) |
| Koren and Maudal Norway[65] | 80 kv, 180 mAs FFD = 100 cm 3 films per examination | Phantom | | 7·8 | 120 |
| Larsson Sweden[9] | Female 4–13 films per examination. Male 3–7 films per examination. Sometimes fluoroscopy, 1·5–2 min. | Patients: 7 male 7 female | | 450–2725 | 18–1280 |
| Laughlin and Pullman 1957) U.S.A.[10] | Abdomen and colon radiography | | Years: 0– 2 2– 7 7–12 12–30 | 450 930 750 10–200 | 240 390 720 460–500 |
| Stanford and Vance (1955) U.K.[58] | 72 kv, 100 mAs FFD = 90 cm | | AP | 69 | 200 |
| | 80 kv, 150 mAs FFD = 90 cm | Patients | Obstetric | | 200 |
| Ardran and Crooks (1957) U.K.[25] | 75 kv, 60 mAs FFD = 110 cm 3 mm Al-filter added | Male: patients Female: phantom | AP | 0·5* | 75 |

* With lead rubber protection.

## Table XI. Barium enema

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| LeFebvre and Serra (1957) France | 15 films 7 films 9 films | Patients | Children: 3 months 3 years 6 years | 450 700 900 | 400 455 800 |
| Larsson Sweden[9] | About 10 films: mean fluoroscopy time 7 min. | Patients: 31 male 15 female | | 255 (52–485) | 2065 (1075–2920) |
| Laughlin and Pullman (1957) U.S.A.[10] | Radiography | | Abdomen & colon 12–30 years | 140–200 | 420–500 |
| | Fluoroscopy | | Lower G.I.T. 12–30 years | 0–750 | 420–1500 |
| | Fluoroscopy | | Lower G.I.T. Children | 420–750 | 420–1500 |
| Stanford and Vance (1955) U.K.[58] | Fluoroscopy: 70 kv, 2 mA 3 min. | Patients | | 40 | 20 |

TABLE XII. BARIUM SWALLOW AND MEAL

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| LeFebvre and Serra (1957) France | 20 films | Patients | Children: 3 months | 220 | |
| | 16 films | | 3 years | 496 | |
| | 20 films | | 6 years | 220 | |
| Koren and Maudal Norway[65] | 75 kv, 60mAs FFD = 60 cm 12 films per examination | Phantom | | 2·9 | 144 |
| | Fluoroscopy: 70 kv, 3 mA, 3 min. FSD = 40 cm | Phantom | | 1·2 | 45 |
| Larsson Sweden[9] | 80–110 kv 40–80 mAs 10–15 films | Patients: 25 male 25 female | Hospital 1 | 12·5 (2·7–29) | 33 (8·5–55) |
| | Mean fluoroscopy time 7 min. | Patients: 25 male 25 female | Hospital 2 | 4·3 (2·1–13·6) | 31 (7·8–78) |
| Laughlin and Pullman (1957) U.S.A.[10] | Radiography | | Stomach & upper G.I.T. 12–30 years | 60–200 | 200–300 |
| | Fluoroscopy | | Upper G.I.T. 12–30 years | 0–500 | 200–750 |
| | | | Upper G.I.T. Children | 200–500 | 200–750 |
| Stanford and Vance (1955) U.K.[58] | Fluoroscopy 70 kv, 2 mA 3 min. | Patients | | 20 | 9 |
| Ardran and Crooks (1957) U.K.[25] | Fluoroscopy with image intensifier 75 kv, 0·5 mA 5 min. 5 mm Al-filter added | Male: patients Female: phantom | | 5 | 5 |

TABLE XIII. CHOLECYSTOGRAPHY

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| Koren and Maudal Norway[65] | 80 kv, 125 mAs FFD = 100 cm 5 films per examination | Phantom | | 6·7 | 260 |
| Larsson Sweden[9] | 60–80 kv 35–200 mAs 4–6 films per examination. | Patients: 26 male 25 female | Hospital 1 | 3·1 (1·3–6·5) | 19 (10–41) |
| | Fluoroscopy 80 kv, 3 mA, 1·2–2·5 min. | Patients: 16 male | Hospital 2 | 7·1 (4·3–11) | |
| Laughlin and Pullman (1957) U.S.A.[10] | Radiography | | 12–30 years | 0–10 | 75–200 |
| Stanford and Vance (1955) U.K.[58] | 70 kv, 150 mAs FFD = 90 cm 3 films per examination | Patients | | 1·8 | 15·6 |

TABLE XIV. CHEST

| Reference | Technical data | Measurements made on | Remarks | Gonad dose per film (mrad) | | Gonad dose per examination (mrad) | |
|---|---|---|---|---|---|---|---|
| | | | | Male | Female | Male | Female |
| LeFebvre and Serra (1957) France | | Patients | Children: 3 months | 5 | | | |
| Koren and Maudal Norway[65] | 80 kv, 27 mAs FFD = 150 cm | Phantom | PA | <1 | 1·0 | <1 | 1·0 |
| | 95 kv, 60 mAs FFD = 150 cm | | Lat. | <1 | 1·5 | <1 | 1·5 |
| Larsson Sweden[9] | 3–5 films per examination & fluoroscopy 70–80 kv, 2–2·5 mA 1–3 min | Patients: 78 male 22 female | | | | 1·6 (0·9–2·7) | 4·6 (2·6–10·8) |
| Laughlin and Pullman (1957) U.S.A.[10] | Radiography | | Years: 0– 2 | | | 0–450 | 0–240 |
| | | | 2–12 | | | 0–5 | 0–5 |
| | | | 12–30 | | | 0–1·2 | 0–0·3 |
| | Fluoroscopy | | | | | 0–40 | 0–30 |
| Sanford and Vance (1955) U.K.[58] | 68 kv | Patients | PA | 0·36 | 0·07 | 0·36 | 0·07 |
| Ardran and Crooks (1957) U.K.[25] | Radiography FFD = 180 cm 3 mm Al-filter added. | Male: patients Female: phantom | PA | 0·01 | 0·02 | 0·01 | 0·02 |
| | Fluoroscopy with image intensifier 75 kv, 0·5 mA 3 min., 5 mm Al-filter added | Male: patients Female: phantom | | | | 3·0 | 3·0 |

## REFERENCES


1. International Commission on Radiological protection (ICRP) and International Commission on Radiological Units and Measurements (ICRU), Joint Study Group report on *Exposure of man to ionizing radiation arising from medical procedures.* Physics in Medicine and Biology, *2,* 107-151 (1957). See also UN document A/AC.82/G/R.117.
2. Martin, J. H.: *The contribution to the gene material of the population from the medical use of ionizing radiations.* Medical Journal of Australia, in print.
3. Austria: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, on radiological data, UN document A/AC.82/G/R.102.
4. Hammer-Jacobsen, E.: *Gonadedoser i diagnostisk radiologi* (Gonad doses in diagnostic radiology). Ugeskrift for Laeger (Denmark), *119,* 279-290 (1957), see also UN document A/AC.82/G/R.221.
5. Osborn, S. B. and Smith, E. E.: *The genetically significant dose from the diagnostic use of X-rays in England and Wales.* The Lancet, 16 June, 949-953 (1956). See also UN document A/AC.82/G/R.51.
6. Reboul, J. and Istin, J.: *Doses gonades en radiodiagnostic.* Bordeaux (1958) UN document A/AC.82/G/R.194).
7. Japan: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, on radiological data, UN document A/AC.82/G/R.70.
8. Norway: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, on radiological data, UN document A/AC.82/G/R.106 and A/AC.82/G/R.106/Add.1.
9. Larsson, L.-E.: *Radiation doses to the gonads of patients in Swedish roentgen diagnostics.* Acta radiologica, Supplement No. 157 (1958), see also UN document A/AC.82/G/R.182.
10. Laughlin, J. S. and Pullman, I.: *Gonadal dose produced by the medical use of X-rays,* UN document A/AC.82/G/R.74.
11. Court-Brown, W. M. and Doll, R.: *Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis.* Medical Research Council (U.K.) Special Report Series, No. 295 (1957). See also UN document A/AC.82/G/R.105.
12. Martin, J. H.: *An estimate of the potential leukaemogenic factor in the diagnostic use of X-rays.* Medical Journal of Australia, in print.
13. International Commission on Radiological Protection (ICRP): *Recommendations,* revised 1 December 1954. Brit. J. Radiol. Suppl. 6 (1955).
14. Clark, K. C.: *Positioning in radiography.* 7th ed., Grune and Stratton Inc., New York and London (1956).
15. Sante, L. R.: *Manual of roentgenological techniques,* 15th ed. revised, Edwards Bros. Inc., Ann Arbor (1946).

16. Webster, E. W. and Merril, O. E.: *Measurements of gonadal dose in radiographic examinations,* New England Journal of Medicine, 257, 811-819 (1957).

17. Ritter, V. W., Warren, S. R. and Pendergrass, E. P.: *Roentgen doses during diagnostic procedures.* Radiology, *59,* 238-249 (1952).

18. Ardran, G. M. and Crooks, H. E.: *A comparison of radiographic techniques with special reference to dosage.* Brit. J. Radiol., *26,* 352-357 (1953).

19. Ecyleshym, A. C. and Schoemaker, D. M.: *A cross-section anatomy.* Appleton-Century Crofts Inc., New York (1938).

20. Johns, H. E., Epp, E. R. and Fedoruk, S. O.: *Depth dose data, 75 kVp to 140 kVp.* Brit. J. Radiol., *26,* 32-37 (1953).

21. Jones, D. E. A. and Ellis, R. E.: *The measurement of the dose-contributions from the main treatment fields.* Appendix B to ref. 28.

22. Laughlin, J. S., Meurk, M. L., Pullman, I. and Sherman, R. S.: *Bone, skin and gonadal doses in routine diagnostic procedures.* American Journal of Roentgenology, *78,* 961-982 (1957).

23. Lorentzon, L.: *Some notes on skin doses and bone marrow doses in mass miniature radiography.* UN document A/AC.82/G/R.176.

24. Martin, J. H.: *Radiation doses to the gonads in diagnostic radiology and their relation to the long-term genetic hazard.* Medical Journal of Australia, *2,* 806-810 (1955).

25. Ardran, G. M. and Crooks, H. E.: *Gonad radiation dose from diagnostic procedures.* Brit. J. Radiol., *30,* 295-297 (1957).

26. Ardran, G. M.: *Dose reduction in diagnostic radiology.* Brit. J. Radiol., *30,* 436-438 (1957).

27. Christensen, H.: *Patienters udsaettelse for ioniserende strålning* (The exposure of patients to ionizing radiation). Ugeskrift for Laeger (Denmark), *119,* 290-295 (1957).

28. Martin, J. H.: *Radiation doses received by the skin of a patient during routine diagnostic X-ray examinations,* Brit. J. Radiol., *20,* 279-283 (1947).

29. Tubiana, M.: *Doses reçues par les organes genitaux au cours des examens radiographiques effectués chez l'enfant.* UN document A/AC.82/G/R.186.

30. Camerman, J.: *Examens radiographiques et danger des radiations.* Journal Belge de Radiologie, *39,* 165-178 (1956).

31. Bacq, Z. M.: *Du danger des examens radioscopiques pour les malades* (see also discussion following text). Journal Belge de Radiologie, *39,* 687-695 (1956).

32. Baily, N. A.: *Patient exposure to ionizing radiation in dental radiography.* Radiology, *69,* 42-45 (1957).

33. Trout, E. D., Kelley, J. P., Cathery, G.: *The use of filters to control radiation exposure to the patient in diagnostic roentgenology.* American Journal of Roentgenology, *67,* 946-962 (1952).

34. Ardran, G. M. and Kemp, F. H.: *Protection of the male gonads in diagnostic procedures.* Brit. J. Radiol. *30,* 280 (1957).

35. Etter, L. E.: *Radiation dose reduction by higher voltage dental roentgenography.* Journ. Amer. Dental Association, *53,* 305-309 (1956).

36. Martin, J. H.: *Necessity and means of protecting patients in diagnostic and therapeutic radiology.* Proceedings of the College of Radiologists of Australasia, *1,* 103-112 (1957).

37. Clark, S. H.: *Genetic radiation exposures in the field of medicine.* Bulletin of the Atomic Scientists, *12,* 14-18 (1956).

38. Purser, P. R. and Quist, C. F.: *An estimate of the genetic dose from radiotherapy.* Acta. radiol. *48,* 267-272 (1957).

39. Chamberlain, R. H.: *Gonadal radiation in the genetically significant portion of the population derived from the radioactive isotope procedures in medicine.* Hearings before the special sub-committee on radiation of the Joint Committee on Atomic Energy, U.S. Congress, Part 1, 885-888 (1957). See also UN document A/AC.82/G/R.130.

40. Johns, H. E. and Taylor, R. M.: *Dose from unsealed radio-nuclides.* UN document A/AC.82/G/R.129.

41. International Labour Office: *Code of practice for radiation protection in luminizing work.* Geneva (1957).

42. Hursh, J. B., Steadman, L. T., Looney, W. B. and Colodzin, M.: *The excretion of thorium and thorium daughters after Thorotrast administration.* Acta radiol., *47,* 482-498 (1957).

43. Rotblat, J. and Ward, G.: *The radioactivity from Thorotrast and its retention in tissue.* Physics in Medicine and Biology, *1,* 125-137 (1956).

44. Service d'hygiène atomique et de radio-pathologie du C.E.A.: *Étude de l'irradiation professionelle en France en 1955.* UN document A/AC.82/G/R.16, Part III.4.

45. New Zealand: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, on radiological data, UN document A/AC.82/G/R.185.

46. Medical Research Council (U.K.): *The hazards to man of nuclear and allied radiations,* London (1956). See also UN document A/AC.82/G/R.2.

47. Swedish government official report: *Strålskydd* (Radiation protection), Statens Offentliga Utredningar 1956:38, Stockholme (1956).

48. Australia: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, on radiological data, UN document A/AC.82/G/R.29.

49. Larrson, L. E.: *Radiation doses to patients and personnel in modern roentgen diagnostic work,* Acta radiologica, *46,* 680-689 (1956).

50. Mayneord, W. V.: Some problems of radiation protection. Brit. J. Radiol., *24,* 525-537 (1951).

51. U.S. Atomic Energy Commission: *Occupational radiation exposures in U.S. atomic energy projects.* UN document A/AC.82/G/R.71.

52. Boulenger, R.: *Doses moyennes reçues par le personnel du C.E.N. Mol de 1954 à 1957.* UN document A/AC.82/G/R.210.

53. New Zealand: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, on radiological data. UN document A/AC.82/G/R.107.

54. Belgium: *Rapport sur la protection sanitaire dans l'exploitation des minerais uranifères au Katanga,* UN document A/AC.82/G/R.116.

55. International Labour Office: *General code of practice for industrial radiation protection,* Geneva (1957).

56. Libby, W. F.: *Dosages from natural radioactivity and cosmic rays,* Science, *122,* 57-58 (1955). See also UN document A/AC.82/G/R.109.

57. Dyson, E. D.: *Shoe-fitting X-ray fluoroscopes—radiation measurements and hazards.* British Medical Journal, *2,* 269-272 (1956).

58. Stanford, R. W. and Vance, J.: *The quantity of radiation received by the reproductive organs of patients during routine diagnostic X-ray examinations.* Brit. J. Radiol., *28,* 266-273 (1955).

59. Spiers, F. W.: *Measurement of the gonadal dose in the medical use of X-rays.* Physics in Medicine and Biology, *2,* 152-156 (1957).

60. Turpin, R., Mille M. Dupire, Jammet, H. and Lejeune, J.: *Etude de la dose/gonade, lors des examens radio-photographiques systematiques.* UN document A/AC.82/G/8.211.

61. Hammer-Jacobsen, E.: *Gonad dose measurements in Denmark,* UN document A/AC.82/G/R.219.

62. Hammer-Jacobsen, E.: *Risk of parenthood and risk of subsequent parenthood,* Denmark 1955 and 1956, UN document A/AC.82/G/R.220.

63. Verbal communication by the delegation of the United Kingdom.

64. Kopp, H.: *Strålebeskadigelse forårsaget af pedoskop. Overvejelser over forøgelse af den totale gonadestråledosis fra pedoskoper* (Radiation damage from pedoscopes. Increase of total gonad dose from pedoscope). Ugeskrift for Laeger, *119,* 766-770 (1957).

65. Koren, K. and Maudal, S.: *Gonad doses received during the medical application of roentgen radiation.* Acta radiol., *48,* 273-279 (1957).

66. Klumpar, J.: *Physical aspects of protection in roentgen and radium therapy.* Acta radiol. et cancerol. Bohemoslovenica, *4,* 152 (1949).

67. Hansen, P. B. and Madsen, C. B.: *Tolerance dose problem in radiological work.* Acta radiol., *34,* 519-528 (1950).

# Annex D
# ENVIRONMENTAL CONTAMINATION

TABLE OF CONTENTS


*Paragraph*

I. RADIOACTIVE FALL-OUT ..... 1
Fall-out mechanisms ..... 6
Measurement of fall-out ..... 9
Airborne activity ..... 10
Fall-out deposit ..... 12

II. COMPUTATION OF EXTERNAL DOSE FROM FALL-OUT DEPOSIT ..... 20

III. $Sr^{90}$ AS AN INTERNAL SOURCE ..... 26
Evaluation of $Sr^{90}$ as an internal hazard ..... 28
$Sr^{90}$ in soil ..... 29
$Sr^{90}$ in food-chains ..... 33
Discrimination factors ..... 34
The soil-vegetation step in food-chains ..... 37
Concentration of $Sr^{90}$ in foodstuffs ..... 48
Calcium sources in diet ..... 50
Stable strontium sources in diet ..... 52
Daily intake of $Sr^{90}$ in man ..... 53
$Sr^{90}$ in human bone ..... 55
The importance of the stable strontium determination ..... 56
$Sr^{90}$ distribution in different bones of the skeleton ..... 57
Uniformity of $Sr^{90}$ distribution in bone ..... 58
The problem of computing skeleton dose from $Sr^{90}$ ..... 63
Concentrations of $Sr^{90}$ in man ..... 66

IV. $Cs^{137}$ AS AN INTERNAL SOURCE ..... 68
Methods for measurement of concentrations of $Cs^{137}$ ..... 71
Concentrations of $Cs^{137}$ in foodstuffs ..... 73
Daily intake of $Cs^{137}$ in man ..... 74
Concentrations of $Cs^{137}$ in man ..... 75
Dose rate from $Cs^{137}$ in man ..... 76

V. DOSES FROM TROPOSPHERIC FALL-OUT ..... 77
External sources ..... 78
Internal sources ..... 79
$Sr^{89}$ and $Ba^{140}$ as internal sources ..... 80
$I^{131}$ as an internal source ..... 84

VI. ESTIMATION OF DOSES FROM FUTURE FALL-OUT ..... 91
Estimation of fall-out rate and deposit in the future ..... 94
Case 1: Tests stop at the end of 1958 ..... 102
Case 2: Tests continue ..... 103
Values of $F_r(0)$ and $F_d(0)$ ..... 107
Methods for dose estimations ..... 111
External irradiation of gonads caused by $Cs^{137}$ ..... 113
Internal irradiation of gonads caused by $Cs^{137}$ ..... 114
Total irradiation of gonads cause by $Cs^{137}$ ..... 115
Internal irradiation of bone marrow caused by $Sr^{90}$ ..... 116
Estimated doses ..... 124

VII. CALCULATION OF BIOLOGICAL EFFECTS ..... 127
Leukemia, assuming a linear dose response relationship and no threshold ..... 128
Leukemia, assuming a threshold of 400 rem ..... 129
Major genetic defects ..... 130

VIII. NOTE ON INFORMATION DOCUMENT ..... 131

REFERENCES

TABLES

## I. Radioactive fall-out

1. In a nuclear explosion, several hundred radioactive isotopes are produced from fission. With exception of a small number of isotopes they have short half-lives and decay rapidly. In addition to fission products and residual fissionable material, a number of neutron-induced radioisotopes are produced. Their nature depend on the surrounding materials. Also, most of the radioisotopes formed by neutron-induction have short half-lives, usually less than a few hours.

2. The radioisotopes formed in a nuclear explosion are distributed by meteorological processes and eventually reach the surface of the earth. They enter the human body in several ways: first, by direct inhalation of airborne material; second, through uptake and deposition on vegetation eaten by humans; third, by transfer through animals and, fourth, by contamination of water supplies.

3. In addition to considering the exposure from material taken into the body, it is necessary to consider external radiation exposure. Except at the immediate site of the explosion, external radiation from airborne material is negligible in comparison with the external radiation from fission products deposited on the ground. The external radiation from deposited fission products depends mainly on their activity, half-lives and gamma emission characteristics.

4. Materials entering the human body deliver a dose which is closely related to the time they are retained by the body. This means that many of the isotopes produced in fission do not present radiation hazards since they do not enter significantly into metabolic processes. Attention has therefore been centred on isotopes which are potentially hazardous by reason of: (1) high fission yield, (2) fairly long physical half-life, (3) high absorption by the body and (4) long biological retention time. Special consideration is given to elements that concentrate in specific tissues, even though they do not have all the characteristics described. Using these criteria, the most important isotopes would be expected to be $Sr^{90}$ and $Cs^{137}$.

5. In addition to the fission products and certain neutron-induced activities, some of the residual fissionable material, such as isotopes of uranium and plutonium, will also be distributed by meteorological processes and can be hazardous since they are alpha emitting bone seekers. However, the absorption by the body is very low and at present there is no evidence of any uptake of these materials in human tissues.

### *Fall-out mechanisms*

6. The fireball from a nuclear explosion in the megaton* range cools so slowly that a major part of the fission products enter the stratosphere, where they become widely distributed. From this reservoir, the fission products fall onto the earth's surface over a period of many years (stratospheric fall-out). These fission products therefore consist mainly of long-lived isotopes. The mechanism of transfer from the stratosphere to the troposphere is not completely understood.

7. The heat of the fireball from explosions in the kiloton* range is dissipated quite rapidly and the fission products do not normally rise above the tropopause. The radioactive cloud from an explosion may travel many times around the earth and, during this time, the tropospheric fall-out is deposited at latitudes fairly close to that of the explosion. The relative magnitude of the contribution of the stratospheric and tropospheric components to the deposit therefore is different for different localities. Half the radioactive material in the troposphere is removed by deposition, mainly through rainfall, in about three weeks[1] and the deposition is effectively complete within three months. This deposit consists mainly of isotopes of fairly short half-life. At the present time the tropospheric fall-out is deposited intermittently during the year and a certain deposit of short-lived activities is built up and maintained. Isotopes of special concern for this report are $Sr^{89}$, $Zr^{95}$, $Ru^{103}$, $Ru^{106}$, $Ba^{140}$ and $Ce^{144}$.

8. If the fireball touches or comes close to the ground in a nuclear explosion, there will be a local fall-out that constitutes a significant fraction of the total activity produced. This type of fall-out consists of radioactivity carried down by relatively large particles and in addition to fission products, contains shortlived isotopes produced by neutron induction in the material from the ground drawn into the fireball. This annex is concerned mainly with stratospheric and tropospheric fall-out.

### *Measurement of fall-out*

9. Measurements have been undertaken to determine concentrations of radioactivity due to fall-out in air, soil and biological material, especially foodstuffs and human bone. Emphasis has been placed on a determination of the world-wide distribution of $Sr^{90}$. A survey of methods which have been found to be valuable in relation to the work of this Committee is given in annex E, and all relevant data from fall-out measurements that are submitted to this Committee are collected in tables XIV to XX and in the map at the end of the volume.

### *Airborne activity*

10. Air samples can be obtained by filtration of air or by electrostatic precipitation. Studies of vertical distribution of fission products in the atmosphere have been made using filters carried by aircrafts or balloons. The samples are counted for total beta activity after decay of natural radioactivity or analysed for individual nuclides after radiochemical separation. One cause of uncertainty in the measurement of airborne activity at high altitude is in many cases the insufficient knowledge of the collection efficiency for this particulate activity.

11. Measurements at ground level in 1956-1957 show a concentration of $Sr^{90}$ from $10^{-10}$ to $10^{-17}$ c/l of air[2-5]. For altitudes up to about 10,000 metres, the amount of fission products per kg of air increases slowly with altitude, but the rate of increase is much greater above the tropopause[2,6,7]. At the present time there are too few data available to permit a complete inventory of the stratospheric content.

Note: Throughout this report and its annexes cross-references are denoted by a letter followed by a number: the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

* 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 ($10^3$ tons) of TNT, namely of about $10^{12}$ calories. A 1 megaton explosion similarly would correspond to the explosion of 1 megaton ($10^6$ tons) of TNT.

*Fall-out deposit*

12. Fall-out deposit measurements are necessary to estimate the external irradiation of man and the amount of specific isotopes likely to enter the biological food-chains and so eventually the body.

13. Many countries are measuring fall-out rate and accumulated deposit. At present, there are available to this Committee results from about 350 stations. However, large areas of the earth are not covered by the survey and not all the stations and laboratories operate at the same technical level. The results received by the Committee, however, allow a number of useful calculations to be made.

14. Soil analysis[D29] and various types of collectors, are used for studying fall-out deposit. Table I gives some technical information on these collectors. The agreement between results obtained by different methods of collection is reasonably good.

15. The location of sampling stations is of the utmost importance in obtaining representative samples. The location of new stations should be determined in consultation with meteorologists to assure a representative collection of precipitation (especially in areas where snow-fall is important).

16. With daily collection on gummed film or gauze, the amount of long-lived nuclides in the samples is generally very low; and, owing to the large soluble fraction, the washing effect of rainfall is considerable. For these reasons the radiochemical determination of $Sr^{90}$ in these samples is valueless. The $Sr^{90}$ content can, however, be computed by measuring the total beta activity of the samples and following its decay (assuming that all the activity originated in a single test).[8] However, in the present situation, with stratospheric mixture of materials from different tests, this computational method is unreliable unless it is repeatedly calibrated against radiochemical determinations on samples collected by the pot method.[9,10] A more refined method for the computation, taking into account the stratospheric reservoir, has recently been worked out, but this method is based on data that are not generally available.[10] The advantages of the gauze or gummed film is that they allow a daily survey of fall-out at many different stations.

17. Results reported to the Committee up to March 1958 are shown in tables XIV, XV and XVII and in the map at the end of the volume where the fall-out deposit at 1 July 1957 is plotted.

18. The world-wide fall-out rate and deposit of $Sr^{90}$ is uneven and there are variations with latitude which show maxima in the region between 30° and 50° North and South, with a minimum near equator, as shown by the curve on figure 1. This curve, showing the fall-out rate during 1956 and 1957, is based on data obtained by radiochemical analysis. Data from soil analysis[12] and from gummed film measurements[10] give the same overall picture for fall-out deposit, although the peak in the northern hemisphere seems to be somewhat broader. The computation of a world-wide average of fall-out rate and deposit is rendered difficult by the existence of large areas not covered by surveys.[D103-109] It is clear, however, that the southern hemisphere has accumulated deposits that are lower than the average, while areas in the northern hemisphere (Japan, the United Kingdom, the United States) have deposits of about three times the world average.[10-15] It should further be pointed out that the large deviations from the average are towards the low side.

19. It has been reported that the fall-out rate in some countries shows seasonal variations,[13] apparently correlated with the known ozone fluctuations. This is, however, not supported by data from other countries.

## II. Computation of external dose from fall-out deposit

20. The fall-out deposit contains gamma-emitters and is therefore an external source of radiation. The composition of the fission products and the corresponding gamma intensities change with time after an explosion. In the tropospheric component there is a large number of short-lived gamma-emitting isotopes and in the stratospheric component $Cs^{137}$ is predominant.

21. It is impossible to make direct measurement of the very low exposure rate from fall-out except at areas close to test sites. Therefore, more indirect methods must be used.

22. To compute the exposure rate from deposited fission products, it is customary to assume that they are uniformly distributed over an infinite plane. The exposure rate from primary radiation is approximately independent of the distance above the ground, provided

Table I. Methods for collection and measurement of fall-out activity

| *Method* | *Evaporation sampling (from pot collection)* | *Filtration and ion exchange* | *Gummed film* | *Gauze* |
|---|---|---|---|---|
| Collection | Rain water and dust | Rain water and dust | Dust | Dust |
| Area, approx. range in $m^2$ | 0.05 to 17 | 0.07 to 3.1 | 0.1 | 0.3 |
| Time of collection | 1 to 30 days or during precipitation, also 3 months' samples | 4 to 30 days or during precipitation | 1 day | 1 day |
| Sample preparation and evaluation | The water is evaporated and the residue mounted for counting or first ashed or radio-chemically analysed. | The water is passed through paper, pulp, paper filter, anion exchanger and cation exchanger. The paper and the exchangers are separately ashed and mounted for counting. | The gummed film is ashed and the residue mounted on planchet or sealed between plastic films for counting. | The gauze is ashed and subsequently treated as the gummed film. |
| Efficiency of collection in per cent | 100[a] | 95[b] | 63[c] | 36[c] |

[a] Assumed 100 per cent effective.
[b] Determined by measurement of effluent water.
[c] The pot collection method is used as reference.

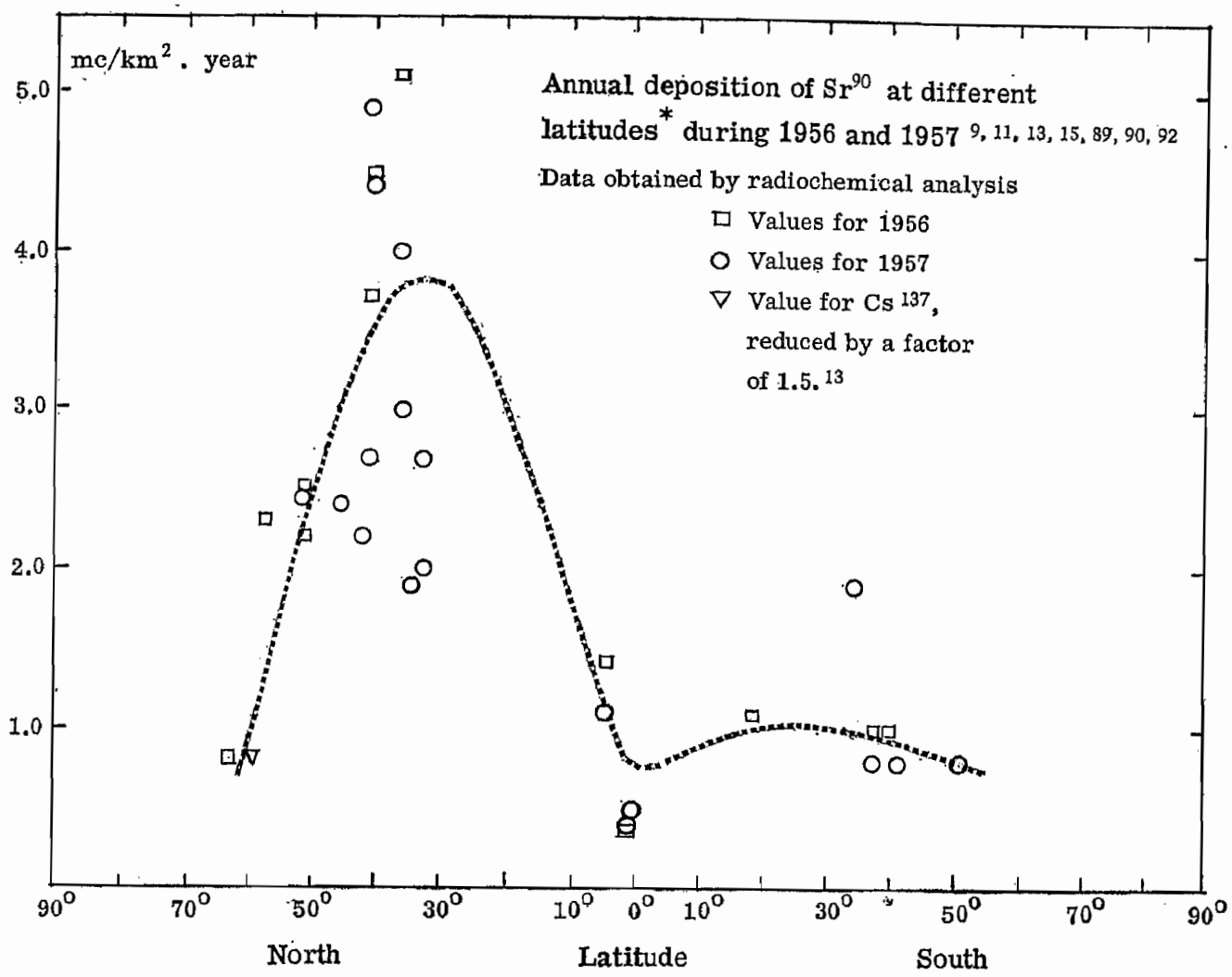



*Figure 1.* Meteorological factors for the different places of observation have not been taken into account

this does not exceed a few metres. One gets the expression:

$$I = c \times \bar{E}\gamma \times F_d^T(t) \qquad (1)$$

where

I is the exposure rate (mrad/year)

$c \approx 0.1 \quad \frac{\text{mrad.km}^2}{\text{year.mc.Mev}}$

$E\gamma$ is the average gamma energy emitted per disintegration (Mev)

$F_d^T(t)$ is the total activity of the deposit (mc/km²)

This formula can be used for individual $\gamma$—emitters such as $Cs^{137}$, or for mixtures if $\bar{E}\gamma$ and $F_d^T(t)$ are known.

23. Two computation methods for the exposure rate from composite fall-out deposits have been used. One computation is based on measurements of total beta-activity of daily gummed film or rainwater samples.[16] This method has been shown to be reasonable at present even though the radioactive fall-out now is a mixture from several explosions.[10]

24. The other method takes into account that the exposure is derived from two components: (1) a "fresh" component of tropospheric origin and (2) a "long-lived" component ($Cs^{137}$) mainly of stratospheric origin.[17] It is shown that the 30-year dose** can be expressed with reasonable accuracy as:

$$D_{30} = aA_t + bA_{Cs137} \qquad (2)$$

where *a* and *b* are constants, $A_t$ is the total beta activity (mc/km²) and $A'_{Cs137}$ is the activity of $Cs^{137}$ (mc/km²). The values of the constants depend on the collection time and the time before the beta counting is done.

25. Values obtained for the infinite plane 30-year exposure due to fall-out deposited up to the end of 1957 are shown in table XIV and are of the order of 10 to 180 mr. The dose delivered to the gonad and bone marrow must be computed taking into account shielding, weathering and leaching factors. The shielding factor accounts for the reduced dose rate during the time the population spend indoors where the dose rate from fall-out deposit is reduced, whereas the weathering and leaching factors account for movement of the deposited gamma-emitting isotopes from the upper layers of the earth's surface, for example to lower layers of the soil. Taking all these effects into account, composite reduction factors ranging from 3 to 21 have been used in reports received by the Committee.[1,15,94,95] Using an average reduction factor of 10, the 30-year genetically significant

** The 30-year dose, which is approximately the genetically significant dose, is the dose received by an individual for the first 30 years of his life.

dose would be about 1 to 18 mrem. It should be emphasized that this is only the dose from what is already deposited, and that the total dose from what has been injected into the atmosphere will be higher, as discussed in paragraphs 94 to 115. Including the tropospheric component, the total dose from the external component will be of the same order of magnitude as the dose from fall-out isotopes taken up by the body.

## III. $Sr^{90}$ AS AN INTERNAL RADIATION SOURCE

26. Among the fall-out isotopes, $Sr^{90}$ is of particular interest on account of the biological hazard that this isotope presents. Strontium is an element of the alkaline-earth group, and its chemical properties are in many ways similar to those of calcium, barium and radium. Thus $Sr^{90}$ co-precipitates with calcium as phosphate or carbonate, and is included in the bone structure. Once included, $Sr^{90}$ may remain in the bone structure for many years, the exact time not being known.[18] The osteocyte and bone marrow cells will be irradiated by the $\beta$ particles from $Sr^{90}$ and its daughter product $Y^{90}$. The ultimate question to be answered is the size of bone and bone marrow doses delivered by these isotopes.

27. To evaluate the present hazard from $Sr^{90}$ the concentration in the bone must be determined. For hazard in the future, however, the change in this concentration, together with the concentration of $Sr^{90}$ in different foodstuffs, should be determined. Of course, $Sr^{90}$ primarily follows stable strontium through the food-chain, i.e., from the deposit on the ground, through uptake by plants and transfer through animals. For practical reasons, however, it is the calcium contributors to the national diet that are mostly studied.

### *Evaluation of $Sr^{90}$ as an internal hazard*

28. A $Sr^{90}$ programme should attempt to take up the following problems:

(*a*) Amount of $Sr^{90}$ so far deposited;
(*b*) Amount of $Sr^{90}$ to be deposited;
(*c*) Rate of deposition of $Sr^{90}$;
(*d*) As a result of (*a*), (*b*) and (*c*):
Eventual total accumulation of $Sr^{90}$ on the ground;
(*e*) Kinetics of strontium in the biological cycle;
(*f*) Present bone level of $Sr^{90}$;
(*g*) Future bone level of $Sr^{90}$.

To this end, the determination of $Sr^{90}$ in the following materials is needed:

(*a*) Human bone;
(*b*) Components of the human food-chains;
(*c*) Fall-out materials (collected by the pot method);
(*d*) Air (atmosphere and stratosphere);
(*e*) Soils, grazing grounds and waters.

The determinations of stable calcium and strontium in the above-mentioned materials are of importance since their concentration is of value in interpreting the $Sr^{90}$ results.

### *$Sr^{90}$ in soil*

29. Soil analysis is useful for the determination of accumulated $Sr^{90}$, as soil can be considered as a primary collector. For determination of fall-out rate, however, this method is not sufficiently accurate. In addition, the soil analysis has little value for the direct estimation of present $Sr^{90}$ hazard owing to the difficulty of estimating the relative importance of the uptake of $Sr^{90}$ in plants from soil and from foliage retention, that is, from uptake of $Sr^{90}$ deposited directly on the leaves.

30. The extraction of $Sr^{90}$ from the soil for analysis is difficult and many techniques are used, such as alkaline fusion, acid leaching, ammonium acetate leaching and electrodiolysis. The large amount of soil needed for analysis makes the alkaline fusion impracticable and the acid leaching method is very much preferred.[B13]

31. The upper 5 cm of the soil retain at present about 70-80 per cent of the deposited $Sr^{90}$, the exact value varying somewhat with the type of soil.[12,19-23] The total amount of $Sr^{90}$, as determined in different countries, is given in table II. Where only the upper 5 cm of the soil was analysed, a factor of 1/0.7 has been used to calculate the total amount. The numbers given are the average and the range of reported values. The values are in reasonable agreement with values for total deposit of $Sr^{90}$ obtained by other methods of measurement.[5,11,13,15]

32. For the study of the behaviour of $Sr^{90}$ in food-chains, it is useful to express the $Sr^{90}$ concentration in activity per gram of available calcium.** The amount of calcium per kg of soil is extremely variable; for example, different areas in the United Kingdom show a range from 0.1 to 150 g calcium/kg soil,[22] although a small part only of the calcium is likely to be labile and available to plants in soils with the higher concentrations. Also, the available fraction of calcium is very variable; for example, in two different localities in the United States 3 and 42 per cent respectively of the calcium is available.[20] The availability to plants may also vary if its chemical form in the soil changes with time or under different conditions. Similarly the chemical form of stable strontium will influence its availability to plants.

### *$Sr^{90}$ in food-chains*

33. From the environment to the human skeleton, strontium follows a long path accompanying calcium. The problems to be considered are the transfer of $Sr^{90}$ and stable strontium in food-chains and the transfer from soil to plant.

#### *Discrimination factors*

34. The chemical similarities between strontium and calcium make the use of $Sr^{90}$/calcium ratio convenient for following $Sr^{90}$ from the environment to human

** For concentrations of $Sr^{90}$ the unit 1 micro-microcurie ($\mu\mu$c) $Sr^{90}$ per gram calcium is used (1 strontium unit, 1 S.U.).

TABLE II. AMOUNT OF $Sr^{90}$ IN SOIL

| Country | Japan[23] | Sweden[9] | UK[22, 89] | USA[20, 88] | USSR[5] |
|---|---|---|---|---|---|
| Period of measurement | January–May 1957 | Mid-1956 | July 1957 | October 1957 | February–July 1957 |
| $Sr^{90}$ in mc/km$^2$ | 2.5–6.3 | 1.2[a] (0.6–2.0) | 5.3 (3.5–14.5) | 9.7 (3.2–13) | 6.0 (3.0–12) |

[a] These preliminary data are probably too low, as an ammonium acetate leaching method was used for the extraction of $Sr^{90}$ from soil.

TABLE III. DISCRIMINATION FACTORS

| *Species* | *Diet* | *Method* | *Remarks* | *Classification*[a] | *Value*[b] | *Reference* |
|---|---|---|---|---|---|---|
| Man..... | Milk | Double tracer with each meal | 4 patients, 9 to 73 years old | Diet → bone | 0.54 (0.50–0.62) | 29 |
| Man..... | Normal mixed | Stable Sr/Ca ratio in diet and bone | Average adult diet in U.K. | Diet → bone | 0.25 | 30 |
| Man..... | Normal mixed | Stable Sr/Ca ratio in diet and bone | Average diet in Canada | Diet → bone | 0.5 | 48, 91 |
| Man..... | Normal mixed | Stable Sr/Ca ratios | 1 normal | Diet → bone | 0.24 | 31 |
| Man..... | Non-milk | Double tracer with each meal | 4 patients | Diet → bone | 0.44 (0.37–0.51) | 29 |
| Man..... | Non-milk | Double tracer, single dose | 2 patients | Diet → bone | 0.35 (0.25, 0.45) | 32 |
| Man..... | Normal mixed | $Sr^{90}$/Ca ratio in diet and bone | Indirect calculation | Diet → bone | 0.25 | 33 |
| Man..... | | Stable Sr/Ca ratio in diet and bone (disregarding marine contribution to diet) | Average Japanese diet and average bone concentration | Diet → bone | 0.17 | 34 |
| Sheep..... | Grass from uncultivated pasture | Stable Sr/Ca ratio in grass and bone | 6 animals | Diet → bone | 0.24 (0.15–0.31) | 22 |
| Sheep..... | Grass from uncultivated pasture | $Sr^{90}$/Ca ratio in grass and bone | 6 animals | Diet → bone | 0.23 (0.09–0.42) | 22 |
| Goat..... | Non-milk | Double tracer, daily dose | 2 animals | Diet → bone | 0.23 | 35 |
| Rat..... | Milk | Double tracer in dietary | | Diet → bone | 0.57±0.02 | 28 |
| Rat..... | Non-milk | Double tracer in dietary | | Diet → bone | 0.27±0.01 | 28 |
| Rat..... | Non-milk | Lifetime feeding of radiostrontium/Ca | | Diet → bone | 0.28 | 27 |
| Rat..... | Non-milk | Stable Sr/Ca ratios | | Diet → bone | 0.27 | 27 |
| Mouse..... | Non-milk | Stable Sr/Ca ratios | | Diet → bone | 0.35 | 27 |
| Guinea pig..... | Non-milk | Stable Sr/Ca ratios | | Diet → bone | 0.22 | 27 |
| Jack rabbit..... | Natural (on desert) | Stable Sr/Ca ratios | | Diet → bone | 0.20 | 27 |
| Cottontail rabbit | Natural (on desert) | Stable Sr/Ca ratios | | Diet → bone | 0.22 | 27 |
| Kangaroo rat... | Natural (on desert) | Stable Sr/Ca ratios | | Diet → bone | 0.16 | 27 |
| Cow..... | | Radiostrontium and radio-calcium at different times | | Diet → milk | 0.14 | 36 |
| Cow..... | | $Sr^{90}$ assay of Wisconsin milkshed, 1953 | | Diet → milk | 0.16 | 37 |
| Cow..... | | $Sr^{90}$ assay of Wisconsin milkshed, 1955 | | Diet → milk | 0.16 | 21 |
| Cow..... | | $Sr^{90}$ assay in U.K., 1955 | | Diet → milk | 0.09 | 26 |
| Goat..... | | Double tracer, daily dose 2 animals 13 days | | Diet → milk | 0.09 (0.08, 0.10) | 35 |
| Rat..... | | Double tracer in dietary | | Plasma → foetus | 0.55–0.65 | 38 |
| Rabbit..... | | Double tracer in dietary | | Plasma → foetus | 0.49 | 38 |

[a] Although some of the following discrimination factors are determined as DF (diet → blood)' they have been written DF (diet → bone)' as DF (blood → bone) is very near unity.[28, 35, 39-42]

[b] The range or mean ± standard error is given where available.

bones. However, the chemical behaviours of strontium and calcium are not identical and, therefore, their utilization varies in biological processes such as assimilation and milk secretion. For example, cows utilize calcium more efficiently than strontium in producing milk. To express quantitatively the preferential utilization of one of these elements in a given process, the following nomenclature is proposed:

$$\text{Discrimination factor}^{\dagger}\ DF_{(\text{precursor}\rightarrow\text{sample})} = \frac{\text{Sr/Ca ratio in sample}}{\text{Sr/Ca ratio in precursor}}$$

This discrimination between strontium and calcium is caused by several physiological factors among which the most important are: preferential absorption of calcium from the gastrointestinal tract; preferential urinary excretion of strontium; preferential secretion of calcium from blood into milk and preferential transfer of calcium across the placental barrier. The quantitative evaluation of the contributions of these physiological processes has been made under certain conditions.[24] It is possible to define an over-all discrimination factor for a given food-chain as the product of the discrimination factors for each step of the chain, under the condition that there is no additional entrance of strontium or calcium from other sources into any of the intermediate steps. For example, in the chain: soil → grass → cow's milk → human bone, the over-all discrimination factor is:

$$DF_{(\text{soil}\rightarrow\text{bone})} = DF_{(\text{soil}\rightarrow\text{grass})} \times DF_{(\text{grass}\rightarrow\text{cow's milk})} \times DF_{(\text{cow's milk}\rightarrow\text{human bone})}.$$

35. Various methods have been described for measuring the discrimination factors:

(*a*) By measuring the stable strontium/calcium ratio in precursor and in sample;[25]

(*b*) By measuring the radiostrontium/calcium ratio, for example $Sr^{90}$/calcium in precursor and in sample in equilibrium, either under field conditions[22,26] or in dietary experiments;[27]

(*c*) By double tracer experiments, for example, using $Ca^{45}$ and $Sr^{85}$.[28]

36. In the case of $Sr^{90}$ transfer from fall-out deposit to human bone, the problem is complicated at present by the possibility that the human bone may often not be in equilibrium with the environment. The discrimination factors obtained by technique (*a*) give inherently the equilibrium value and this technique is therefore very important for the evaluation of future risk. For this reason, the determination of stable strontium and calcium in the steps of the food-chains is fundamental. It is important, however, that the subjects have lived on a diet with a constant stable strontium/calcium ratio and that the entire diet is analysed. Some values for discrimination factors are summarized in table III and in paragraph 47.

*The soil-vegetation step in food-chains*

37. It is very difficult to compute an over-all discrimination factor for the soil-vegetation step. The plants receive $Sr^{90}$ from soil through the roots and also directly from fall-out deposited on the leaves and the concentration may not be uniform throughout the plant.[19,20] With information available at present it is difficult to estimate the relative importance of the two routes of entry as:

(*a*) The accumulated deposit is at present increasing, whereas the fall-out rate has been approximately constant for the last four years.[D104]

(*b*) The mechanism of deposition (dry fall-out, continuous slow precipitation, heavy showers) may change the efficiency of foliar retention.

(*c*) The type and condition of the foliage may change the efficiency for retention of direct deposit.

(*d*) There are great differences in the growing periods and, therefore, in the exposure time of different plants.

(*e*) The accumulation of fission products at the stems of plants may influence the relative significance of the two factors, as this accumulation will depend on the fall-out rate for some previous years.[D44]

(*f*) There are indications that in soils with low available calcium contents, the root uptake of $Sr^{90}$ is more important than in soils with more available calcium.[D44]

(*g*) The depth of the root penetration, the soil type, the water supply and the depth of ploughing may change the root uptake.

38. For the indirect evaluation of the relative importance of the two components, both stable strontium and calcium data are useful. A possible approach is based on the measurement of the specific activity of $Sr^{90}$ in plant and in soil ($\mu\mu c\ Sr^{90}$/g stable strontium). As the $Sr^{90}$ retained by the foliage is carrier-free the ratio:

$$\frac{\text{specific activity of } Sr^{90} \text{ in soil}}{\text{specific activity of } Sr^{90} \text{ in plant}}$$

gives the fraction of the total $Sr^{90}$ in the plant that comes from soil. If the specific activity of the soil is computed from the total strontium content and not from the amount of strontium available to the plant, this fraction will represent a lower limit, and the available strontium may in certain circumstances represent a small proportion only of the total strontium.

39. An experiment has been reported on the direct determination of the surface contamination of grain of the 1956 harvest in the Soviet Union. The grain was washed with 0.5 per cent hydrochloric acid and water, which removed at least 50 per cent of the total $Sr^{90}$.[5]

40. Another approach to the problem depends on a direct correlation of the rate of deposition of $Sr^{90}$, the accumulated deposit and the $Sr^{90}$ content in any particular food. This has been attempted for milk[43] in the following way, taking yearly averages to avoid seasonal effects, and assuming that the $Sr^{90}$ in milk comes from the following sources:

(*a*) Uptake by vegetation through the roots, assumed to be proportional to the accumulated deposit in soil ($F_d$, in mc/km², the value at the beginning of the one-year period);

(*b*) Direct deposits on leaves, assumed to be proportional to the fall-out deposit in a one-year period ($f_d$, in mc/km²).

The average $St^{90}$ level in milk in a one-year period $C_M$ is then given by:

$$C_M = a_M(F_d + 1/2f_d) + b_M f_d \qquad (3)$$

where $a_M$ and $b_M$ are proportionality constants.

41. Using data from Perry, N. Y., U.S.A., a set of constants $a_M$ and $b_M$ can be computed. The values for $F_d$ and $f_d$ are estimated from New York City pot data corrected by a factor derived from gummed film data from places near Perry and in New York City.

† A system of nomenclature has been earlier proposed[24]; in this system the term "Observed Ratio" (OR) was proposed for the over-all discrimination between a precursor and sample and the term "Discrimination Factor" was used to denote the discrimination that is produced by a given physiological process.

TABLE IV. $Sr^{90}$ DATA FROM PERRY, N. Y., U. S. A.

| *Period* | *$Sr^{90}$ in milk, S.U.* | *$F_d$, deposited $Sr^{90}$ in mc/km²* | *$f_d$, annual $Sr^{90}$ deposit, mc/km²,* |
|---|---|---|---|
| April 1954–March 1955 | 1.20 | 0.89 | 2.30 |
| Jan. 1955–Dec. 1955.. | 1.89 | 2.16 | 2.78 |
| Oct. 1955–Sept. 1956.. | 2.86 | 4.57 | 3.36 |
| July 1956–June 1957.. | 3.94 | 7.48 | 3.58 |

From these data one calculates the constants: $a_M = 0.34$ S.U. km²/mc and $b_M = 0.23$ S.U. km²/mc.*

42. In the milk from the four one-year periods, the fractions of $Sr^{90}$ derived from foliar retention are 43, 35, 27 and 21 per cent respectively of the total $Sr^{90}$ content. These fractions need not necessarily be measures of the foliar retention of the plants, as the relative contribution may have been altered by factors such as washing of the grass by rain, and differences in chemical form of the $Sr^{90}$ that the plants had obtained from the two origins. It is likely also that values of $a_M$ may vary with time if the chemical state of radiostrontium in the soil changes progressively.

43. To determine the root uptake directly, crop experiments have been performed in the United Kingdom with $Sr^{89}$ tracer.[90] With the conditions of soil and cultivation in that country, concentration of 1.1 S.U. in grass was found for an accumulated level of 1mc/km² from root uptake alone.[44] This corresponds to a milk concentration of about 0.15 S.U., derived by using the appropriate discrimination factor from table III.[D30] The constant $a_M$ in equation (3) should thus have a value of about 0.15 S.U. km²/mc for the United Kingdom as derived from experiments lasting for one year with $Sr^{89}$ well equilibrated with soil. Experiments also indicate a foliar retention ranging up to 90 per cent of the total herbage contamination.

44. For other food materials and crops, a method similar to that given in paragraph 40 is applicable with three provisions:

(*a*) The relevant period during which the fall-out is averaged should in some cases be limited to the growing period of the plant if this is much shorter than one year, although the fall-out during this period may correlate with the annual fall-out rate.

(*b*) Some plants have leaves at the base of the stem, or a horizontal mat of roots, which may persist for several years and prevent the $Sr^{90}$ fall-out from passing to the soil. If the growing parts of the plant derive $Sr^{90}$ from such a persistent stem base or root mat, the appropriate averaging period for the fall-out rate may need to be several years. Since, at the present time, the fall-out deposited during the last four years is nearly equal to the total fall-out deposit, the formula given above may fail to distinguish between uptake from a stem base or root mat on the one hand and from the accumulated deposit present in the soil on the other.

(*c*) The uptake of $Sr^{90}$ from the soil is likely to be influenced somewhat by the amount of available calcium in the soil. There are indications that in soils which are very deficient in available calcium, the root uptake of $Sr^{90}$ may be greater than from high total calcium soils,[22] and that on such soils the possible formation of root mats may also enhance the uptake. The foliar uptake of $Sr^{90}$ is not, however, influenced in this way by soil calcium. The proportions of $Sr^{90}$ taken up through leaves and through roots will therefore depend on the calcium status of the soil as well as upon the type of plant, conditions of culture and the rate and quantity of $Sr^{90}$ fall-out. It should be emphasized, however, that the $Sr^{90}$ uptake of plants from soil is effected not only by the absolute quantity of calcium present, but also by the degree of saturation of the colloidal complex of the soil by calcium and other cations, such as magnesium, potassium and sodium, and this varies materially from one soil to another.[45]

45. In the important case of rice, the outer layers of the grain become contaminated by carrier-free $Sr^{90}$ deposited on them from fall-out occurring during a very short period before the harvest. The kernel of the grain has an $Sr^{90}$ uptake which appears to be more dependent upon accumulated deposit than upon rate of fall-out;[23] this will be accentuated by the shortness of the growing period, by the ploughing of each season's straw into the upper soil layers and also by the formation of a root mat under certain conditions of growth. The $Sr^{90}$ content of white rice is thus mainly dependent on root uptake, whereas that of brown rice, from which the outer layers have not been removed, is at present more dependent on surface contamination.

46. To distinguish between the amount of $Sr^{90}$ reaching plants through their roots, as compared with that coming from foliar absorption or uptake from the stem base, is important for predicting their relative significance under future conditions. If, in the future, the accumulated deposit of $Sr^{90}$ in the soil has increased considerably relative to the fall-out rate, the relative uptake of $Sr^{90}$ from the soil is likely to become much greater than that by other routes, especially for soil of very low calcium content. Forecasts of plant contamination under such future conditions can, therefore, only be based adequately upon that component of present uptake which depends on the accumulated deposit of $Sr^{90}$.

47. From the preceding paragraphs it may be deduced that an evaluation of a generally valid discrimination factor that includes the step from soil is very difficult at best. For defined conditions, however, some values have been reported. Thus $DF_{(soil \rightarrow diet)}$ has been estimated as 0.5, based on values for stable strontium/calcium ratios in average Japanese soil and diet.[84] Data obtained in the United States indicated that $DF_{(soil \rightarrow plant)}$ may be about unity.[46] A general approach, by using stable strontium/calcium ratios in average rock and soil and in human bones, has given the value $0.07 \pm 0.01$ for $DF_{(soil \rightarrow human\ bone)}$,[47] although this value will vary according to the type of diet.

### *Concentrations of $Sr^{90}$ in foodstuffs*

48. Data submitted to the Committee on concentrations of $Sr^{90}$ in different foodstuffs are collected in table XVI. The data show a wide range, caused both by geographic and seasonal effects. Only selected data are therefore meaningful if one wants to examine the increase of the concentration with time. Some such data for milk are collected in table V. Analysis has shown that dried and fluid milk and cream and skimmed milk from the same whole milk sample have the same $Sr^{90}$/calcium ratio.[48]

49. Cereals and vegetables, as a rule, show higher concentrations of $Sr^{90}$ than milk and milk products, as shown in table VI.

### *Calcium sources in diet*

50. If the dietary habits of a population are known with respect to the main sources of calicum and also the

* The values given in reference 43 were calculated using experimental data from a shorter period. They differ by about 10 per cent from the values above.

concentration of $Sr^{90}$ in the various foodstuffs, the daily uptake of $Sr^{90}$ from vegetation to human bone can be computed, using discrimination factors for the different steps in the food-chains as given in table III.[D36] Table VII, submitted by the Food and Agriculture Organization in consultation with the World Health Organization, gives some data on dietary habits in different countries. Additional data from some of these countries support the values.[23,30,34,52] It should be pointed out that there are only a few countries from which suitable data were available.[51]

TABLE V. AVERAGE CONCENTRATION OF $Sr^{90}$ IN MILK (IN S.U.) IN SOME SELECTED AREAS

| *Location* | *1954* | *1955* | *1956* | *1957* | *Reference* |
|---|---|---|---|---|---|
| Canada | | | | | |
| 6 stations[a] | | | 5.0 | 6.2 | 48, 49 |
| U.K. | | | | | |
| Somerset[b] | | 4.1 | 4.4 | 5.1 | 22, 30 |
| U.S.A. | | | | | |
| Perry, N. Y. (Jan.–Dec.) | | 1.9 | 3.3 | 3.9 | 92 |
| (Apr.–Dec.) | 1.1 | 2.2 | 3.7 | 4.0 | |
| New York City (Jan.–Dec.) | | 2.7 | | 4.5 | 92 |
| (June–Dec.) | 1.4 | 3.7 | | 5.0 | |
| State College, Miss. (May–Sept.) | | 3.8 | 4.8 | | 92 |
| Columbus, Wisc. (Jan.–Oct.) | | | 3.7 | 4.2 | 92 |
| (May–Oct.) | | 2.6 | 4.0 | 5.3 | |
| Mandan, No. Dak. (Jan.–Dec.) | | | 9.2 | 16 | 92 |
| (May–Dec.) | | 7.2 | 9.1 | 22 | |

[a] Monthly data for each station are compared with data from the same month in the two years, altogether 57 values used.
[b] Median values.

TABLE VI. CONCENTRATIONS OF $Sr^{90}$ IN (S.U.) IN CEREALS AND VEGETABLES

| *Location and type of sample* | *1956* | *1957* | *Reference* |
|---|---|---|---|
| Japan | | | |
| Rice, white | 49 (36,62) | | 23 |
| Rice, brown | 154 (81–250) | | |
| Wheat, flour | | 53 | |
| Wheat, brown | | 162 (153,170) | |
| Soviet Union | | | |
| Wheat and rye | 69 (28–140) | | 5 |
| United Kingdom | | | |
| Vegetables | | 11 (6–35) | 30 |
| United States | | | |
| Different cereals | 14 (4–38) | | |
| Vegetables[a] | 8 (1–29) | 9 (1–23) | 33, 50 |

[a] The samples were frozen vegetables from food plants.

TABLE VII. SOME PRINCIPAL SOURCES OF CALCIUM IN THE AVERAGE DIETS OF A FEW SELECTED COUNTRIES[51]

| *Country* | *Per capita average daily intake, mg calcium* | | |
|---|---|---|---|
| | *Cereals, vegetables, etc.* | *Milk and milk products* | *Fish and marine products* |
| Argentina | 84 | 510 | – |
| Australia | 52 | 570 | 12 |
| Canada | 109 | 780 | – |
| Japan | 264 | 20 | 106 |
| Philippines | 53 | 32 | – |
| Union of South Africa | 56 | 260 | 7 |
| United Kingdom | 370 | 585 | 12 |

51. The data in table VII should only be taken to indicate the order of magnitude of the calcium supplies in the different countries. The main contribution to the human diets vary widely from one country to another, and there are wide variations within the same country in accordance with many general and local differences in food supplies, dietary habits and economic conditions.[51] Milk and milk products are the major source of calcium intake in most Western countries (giving about 70-85 per cent of the total calcium), whereas they play a very minor role in most of the countries in Asia and Africa, where other foods such as cereals, vegetables and also fish and marine products are the principal sources of calcium in the average diets. Moreover, certain foods not originally rich in calcium are fortified by mineral calcium in many countries.

### *Stable strontium sources in diet*

52. Some data on the content of stable strontium in various types of food are also available and are summarized in table VIII.

TABLE VIII. AVERAGE STABLE STRONTIUM CONTENT IN VARIOUS TYPES OF FOODS

| *Type* | *mg Sr/gCa* | *Reference* |
|---|---|---|
| Cereals and vegetables | 2 | 22, 23 |
| Milk and milk products | 0.3 | 20, 22, 48 |
| Marine fish | 3 | 23 |
| Fresh water fish | 1 | 23 |

These data show that the stable strontium/calcium ratio of certain foods may be up to ten times higher than in milk and milk products. Therefore milk may not be the main source of stable strontium in diet although it may be the main source of calcium (see table IX).

### *Daily intake of $Sr^{90}$ in man*

53. Daily intake of $Sr^{90}$ has been reported from some places. Table IX shows data from the United Kingdom, together with data on stable calcium and strontium intake.

TABLE IX. AVERAGE DAILY INTAKE OF CALCIUM, STABLE STRONTIUM AND $Sr^{90}$ IN ADULT DIET IN UNITED KINGDOM[30]

| *Food* | *Calcium intake, mg/day* | *Stable strontium intake, µg/day* | *$Sr^{90}$ intake µµc/day* |
|---|---|---|---|
| Milk | 667 | 193 | 3.64 |
| Flour and bread[a] | 332 | 714 | 0.66 |
| All other foods | 200 | 526 | 2.35 |
| TOTAL | 1199 | 1433 | 6.65 |

[a] Fortified with mineral calcium.

54. Wide variation can be expected because of different food habits and living conditions, as illustrated by computations from Japan.[34] They show that whereas the majority of the population have an average daily intake of 3.3 to 5.8 µµc $Sr^{90}$ per day, there is a substantial number of people, who either eat unpolished brown rice or drink and prepare food with unfiltered rainwater, which may cause a daily intake of 23 to 26 µµc $Sr^{90}$ per day.

### *$Sr^{90}$ in human bone*

55. The measurements of $Sr^{90}$ concentrations in human bone give the data that are most needed for the estimation of present risks from fall-out. The interpretation of bone $Sr^{90}$ results is complicated by four important factors, which will be discussed in the following paragraphs.

(1) Due to lag in contamination of calcium sources with $Sr^{90}$, human bone is not yet in equilibrium with the environment. To correlate the $Sr^{90}$ content of human bone with the contamination level of the environment and to predict future risks, it is necessary to know how close the system bone-environment is to equilibrium. For this purpose stable strontium measurements are very useful.

(2) If $Sr^{90}$ were unevenly distributed in the human skeleton the measurement of a single bone would not be representative of the average skeleton value.

(3) Uneven distribution of $Sr^{90}$ within the bone would also make the relevant dose computation difficult.

(4) The average $Sr^{90}$ content of bone may also vary with age.

*The importance of the stable strontium determination*

56. Using the stable strontium/calcium ratios in different steps of the food-chains and in bone, it is possible to determine the discrimination factors$^{D35}$ and compute the equilibrium concentration in bone. The determination of stable strontium in bone can be done by spectography[47,53,54] or by activation analysis.[55,56] The reported values differ somewhat, and this may partly be explained by a small but significant difference observed from one locality to the next.[47] An average of 450 $\pm$ 100 $\mu$g strontium/gram calcium has been found using 756 samples from all over the world.[47] Investigations in Canada and the United Kingdom have given average values from 290 to 370 $\mu$g strontium/gram calcium using a limited number of samples (16 to 35).[22,49,50] Young children apparently have somewhat lower strontium concentrations in bone than adults,[22,50] which should be expected as a result of foetal discrimination against strontium.[38]

*$Sr^{90}$ distribution in different bones of the skeleton*

57. The problem of non-uniformity in the distribution of stable strontium in different bones in the skeleton of man has also been investigated by stable strontium measurements. It seems that there is a uniform distribution,[47,56] which should mean that the distribution of $Sr^{90}$ should also be uniform when the skeleton has reached equilibrium with a contaminated environment. This has been confirmed for goats fed by $Ca^{45}$ and $Sr^{89}$ over an extended period,[35] and by measurements on the distribution of $Sr^{90}$ in cow's bones.[48] In man, however, there are experiments showing non-uniformity by single injections of double tracers and also in the $Sr^{90}$ distribution at present in adults.[33,57]

*Uniformity of $Sr^{90}$ distribution in bone*

58. It seems clear that $Sr^{90}$ would be distributed uniformly with calcium throughout the bones of a child whose calcium intake had been contaminated with $Sr^{90}$ at constant concentration during the whole of its life since, in these circumstances, all bone formed would be derived from calcium of equal $Sr^{90}$ content.

59. Non-uniform deposition would arise from two main causes:

(*a*) A progressive change in the $Sr^{90}$ contamination of dietary sources will lead to a corresponding change in $Sr^{90}$ level of new deposits of bone, which contain the most sensitive cells. With rising dietary levels, the bone concentrations in young children will indicate the current dietary conditions. Much of the bone of older children and of adults will, however, be contaminated at lower levels corresponding to the lower levels in diets of earlier years. In this sense, the maximum bone concentrations in young children may be in equilibrium with their current diet, although the amount of bone contaminated at this concentration may well be only a fraction of the whole skeleton. Correction for non-uniformity of $Sr^{90}$ distribution is not, however, required if the concentration in young children is used as an indication of the maximum concentrations being reached in new bone deposited in older children or adults.

(*b*) Any change in source of calcium intake may involve an alteration of $Sr^{90}$ level in this intake and thus in bone that is currently being formed. An important instance arises in young children, whose bone calcium will have been derived from three different sources:

(i) From the mother during gestation;

(ii) From the mother's milk during maternal feeding;

(iii) From the subsequent dietary sources.

60. Some indication may be given as to the importance of these factors. Calcium derived during gestation appears at present to be somewhat lower in $Sr^{90}$ levels (about one half) than the child's subsequent diet, since the level in the bones of stillborn children is rather less than in children 1 to 2 years old (table X). The $Sr^{90}$ content of the bones of a child of 2 years would be only slightly lowered for this reason since at this age only about 15-20 per cent of the bone calcium and associated $Sr^{90}$ will have been derived during gestation.[58]

61. Maternal milk contains about 40 per cent of the level of $Sr^{90}$ in the diet of the mother.[59] Since about 25 per cent or less of the bone of a 2-year-old child, previously breastfed for half a year, will have been derived from maternal milk, this factor would only lower the average bone $Sr^{90}$ level by about 15 per cent or less from an equilibrium condition with the diet.[58]

62. Thus the highest radiation doses delivered to bone from radiostrontium are likely to be those in the new bone, that is at present being laid down in children aged over 1 year. If the concentration remains constant, the absolute quantity of strontium in the body increases with the size of the skeleton up to 20 years, and on the assumption of a linear dose effect relationship, the probability of somatic mutation in bone-marrow cells increases with the size of the skeleton.

*The problem of computing skeleton dose from $Sr^{90}$*

63. As a first approximation, $Sr^{90}$ will be considered to be uniformly distributed in the skeleton and it will be assumed that the whole radiated energy is absorbed by the bone. The mean particle energy of the pair $Sr^{90}$ and $Y^{90}$ is 1.13 Mev[59], so that a skeleton containing 1g calcium per 7g bone will receive an average dose rate in compact bone of 2.7 mrem/year per strontium unit.[60] In the skeleton about 10 to 13 per cent is spongious bone, having a dose rate of about 0.9 mrem/year per strontium unit. The average dose rate to the compact and spongious bone of 2.5 mrem/year will be used in the following calculations.[61,62]

64. The bone marrow dose from $Sr^{90}$ deposited in the bone will be lower than the bone dose, depending on the size of the marrow cavity. A calculation of a mean marrow dose is therefore a very complex problem.[60-62] In the following it will be assumed that 1 strontium unit will cause a mean bone marrow dose rate of 1 mrem/year. The true value of the mean marrow dose** might

** The computation of the mean marrow dose is difficult and approximate only.

TABLE X. AVERAGE CONCENTRATION OF $Sr^{90}$ IN MAN (STRONTIUM UNITS)[a]

| Age Group | Canada[48, 49] 1956–1957 | United Kingdom[22, 89] 1956 | United Kingdom[22, 89] 1957 | United States[33,b] 1955–1956 | United States[33,b] 1956–1957 |
|---|---|---|---|---|---|
| Stillborn to 1 month | 0.7 (3) | 0.44 (5) | 0.55 (42) | | |
| 1 month to 1 year | 1.6 (2) | 0.70 (11) | 1.1 (19) | | |
| 1 year to 5 years | 2.1 (4) | 0.83 (13) | 1.2 (17) | 0.56 (10) [c] | 0.67 (30) [c] |
| 5 years to 20 years | 0.1 (1) | 0.25 (12) | 0.45 (19) | 0.26 (17) | 0.54 (32) |
| More than 20 years | 0.4 (3) | 0.11 (5) | 0.1 (4) | 0.07 (137) | 0.07 (62) |

[a] The number of samples in each age group is given in parentheses.

[b] Including a few data from North America outside the United States.

[c] Age group 0 to 5 years.

however, be as low as 0.5 or as high as 2 mrem/year per strontium unit.*

65. It should be emphasized that bone marrow cells which are almost surrounded by bone will receive doses which may be equal to those in compact bone. Taking into account all causes for non-uniformity, i.e. the non-uniform deposition in the mineralized zones, the variation in bone layer widths and geometrical factors (corners), the bone marrow level is probably five times the figures quoted above.

*Concentration of $Sr^{90}$ in man*

66. The knowledge of average values is not sufficient for risk evaluation and individual data are extremely useful. It is emphasized that data on bone concentrations should be accompanied by the following information:

(*a*) Date of death or biopsy;

(*b*) Age at death or biopsy;

(*c*) Precise origin;

(*d*) In case of children: methods of feeding.

67. Not all the data obtained so far include complete information, and further studies are required. Table X gives some of the bone concentrations measured in different countries (see also table XVII).

## IV. $Cs^{137}$ AS AN INTERNAL SOURCE

68. The similarity between the nature of the precursors, half-lives and fission yields of $Sr^{90}$ and $Cs^{137}$ suggests that the distribution of these two isotopes is similar in fall-out. On the other hand, their different chemical properties make their behavour in food-chains and in the body different.

69. $Cs^{137}$ is poorly taken up from soil by plants.[10,64,65] Therefore, the contamination of food sources should depend largely on fall-out rate. The biological half-life of caesium is comparatively short (about 140 days in man[65] and 20 days in cow[66]), thus indicating that the level of the isotope in the human body will approach equilibrium with the environment relatively quickly.

70. $Cs^{137}$ concentrations are often expressed by the $Cs^{137}$/potassium ratio. Some evidence exists, however, that the metabolism and routes of entry into the human body of these elements are to some degree different. For example, in man, the biological half-life of potassium (35 days)[67] is apparently shorter than that of caesium. An analogy of $Sr^{90}$/calcium ratios should therefore not be implied.

*Methods for measurement of concentrations of $Cs^{137}$*

71. Measurements of concentrations of $Cs^{137}$ can be made without radiochemical separations. $Cs^{137}$ has a gamma-emitting daughter product, $Ba^{137}$, which can be determined using gamma-spectroscopy, as can $K^{40}$.[E15] The large difference in energy of the gamma rays emitted from $Cs^{137}$ (0.66 Mev) and $K^{40}$ (1.46 Mev) makes the discrimination adequate even with crystal detectors of low energy resolution. Radiochemical methods are also in use for separation of caesium from other material.[E15]

72. The present burden of $Cs^{137}$ in man can be determined *in vivo* with whole body spectrometry or gamma spectroscopy.[E15] Large liquid scintillators have the advantage of being geometrically efficient, but the energy resolution is relatively poor. Sodium iodide crystals have good energy resolution, but even with the largest crystals available, the counting rate is not as high as with the large liquid scintillators. To obtain the maximum of information, both types of counter seem necessary.[68]

*Concentration of $Cs^{137}$ in foodstuffs*

73. As in the case of $Sr^{90}$ it should be possible to relate the $Cs^{137}$ burden in man to the concentration in the diet. In some areas (i.e. the United States), milk contributes about 50 per cent of the human uptake[65] and can therefore be used for comparative purposes. During 1956-1957, milk in different countries showed a general $Cs^{137}$ concentration of 20 to 70 $\mu\mu$c $Cs^{137}$/g potassium.[23,65,73,74,86,87] The wide range is partly caused by variation with geographic locality. Measurement of rice in Japan 1956-1957 showed a concentration of about 50$\mu\mu$c $Cs^{137}$/g potassium.

*Daily intake of $Cs^{137}$ in man*

74. Estimations of daily intake of $Cs^{137}$ have been made for Japan and the United States, giving about 30 to 50 $\mu\mu$c $Cs^{137}$/day.[23,65] Because of the short biological half-life for $Cs^{137}$, variations in the diet will change the $Cs^{137}$ level in man rapidly. With the constant concentration in the diet, the equilibrium burden in man is reached in about two years.

*Concentrations of $Cs^{137}$ in man*

75. The measurements of $Cs^{137}$ in man show a range of 25 to 70 $\mu\mu$c $Cs^{137}$/g potassium in the north temperate zone during 1956-1957 with an average of about 35 $\mu\mu$c $Cs^{137}$/g potassium.[65,69] During periods shortly after tests, a slight increase has been observed.[65] Concentrations in the diet and in man are apparently rather similar, which is unexpected because of the longer biological half-life of caesium as compared to potassium.[65]

*Dose rate from $Cs^{137}$ in man*

76. Since the average potassium content of a standard man (70 kg body weight) is about 150 g,[67,69,70] the average $Cs^{137}$ gonad dose rate amounts to about

* Higher mean marrow doses are possible and higher doses in small foci of bone can be expected.

1 mrem/year (ranging from about 0.5 to 2 mrem/year).[65] Uniform distribution of caesium in soft tissue is assumed as is indicated by stable caesium measurements.[71]

## V. Doses from tropospheric fall-out

77. Fall-out from the troposphere consists mainly of short-lived isotopes and the dose contributions are therefore primarily dependent on fall-out rate rather than on accumulated deposit. The latitudes where the tropospheric fall-out is deposited are mainly determined by the latitude of the test sites. The doses from tropospheric fall-out material vary with geographic location roughly in the same manner as the dose from stratospheric fall-out.

### *External Sources*

78. The tropospheric material has an observed mean residence time of two to four weeks[1] and although it is deposited intermittently during the year, a certain deposit of short-lived activities is built up and maintained. The reported values indicate that a level of short-lived radioactivity is maintained at about 50 to 200/mc/km$^2$ (See table XIV). Allowing a factor of 10 for shielding and weathering and assuming an average $\gamma$-energy of about 0.5 Mev[16], the annual gonad and mean bone marrow dose should be of the order of 0.25 to 1 mrem/year.[D22]

### *Internal Sources*

79. The air concentration of fission products at ground level has been reported to be about $10^{-15}$c/l during 1956 to 1957 (See table XVI). Assuming that this material has the same composition as the fall-out, the annual dose resulting from inhalation has been computed[72] using data for retention, volume of inhaled air, weight of critical organs, etc., based on I.C.R.P.—criteria.[67] The annual doses, according to the calculations, are:

| | | |
|---|---|---|
| Whole body dose | 0.2 | mrem |
| Lung dose (if material soluble) | 0.1 | mrem |
| (if material insoluble) | 1.5 | mrem |
| Thyroid dose | 0.6 | mrem |
| Bone dose ($Sr^{89}$, $Sr^{90}$, $Ba^{140}$) | 0.15 | mrem |
| Average bone marrow dose ($Sr^{89}$, $Sr^{90}$, $Ba^{140}$) | 0.05 | mrem |
| Average gut dose | 0.03 | mrem |

### *$Sr^{90}$ and $Ba^{140}$ as internal sources*

80. Dose contribution from short-lived activities can be introduced through food-chains when the food has not been stored for a long time. Storage of food reduces the activity of short-lived isotopes, which makes it very difficult, if not impossible, to give world-wide average annual doses from tropospheric material.

81. It has been reported that $Sr^{89}/Sr^{90}$ activity ratios in milk show fluctuations in the range 1 to 25.[20,22,48,49,73,74] There are marked seasonal variations, largely dependent on whether the cows were on pasture. Thus the average $Sr^{89}$ concentration in milk has been reported as 3 to 12 $\mu\mu$c $Sr^{89}$/g calcium in January to April, whereas it was of the order of 100 to 150 $\mu\mu$c $Sr^{89}$/g calcium in September and October in Canada in both 1956 and 1957. The $Sr^{90}$ concentration was all the time of the order of 4 to 8 $\mu\mu$c $Sr^{90}$/g calcium.[48,49]

82. Computation of the relative doses from the two isotopes, using the range of values observed in milk for the $Sr^{89}/Sr^{90}$ ratios, show that the doses from $Sr^{89}$ give rise to a bone dose ranging from about 1 to 20 per cent of that from $Sr^{90}$.† $Ba^{140}$ in the amount that corresponds to the mean residence time of the tropospheric fall-out (3 weeks), gives a dose contribution that is less than 10 per cent of the dose from $Sr^{89}$.

83. Data from measurements in Canada, show the presence of $Sr^{89}$ in bone from man and animals, as given in table XI.

Table XI. Concentrations of $Sr^{89}$ and $Sr^{90}$ in bone[48]
($\mu\mu$c per g calcium)

| *Sample and date of death* | *Age* | *$Sr^{89}$* | *$Sr^{90}$* |
|---|---|---|---|
| *Human bone* | | | |
| December 1956 | 5 months | 5.4±0.6 | 1.8±0.2 |
| December 1956 | 10 months | 3.7±0.4 | 1.4±0.2 |
| November 1956 | 22 months | 5.7±0.3 | 3.8±0.2 |
| *Cow bone* | | | |
| October 1956 | Foetal | 144 | 8.6 |
| October 1956 | 3 weeks | 28.3 | 5.3 |
| October 1956 | 4 weeks | 43.4 | 5.1 |
| October 1956 | 6 years | 15.6 | 8.1 |
| October 1956 | 13 years | 18.7 | 3.8 |
| August 1956 | Old | 6.3 | 3.3 |
| August 1956 | Old | 8.4 | 6.9 |

### *$I^{131}$ as an internal source*

84. Measurements of $I^{131}$ are of interest because of the selective concentration of iodine by the thyroid glands of man and animals. The normal human thyroid weighs 20-35 g and contains about 10 to 15 mg of stable iodine. All soft tissue has small amounts of stable iodine and blood plasma contains about 0.05 $\mu$g/cm$^3$.[75] The effective half-life of $I^{131}$ in the body is very close to the radioactive half-life, 8 days.[67]

85, Since 1954, many laboratories have measured activities of $I^{131}$ from fall-out in human and cattle thyroids.[76–80] The thyroid samples obtained from autopsies are counted with scintillation counters calibrated against $I^{131}$ standards. In some cases the results are corrected using values from muscle measurements to eliminate the $K^{40}$ and $Cs^{137}$ contributions.

86. Apparently the cattle contamination is from two sources; inhalation and feeding on contaminated pastures. Results obtained by feeding cattle on fresh fodder or with barn fodder during the same periods suggest that 70 per cent of the $I^{131}$ uptake is from intestinal absorption,[80] but there are other experiments that indicate both higher[81] (up to 95 per cent) and lower[77] percentage from this route of entry.

87. Results of measurements of the $I^{131}$ content in cattle thyroids from various laboratories show a large spread of values. Neglecting high values from areas near test sites, average results for cattle from different geographical locations are comparable, and are of the order of 1 to 100 $\mu\mu$c/g thyroid for the period May 1955 to the end of 1956.[76,78] On account of the short half-life, $I^{131}$ concentrations in thyroids vary with time as related to weapon tests.[79,80]

88. $I^{131}$ activities in human thyroids are lower than in those of cattle from the same area and show less spread in the values. Considering only the $I^{131}$ activities from a group of barn-fed cattle and correcting for different respiratory volumes, values similar to those of human thyroids are obtained.[80] This supports the idea that the human $I^{131}$ intake is through inhalation. In some areas of the United States away from test sites, the $I^{131}$ concentrations in human thyroids averaged about 4 $\mu\mu$c/g thyroid during May 1955.[80] The human thyroids measured were mostly from adults (more than 50 years old), but a few samples from persons of different ages

† A biological half-life of strontium of 11 years is used.[67]

suggested that the $I^{131}$ activity increased slightly with age.[80] The human thyroid concentrations also vary with time according to weapon test periods. It is therefore difficult to estimate the integral thyroid dose over a period of time.

89. Considering the linear dimensions of the normal thyroid gland, it can be computed that the gamma contribution to the average thyroid dose is about 10 per cent of the beta contribution.[82] Integrating the data for the United States, excluding areas immediately adjacent to test sites, average doses of the order of 5 mrem/year are found in man for the years 1955 and 1956.[80] Dose from $I^{131}$ in soft tissues is of the order of $10^{-4}$ times the thyroid dose.[D84] Therefore the average annual gonad dose in the United States for the years 1955 and 1956 was of the order of $\mu$ rem.

90. In areas near test sites, short-lived iodine isotopes will reach the thyroids. From the half-lives and average energies of these isotopes, the thyroid dose delivered can be computed as 4 times the dose from $I^{131}$ if radioiodine is inhaled about 10 hours after the nuclear explosion,[83] but after 10 days the contribution is negligible.

## VI. Estimation of doses from future fall-out

91. Data on present fall-out rates and accumulated deposits and the human burden of fission products allow the estimation of present dose rates. However, for evaluation of future genetic and somatic effects it is required to estimate the 30-year and 70-year doses. This estimation can of course be based on computations only of future fall-out rate and deposit and not on experimental data. It is possible, however, to make these computations using available data and certain assumptions which have at present little if any support in physical data. The results must therefore be considered only in connexion with these assumptions and necessarily cannot be any more valid than these.

92. Once the values for the future average world-wide fall-out rate and deposit have been calculated, the next step is to evaluate the doses received by human beings. This requires calculations based on factors, some of which are uncertain and others which cannot be generalized for the world's population, such as agricultural conditions and practices or living and dietary habits.

93. Owing to all these factors the evaluation of doses is rather uncertain. Furthermore, no indication, based on experiments, can be given as to the degree of uncertainty involved in the evaluations, but an attempt has been made to choose the more pessimistic of the possible alternative assumptions, and the over-all calculations may therefore overestimate the doses to be expected from future fall-out.

### *Estimation of fall-out rate and deposit in the future*

94. A major part of the long-lived components of fall-out arises from the stratospheric reservoir, which is built up by "high yield explosions".[D6] It has been reported that about 10 per cent of the deposited $Sr^{90}$ comes from tropospheric fall-out[9,13] in areas far from test sites (Sweden and United Kingdom). In the United States the contribution is estimated to be about 30 per cent,[12] which may be taken as representative for areas relatively close to test sites. Only a small error, therefore, is introduced in considering that all the $Sr^{90}$ fall-out arises from the stratospheric reservoir. As $Cs^{137}$ and $Sr^{90}$ have approximately the same half-life and fission yield, and similar gaseous precursors in the fission chain, the following evaluation will be assumed to apply for both isotopes.

95. The material balance of $Sr^{90}$ in the stratosphere-earth system can be described by the following general equations:

$$\frac{d\overline{Q}(t)}{dt} = n - \lambda\overline{Q}(t) - \overline{F}_r(t) \qquad (4)$$

$$\frac{d\overline{F}_d(t)}{dt} = \overline{F}_r(t) - \lambda\overline{F}_d(t) \qquad (5)$$

where:

n is the injection rate of $Sr^{90}$ into the stratosphere per unit area (mc/km²·year). (*n* is as a convention assumed to be uniform for all the earth's surface. This assumption implies a relatively fast latitudinal stratospheric mixing.)

$\overline{Q}$ (t) is the $Sr^{90}$ content of the stratosphere, expressed per unit area (mc/km²).

$\overline{F}_r(t)$ is the world-wide average fall-out rate of $Sr^{90}$ per unit area (mc/km²·year).

$\overline{F}_d(t)$ is the world-wide average accumulated deposit of $Sr^{90}$ per unit area (mc/km²).

$\lambda$ is the disintegration constant of $Sr^{90}$ (0.025/year).

96. These equations do not imply any particular relation between the stratospheric content and the fall-out rate, nor do they imply any specific function for the variation of *n* with time. The equations, therefore, cannot be fully resolved. At present, data on *n* are not available to the Committee. The computations will therefore be carried out for hypothetical cases of future values for *n*. Equation (5) implies that no leaching or weathering occurs.

97. Analysis of fall-out material has shown that $Sr^{90}$ can remain in the stratosphere for many years before being deposited on the earth. The depletion mechanism of the stratospheric reservoir is not yet adequately known. It has been estimated from measurement of fall-out rate and stratospheric content that the annual $Sr^{90}$ fall-out is about 12 per cent of the stratospheric content.[2] This annual fraction corresponds to a mean residence time of about 8 years, which is in agreement with a value of 10 ± 5 years derived from unpublished data.[37] The concept of a constant fractional removal per year of the stratospheric content is inconsistent with meteorological principle. However, nothing better can be offered at present. If the concept is to be used, a mean residence time of about 5 years appears to be the best value and a reasonable upper limit is about 10 years.[84] The latter value has been used in the calculations to follow, since it tends to yield results on the pessimistic side.

98. For the calculations it will be introduced as working hypothesis that the annual fraction does not change with time:

$$\overline{F}_r(t) = k\,\overline{Q}(t)$$

where k = 0.1/year. It can be seen that all the following equations for $\overline{F}_r(t)$ and $\overline{F}_d(t)$ that depend on the value of *k* will give higher results for lower values of *k**.

99. As the radioactive material is in the form of microscopic particles of various sizes, it might be expected that the residence time of this material in the stratosphere will be a function of the size spectrum of the particles. This has importance especially in the event that no new material is introduced into the stratosphere, because the depletion would then continuously change the size distribution.

* Using k = 0.2/year in the following computations gives doses that are 0 to 40 per cent lower than those obtained using k = 0.1/year.

100. It is now possible to present a model in which equations (4) and (5) can be integrated. The hypotheses of the model are the following:

(*a*) All the $Sr^{90}$ fall-out comes from the stratospheric reservoir;

(*b*) The fall-out rate is proportional to the stratospheric content;

(*c*) The $Sr^{90}$ deposited on the earth is not acted upon by weathering effects or leaching;

(*d*) The injection rate of $Sr^{90}$ into the stratosphere $n$ will be constant in the future. Two hypothetical cases giving two different values of $n$ will be discussed below.

101. The general solutions of equations (4) and (5), using equation (6), are:

$$\bar{F}_r(t) = \bar{F}_r(0)\, e^{-(k+\lambda)t} + \frac{kn}{k+\lambda}(1 - e^{-(k+\lambda)t}) \qquad (7)$$

$$\bar{F}_d(t) = \bar{F}_d(0)\, e^{-\lambda t} + \frac{\bar{F}_r(0)}{k}(e^{-\lambda t} - e^{-(k+\lambda)t}) + \frac{n}{\lambda}\left(\frac{k}{k+\lambda} + \frac{\lambda}{k+\lambda} e^{-(k+\lambda)t} - e^{-\lambda t}\right) \qquad (8)$$

$\bar{F}_r(0)$ and $\bar{F}_d(0)$ are the values

for the fall-out rate and accumulated deposit at the time $t = 0$, which in the following will be taken as the end of 1958.

*Case 1: The tests stop at the end of 1958*

102. This implies that $n = 0$ for any subsequent time. Using this relation, equations (7) and (8) will be:

$$\bar{F}_r(t) = \bar{F}_r(0)\ e^{-(k+\lambda)t} \qquad (9)$$

$$\bar{F}_d(t) = \bar{F}_d(0)\, e^{-\lambda t} + \frac{\bar{F}_r(0)}{k}(e^{-\lambda t} - e^{-(k+\lambda)t}) \qquad (10)$$

Equations (9) and (10) show that the fall-out rate decreases exponentially from the moment of interruption of tests, while the fall-out deposit increases, goes through a maximum at a time:

$$t_{max} = \frac{1}{k} \ln \frac{\bar{F}_r(0)\,(k+\lambda)}{(\bar{F}_d(0) + \bar{F}_r(0)/k)k\lambda} \qquad (11)$$

(about 13 years after tests stop) and then decreases, eventually with the half-life $Sr^{90}$.

*Case 2: Tests continue*

103. For the calculations of future fall-out rate and deposit two assumptions are used: (*a*) the rate of fall-out of $Sr^{90}$ will remain in the future at the constant value observed for the last four years, or (*b*) the rate of injection of $Sr^{90}$ into the stratosphere will remain in the future at a value equal to the mean value for the years 1954 to 1958 inclusive. If tests are stopped at any subsequent time T, then $\bar{F}_r(t)$ and $\bar{F}_d(t)$ would from that moment on, with either assumption, be determined by the equations:

$$\bar{F}_r(t) = \bar{F}_r(T)e^{-(k+\lambda)(t-T)} \qquad (12)$$

$$\bar{F}_d(t) = \bar{F}_d(T)e^{-\lambda(t-T)} + \frac{\bar{F}_r(T)}{k}(e^{-\lambda(t-T)} - e^{-(k+\lambda)(t-T)}) \qquad (13)$$

104. *Assumption* (a). In the model adopted, this assumption implies that Q will remain at an equilibrium value, which has been caused by large initial injections, followed by a constant injection rate that compensates

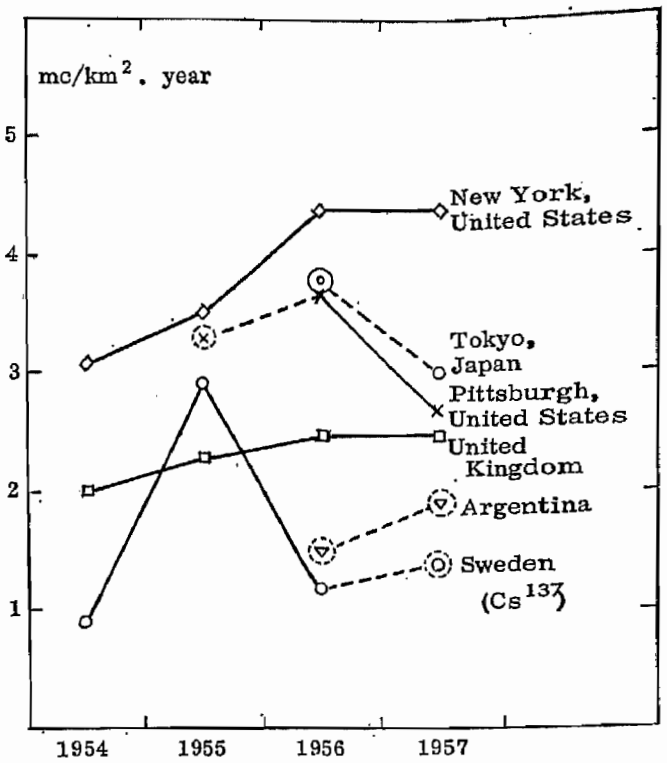



*Figure 2.* Fall-out rate of $Sr^{90}$ determined by radiochemical analysis.[9,11,15,87,90,92] Values obtained by extrapolation of data for part of year are encircled.

for the stratospheric depletion. This might have been the situation during the last four years, as illustrated in figure 2. From equations (4) and (6) it follows that:

$$n = \bar{F}_r(0)\,\frac{k+\lambda}{k} \qquad (14)$$

Using this relation, equations (7) and (8) will be:

$$\bar{F}_r(t) = \bar{F}_r(0) \qquad (15)$$

$$\bar{F}_d(t) = \bar{F}_d(0)e^{-\lambda t} + \frac{\bar{F}_r(0)}{\lambda}(1 - e^{-\lambda t}) \qquad (16)$$

If the tests go on indefinitely, $\bar{F}_d(t)$ will reach an equilibrium value of:

$$\bar{F}_d(\infty) = \frac{\bar{F}_r(0)}{\lambda} \qquad (17)$$

The 90 per cent equilibrium value will be reached in about 70 years.

105. *Assumption* (b). The period from the beginning of 1954 to the end of 1958 has been chosen[D103] because the values of $\bar{F}_r(t)$ and $\bar{F}_d(t)$ were small before 1954 and the error introduced assuming both to be equal to zero would be small. The estimation of an average $n$ for the period 1954 to 1958 inclusive implies in our model computing a constant $n$ such that it would produce, in five years, the observed values of $\bar{F}_r(0)$ and $\bar{F}_d(0)$ at the end of 1958.

106. The total amount of $Sr^{90}$ in the environment is $\bar{F}_d(t) + \bar{Q}(t) = \bar{F}_d(t) + \frac{\bar{F}_r(t)}{k}$. Therefore $\bar{n}$ (average for the period 1954 to 1958) is an $\bar{n}$ determined by:

$$\bar{F}_d(0) + \frac{\bar{F}_r(0)}{k} = \frac{\bar{n}}{\lambda}(1 - e^{-\lambda r}) \qquad (18)$$

where $r$ is 5 years, and $\bar{F}_r(0)$ and $\bar{F}_d(0)$ are the fall-out rate and deposit at the end of 1958. Under this assumption the solution of equations (7) and (8) is:

$$\bar{F}_r(t) = \bar{F}_r(0)e^{-(k+\lambda)t} + \frac{\bar{n}k}{k+\lambda}(1-e^{-(k+\lambda)t}) \quad (19)$$

$$\bar{F}_d(t) = \bar{F}_d(0)e^{-\lambda t} + \frac{\bar{F}_r(0)}{k}(e^{-\lambda t}-e^{-(k+\lambda)t}) + \frac{\bar{n}}{\lambda}\left(\frac{k}{k+\lambda} + \frac{\lambda}{k+\lambda}e^{-(k+\lambda)t} - e^{-\lambda t}\right) \quad (20)$$

If tests go on indefinitely $\bar{F}_r(t)$ and $\bar{F}_d(t)$ will reach the equilibrium values:

$$\bar{F}_r(\infty) = \frac{\bar{n}k}{k+\lambda} \quad (21)$$

$$\bar{F}_d(\infty) = \frac{\bar{n}k}{\lambda(k+\lambda)} \quad (22)$$

The 90 per cent equilibrium values will be reached in about 15 and 100 years, respectively.

*Values of $F_r(0)$ and $F_d(0)$*

107. It is difficult from the available data to compute a world-wide fall-out rate and deposit, partly because large areas of the earth are insufficiently covered by the net-work of stations collecting data and partly because the different stations and laboratories do not all operate with comparable collection and evaluation methods. The estimation is especially difficult for the fall-out deposit, as many stations have only operated for less than two years.

108. The world-wide average of the fall-out rate of $Sr^{90}$ was estimated from the latitude distribution curve, figure 1.[D18] It was assumed that the fall-out rates at the poles were zero. As measurements seem to indicate that the fall-out rate has been fairly constant over the last four years (see figure 2),[D104] the rate of 1.5 mc/km²·year obtained from the data from 1956 and 1957 has also been assumed valid for 1958.

109. The world-wide average of the accumulated fall-out deposit of $Sr^{90}$ has been obtained from soil, pot and gummed film data.[5,9–13,20,22,23] The values obtained were extrapolated to the end of 1958 using the quoted value 1.5 mc/km²·year for the average fall-out rate, giving as an average about 5 mc/km² as the average accumulated deposit at the end of 1958.

110. Population weighted averages have been calculated using the same data as in paragraphs 108 and 109, and the latitudinal distribution of the world's population as obtained from a detailed population map.[85] At present, the maximum fall-out level occurs at the same latitude as the maximum population density and the population weighted averages for fall-out rate and deposit are at present higher than the area weighted averages by a factor of about 2. It is possible that this may change in the future and that in the event of cessation of tests it may approach unity. However, no allowance for this possible reduction has been made in the present calcula-

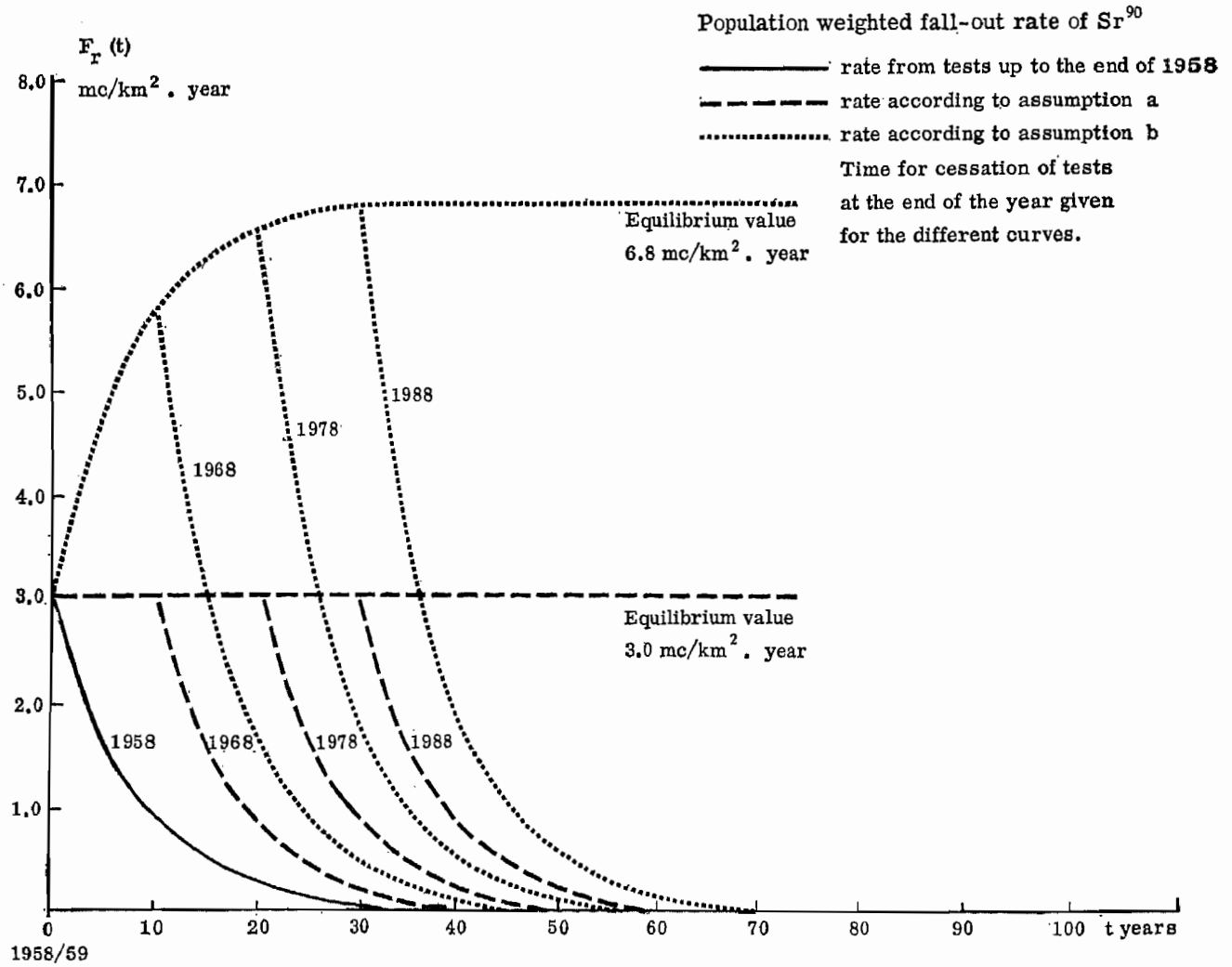



*Figure 3*

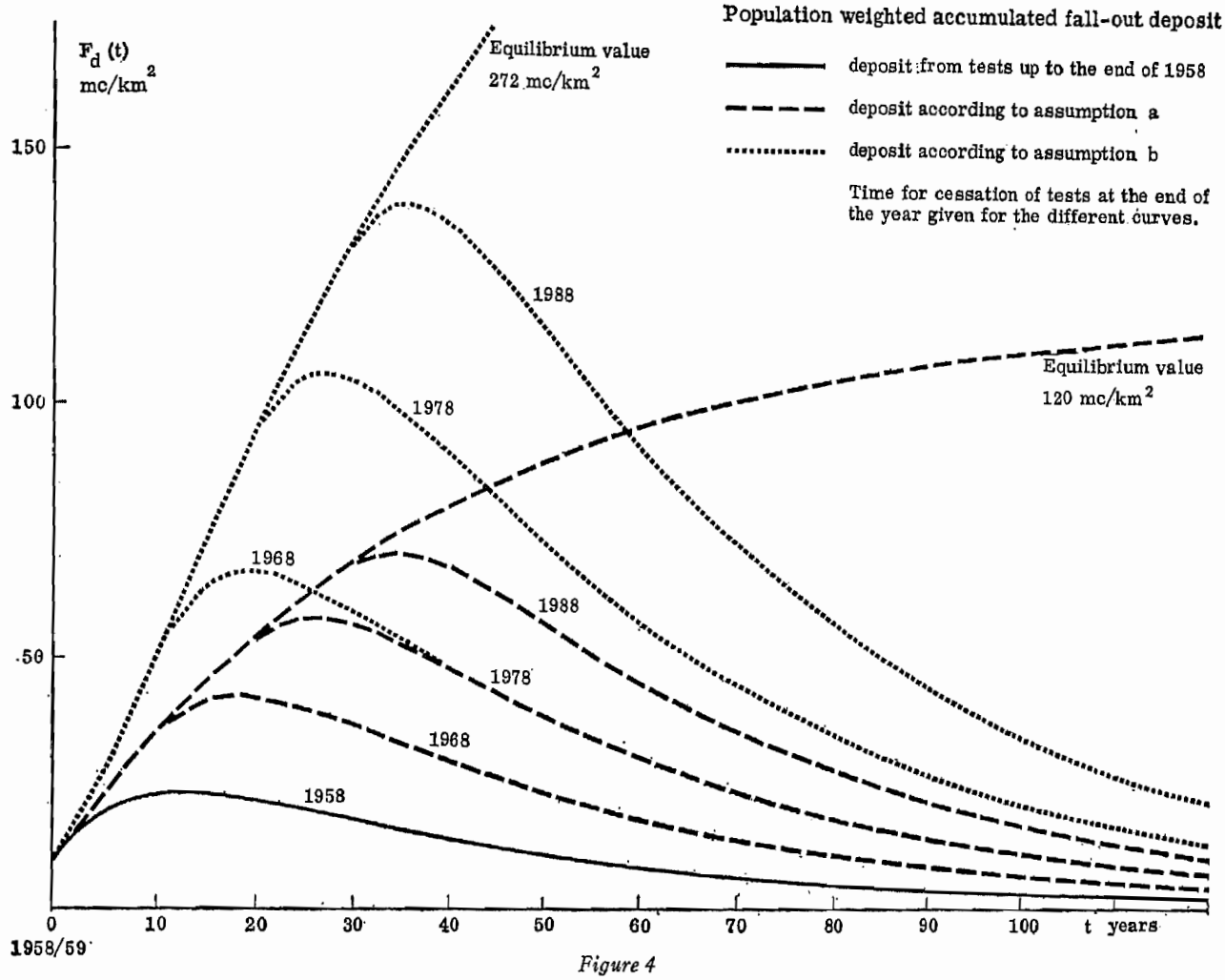



*Figure 4*

tions.** The population weighted values of the fall-out rate and of the accumulated deposit at the end of 1958 are accordingly taken as:

$$F_r(0) = 3 \text{ mc/km}^2 \cdot \text{year}$$

$$F_d(0) = 10 \text{ mc/km}^2$$

*Methods for dose estimations****

111. The equations derived above give the variation of the fall-out rate and deposit with time for the different cases studied (see figures 3 and 4). The computation of doses to human beings also requires information on the behaviour of $Sr^{90}$ and $Cs^{137}$ in the food-chain, and this introduces new uncertainties. The main information required is the extent to which the dose rate is correlated to fall-out rate and to fall-out deposit and the values of these correlation factors. At present the available information is insufficient and has to be complemented by some assumptions.

112. In the following paragraphs dose computations will be considered for:

(*a*) External irradiation of gonads caused by $Cs^{137}$;

(*b*) Internal irradiation of gonads caused by $Cs^{137}$;

(*c*) Internal irradiation of bone marrow caused by $Sr^{90}$.

In addition to the cases of (1) cessation of tests at the end of 1958 and (2) continuation of tests until equilibrium is reached, the doses for cases of (3) interruption of tests at different times in the future are also given as percentages of the equilibrium dose.

*External irradiation of gonads caused by $Cs^{137}$*

113. Equation (1)[D22] shows that the exposure rate from external irradiation is proportional to the accumulated fall-out deposit:

$$I = c \times \overline{E}_\gamma \times F_d^T(t) \qquad (1)$$

Taking into account a reduction factor $c^1$ to take care of shielding, leaching and weathering effects, the dose rate is given by:

$$\left(\frac{dD}{dt}\right)_e = c \times c^1 \times E_\gamma \times F_d^T(t) = g_e \times F_d^T(t) \qquad (23)$$

Here $c \approx 0.1 \frac{\text{mrad} \cdot \text{km}^2}{\text{year} \cdot \text{mc} \cdot \text{Mev}}$ and $c^1$ will be assumed to be 0.1.[D25] In the case of exposure from $Cs^{137}$ the value to

** For population weighted average fall-out rate and accumulated deposit the symbols $F_r(t)$ and $F_d(t)$ are used (without bar). As $F_r(0)$ and $F_d(0)$ are a factor of 2 higher than $\overline{F}_r(0)$ and $\overline{F}_d(0)$, respectively, it can be seen from equations (7), (8), (14) and (18) that also $F_r(t)$ and $F_d(t)$ are a factor of 2 higher than $\overline{F}_r(t)$ and $\overline{F}_d(t)$.

*** For the dose estimations population weighted average fall-out rate and accumulated deposit $F_r(t)$ and $F_d(t)$ will be used.

be used for $\bar{E}\gamma$ is 0.92 × 0.89 × 0.661 Mev (92 per cent of the disintegrations give $\gamma$-rays of energy 0.661 Mev and of these $\gamma$-rays 11 per cent are converted.) The dose rate from deposited $Cs^{137}$ is therefore:

$$\left(\frac{dD}{dt}\right)_e = g_e \times F_d(t) = 0.005 \times F_d(t) \text{ mrem/year} \quad (24)$$

*Internal irradiation of gonads caused by $Cs^{137}$*

114. The human burden of $Cs^{137}$ at present depends primarily on the fall-out rate of $Cs^{137}$,[D69] thus giving the dose rate:

$$\left(\frac{dD}{dt}\right)_i = g_i \times F_r(t) \quad (25)$$

Calculations from experimental data show that the average gonad dose rate amounts to about 1 mrem/year in the United Kingdom and the United States during 1956 and 1957.[D70] The observed fall-out rate of $Sr^{90}$ in those countries was about 3 mc/km² during the same years (figure 2).[D104] Assuming the same fall-out rate for $Cs^{137}$ as for $Sr^{90}$ (probably an underestimate), the dose rate due to internal irradiation from $Cs^{137}$ is 0.3 mrem/year for a fall-out rate of 1 mc/km². If in the future the dose rate is proportional to the fall-out rate, then:

$$\left(\frac{dD}{dt}\right)_i = g_i \times F_r(t) = 0.3 \times F_r(t) \quad (26)$$

*Total irradiation of gonads caused by $Cs^{137}$*

115. The total dose rate for the gonads from $Cs^{137}$ is

$$\frac{dD}{dt} = g_e F_d(t) + g_i F_r(t) \quad (27)$$

The 30-year doses for the two assumed injection rates (assumptions *a* and *b*) and for the different cases considered for cessation of tests are therefore given by

$$D_{30} = \int_0^{30} \frac{dD}{dt} dt = g_e \int_0^{30} F_d(t)dt + g_i \int_0^{30} F_r(t)dt \quad (28)$$

The equations for $F_d(t)$ and $F_r(t)$ to be inserted in the different cases can be found elsewhere in annex D, identified by their numbers as given in table XII.

TABLE XII. EQUATIONS FOR USE IN FORMULAS (28), (34) AND (35)

| | $F_d(t)$ | | $F_r(t)$ | |
|---|---|---|---|---|
| | *Assumpt.* a | *Assumpt.* b | *Assumpt.* a | *Assumpt.* b |
| Tests stop end of 1958..... | (10) | | (9) | |
| Tests stop end of 1968, T=10 | (16) and (13) | (20) and (13) | (15) and (12) | (19) and (12) |
| Tests stop end of 1978, T=20 | (16) and (13) | (20) and (13) | (15) and (12) | (19) and (12) |
| Tests stop end of 1988, T=30 | (16) and (13) | (20) and (13) | (15) and (12) | (19) and (12) |
| Tests continue..... | (16) | (20) | (15) | (19) |

The 30-year doses become functions of the time for the start of integration, i.e., of the time of birth of the persons concerned. It can be shown that the maximum occurs for persons born at the end of 1958.† If tests continue, the maximum doses occur when equilibrium conditions are reached for fall-out rate and deposit. In order to compute the total of individuals genetically affected by a given series of tests, it is necessary to add up the $D_{30}$ values for all population groups born in successive years. Because the doses are almost completely delivered over only a few decades for tests ceasing at the end of 1958, these sums of $D_{30}$ values over all successive population groups are satisfactorily approximated for the present purpose by the maximum values of $D_{30}$ in table XIII, if these are assumed to apply over a period of 30 years.

*Internal irradiation of bone marrow caused by $Sr^{90}$**

116. Any estimation of future levels of $Sr^{90}$ in human bone is extremely difficult because it depends both on estimations of the $Sr^{90}$ fall-out rate and deposit in the future and on estimations of how these levels will influence the concentration of $Sr^{90}$ in bone. This last problem is particularly uncertain, as the uptake in the bone is very much dependent on the dietary habits and the food technology in a given region.[D50-D54] As it has been discussed in paragraphs 37 to 46, the uptake of $Sr^{90}$ in different plants at different locations may be dependent on a number of factors, such as fall-out rate, accumulated deposit and the amount of available calcium in soil.

117. The following paragraphs provide calculations of the equilibrium diet-bone concentrations to be expected in humans subsisting on each of two foods: milk and rice. In actual practice, a population does not subsist entirely on either milk or rice, and these calculations should, therefore, be accepted as approximations based on conditions which would not in practice be realized.

118. The concentration of $Sr^{90}$ in human bone in equilibrium with contaminated food can be estimated using formula (3) in paragraph 40 if milk is the main source of calcium in the diet:

$$C_M^B = DF_{(\text{milk} \to \text{bone})} \times C_M = DF_{(\text{milk} \to \text{bone})} \times (a_M(F_d + \tfrac{1}{2}f_d) + b_M f_d) \quad (29)$$

where $C_M^B$ is the concentration of $Sr^{90}$ in newly formed bone, $DF_{(\text{milk} \to \text{bone})}$ the discrimination factor from milk to bone and the rest of the symbols are as in paragraph 40.

119. It will be assumed that, in the future, the accumulated deposit, $F_d(t)$, will be the determining factor for the milk contamination.[D46] Using a value of $a_M$ intermediate between those determined for Perry, N. Y.,[D41] and in the United Kingdom,[D43] and $DF_{(\text{milk} \to \text{bone})} = 0.5$ (table III),[D36] a simplified equation will be:

$$C_M^B \approx 0.15 \times F_d(t) \quad (30)$$

where $C_M^B$ is given in strontium units when $F_d(t)$ is in mc/km².

† This becomes slightly incorrect when the cessation date is later than about 1978. Even for cessation in 1988, however, the approximation is good if the tropospheric contribution to the doses is added.

* The bone marrow dose from external and internal $Cs^{137}$ can be calculated by integration of equation (27) over 70 years. The dose contribution is of the order of 10 per cent or less than that from $Sr^{90}$ in bone and has accordingly been neglected in table XIII.

120. In the cases where rice is the main source of $Sr^{90}$ in the diet, a formula has been derived to cover the rather unusual method of farming this grain in Japan, where most of the plant material from earlier crops is ploughed down in a homogeneously cultivated soil.[34]

$$C_R^B = DF_{(soil \rightarrow rice)} \times DF_{(rice \rightarrow bone)} \times \frac{1}{A} \times F_d(t) \quad (31)$$

$C_R^B$ is the concentration of $Sr^{90}$ in newly formed bone. $DF_{(soil \rightarrow rice)}$ and $DF_{(rice \rightarrow bone)}$, the discrimination factors from soil to rice and from rice to bone, are taken as 0.5 and 0.17 respectively[D36,D47]. $A$ is the amount of available calcium in the soil, approximately $95 \times 10^6$ g/km$^2$ (with outer limits approximately $30 \times 10^6$ and $230 \times 10^6$ g/km$^2$).[34] The formula will in this case be:

$$C_R^B \approx 0.9 \times F_d(t) \quad (32)$$

where $C_R^B$ is given in strontium units when $F_d$ is in mc/km$^2$.

121. It is evident that the equations (30) and (32) for concentrations of $Sr^{90}$ in bone are uncertain. The neglect of foliar retention and of sources of $Sr^{90}$ other than milk tend to give bone concentrations that are too low, especially in the immediate future. It must be emphasized that the bone concentrations are calculated only for newly formed bone.[D118]

122. The mean bone marrow dose is assumed to be 1 mrem/year for a bone concentration of 1 strontium unit.[D64] Therefore the dose rate in bone from $Sr^{90}$ will be:

$$\frac{dD}{dt} = C^B \quad (33)$$

where $C^B$ is the concentration of $Sr^{90}$ in newly formed bone, as given by equations (30) and (32) for the two diets considered. The 70-year doses for the two assumed injection rates (assumptions *a* and *b*), and for the different cases considered for cessation of tests are therefore obtained by integration over 70 years of equation (33), giving, for the hypothetic milk diet:

$$(D_{70})_M = 0.15 \int_0^{70} F_d(t)\, dt \quad (34)$$

and for the hypothetical rice diet:

$$(D_{70})_R = 0.9 \int_0^{70} F_d(t)\, dt \quad (35)$$

The equations for $F_d(t)$ to be inserted in the different cases can be found elsewhere in annex D, identified by their numbers as given in table XII. The doses are calculated for persons born at the end of 1958, which give approximately the maximum 70-year doses. If tests continue, however, the maximum doses occur when equilibrium conditions are reached for accumulated deposit, and have accordingly been calculated for that case.

123. To use the equations (30) and (32) in these computations implies the assumption that the whole skeleton has, at any time, the same concentration of $Sr^{90}$ as bone which is newly formed at that time. The Committee is aware that this assumption is not consistent with the rather long biological half-lives of calcium and strontium. It is, however, a satisfactory approximation for the purpose of the present calculations, which it greatly simplifies. Moreover, this extreme assumption tends to over-estimate the average 70-year dose, and so the calculations may be taken as an upper limit for those population cohorts receiving the maximum 70-year exposure.

*Estimated doses*

124. Table XIII shows the results of the computations for the different cases. The numbers should only be considered in connexion with all the assumptions and uncertain factors discussed in the preceding and following paragraphs.

125. For the estimations of future fall-out rate and accumulated deposit the regional values can be expected to differ by a factor of about ⅕ to 2 depending mainly upon latitude.[D18] In some areas of the world the tropospheric fall-out may tend to raise the upper limit of this range, especially in the vicinity of test sites.

126. The uncertainties in the calculations of doses, based on the estimated fall-out levels, may be considerable, but are difficult to evaluate because of insufficient experimental data. It seems, however, that the experimental data indicate an uncertainty in the *per capita* mean marrow doses of a factor of about 3 merely because of regional variations in the conversion factors from fall-out deposit to bone concentration of $Sr^{90}$.[D119-120]

## VII. Calculation of biological effects**

127. The frequency of certain possible consequences of radiation has been estimated on the following basis:

*Leukemia, assuming a linear dose response relationship and no threshold*

128. In this case, the number of individuals affected annually ($R_1$) is calculated from the appropriate 70-year mean marrow dose ($D_{70}$), the dose effect constant ($K_1$) for leukemia as derived in annex G, paragraph 50, and the assumed world population (P), and dividing by 70 to give a mean annual rate. Thus:

$$R_1 = \frac{D_{70} \times K_1 \times P}{70} \quad (36)$$

$K_1$ is here calculated on the assumption that a leukemia incidence of 1.5 cases per million per year per rem continues after each element of radiation exposure for the remaining life of the individual, or for an average period of 35 years in a population living to age 70. $K_1$ has thus a value of 52 cases per million per rem.

(*a*) In estimating on this basis leukemia ascribable to natural radiation, $D_{70}$ is 7 rem (annex C, table XXV) and $R_1$ is calculated for $P = 3 \times 10^9$ and $5 \times 10^9$, giving values of $R_1$ of 15,800 and 26,200. (The natural occurrence of leukemia is calculated on a basis of 50 deaths per million per year.)

(*b*) Leukemia ascribable to fall-out from weapon tests, if such tests stop in 1958, is calculated with $P = 3 \times 10^9$ and with values of 0.16 and 0.96 for $D_{70}$. These are estimates for milk and for rice diets (table XIII), and would correspond to incidences of 360 and 2,160 cases per year. Because most of the dose is actually delivered during a few decades, the total of induced cases would about equal $70R_1$ and so would be 25,200 to 151,000.

(*c*) Leukemia attributable to fall-out in equilibrium conditions reached after prolonged testing is calculated for $P = 5 \times 10^9$. The values of $D_{70}$ (table XIII) range from 1.3 rem under assumption *a* and with a milk diet, to 17 rem under assumption *b* and with a rice diet, giving incidences of 4,880 and 63,800 cases per year.

** For the purpose of table II, chapter VII, of the report the figures calculated in the following paragraphs have been rounded off.

TABLE XIII. ESTIMATED DOSES FROM STRATOSPHERIC FALL-OUT[a] (computed from population weighted world-wide average values of stratospheric fall-out rate and deposit)[b]

| | *Genetically significant dose: Maximum for any 30-year period (rem)* | | Per capita *mean marrow dose: Maximum for any 70-year period (rem)* | | | |
|---|---|---|---|---|---|---|
| | | | *Estimates for countries deriving most of dietary calcium from milk*[c] | | *Estimates for countries deriving most of dietary calcium from rice*[c] | |
| Weapon tests cease at end of 1958 | 0.010 | | 0.16 | | 0.96 | |
| | *Assump. a*[d] | *Assump. b*[d] | *Assump. a*[d] | *Assump. b*[d] | *Assump. a*[d] | *Assump. b*[d] |
| Weapon tests continue until equilibrium is reached in about a hundred years | 0.045 | 0.10 | 1.3 | 2.8 | 7.5 | 17 |

| | *Estimated percentages of the maximum doses for continued weapon tests* | | | |
|---|---|---|---|---|
| | *Assump. a*[d] | *Assump. b*[d] | *Assump. a*[d] | *Assump. b*[d] |
| Weapon tests cease: | | | | |
| 1958 | 22 | 10 | 13 | 6 |
| 1968 | 45 | 33 | 24 | 16 |
| 1978 | 63 | 55 | 34 | 26 |
| 1988 | 72 | 62 | 42 | 35 |
| Weapon tests continue | 100 | 100 | 100 | 100 |

[a] The methods used for calculation of these doses are given in paragraphs 91 to 123.

[b] Regional values may differ by a factor of 1/5 to 2 from the estimated population weighted world-wide average values because of the latitudinal variation of fall-out rate and deposit. In some areas of the world the tropospheric fall-out may tend to raise the upper limit of this range, especially in the vicinity of test sites.

[c] The extent to which these estimates apply to populations of different dietary habits and to those living in areas of differing soil conditions is discussed in paragraphs 116–121.

[d] Assumption *a* is that the injection rate is such as to maintain a constant fall-out rate of $Sr^{90}$ and $Cs^{137}$, whereas assumption *b* is that weapon tests equivalent in release and stratospheric injection of fission products to the whole sequence of weapon tests from the beginning of 1954 to the end of 1958 will be repeated at constant rate. This second assumption will give an equilibrium value for the fall-out rate and deposit approximately a factor of 2 higher than that calculated by using the first assumption.

Estimates for milk diet with assumption *b* and for rice diet with assumption *a* are 10,500 and 28,200 cases per year.

*Leukemia, assuming a threshold of 400 rem*

129. On this hypothesis, cases of leukemia might result if the 70-year dose exceeded 400 r at any point in the marrow. The maximum dose in marrow might, in a small cavity, equal that in surrounding bone; and it is possible that such bone might, owing to irregularities in mineralization, receive a dose of up to twice the mean bone dose, which in turn is estimated to be about 2.5 times the mean marrow dose (taking a mean bone dose of 2.5 mrem per year per strontium unit*** and a mean marrow dose of 1 mrem per year per strontium unit). The maximum marrow dose might thus equal 5 times the mean marrow dose.

(*a*) With natural radiation, a threshold of 400 rem will only be exceeded in an individual receiving 400/7, or 57 times the normal $D_{70}$ of 7 rem.

(*b*) With fall-out from tests ending in 1958, the mean marrow doses of 0.16 and 0.96 on milk and rice diets correspond to maximum marrow doses of 0.80 and 4.8. The threshold would thus be exceeded by individuals receiving 400/0.8 and 400/4.8, or 500 and 83 times, the average values of $D_{70}$.

(*c*) Under equilibrium conditions of fall-out after prolonged continuation of tests, the mean 70-year marrow doses would range from 1.3 to 17 rem, and the corresponding maximum marrow doses would be 6.5 and 85 rem. A threshold of 400 rem would thus be exceeded by individuals receiving 62 times the average value for milk diet with assumption *a*, and 4.7 times this value for rice diet with assumption *b*.

*** A mean osteocyte dose of 2.5 mrem per year per strontium unit has also been used for the purpose of the calculations of the numbers given in note to table II, chapter VII.

This report affords only very incomplete evidence as to the likely variation of individual marrow doses from the mean values, and no estimate is given of the way in which the risk of leukemia might increase once a threshold dose was exceeded. These results, on the hypothesis that a 400 rem threshold exists, therefore give only a general indication of the relative hazards in different circumstances.

*Major genetic-defects*

130. For the purpose of these calculations it is assumed that, by the time any mutations currently occurring came to be expressed as damage in the population, the world population would have become stabilized at $P = 5 \times 10^9$, half of whom were below the mean age of reproduction.

The total number of births would be $5 \times 10^9/70$ and a part ($K_g$) of these would be affected by major genetic defects (annex H, table XI), the value of $K_g$ being assumed from present experience to lie between 1 and 4 per cent of all births. The normal occurrence of such defects would thus be from 715,000 to 2,860,000 per year.

The total number of births affected by a 30-year gonad dose $D_{30}$ is given by

$$\frac{D_{30}}{\overline{D}_2} \times K_g \times \frac{P}{2} \qquad (37)$$

where $\overline{D}_2$ is the representative doubling dose and is assumed to lie in the range 10 to 100 rem. Under equilibrium conditions, the evaluated rate of such births would be

$$\frac{D_{30}}{\overline{D}_2} \times K_g \times \frac{P}{2 \times 30} \qquad (38)$$

(a) *Radiation from natural sources*

For $D_{30}$ = 3 rem (annex B, table XXV) the rate of

affected births is $\frac{3}{(10 \text{ to } 100)} \times \frac{(1 \text{ to } 4)}{100} \times \frac{2.5 \times 10^9}{30}$
= 25,000 to 1,000,000 per year.

(b) *Fall-out, tests stopping in 1958*

The total gonad dose is about equal to the maximum 30-year dose of 0.01 rem (table XIII) so that the total number of affected births is $\frac{0.01}{(10 \text{ to } 100)} \times \frac{(1 \text{ to } 4)}{100} \times 2.5 \times 10^9$ = 2,500 to 100,000 births.

No rate can appropriately be given since these births will occur over a period prolonged beyond the 30-year interval over which the dose is integrated.

(c) *Fall-out, tests continuing for a prolonged period*

The values of $D_{30}$ are 0.06 rem and 0.12 rem on assumption *a* and *b* (table XIII)†, giving rates of

$$\frac{(0.06 \text{ or } 0.12)}{(10 \text{ to } 100)} \times \frac{(1 \text{ to } 4)}{100} \times \frac{2.5 \times 10^9}{30}$$

Rates are thus 500 to 20,000 on assumption *a* and 1000 to 40,000 on assumption *b*. Rates can here be given since equilibrium conditions are postulated.

## VIII. Note on information document

131. A document (A/AC.82/INF.3) entitled: "An approach to a general method of computing doses and effects from fall-out" was prepared by the Secretariat of the United Nations in collaboration with a group of experts of the Committee, as a working paper. It was completed just before the Committee's last session (9-14 June, 1958). The Committee has not had sufficient time to study and eventually to accept this work which was considered to be of substantial scientific interest; it has decided to make this paper available because it will be useful to scientists engaged in calculations of gonad or bone marrow doses and their biological effects.[97]

## References


1. Marley, W. G., *The long-range fall-out from nuclear test explosions.* Medical Research Council (U.K.): The hazard to man of nuclear and allied radiations, London (1956), p. 121-125. UN document A/AC.82/G/R.2.
2. Stewart, N. G., Crooks, R. N., and Fisher, E. M. R., UN document A/AC..82/G/R.20.
3. Martell, E. A., UN document A/AC.82/G/R.21.
4. Doke, T., UN document A/AC.82/G.R.136.
5. Kurchatov, B. V., UN document A/AC.82/G/R. 199.
6. Aler, B., Björnerstedt, R., Edvarson, K., and Löw, K., UN document A/AC.82/G/R.15. Part 9.
7. Hvinden, T., UN document A/AC.82/G/R.144.
8. Hunter, H. F. and Ballou, N. E., Nucleonics *9*, No. 5. C2-7(1951).
9. Löw, K. and Edvarson, K., UN document A/AC. 82/G/R.146.
10. Eisenbud, M. and Harley, J. H., United States Atomic Energy Commission report HASL-24 (1958).
11. Hardy, Jr., E. P., United States Atomic Energy Commission report HASL-22(1958).
12. Eisenbud, M., *Measurement of strontium-90 in geophysical and biological material.* Hearings before the special subcommittee on radiation of the Joint Committee on Atomic Energy, Congress of the United States. Part 1, 554-575 (1957), and UN document A/AC.82/G/R.130.
13. Stewart, N. G., Osmond, R. G. D., Crooks, R. N., and Fisher, E. M., UN document A/AC.82/G/ R.143.
14. Nussis, N., Henkel, C., and Menis, M., UN document A/AC.82/G/R.157.
15. Miyaka, Y., Sugiura, Y., Saruhashi, K., and Kanazawa, T., UN document A/AC.82/G/R.172.
16. Hallden, N. A., and Harley, J. H., United States Atomic Energy Commission report NYO-4859 (1957), and UN document A/AC.82/INF.1.
17. Aler, B. and Herrlander, C. J., UN document A/ AC.82/G/R.150.
18. Neuman, W. F. and Neuman, M. W.: *Chemical dynamics of bone mineral.* Monograph. University of Chicago Press (1958).
19. Klechkovsky, V. M., editor, UN document A/AC. 82/G/R.41.
20. Harley, J. H., Hardy, Jr., E. P., Whitney, I. B., and Eisenbud, M., UN document A/AC.82/G/R.93.
21. Martell, E. A., UN document A/AC.82/G/R.153.
22. Bryant, F. J., Chamberlain, A. C., Morgan, A., and Spicer, G. S., UN document A/AC.82/G/R.126.
23. Hiyama, Y., editor, UN document A/AC.82/G/ R.141 and Add. 1.
24. Comar, C. L., Scott Russel, R., and Wasserman, R. H., Science *126,* 485-492 (1957).
25. Alexander, G. V., Nusbaum, R. E., and MacDonald, N. S., J. Biol. Chem. *218,* 911-919 (1956).
26. Bryant, F. J., Chamberlain, A. C., Morgan, A., and Spicer, G. S., UN document A/AC.82/G/R.30.
27. Comar, C. L., Whitney, I. B., and Lengemann, F. W., Proc. Soc. Exptl. Biol. Med. *88,* 232-236 (1955).
28. Comar, C. L., Wasserman, R. H., and Nold, M. H., Proc. Soc. Exp. Biol. Med. *92,* 959-863 (1956).
29. Comar, C. L., Wasserman, R. H., Ullberg, S., and Andrew, G. A., Proc. Soc. Exptl. Biol. Med. *95,* 386-391 (1957).
30. Chamberlain, A. C., Spicer, G. S., and Webb, M. S. W., British Medical Journal, in press.
31. Harrison, G. E., Raymond, W. H. A., and Tretheway, H. C., Clin. Sci. *14,* 681-695 (1955).
32. Spencer, H., Laszlo, D., and Brothers, M., J. Clin. Invest. *36,* 680-688 (1957).
33. Eckelman, W. R., Kulp, J. L., and Schulert, A. R., Science *127,* 266-274 (1958).
34. Hiyama, Y.: UN document A/AC.82/G/R.168.
35. Wasserman, R. H., Lengemann, F. W., and Comar, C. L., J. Dairy Science, in press.
36. Comar, C. L. and Wasserman, R. H., Progress in Nuclear Energy. Series VI. Biological Sciences. Pergamon Press, Ltd., London, *1,* 153-196 (1956).


† The values for the 30-year dose have been corrected for tropospheric fall-out in accordance with paragraphs 78 and 79, using a value of 0.5 mrem/year for the period of testing.

37. Libby, W. F., Proc. Natl. Acad. Sci. *42,* 365-390 (1956), and UN document A/AC.82/G/R.131.
38. Wasserman, R. H., Comar, C. L., Nold, M. M., and Lengemann, F. W., Am. J. Physiol. *189,* 91-97 (1957).
39. Lengemann, F. W., Proc. Soc. Exptl. Biol. Med. *94,* 64-66 (1957).
40. Talmage, R. V., Schooley, J. C., and Comar, C. L., Proc. Soc. Exptl. Biol. Med. *95,* 413-417 (1957).
41. Bauer, G. C. H., Carlsson, A., and Lindquist, B., Acta Physiol. Scand. *35,* 56-66 (1955).
42. MacDonald, N. S., Noyes, P., and Lorick, P. C., Am. J. Physiol. *188,* 131-136 (1957).
43. Tajima, E., Science, in press.
44. Communicated by W. G. Marley, 1958.
45. Food and Agriculture Organization of the United Nations, UN document A/AC.82/G/R.165.
46. Menzel, R.: Private communication, as given in reference 47.
47. Thurber, D. L., Kulp, J. L., Hodges, E., Gast, P. M., and Wampler, J. M., Science, in press.
48. Canada: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, UN document A/AC.82/G/R.99.
49. Grummitt, W. E. and Mar, P. G., Atomic Energy of Canada Limited and Department of National Health and Welfare Report CRC 786 (1958).
50. Kulp, J. L. and Slakter, R., Science, *125,* 85-86 (1958).
51. Food and Agriculture Organization of the United Nations, UN document A/AC.82/G/R.76/Rev.1.
52. Argentina: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, UN document A/AC.82/G/R.127.
53. Hodges, R. H., MacDonald, N. S., Nusbaum, R. E., Stearns, R., Ezmirlian, F., Spain, P., and McArthur, C., J. Biol. Chem. *185,* 519-524 (1950).
54. Turekian, K. K. and Kulp, J. L., Science *124,* 405-407 (1956).
55. Harrison, G. E. and Raymond, W. H. A., J. Nucl. Energy, 290-298 (1955).
56. Sowden, E. M. and Stich, S. R., Biochem. J. *67,* 104-109 (1957).
57. Kulp, J. L., Eckelmann, W. R., and Schulert, A. R., Science *125,* 219-225 (1957) and UN document A/AC.82/G/R.91.
58. Mitchell, H. H., Hamilton, T. S., Steggerda, F. R., and Beau, H. W., J. Biol. Chem. *158,* 625-637 (1945).
59. Hine, G. J. and Brownell, G. L., editors: *Radiation dosimetry.* Academic Press, Inc., New York (1956), p. 899.
60. Hindmarsh, M., Lamerton, L. F., Owen, M., Spiers, F. W., and Vaughan, J., UN document A/AC.82/G/R.114.
61. Engström, A., Björnerstedt, R., Clemedson, C.-J., and Nelson, A.: *Bone and radiostrontium.* Almquist and Wiksell, Stockholm; John Wiley and Son, Inc. New York (1958).
62. Communicated by R. Björnerstedt and A. Engström, 1958.
63. Communicated by W. G. Marley, 1958.
64. Nishita, H., Kowalewsky, B. W., Steen, A. J. and Larson, K. H., Soil Sci. *81,* 317-326 (1956).
65. Anderson, E. C., Schuch, R. L., Fisher, W. R., and Langham, W., Science *125,* 1273-1278 (1957) and UN document A/AC.82/G/R.123.
66. Hood, S. L. and Comar, C. L. University of Tennessee Report ORO-91 (1953), also Arch. Biochem. Biophys. *45,* 423-433 (1953).
67. International Commission on Radiological Protection, Recommendations, revised December 1, 1954. Brit. J. Radiol. Suppl. 6 (1955).
68. Burch, P. R. J., Brit. J. of Radiol. Suppl. 7, 20-26 (1957).
69. Rundo, J., UN document A/AC.82/G/R.167.
70. Sievert, R. M., Proc. Int. Conf. Peaceful Uses Atomic Energy, United Nations *13,* 187-195 (1956).
71. Communicated by I. H. Tipton, 1958.
72. Communicated by W. G. Marley and E. E. Pochin, 1958.
73. Bergh, H., Finstad, G., Lund, L., Michelson, O., and Ottar, B., UN document A/AC.82/G/R.113.
74. Bergh, H., Finstad, G., Lund, L., Michelson, O., and Ottar, B., Norwegian Defence Research Establishment Reports No. KIR-175/57, KIR-176/57, KIR-177/57, KIR-183/57, KIR-186/57, KIR-195/58 (1957-1958).
75. Best, C. H. and Taylor, N. B.: *The physiological basis of medical practice,* 6 ed. The Williams and Wilkins Comp., Baltimore (1955) p. 806-817.
76. Egypt: Preliminary Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, UN document A/AC.82/G/R.46.
77. Gunther, R. L. and Jones, H. B., United States Atomic Energy Commission report UCRL-2689 and addendum, (1954).
78. White, M. R. and Dobson, E. L., United States Atomic Energy Commission report UCRL-3355 (1956).
79. Van Middelsworth, L., Science *123,* 982-983 (1956).
80. Comar, C. L., Trum, B. F., Kuhn III, U.S.G., Wasserman, R. H., Nold, M. M., and Schooley, J. C., Science *126,* 16-18 (1957).
81. Communicated by W. G. Marley, 1958.
82. Hine, G. J. and Brownell, G. L., editors: *Radiation dosimetry.* Academic Press Inc., New York (1956) p. 868.
83. Dunning, G. M., Nucleonics *14,* No. 2, 38-41 (1956).
84. Communicated by L. Machta, representative of the World Meteorological Organization to the United Nations Committee on the Effects of Atomic Radiation, 1958.
85. Lewis, C.: *The American Oxford Atlas.* Oxford University Press, New York (1951).
86. Sievert, R. M., Gustafsson, S., and Rylander, C. G., Arkiv för fysik *12,* 481-499 (1957) and UN document A/AC.82/G/R.147.
87. Alba, F., Brody, T., Palacios, A., and Tejera, A., UN document A/AC.82/G/R.187.
88. Data submitted by the United States delegation to the United Nations Committee on the Effects of Atomic Radiation (1958).
89. Data submitted by the United Kingdom delegation to the United Nations Committee on the Effects of Atomic Radiation (1958).
90. Data submitted by the Japanese delegation to the United Nations Committee on the Effects of Atomic Radiation (1958).

91. Communicated by W. E. Grummitt, 1958.
92. Hardy, Jr., E. P., United States Atomic Energy Commission Report HASL-38 (1958).
93. Communicated by J. H. Harley, 1958.
94. Alba A., F., Brody, T. A., Cameras, R., Palacios, A., Rickards C., G., Tejera R., A., and de Velarde, E. G. B., UN document A/AC.82/G/R.164.
95. Blok, J., UN document A/AC.82/G/R.184.
96. Russell, R. S. and Milbourn, G. M., Nature, *180*, 322-324 (1957).
97. UN document A/AC.82/INF.3. Copies of the document may be obtained by writing to the United Nations, New York 17, N. Y., U.S.A.

## Tables containing data on fall-out from reports submitted to the United Nations Scientific Committee on the Effects of Atomic Radiation

### Table XIV. External irradiation due to fall-out

| *Country* | *Argentina* | *Denmark* | *France* | *Japan* | *Mexico* | *Netherlands* | *Norway* | *Sweden* | *United States* |
|---|---|---|---|---|---|---|---|---|---|
| Sampling method | Stainless steel pot | Plate | Funnel combined with gummed film | Polyethylene sheet and porcelain tray | Gummed film | Stainless steel pot | Stainless steel pot | Funnel | Gummed film |
| Sampling period | 1 month | 24 hours (if more than 0.5 mm precipitation is collected) | 1 month or after each precipitation | Dust: 24 hrs., water after each precipitation | 2 to 3 days | 2 days | 24 hours | 4 to 30 days or during precipitation | 24 hours |
| Period of measurement | Jan. to Sept. 1957 | Jan. to Dec. 1956 | April 1955 to July 1957 | May 1954 to June 1957 | May 1956 to Oct. 1957 | Nov. 1955 to Oct. 1957 | Oct. 1956 to Sept. 1957 | April 1953 to June 1957 | Oct. 1952 to June 1957 |
| Total accumulated activity from fall-out (mc/km²)[a] | 41[b] | 60 | 50[b] | | 150[b] | | 94–377 | 70 | |
| "Infinite plane" exposure during a 30-year period, from the total fall-out during the period of measurement (mrad). | | | | 123[c] | 9 (4–13)[d] | 24[c] | | 25 | 55[c] (20–180) |
| Factor of reduction due to weathering | | | | 3 | | 2 | | | |
| Factor of reduction due to shielding by buildings | | | | 1 | | 3 | | | |
| Total reduction factor | | | | 3 | 7 | 6 | | | |

[a] Activity at the end of the period of measurement, comprising local tropospheric and stratospheric fall-out deposited during that period.
[b] Extrapolated to 1 January 1958.
[c] Dose for infinite time. This dose is only slightly different from the 30-year dose.
[d] From fall-out during the period March–October 1957.

## TABLE XV. $Sr^{90}$ FALL-OUT ON THE GROUND

| Country | Argentina | Belgium | France | Japan | Mexico | Netherlands | Norway | Union of South Africa | Union of Soviet Socialist Republics | United Arab Republic (Egypt) | United Kingdom | United States |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sampling method..... | Stainless steel pot | Aluminium pot | Funnel combined with gummed film | Polyethylene sheet and porcelain tray | Gummed film and pot | Stainless steel pot | Stainless steel pot | Porcelain pot | Gauze | Gummed film | Funnel | (a) Gummed paper<br>(b) Stainless steel pot<br>(c) Galvanized tub |
| Sampling period..... | 1 month | 24 hours | 1 month, or after each precipitation | Dust: 24 hrs., water after each precipitation | 2 to 3 days | 2 days | 24 hours | 24 hours | 24 hours | 24 hours | 1 month | (a) 24 hours<br>(b) 1 wk.–1 mo<br>(c) 3 to 7 days |
| Period of measurement.. | Jan.–Sept. 1957 | Apr.–Nov. 1957 | Apr. 1955–July 1957 | (a) May 1954–Aug. 1956<br>(b) Oct. 1956–June 1957 | Mar.–Oct. 1957 | (a) July 1955–Nov. 1956<br>(b) Dec. 1956–Nov. 1957 | Mar.1956–June 1957 | Jan.–Apr. 1956 | (a) Up to end 1955<br>(b) July–Sept. 1957 | Mar.–Dec. 1957 | May 1954–Apr. 1957 | (a) Oct. 1951–June 1957<br>(b) Feb. 1954–Sept. 1957<br>(c) Mar. 1955–Nov. 1957 |
| Method of determination of $Sr^{90}$..... | Rad.chem. analysis | Rad.chem. analysis | Calculation[a] | (a) Calculation[a]<br>(b) Rad.chem. analysis | Calculation[a] | (a) Calculation[a]<br>(b) Radiochem. analysis | Calculation[a] | Rad.chem. analysis | Rad.chem. analysis of pooled samples | Rad.chem. analysis of pooled samples | Rad.chem. analysis | (a) Calculation[a] (improved)<br>(b) and (c) Rad.chem. analysis |
| Accumulated deposit of $Sr^{90}$ during the period of measurement (mc/km²)..... | 1.4 | 1.5 | 2.0 | 8.0[b] | 0.6 (0.3–0.9) | Approx. 5.3 | 2.4 | 0.28 | (a)1.6 (0.8–3.2) | | 7.5[c] | (a) 8.8(4.2–21)<br>(b) 15[d]<br>(c) 9.0[e] |
| Fall-out rate of $Sr^{90}$ (mc/km²· year) ..... | | | 1955: 0.6<br>1956: 0.7 | 1954: 1.0<br>1955: 0.7<br>1956: 3.8 | | (a) Approx. 2.3<br>(b) 2.3 | Sept. 1956–Aug. 1957: 0.9 | | (b) 2.8 (2.2–4.3) | 1.4 | 1954: 2.0<br>1955: 2.3<br>1956: 2.4[f] | 1957 3.9[g] (1.9–6.2) |

[a] Using Hunter and Ballou curves [8].
[b] Assumed a deposit of 0.4 mc/km² prior to May 1954.
[c] Assumed a deposit of 0.7 mc/km² prior to May 1954.
[d] New York City.
[e] Pittsburgh.
[f] Mean value from 4 funnel stations.
[g] Mean value from 8 pot stations.

## TABLE XVI. MISCELLANEOUS DATA ON $Sr^{90}$

| *Country* | *Argentina* | *Brazil* | *Canada* | *Japan* | *Mexico* | *Norway* | *Sweden* | *Union of Soviet Socialist Republics* | *United Kingdom* | *United States* |
|---|---|---|---|---|---|---|---|---|---|---|
| $Sr^{90}$ in air at ground level ($10^{-19}$ c/l) | | | | Nov. 1955 to Nov. 1956: 53 (28–106)[a] | | | | Mar. to Dec. 1955: 60–140 Sept.–Nov. 1957: 6.3–100 | April 1952 to Jan. 1956: 4[a] | 1953: 6.4 (3.0–11.2) 1954: 20 (1.0–60) 1955: 41 (3.6–120) June to Aug. 1956: 75 |
| $Sr^{90}$ in soil (mc/km²) | | | | 1957: 3.6 (2.5–6.3) | | 1956: 4.6 (4.5, 4.6) | Summer 1956: 1.2[b] (0.6–2.0) | Feb. to July 1957: 6.0 (3.0–12) | March 1955: 1.7(0.5–2.9) July 1956: 4.7 (1.9–10) | 1953: 1.5 (0.4–24)[c] 1955: 4.6 (0.8–7.5)[c] 1956: 6.9 (2.9–12)[c] |
| $Sr^{90}$ in drinking water ($10^{-14}$ c/l) | | | | 1957: 200 | | 1957: 35 (15–55) | | | | 1954: 6.1 (4.5–9.0) 1955: 10.1 (4.9–33) 1956: 15.4 (1.4–26) 1957: 17.6 (0.7–27.2) |
| $Sr^{90}$ in milk ($\mu\mu$c/gCa) | Apr. to June 1957: 3.5 (3.1, 3.9) | First months 1957: 2.7±0.3 | 1956: 5.0 (1.5–11.6) 1957: 6.2 (2.5–19.8) | 1956: 2.4 (2, 1, 2.7) 1957: 2.9 | Oct. to Dec. 1956: 1.2(0.5–1.5) Oct. to Dec. 1957: 3.0(2.5–3.5) | 1957: 7.9[d] (4.5–15.5) | | July 1956 to June 1957: 4.9 (2.2–8.0) | 1955: 3.9 (1.8–6.4) 1956: 5.4 (2.9–10.3) | 1954: 1.3 (0.5–2.3) 1955: 3.2 (0.3–3.10) 1956: 5.0 (1.3–17) 1957: 8.0 (1.9–33) |
| $Sr^{90}$ in plants ($\mu\mu$c/gCa) | | | | 1956: Vegetables: 9.4 (1.1–23) White rice: 49 (36, 62) Brown rice: 154 (81–250) Rice bran and chaff: 450 (390–540) 1957: Brown wheat: 162 (153, 170) Wheat flour: 53 | | | | Cereals, 1956: 69 (28–140) | Grass 1955: 34 (5.5–53)[e] 1956: 39 (11–77)[e] 516(91–2100)[f] | Hay: 1954: 1.3 (0.5–2.3) 1955: 3.2 (0.3–10) 1956: 5.1 (1.3–17) 1957: 8.0 (1.9–33) |
| $Sr^{90}$ in animal skeleton ($\mu\mu$ c/g Ca) | | | Cows, 1956: 5.2 (2.2–8.6) | Deer horn, grown 1954: 4.4 (1.6–9.9) 1955: 4.7 (1.0–11.7) 1956: 2.6 Fish, 1956 to 1957: Freshwater: 3.4 (0.4–11.4) Marine: 0.29 (0.19, 0.38) | | Sheep, 1956: 24 (10–77) | | | Sheep 1955: 11.0 (8.0–13.9)[g] 52(5.7–183)[h] 1956: 13.0 (7.8–15.8)[g] 48(24–160)[h] | Cows and Sheep 1954: 3.3 (1.7–7.0) 1955: 7.8 [g] (0.51–24) |

[a] Calculated from total $\beta$-activity measurements.
[b] Preliminary data, probably too low because of the leaching method used (1M ammonium acetate).
[c] Sampled in October each year.
[d] In units of $\mu\mu$c/l.
[e] Grown on normal soil.
[f] Grown on acid hill soil.
[g] Lowland sheep.
[h] Highland sheep.

TABLE XVII. $Sr^{90}$ IN HUMAN SKELETON
($\mu\mu c/gCa$)

| *Country* | *Canada* | *Japan* | *Norway*[a] | *Union of Soviet Socialist Republics* | *United Kingdom* | | *United States* |
|---|---|---|---|---|---|---|---|
| Period of measurement.... | June 1956 to June 1957 | Dec. 1956 to May 1957 | Oct. 1956 to Dec. 1957 | Second half 1957 | Oct. 1955 to Dec. 1956 | Jan. to June 1957 | Dec. 1955 to July 1956 |
| Age group | | | | | | | |
| Stillborn to 1 month..... | 0.7 (0–1.1) | 4.6 (4.1–4.6) | 0.5 | | 0.44 (0.15–0.8) | 0.54 (0.4–0.7) | 0.57 (0.45, 0.70) |
| 1 month to 1 year..... | 1.6 (1.4, 1.8) | | 0.8 (0–1.3) | | 0.70 (0.15–1.3) | 1.5 (0.9–2.4) | 0.83 (0.71–0.97) |
| 1 year to 5 years..... | 2.1 (0.1–3.8) | | 0.7 (0.2–1.1) | 2.3 (1.6–3.2)[b] | 0.85 (0.54–1.45) | 1.3 (0.4, 2.2) | 0.51 (0.10–1.7) |
| 5 years to 20 years..... | 0.1 | 0.73 (0.2–1.25) | 0.4 (0.3–0.5) | | 0.26 (0.15–0.53) | 0.39 (0.3–0.5) | 0.47 (0.13–1.4) |
| More than 20 years..... | 0.4 (0.1–0.6) | 0.41 (0.04–1.75) | 0.3 (0–0.7) | | 0.11 (0.06–0.2) | | 0.04 (0.02–0.11) |

[a] Preliminary data, determined without using low-level counter. [b] Age 0 to 5 years.

TABLE XVIII. $Cs^{137}$ FALL-OUT ON THE GROUND
(Determined by radiochemical analysis)

| *Country* | *Japan* | *Sweden* | *United Kingdom* |
|---|---|---|---|
| Sampling method..... | (*a*) Precipitation collection<br>(*b*) Soil | Funnel | Funnel |
| Sampling period..... | (*a*) 40 to 83 days | 4 to 30 days or during precipitation | 3 months |
| Period of measurement..... | (*a*) March to June 1957<br>(*b*) Aug. 1957 | April 1953 to June 1957 | Jan. 1956 to March 1957 |
| Accumulated deposit of $Cs^{137}$ during the period of measurement ($mc/km^2$)..... | (*b*) 6.5 | 6.0 | 5.3<br>(3.8–6.7) |
| Fall-out rate of $Cs^{137}$ ($mc/km^2 \cdot year$)..... | (*a*) 2.3 | July 1955 to June 1957: 1.3 | |

TABLE XIX. $Cs^{137}$ IN FOODSTUFFS AND THE HUMAN BODY
(In units of $\mu\mu cCs^{137}/gK$)

| *Country* | *Japan* | *Mexico* | *Norway* | *Sweden* | *United Kingdom* | *United States* |
|---|---|---|---|---|---|---|
| Period of measurement..... | 1956 to 1957 | Dec. 1956 | 1957 | 1956 | June 1956 to July 1957 | 1956 |
| Milk..... | 81<br>(44–140) | 40[a]<br>(20, 60) | 33[a]<br>(4.0–107) | 60[a] | | 25<br>(4–96) |
| Vegetables and fruit..... | 6.4<br>(3.3–11) | | | | | 13<br>(3–38) |
| Cereals and rice..... | 48<br>(31–65) | | | | | 20<br>(3–32) |
| Human body..... | 30–60 | | | | 34<br>(20–44) | 30–70 |
| Human urine..... | 34<br>(9–78) | | | | | 11<br>(7.2–14) |

[a] In units of $\mu\mu cCs^{137}/l$.

TABLE XX. MISCELLANEOUS DATA ON FALL-OUT

| *Country* | *Belgium* | *Brazil* | *Denmark* | *France* | *India* | *Italy* | *Japan* | *Netherlands* | *Norway* | *Sweden* | *United Arab Republic (Egypt)* | *United Kingdom* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period of measurement of air concentrations of fission products | 1957 | May to July 1956 | 1956 | 1957 | Feb. to Aug. 1956 | Nov. 1956 to Jan. 1958 | a) 1955<br>b) 1956<br>c) 1957 | May 1956 to Dec. 1957 | Mar. 1956 to Oct. 1957 | | | April 1952 to Jan. 1956 |
| Maximum concentration of fission products in air at ground level ($10^{-16}$c/l) | 14.8[a] | | 21.9[b] | 87[b] | 17.9[b] | 33.2[a] | a) 14.7[a]<br>b) 177.3[a]<br>c) 153.6[a] | 120[b] | 18[b] | | | 113[b] |
| Mean concentration of fission products in air at ground level ($10^{-16}$cll) | 7.5 | 0.5 | 2.8 | 10 | 5.6 | 12.6 | a) 5.9<br>b) 37.1<br>c) 54.1 | 9 | 7 | | | 2.3 |
| Content of $I^{131}$ in thyroids of cattle ($\mu\mu$c/g) | | | | | | | | | | Sept. 1956<br>100–800 | May to Sept. 1956<br>11 (0–129)<br>Oct. 1956<br>344 (3–1290) | |
| $I_{131}$ in milk ($\mu\mu$c/l) | | | | | | | | | 1957<br>82<br>(0–1350) | | | |

[a] Average over 1 month. [b] Average over 24 hours.

# Annex E
# METHODS OF MEASUREMENT

TABLE OF CONTENTS


*Paragraphs*

I. INTRODUCTION ..... 1
Direct measurements ..... 3
Indirect measurements ..... 5
II. SAMPLING ..... 6
III. RADIOCHEMISTRY AND ACTIVITY MEASUREMENT ..... 11


## I. INTRODUCTION

1. The ultimate purpose of radiological measurements of concern to the Committee is the estimation of tissue dose from natural sources, man-made sources and environmental contamination. In some cases, however, measurements of radioactivity are also of primary concern. It is emphasized that new and improved methods are constantly being developed.

2. It is customary to classify measurements of this nature into categories relating to the method used, i.e., direct or indirect. Direct exposure rate measurements are those made with ionization chambers or instruments calibrated in terms of air ionization. Indirect methods are those where exposure rate is calculated from activity measurement. The rates of exposure from medical and industrial practice and from terrestrial and cosmic radiation are sufficiently high to allow direct measurement. Exposure rates from other sources are low and the dose rate must usually be estimated indirectly by activity measurement and subsequent calculation.

### *Direct measurements*

3. Routine direct determination of external exposures usually involves the measurement of gas ionization, as the relationship between energy absorption and ionization is relatively independent of energy. Any ionization chamber with an air equivalent wall may be used for the measurement, but it must be standardized periodically against a free air chamber.[1]

4. Scintillation counters, films and geiger counters can be used for rough estimation of exposure or exposure rate, but they can give erroneous results in mixed radiation fields. They can be valuable, however, if the composition of the field is known and they have been calibrated under similar conditions.

### *Indirect measurements*

5. The indirect determination of exposures from radioactive sources, such as deposited fall-out or radioisotopes in the body, is more complex. It involves consideration of methods of sampling, radiochemistry and activity measurement. Methods for these are outlined in the following sections. The necessary dose computations are described in annexes B, C, and D.

NOTE: Throughout this report and its annexes cross-references are denoted by a letter followed by a number: the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

## II. SAMPLING

6. The determination of activity in the atmosphere, fall-out deposit, soil, foodstuff and human tissue requires the collection of samples representative of a given geographic region. Although this is difficult from a technical and statistical viewpoint, there are recognized methods.[2,3] It is recommended that the sampling of the environment and the biological materials be co-ordinated.

7. Radioactive material may be present in the atmosphere in gaseous or particulate form, each requiring its own sampling method. For measurement of radioactive gases, the sample must be obtained by collecting a measured volume of air in a suitable container[4–7] or by drawing a measured volume of air through an activated charcoal trap.[4,5,8] Both filters[4,5,9–14] and electrostatic precipitators are suitable for collection of airborne particulates.[5,11] These methods may also be used for very rough estimates of gaseous activities having solid daughters.[15,16] Deposited fall-out activity may be collected periodically by a high-walled pot[12–14,17–21] or high-walled funnel,[22–24] or the accumulated deposit may be obtained from soil samples.[25,26,D14]

8. It is not possible at present to state the absolute efficiency of any device for the collection of fall-out deposition. The high-walled pot is recommended as an arbitrary basis of comparison for other methods.

9. Samples of foodstuff should represent the regional diet, and should be selected with reference to the isotope of interest. Although it is advisable to take samples frequently, it is more economical to analyse a composite representing one or more months' collection.

10. The *in vivo* measurement of radioactive strontium or radium by whole body spectrometry is inadequate at present. Therefore samples of bone are required for estimation of the skeletal burden in man. Specifications for sampling have been given.[25,D66]

## III. RADIOCHEMISTRY AND ACTIVITY MEASUREMENT

11. Radon may be measured by alpha counting in an ionization chamber[11,27,28] or scintillation counter.[29,30] The techniques suitable for air samples are also adequate for samples of exhaled breath for evaluation of

the radium body burden. Standards may be prepared from commercially available radium solutions.[31,32]

12. The determination of strontium activity in the various materials described above involves preparation of the sample, separation of strontium and measurement of the activity.

13. The preparation depends on the type of sample: (*a*) soil from which strontium is removed satisfactorily by a 6M HCl leach; and (*b*) rainwater, foodstuffs and bone, which are best treated by wet or dry ashing with subsequent solution in mineral acid. Following this treatment strontium is radiochemically purified. $Y^{90}$ is allowed to grow to equilibrium, is separated from the parent and measured in a beta counter, thus giving the $Sr^{90}$ content of the sample.[25,20,33-39] The activity of any $Sr^{89}$ present can be determined by difference. A moderately low background counter (5 to 10 cpm) is satisfactory for all samples but human bone, which requires counters with a background of about 1 cpm. The counting procedure must be calibrated with an absolute standard in order to convert the values obtained to disintegration rate. Reference samples for $Sr^{90}$ are available for inter-calibration purposes through the Secretariat of the United Nations Scientific Committee on the Effects of Atomic Radiation and also commercially.[81]

14. The determination of total beta activity involves only preparation of the sample and measurement of the activity. Rainwater activity may be concentrated satisfactorily by evaporation[33,38] or by absorption on ion exchange resins.[23,24] Air filters or the residues from rainwater may be counted directly or dry-ashed prior to measurement of activity.[23,33,38,40] Useful information may be obtained by determination of beta or gamma activity. The conversion of counting data to disintegration rates is difficult; the best standardization is accomplished with mixed fission products from a short irradiation but natural potassium is more generally available and has suitable radiation characteristics.

15. The $Cs^{137}$ burden of humans living in a contaminated environment can best be measured *in vivo* with a whole body spectrometer.[41-45] Gamma spectroscopy is also useful for direct determination of this radioisotope in other materials.[46,47] Radiochemical separation techniques have been described which allow measurement of the caesium beta or gamma activity without energy discrimination.[33,35,38,39] Adequate standards have not been available until recently.[31] An accuracy of ± 25 per cent may be obtained by comparison of the beta activities of the $Cs^{137}$ with a $Sr^{90}$ standard. An intercomparison programme for development of $Cs^{137}$ standards is desirable.

16. The $I^{131}$ burden in humans can best be measured *in vivo* by scintillation counting of the thyroid with energy discrimination.[48-51] Also, gamma spectroscopy is useful for direct determination of this radioisotope in other materials, though radiochemical techniques have been described which allow measurement of the separated iodine activity.[52,53] Adequate standards are commercially available.[54]

17. The determination of radium involves preparation of a sample solution as for $Sr^{90}$ followed by measurement either by a radon emanation technique[55] or by radiochemical separation and alpha counting of the radium.[56,57] Standards are commercially available.[31,32]

18. The current radiochemical literature describes methods for many other nuclides, (fission products, induced activities, fissionable materials and natural isotopes) which would appear to be completely satisfactory in most instances.

## References


1. United States Department of Commerce, National Bureau of Standards Handbook 62: *Report of the International Commission on Radiological Units and Measurements (ICRU)* (1957).
2. Deming, W. E.: *Some theory of sampling.* John Wiley and Sons, Inc., New York (1950).
3. Snedecor, G. W.: *Statistics.* Iowa State College Press, Ames, Iowa, 4th ed. (1946).
4. Goldman, F. H., and Jacobs, M. B.: *Chemical methods in industrial hygiene.* Interscience, London (1953).
5. Elkins, H. B.: *The chemistry of industrial toxicology.* John Wiley and Sons, Inc., New York (1950).
6. Harley, J. H., Jetter, E., and Eisenbud, M., A.M.A. Archives of Ind. Hyg. and Occupat. Med., *4,* 1-9 (1951).
7. Grove, W. P., and Clack, B. N., Brit. J. of Radiol., Suppl. 7, 120-123 (1957).
8. Hursh, J. B., Nucleonics *12,* No. 1, 62-65 (1954).
9. Harris, W. B., LeVine, H. D., and Eisenbud, M., A.M.A. Archives of Ind. Hyg. and Occupat. Med., *7,* 490-502 (1953).
10. Steward, N. G., Crooks, R. N., and Fisher, E. M. R., UN document A/AC.82/G/R.20.
11. Hultqvist, B.: *Studies on naturally occurring ionizing radiations.* Kungl. Svenska Vetenskapsakademiens Handlingar, Series 4, vol. 6, No. 3. Stockholm (1956) and UN document A/AC.82/G/R.15, Part 4.
12. Alba A., F., Beltrán, V., Brody, T. A., Lezama, H., Moremo M., A., Tejera, A., and Vásquez B., M., UN document A/AC.82/G/R.5.
13. Labeyrie, J., UN document A/AC.82/G/R.16, Part I-1.
14. Martell, E. A., UN document A/AC.82/G/R.21.
15. Wilkening, M. H., Rev. Sci. Inst. *23,* 13-16 (1952).
16. Harley, J. H., Nucleonics, *11,* No. 7, 12-15 (1953).
17. Shirvaikar, V. V., and Vohra, K. G., UN document A/AC.82/G/R.32.
18. Hvinden, T., UN document A/AC.82/G/R.92.
19. Harley, J. H., Hardy, Jr., E. P., Whitney, I. B., and Eisenbud, M., UN document A/AC.82/G/R.93.
20. Blok, J., UN document A/AC.82/G/R.184.
21. Boulenger, R., UN document A/AC.82/G/R.209.
22. Stewart, N. G., Osmond, R. G. D., Crooks, R. N., and Fisher, E. M., UN document A/AC.82/G/R.143.
23. Edvarson, K., UN document A/AC.82/G/R.149.
24. Welford, G. A., and Harley, J. H., Presented at the American Chemical Society Meeting in San Francisco on April 14, 1958. To be published in Analytical Chemistry.
25. Bryant, F. J., Chamberlain, A. C., Morgan, A., and Spicer, G. S., UN document A/AC.82/G/R.30.
26. Hamada, G. H., and Hardy, Jr., E. P., United States Atomic Energy Commission report HASL-33 (1958).
27. Curtiss, L. F., and Davis, F. J., J. Res. Nat. Bur. Stand. *31,* 181-195 (1943).
28. Pradel, J., UN document A/AC.82/G/R.16, Part I-3.
29. Pittendrigh, L. W. D., Atomic Energy Research Establishment, Harwell, England, report AERE HP/M 83 (1954).

30. Van Dilla, M. A., and Taysum, D. H., Nucleonics *13*, No. 2, 68-69 (1955).
31. Standard samples are available at National Bureau of Standards, United States Department of Commerce, Washington 25, D.C., U.S.A.
32. Standard samples are available at The Radiochemical Centre, Amersham, England.
33. Health and Safety Laboratory, *Manual of Standard Procedures*. United States Atomic Energy Commission report NYO-4700 (1957).
34. Michon, G., UN document A/AC.82/G/R.16 Part I-2.
35. Kurchatov, V. V., UN document A/AC.82/G/R.40.
36. Canada: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, UN document A/AC.82/G/R.98.
37. Netherlands: Report to the United Nations Scientific Committee on the Effects of Atomic Radiation, UN document A/AC.82/G/R.110.
38. Osmond, R. G., Pratchett, A. G., and Warricker, J. B., UN document A/AC.82/G/R.132.
39. Saito, N., UN document A/AC.82/G/R.135.
40. Lockhart, Jr., L. B., Baus, R. A., and Blifford, Jr., I. H., UN document AC.82/G/R.124.
41. Anderson, E. C., Brit. J. of Radiol., Suppl. 7, 27-32 (1957).
42. Burch, P. R. J., Brit. J. Radiol., Suppl. 7, 20-26 (1957).
43. Rundo, J., 1956/1957, UN document A/AC.82/G/R.167.
44. Owen, R. B., Brit. J. Radiol. Suppl. 7, 33-37 (1957).
45. Marinelli, L. D., Brit. J. of Radiol. Suppl. 7, 38-43 (1957).
46. Iredale, P., and Humphreys, D. L. O., UN document A/AC.82/G/R.152.
47. Booker, D. V., Phys. in Med. and Biol. *2*, 29-35 (1957).
48. Gunther, R. L., and Jones, H. B., United States Atomic Energy Commission report UCRL-2689 and addendum (1954).
49. Franco, V. H., Botelho, L., Clode, W., Baptista, A. M., Fernandez, M. A. P., and Martins, M. L., Proc. Int. Conf. Peaceful Uses Atomic Energy, United Nations *10*, 298-307 (1956).
50. Francis, J. E., and Bell, P. R., Proc. Int. Conf. Peaceful Uses Atomic Energy, United Nations *11*, 193-203 (1956).
51. Hine, G. J., Burrows, B. A., and Ross, J. F., Nucleonics, *15*, No. 1, 54-56 (1957).
52. Schrodt, A. G., Proceedings of the Second Annual Meeting on Bio-Assay and Analytical Chemistry, October 11 and 12, 1956. Los Alamos Scientific Lab., N. Mex., report WASH-736 (1957).
53. Bergh, H., Finstad, G., Lund, L., Michelsen, O., and Ottar, B., UN document A/AC.82/G/R.113.
54. Standard samples can be obtained from Nuclear-Chicago Corporation, 223 West Erie Street, Chicago 10, Ill., U.S.A.
55. Hudgens, J. E., Benzing, R. O., Cali, J. P., Moyer, R. C., and Nelson, L. C., Nucleonics, *9*, No. 2, 14-21 (1951).
56. Harley, J. H., and Foti, S., Nucleonics, *10*, No. 2. 45-47 (1952).
57. Kirby, H. W., Anal. Chem. *25*, 1238-1241 (1953).

# ANNEX F
# FUNDAMENTAL RADIOBIOLOGY

TABLE OF CONTENTS


| | Paragraphs |
|---|---|
| I. DISSIPATION OF PHYSICAL ENERGY | |
| Introduction—Direct and indirect effects | 1 |
| LET and RBE | 4 |
| Dose-effect relations | 8 |
| Time intensity factor | 12 |
| Inactivation by transmutation of radioactive elements | 15 |
| II. RADIATION CHEMISTRY | 17 |
| Indirect effects | 18 |
| Direct effects | 28 |
| Effect of LET | 36 |
| Oxygen effect | 38 |
| After-effects | 39 |
| Radioprotection | 42 |
| Restoration | 48 |
| Present status of the "target" theory | 51 |
| III. BIOCHEMICAL EFFECTS | 52 |
| Cellular constituents | 53 |
| Biochemical mechanisms | 59 |
| IV. CYTOLOGICAL EFFECTS | 66 |
| Nucleus | 67 |
| Cytoplasm | 72 |
| V. BIOLOGICAL EFFECTS | 87 |
| Homogeneous cell populations | 88 |
| Differentiating cell populations | 113 |
| Adult organisms | 120 |
| VI. VARIABLES IN RADIATION EFFECTS | |
| Physiological conditions | 128 |
| Comparative sensitivity of living organisms | 138 |
| Adaptation to radiation | 146 |
| Secondary effects | 153 |
| VII. ALTERATIONS OF RADIATION EFFECTS BY FOREIGN AGENTS | |
| Protection | 159 |
| Sensitization | 170 |
| Recovery | 173 |
| VIII. CONCLUSIONS | 188 |


## I. DISSIPATION OF PHYSICAL ENERGY
(Space and time factors)

### *Introduction—Direct and indirect effects*

1. The effect of radiation is induced by the processes of absorption, when the energy of radiation is dissipated in the irradiated matter. Apart from excitation, the ionization of molecules is believed to be largely responsible for the initiation of primary chemical reactions. There are at present two major theories of the mechanism of action of radiations on living organisms: the theories of direct and indirect action. The first one claims that effective ionizations take place *in* key cellular structure or in their immediate vicinity: the probability that their alteration causes cellular damage is dependent on their biological specificity. This has often been called the "target theory", and, since Dessauer, Crowther, Holweck and Lacassagne, Timofeeff-Ressovsky and Lea, the concept has had the support of many physicists; it is being constantly revised to take into account many new fundamental acquisitions.[1,2,3,4,5,6,7]

2. The "theory of indirect action," on the contrary, claims that the biologically specific cellular structures are altered as a result of their chemical reaction with free radicals formed in irradiated water or other molecules not belonging to these structures.[8] As with most conflicting theories which have had ardent supporters on both sides (another good example is the corpuscular and electromagnetic theories of light), it is very probable that the two are complementary. Indeed, it is almost certain that the same cellular component can be affected in a way which is liable to produce identical biological effects by both mechanisms.[9,10,11] Methods have been

developed in recent years which enable the existence of unpaired electrons resulting from the ionization process to be demonstrated not only in crystalline amino acids and other small molecules, but also in proteins, plant embryos and other kinds of cells.

3. An attempt will be made to draw a brief picture of some fundamental aspects of the problem.

*Linear energy transfer (LET) and relative biological effectiveness (RBE) of different kinds of radiation*

4. The efficiency of radiation *per ionization* to induce a particular effect is often found to vary for different types of radiation. Let us at first consider an event which is caused by one ionization such as the inactivation of an enzyme or virus: in the case of small structures *in vitro,* the radiation producing a low ion density will be more effective than that giving a high ion density, because some of the ionizations of the latter will be wasted. On the contrary, a radiation with a high density of ionization will be more effective when several ionizations are simultaneously or in a relatively short time needed in the sensitive structure. Thus, the *relative biological effectiveness* (RBE) of radiations varies with their *linear energy transfer* (LET). This term describes the spatial distribution of the transfer of physical energy in matter—and accounts for the loss of energy of the radiation, not only through ionizing processes, but also through other processes such as dissipation of heat or excitation of atoms. It is a theoretical implication of these facts that some of the primary effects of radiations take place within a shorter time than that needed for the processes initiated by ionization or excitation to lose their initial spatial distribution (perhaps as short as 1 millionth of a second); and also that the primary biological receptors of radiation are not themselves homogeneously distributed throughout the cell.[12]

5. In mice, the relative biological efficiency (RBE) increases greatly with ion density, for killing with low intensity radiation, for shortening of the life-span, for inhibition of tumour growth, and for cataract induction; the increase, however, is smaller when one considers effects on the gonads (sterilization), on the skin (epilation), on the blood white-cell count, or on the induction of many chromosome abnormalities in Drosophila.[12,14,15] Some chromosome abnormalities in Tradescantia have a very high incidence with high density irradiation.[13] Mutations in micro-organisms and some in Drosophila are only slightly influenced by the LET.[12]

6. Reviews on the subject by Lea[1] and Zirkle[12] have shown that much could theoretically be achieved by comparing the effects of ion density. Lea had attempted to use the data available to him at the time, on the decrease in incidence of chromosome breakage with decreasing ion density, as an argument for the target theory. However, it appears from Zirkle's paper that changes in RBE for comparable effects are often very difficult to include in a general theory, because in many instances the direction of change in RBE is not the same for similar effects in different materials and the RBE may be strongly dependent on conditions of irradiation such as the oxygen tension. It is at present very difficult to make definite generalizations.

7. The mode of dissipation of radiation energy inside living cells is not yet understood, although our knowledge of the physical aspects of energy loss is adequate and hypotheses on the distribution of free radicals along the radiation tracks have been suggested. However, it is not clearly understood how this physical energy becomes apparent in chemical changes such as ionization and excitation. It might be of interest to use inert structural models or do such experiments as comparing the LET for a virus inside and outside the host cells to get a better picture of the sequence of events. When completely understood, the use of radiations of different LET may lead to precise estimates concerning the size of the biological structures affected.

*Dose-effect relations*

8. When a homogeneous substrate is irradiated, the energy is distributed in an unpredictable way and the probability of a molecule being hit depends on its concentration and on its volume. The concentration of the intact substrate decreases as radiolysis proceeds, and it can be predicted on theoretical grounds for low density radiations that, if one ionization suffices to cause the effect, the expression relating the remaining intact structures ("survivors") to dosage will be *exponential.* When a relatively small number of ionizing events is needed, the number of responses observed will, however, be approximately proportional to the dosage.[16,17,18] This sort of effect has no *threshold*—which means that any dosage, however small, is effective in producing some alteration.

9. On the contrary, if several ionizing events or "hits" are needed, the response only becomes manifest after a certain dosage has been accumulated in the sensitive structure: the dose effect curve is then *sigmoid.*[16,17,18,19] In this case there is a *threshold* which, however, may only be statistical, as when two identical cellular structures need to be *irreversibly* altered for the effect to become manifest, which is so for recessive lethal mutations in yeasts.[16] Other threshold effects appear when recovery of the altered structure or replacement of killed cells takes place, as is often the case in multicellular organisms where many interferences may take place between the primary physical event and its biological expression.

10. The meaning of the dose-effect relationship is often difficult to understand because the curve may change quite dramatically when the conditions of irradiation are altered (aerobic or anaerobic irradiation; change of culture medium); this difficulty is most likely to occur when one studies a complex phenomenon like cell death, whose cause may be multiple and not identical in different circumstances.[20]

11. However, several radiobiological processes are known to give exponential dose-effect curves under specific environmental conditions, as in the case of many lethal effects on viruses and on micro-organisms.[21,22] Diploid yeast cells[19,23] or mammalian cells[24] in tissue culture have a sigmoid dose-effect curve when x-irradiated. In the case of diploid cells, the sigmoid type of curve is consistent with a 2 hit process, the exponential response being explained on the assumption of a single hit. One of the best present arguments for the "target" concept comes from the fact that in the case of small viruses the "target" size can be estimated with a good approximation[21] and that survival curves of protected bacteriophage are very similar *in vitro* and during the very first minutes of infection.[22] These results can be

explained on the basis that the primary ionization takes place inside the sensitive structure. In the case of a mutation this is the gene. It is, however, difficult to accept the concept without modification at the present time, on account of the possible contribution of diffusable radicals from water or other molecules in the immediate vicinity of the target. However, it is believed that radicals only diffuse for distances of about 30Å. As most effects have not been fully expressed when the radiation has ceased to be delivered, there is a time interval during which restoration may occur, and whether this takes place or not may alter the dose-response curve. Very little is known about what happens during this time: the chain of events may be relatively "simple" in the expression of a point mutation in micro-organisms or perhaps even in a mammalian germinal cell, but it is certainly very complex when the induction of malignant growths is considered. The number of *mutations* in bacteria,[21] Drosophila,[25] and perhaps mouse populations,[26] *increases* linearly with radiation up to moderate dosages, as do certain of the chromosome aberrations[27] and perhaps the induction of leukemia.[28,29] However, the determinations do not extend as low as the background radiation, and much uncertainty remains at these low levels, although it is highly probable that the background radiation causes some of the mutations which occur naturally, thus contributing to some extent to the evolution of living organisms and to their load of mutational hazards. *This means that as far as we know at present, biological effects will follow irradiation, however small its amount.* It has thus become very important to establish with great accuracy the shape of the dose-effect curve in the lower dose range, in order to estimate the contribution of the natural radiation for different effects. The number of experimental animals needed to obtain a good accuracy increases enormously as the dose decreases and the response becomes smaller or less frequent. For human populations, as each individual is important, the only reasonable "experimental sample", when small doses are concerned, is the total population of living human beings. In this case, the only sound procedure is to get a better understanding of the fundamental processes which are occurring. *This may actually be the only way of answering some of the basic problems underlying low dosage irradiation.*

*Time intensity factor*

12. The time taken to deliver a given dosage of radiation can be varied in order to give very high or very low *intensities* per unit time. A change in intensity will not affect the end result when separate ionizing events contribute *independently* to the observed effect; this should hold true for some of the exponentially responding events although it is not true for all. On the contrary, in the case of events responding by sigmoid curves, several ionizations may be needed almost *simultaneously* (this is the case when recovery processes exist); here, a given dose becomes less effective if delivered in a long interval of time.[31,32,30] However, this is not always the case, and for inactivation of both homologous chromosome regions of a diploid cell, it is known that protraction of irradiation does not alter the effect.

13. The physiological conditions of *Drosophila* sperm are very constant for a considerable length of time, and it has been found that the induction of mutation by irradiating the males does not vary with the intensity of irradiation.[30] The same is true for the induction of most malformations in the mouse embryo. However, in some cases the severity of malformations is *greater* if a given dose is fractionated.[33] A change of intensity by a factor of one million does not alter the number of phage induced in E. Coli.$K_{12}$.[37,38] In contrast, the number of certain chromosome aberrations in Tradescantia microspores or Vicia seeds[34,36] — like chromosome exchanges, which require the simultaneous occurrence of two breaks —are often highly dependent on the time taken to deliver the dosage: more exchanges are obtained for higher intensities. When the duration of irradiation is increased, one reaches a time for which the effectiveness does not decrease any more; this time is related to the lapse during which the breaks remain open. However, this picture is complicated by the fact that the rate of rejoining depends on respiratory activity.[35] The killing of complex organisms like mammals, being the result of extremely complex cellular damage, is very efficient for high intensities but much less so for low ones.[40,41,42]

14. The time during which radiation is delivered becomes very important if the system being studied undergoes some *change* during this time: the radiosensitivity of many cellular processes varies during the *mitotic cycle* and one can expect a greater radiation effect if the intensity is high during the most sensitive period of this cycle. Secondary biological reactions may interfere with the expression of damage and, if recovery or selection occur, one can expect a greater effect if the intensity is high for the same given dosage. For these reasons, *it does not appear justifiable, unless the fundamental pathways of radiation damage are known, to consider that an effect observed after high intensity irradiation will necessarily follow the application of the same dosage at low intensity.*

*Inactivation by transmutation of radioactive elements*

15. Certain radioactive substances taken up by the organisms in specific structures may affect them not only by the radiation they emit, but also by the fact that the emission of these radiations is often accompanied by recoil effects or transmutation into an atom having new chemical properties. Thus P-32 can be incorporated into important biological structures like viruses or chomosomes, and in the first case it has been shown that the inactivation due to transmutation of P-32 into S-32 is more efficient than the one due to the $\beta$ particles being emitted.[44,45] It is conceivable that strontium could replace calcium or magnesium, which are probably structural constituents of chromosomes.[46] It has been claimed that a low calcium environment increases the number of spontaneous and induced chromosome breaks in Tradescantia.[47,48] If these facts were of general application, the disintegration of strontium-90 or strontium-89 might affect cells not only by emitting $\beta$ radiation, but also by transmuting to yttrium, which has new chemical properties. Such possibilities will have to be discussed, and *the role of trace amounts of metals and of alkaline earths in important cellular structures should be known before one dismisses its possible importance in biological effects of radionuclides which, apart from emitting radiation, have a specific function.*

16. Although Ca-45 has not been found by radioautography in the bone marrow cells of rats previously injected with 200 $\mu$c,[49] nuclear aberrations have been observed in allium which had been grown in the presence of Sr-90,[50] and further work on the subject should be done to settle this problem, which is of great importance in understanding the possible cellular damage induced by radionuclides. Their specific radioactivity inside cellular structures as well as their rate of turnover and their

chemical function may be important in inducing cellular damage.

## II. Radiation chemistry

17. It is only by understanding the mechanisms of action of radiations on the different cellular constituents that one can hope to understand what is happening in irradiated cells and also to use these basic findings in the search for protecting agents. Much useful information on the chemical effects of radiation has been gathered by submitting various chemicals to irradiation *in vitro* (radiation chemistry); however, on account of our very incomplete knowledge of cellular structure and chemistry, biological constituents should be studied after irradiation of the living organisms (radiation biochemistry) if one is looking for full understanding of radiobiological processes. Furthermore, as will be pointed out, specific constituents and not bulk chemical properties should be studied whenever possible. Molecules may be altered by *indirect* and *direct* effects of radiation.

### *Indirect effects*

18. It is known that the most abundant of all biological constituents is water: it constitutes 70 per cent of most living cells except for certain plant seeds and may sometimes constitute more than 95 per cent, but an unknown proportion of it is bound water and constitutes part of the cellular structures. This has prompted much research into the radiochemistry of water.

#### *Effects of radiation on water and substrates in aqueous solution*[51,52]

19. It is usually accepted, although by no means demonstrated, that water when chemically pure undergoes ionization and, as a result of this—and of secondary reactions, the sequence of which is hypothetical—splits into $OH^0$ (hydroxyl radicals) and $H^0$ (hydrogen atoms), which recombine; in the absence of any impurity, nothing apparently will have happened because the radicals cannot enter any other reaction. Traces of $H_2$ and $H_2O_2$ are thought to be formed during this process. The formation of radicals takes place in the short time of $10^{-11}$ -$10^{-12}$ sec.[53]

20. The existence of $OH^0$ radicals has been demonstrated: certain radiation reactions leading to the polymerization of acrylonitrile can best be explained on the basis of an $OH^0$ radical mechanism, as also the oxidation of benzene to phenol.[51,52]

21. On the other hand, the existence of free H atoms is still questioned on account of the high oxidizing power of radiation on substrates in aqueous solutions; several mechanisms of radiolysis have been suggested, which do not make necessary the postulation of the existence of $H^0$ atoms.[51] It may be easier to interpret many biochemical reactions of radiation when a better understanding of the radiolysis of water has been achieved. This should certainly be of great importance for the logical approach to protection mechanisms. Although the existence of a free hydrogen atom is doubted by some, many authors have assumed that it does exist, and much present thinking is based on this assumption. It will make the discussion easier if we tentatively adopt this view, whenever a mechanism involving this radical is suggested. If oxygen is present as it is when a solution is in equilibrium in air, $O_2H^0$ (perhydroxy radical) and $H_2O_2$ (hydrogen peroxide) are also formed in addition to $H^0$ and $OH^0$.[51]

22. When the water contains various solutes, these are the site of chemical reactions due to $H^0$, $OH^0$ and $O_2H^0$ radicals formed in the solution through the radiolysis of water. These radicals have reducing or oxidizing properties and can react with the substrate, oxidizing or reducing it or transforming it in turn to a new free radical. Thus, if many solutes are present, they may be altered by radicals coming either from water or from the other solutes; this last mechanism although not too well studied could very well be of some importance in very complex systems. When macromolecules are irradiated, the yield of altered molecules per ion is usually smaller than expected from what happens to smaller molecules of similar chemical properties; this is thought to be due to the fact that bonds, broken in these structures, are not able to come apart (they are held together by the other intact bonds in the structure or cannot come apart by normal diffusion processes) and the radicals formed presumably recombine. Such a "cage effect" would be chiefly expected in concentrated solution and in complex cellular structures.[54] There are probably also some biologically inert chemical groups whose alteration would not impair the biological activity of some macromolecules.[55]

23. Although some reduction reactions occur when substrates are irradiated, most reactions appear to be oxidative.[52,56] From experimental data it is apparent that a substance is reduced only when it possesses a very high normal redox potential (greater than 0.9 - 1.0 for effects of X-rays in the absence of oxygen).[57]

#### *Nature of the chemical effects*

24. Ionizing radiations may alter inorganic as well as organic substrates. The following reactions can be taken as examples:[51]

*Oxidizing reactions* may be effected by $OH^0$ radicals

(*a*) By simply removing an electron from an ion $Fe^{2+} \rightarrow Fe^{3+}$—a reaction used for chemical dosimetry;

(*b*) By removing an H atom, leaving a radical which can combine with another one[51]
$2CH_3\,COOH \rightarrow 2C^0H_2\,COOH \rightarrow COOH\text{-}CH_2\text{-}CH_2\text{-}COOH$;

(*c*) By substitution of a hydrogen by an $OH^0$ as in the oxidation of benzene to phenol.[51,58]

25. In a similar manner, small organic molecules like alcohols, aldehydes or acids undergo oxidation, and the last-named compounds are often decarboxylated.[51,59,60] They are also sometimes capable of undergoing polymerization by the formation of a chemical bond possibly between two radicals as in the second reaction above: acetic acid is capable of giving succinic and even still more complex organic acids. Amino-acids may be oxidatively deaminated,[51] and if they have sulfhydryl groups these are oxidized to disulfur (S-S)[64] and sometimes to sulfoxide, as in the case of cysteine.[60,61]

26. *Reducing reactions* may be obtained as follows:

(*a*) $OH^0$ radicals may act on strongly oxidizing agents (this is the case for iodate and ceric salts).[51]

(*b*) In certain cases, organic redox indicators have been reversibly bleached in the absence of oxygen.[62] The mechanisms are at present difficult to understand on account of the questionable existence of the free H atom.

(*c*) Coenzyme I (Diphosphopyridine nucleotide) can be reduced by radiation to an abnormal derivative (probably a dimer of the natural molecule) but only in the presence of a hydrogen donor like ethanol.[68]

27. *Complex molecules*, such as enzymes and other proteins,[65] nucleic acids, lipids and polysacharides, are also altered *in vitro* as a result of the action of ionizing radiations; enzymes and desoxyribonucleic acid (in the case of the transforming principle of bacteria) may lose their biological properties.[68,69] In most cases the nature of the reaction has not been analyzed and cannot be until we know more about the structure of these macromolecules.

(*a*) One of the most sensitive chemical groups of proteins is the sulfhydryl group (-SH): two adjacent groups are oxidized by $OH^0$ to -S-S resulting in the loss of biological activity when, as in some enzymes, this activity is associated with the reduced form. S-S bridges also cause cross-linking reactions between two adjacent molecules.[65,81]

(*b*) Other specific oxidation reactions of some macromolecules have been found, including the deamination or decarboxylation of proteins,[66] and the oxidation of structures containing double bonds, as in the case of unsaturated fatty acids;[66] but large dosages have usually been necessary in order to make measurements possible.

(*c*) Cross linking may occur through the formation of a carbon to carbon linkage as the result of the combination of two macromolecular free radicals, possibly formed by direct or indirect action.[71,72] This process has, however, mostly been studied in artificial high polymers like polyvinylalcohol, but it is also very likely to take place in cells where the local concentration or the orientation of macromolecules relative to each other may be advantageous for such a process, as in chromosomes or during the formation of other oriented cellular structures. There is in fact good evidence for its occurrence in protein[73] and in DNA.[74]

(*d*) Some effects of ionizing radiations on complex molecules of biological interest have been definitely shown to be due to $OH^0$ radicals: this is so for the inactivation of ribonuclease, carboxypeptidase or the SH enzymes. These effects can be duplicated by chemically produced $OH^0$.[75] In the case of bacteriophage $S_{13}$[76] or catalase,[78] however, it has been suggested that they become inactivated as a result of a reducing mechanism but, on account of the problematic existence of independent H atoms in usual conditions of irradiation, one can probably not be certain of the exact mechanism, since new experiments[77] may yet lead to other interpretations. In many cases the mechanism of inactivation has not been worked out.

(*e*) The physical chemical properties of these molecules may be altered: the asymmetry of nucleic acids,[66,67,70] of fibrous proteins[80] or of hyaluronic acid[79] may be decreased, possibly but not necessarily as a result of a depolymerization; the absorption spectrum of these various compounds is often altered, indicating a chemical alteration of the chromophore group;[75] the stability of proteins and nucleic acids towards heat or other denaturing agent is usually decreased.[70]

*Direct effects*

28. In the case of a *direct* effect,[1,82] the ionization caused by the radiation concerns the molecule or structure under study. It is probable that the energy released in one part of such a molecule will be transferred over the whole structure and ionization or excitation phenomena will not necessarily occur at the point of first interaction. If the molecule becomes ionized, reactive free radicals may be formed and the existence of unpaired electrons has been proved in experiments using paramagnetic resonance; in the absence of water, these radicals are found to exist for periods as long as weeks or months.[83,84] In the case of water solutions, the life of the radicals is much shorter (a few minutes). Such studies have also been made in irradiated cells, indicating the existence of free radicals.[84,85]

29. Cross-linking between macromolecules may occur, as in polyethylene, probably by the reaction of an ionized molecule on a normal one.[86] The absence of an electron from a chemical bond may make this bond unstable and cause it to be hydrolyzed or broken, and some ions may also react with normal molecules causing them to cross link, as in some synthetic polymers.[73] The absorption of energy from the ionizing radiation does not always result in the expulsion of an electron: when ionization does not occur, the group of atoms may become *excited* for a period perhaps as short as $10^{-8}$ sec. thus being rendered more reactive with other molecules and susceptible to chemical alteration.[87] Excitation is the only process responsible for the alteration of substances by ultraviolet or visible radiations, and the use of these types of radiations is thus extremely useful in this respect.

30. *The physical state of a protein molecule* can be made to vary, and it has been shown that when an originally globular protein like pepsin is unfolded at an air-water interface and is irradiated as a monomolecular layer it is much more sensitive than when the "stretched" molecules have been compressed into fibres.[88]

*Distinction between direct and indirect effects*

*Dilution effect*

31. It is possible to distinguish between direct and indirect effects in a simple system by increasing the concentration of the molecules under study. In the case of indirect effects, the yield of altered solute molecules decreases with increasing concentration of the solute.[89,90] It has thus been calculated that in a 1 per cent solution of the enzyme carboxypeptidase, more than 90 per cent of the inactivation is indirect; in a 20 per cent solution, only 60 per cent of the effect is indirect.[90]

*Desiccation and protection*

32. One can also obtain information on the relative importance of direct and indirect mechanisms by comparing the yield of a radiation reaction on the same substrate after desiccation, in a completely protected solution and in the absence of any protector, although it is probable that one will not be able to secure absolute protection against indirect effects.[91]

*Temperature coefficients*

33. One can expect, if diffusible free radicals play a part in the *indirect* effect, that the contribution of this type of effect could be reduced considerably by freezing the solution.[92] This has been experimentally proved. However, irradiation of dry substances at different

temperatures shows that the *direct* effect of ionizing radiation also varies with the temperature, which makes the use of temperature coefficients more hazardous, but nevertheless useful.[82]

*Oxygen effect*

34. The existence of an oxygen effect (paragraph 38) was considered until recently as a criterion for indirect effects; however, as the radiosensitivity of dried proteins and polymers varies with oxygen tension,[93,94] this is no longer a good test until more is known about the mechanism of oxygen effects.

35. A major problem in radiobiology is to determine the relative contribution of direct and indirect effects[3] and its solution will also be of great help in developing methods of chemical protection. A first attempt has been made with yeasts; it can be shown that when they are irradiated in the dry and hydrated state the order of magnitude of both types of effects is very similar.[95] However, the molecular organization of most structures (chromosomes, cytoplasmic particles, nucleoli, cell membrane) is hardly understood, nor is the contribution to these structures of free or bound water and the possibility of diffusion of the free radicals formed during irradiation into or around them. A better understanding of all these fundamental problems would undoubtedly be of great value.

*Effect of LET*

36. According to the type of radiation used, yields per ion pair formed may vary as a result of different LET. It has been calculatted for water solutions that radiation giving high specific ionizations ($\alpha$ particles, slow neutrons, soft electrons) produce high concentrations of $H^0$ and $OH^0$ radicals along the ionization track;[96] their efficiency per ion pair in water solution will thus be smaller, when they are compared to $\gamma$ or x-rays or high energy electrons. In the first case, the radicals, being more densely distributed in space, will have a higher probability of recombining or neutralizing each other, and this explains the lower yield of reactions such as the oxidation of tyrosine, the inactivation of the enzyme carboxypeptidase or of several viruses when the high specific ionizations are used.[12]

37. These densely ionizing particles form $H_2$, $O_2$, $H_2O_2$ and presumably $HO_2^0$ as a result of the radiolysis of $H_2O_2$ in water, *even in the absence of oxygen* and there are instances where $H_2O_2$ has been shown to be responsible for part at least, of the effect of these particles; it has been estimated that local concentration of $H_2O_2$ may reach molarity along the track of $\alpha$ particles.[96]

*Oxygen effect*

38. In *aerated* water solutions, irradiated with X or $\gamma$ rays, $H_2O_2$ is formed, and it is thought that the radical $O_2H^0$ (perhydroxyl) is also produced as a result of the reduction of molecular oxygen by an $H^0$ atom;[51,97,100] in these, the radio-oxidation yield of many substrates is strikingly increased, sometimes by a factor of 3 to 6. In the case of the more densely ionizing particles, as these radicals are formed even in the absence of oxygen, one finds hardly any oxygen effect.[51,98,99] In some instances, new oxidation products appear, as when irradiated alanine becomes oxidized to pyruvic acid[101] (the latter also occurs as a natural oxidation product of alanine through the action of aminoacid oxidase).[51] In some degradation reactions of polymetacrylate, oxygen is necessary;[97,102] organic hydroperoxides or peracids also arise by the oxidizing action of $O_2H^0$ on organic acids.[51,103,104] The rate of inactivation of certain non-SH enzymes does not appear to depend on the presence of oxygen, but SH enzymes are far more radiosensitive when oxygen is present.[105] Other biological materials such as the desoxyribonucleic acid[67,68,102] or bacteriophage[76] (a desoxyribonucleoprotein) appear to be inactivated by ionizing radiations, by mechanisms chiefly independent of the presence of oxygen. This is also true for the induction of bacteriophage in E. Coli K12.[87,106] But it has been shown that DNA irradiated in the presence of oxygen is capable of forming hydroperoxides which arise almost certainly from the indirect effect of the perhydroxyl radicals on pyrimidine bases.[107] However, the excited DNA molecule itself can form similar compounds by reacting with molecular oxygen and this will result in the direct formation of hydroperoxides.[108] It has recently been shown that *dehydrated proteins* (trypsin) *also show an oxygen effect* when irradiated with sparsely ionizing radiation (X or $\gamma$ rays); this may be due to $O_2^-$ ions.[93]

*After-effects*

39. It has often been observed that the molecules under study continue to undergo alteration *after* the exposure to irradiation has ceased. This is the case for the oxidation of tyrosine,[109] or for the inactivation of some proteins,[110] nucleic acids,[67] bacteriophage,[111] other nucleoproteins[113] hyaluronic acid.[79] Pneumococcal DNA when tested for transforming activity does not appear to show any after-effect after irradiation in 1 per cent yeast extract.[68]

40. The after-effect seems to be the result of a primary process taking place chiefly in the presence of dissolved oxygen but it may not be sufficient in itself to inactivate the molecule. It could be due to the $H_2O_2$[111] or to the organic hydroperoxides[112] formed in the solution, but other hypotheses have been presented.

41. The case of desoxyribonucleic acid has been the most studied: many mechanisms—such as the oxidative formation of labile phosphate links with the sugar rings of the macromolecular chain or the slow unwinding of the double helical structure of desoxyribonucleic acid—have been postulated.[114,115,116] Although $H_2O_2$ formed in the solution does not appear to be necessary in the case of desoxyribonucleic acid,[116] it may have a very pronounced effect on bacteriophage $S_{13}$ which becomes more sensitive to this agent after irradiations; $S_{13}$ also becomes more sensitive to some reducing agent like ascorbic acid.[76] As the after-effect does not appear to occur after irradiation in the dry state (in the case of DNA)[55] it does appear to be the consequence of an indirect effect of irradiation. One will not be able to estimate its contribution in irradiated organisms until one knows more about direct and indirect action *in vivo*.

*Radioprotection*

*In water solution*

42. In a radiation-induced reaction taking place in water, the fact that the major part of the effect is of indirect origin has fundamental as well as important practical consequences.

43. Any other solute, reacting with the free radicals formed at the expense of the water molecules, will render them less available to the substance under study and protect it possibly by a competitive mechanism.[8,117] Many organic or inorganic compounds are efficient *in*

*vitro*, amongst these thiourea, aniline, phenol, cysteamine and its oxydation derivative cystamine,[97] and S-2-Aminoethylisothiuronium$^{0}$ Br$^{0}$HBr (AET).[118]

44. Substances capable of reacting with essential groups of enzymes may, when present during irradiation, protect the group; removal of the agent after irradiation uncovers an unaltered group and this has been shown to be the mechanism in the case of SH enzymes protected *in vitro* by some SH reagents.[65,119] Many enzymes are also protected by their substrate,[120] their coenzyme or by competitive inhibitors,[121,122,123] probably also because the biologically active sites of the enzyme molecules are masked by the protector. It has been suggested, furthermore, that the SH group of cysteamine can protect SH groups of enzymes by becoming linked to them reversibly through S-S bridges. Similar dissociable complexes can be postulated in other instances.[124,125]

45. If organic radicals originating from irradiated molecules are prevented to diffuse from one another, one favours their rejoining. This is also a possible mechanism of radioprotection and it can probably be achieved by freezing at *low temperature*.[126]

46. Reducing the oxygen tension will inhibit those effects of radiation which are known to be increased in oxygen. There are many ways of producing anoxic conditions, including the use of chemicals, such as hydrosulfite, cysteine or cysteamine,[127,129] and of more usual respiratory inhibitors. *In vivo*, many reducing organic substrates which consume the cellular oxygen by way of the normal respiratory processes probably also produce anoxic conditions.[20,128] It is difficult at present to know the exact contribution of these mechanisms in the case of certain protecting agents like cysteine or cysteamine; it is probable that it varies according to the type of substrate, the presence of other solutes and the concentration of the different substances.

*In the dry state*

47. However, it is possible to protect molecules in the dry state. It has been shown that the four first substances listed above, (paragraph 43) when incorporated into a synthetic polymetacrylate, protect it during irradiation even when in the dry state.[55] In the solid state, no water radicals being present, the protective action is probably due to a transfer of energy through the polymer molecules to the radioprotector. This would be the mechanism of protection in the case of a *direct* action of radiation on the molecule. The ribonucleic acid of tobacco mosaic virus also appears to be protected against direct effects by cysteine.[130]

*Restoration*

48. Restoration is a process starting in the irradiated material, by which the original product can be obtained with its normal characteristics.

49. Reducing agents when added after irradiation have been shown to be capable of restoring the full enzymatic activity of a number of SH enzymes. The restoration is complete only at very low dosages; as dosage is increased, reversibility is less and less complete, which shows that different sites of one molecular species are altered with different efficiencies.[65]

50. Although some compounds are normally oxidized or reduced during normal cellular processes, the radiobiological oxidations or reductions may lead to a product which is not the natural one and which cannot be restored to an active biological compound by natural processes.[68] Coenzyme I *is reduced* by X or $\gamma$ irradiation to an unnatural product only in the presence of alcohol which is oxidised to acetaldehyde; the reaction cannot be reversed by enzymatic oxidation. The great majority of radiochemical reactions are apparently irreversible *in vitro*. If a radiation reaction similar to the last one described were to take place *in vivo*, natural enzymatic processes could restore the *substrate* to its natural state, and the acetaldehyde formed could be reduced again to ethanol.

*Present status of the "target" theory*

51. According to its original meaning given by Crowther in 1924, a "target" in radiobiology is a sensitive cellular structure whose inactivation by one or several ionizations (hits) would result in the observed biological effects.[131] When ionization takes place exclusively in the sensitive structure (direct effects) the dosage to effect relationship has enabled one to calculate a target volume. In the case of dry or highly protected small viruses which are inactivated by a single efficient ionization, it has been possible on this basis to measure their volume and molecular weight and obtain values in agreement with those obtained by other methods. As water is a major cell constituent, it can be expected that part of the biological effect of radiations is of an indirect nature: this raises new problems as to the applicability of the target hypothesis to living cells. If all indirect effects could be suppressed, as it is thought they are in dried seeds, there would be no problem. At present there is no certain way of doing this: loading the organism with chemical protectors, freezing the cells or reducing the oxygen tension may not do it efficiently because it cannot be foreseen to what extent a chemical protector will reach the cellular structure under consideration, and because free radicals may remain frozen at or near their site of origin until the cells are thawed for biological assay. Therefore, more knowledge is needed about the relative importance of indirect effects and about the distances over which free radicals may diffuse before being neutralized or before reaching the cellular targets. In order to have a clear-cut criterion which can be observed, the biochemical or biological reactions controlled by the targets should be well defined. Probably, when these conditions are satisfied, it will be possible to use the target concept as a useful analytical tool. Work in this direction is in progress.

## III. Biochemical Effects

52. The *sequence of chemical events* from the moment when the cell constituents are subjected to radiation up to the time the biological effects become apparent can conceivably be discovered with biochemical techniques. The search for an immediate or initial biochemical event will thus be the first step in this attempt. Two approaches have been used by studying the effects on cellular constituents and on biochemical mechanisms.

*Cellular constituents*

53. The search for structural damage to important cellular constituents can be done by assaying, as soon as possible after irradiation, the biological or the physicochemical properties of various cell components of which the integrity appears to be important for the economy of the cell. Enzymes or nucleic acids can be examined in this way, but although high doses have been used no definite clues have so far been reached, despite the very great number of observations. The general conclusion seems to point to the apparent radioresistance of the majority of

cellular proteins; and even sulfhydryl groups, which are very radiosensitive in dilute solution, [132,134] do not appear to be considerably damaged *in vivo*.[126,133] Similarly, essential coenzymes and vitamins do not seem significantly altered immediately after irradiation.[126] This is due to the fact that only a very small percentage of the constituents are affected unless very high dosages are applied.[126]

54. It must be realized that in such attempts to identify radiosensitive molecular species by looking for the oxidation of SH groups or changes in molecular asymmetry these molecules are usually considered in bulk, and even when specific analysis is undertaken, it is often found, as is the case of coenzyme A, that no alteration can be detected.[135] These negative findings do not exclude the possibility that a small number of molecules of a type controlling key mechanisms (cell division for example) or having a particular location may still be altered —but at present, general knowledge about the existence of such specific molecules is lacking.

55. In the case of genetic constituents (desoxyribonucleoproteins), which presumably constitute a class of relatively few molecules each having a very high degree of biological specificity, the alteration of a single unit would result in some cellular damage which would become expressed at the end of the chain of reactions it initiated.

56. The question of the radiosensitivity of nucleic acids *in vivo* seems still to be controversial, although evidence indicates that *nucleoprotein* complexes are probably dissociated in many tissues as a result of moderate irradiation.[67,126] It has been calculated, on the basis of *in vitro* measurements, that a dosage of 100 r could damage 100 to 200 molecules of DNA in a mammalian cell,[137] and this figure does not disagree with the data indicating the stability of pneumococcus DNA when irradiated *in vivo*[136], the dosages used in these experiments not being sufficient to cause any significant inactivation.[60] Thus, a very much lower dosage than 1 r would be theoretically sufficient to alter permanently some genetic constituent in a single cell. In this case, not all cells would have one of their DNA molecules affected. However, nothing is known on the possible interactions that intact cells could have on the affected ones, either by influencing their recovery processes or by competing effectively with them (selection). Knowledge on the behaviour of an affected cell in a normal population would be of great interest to understand low dosage effects.

57. There is no reason to believe that ribonucleoproteins are not as radiosensitive as the desoxyribonucleoproteins, but very little is known about the number of units of each type which a cell is likely to possess and even less of the specific reactions they control. Chromosomal ribonucleoproteins could very well be concerned with the duplication of genetic material in dividing cells, as suggested by recent work on bacteriophage synthesis.[138,139,140]

58. Still less information is available concerning the possibility of other cellular constituents playing key roles; many remain to be discovered and further fundamental research is required.

## *Biochemical mechanisms*

### *Energy-forming systems*

59. More information is available from the study of integrated biochemical reaction chains, like those of *glycolysis* and *respiration*, when studied at various times after irradiation. These systems result in the building up of compounds rich in chemical energy which can be used for biosynthetic reactions and cellular work. In radiosensitive organs like bone marrow, spleen and thymus, such reactions as aerobic phosphorylations seem already to be impaired thirty minutes after irradiation by 50 r (effects on mitochondria), but it cannot yet be stated whether these radiobiological processes are the cause or the result of other biochemical damage.[141,142]

### *Synthetic mechanisms*

60. In dividing tissues, the most constant finding is an inhibition of the synthesis of desoxyribonucleic acid. [131,143,144,145] In micro-organisms like yeasts, the homogenity of the population makes experiments more easily interpretable; and it has been found that this inhibition is only temporary and that synthesis resumes after various lengths of time.[144] In other instances, there may be a short time-lag before this inhibition occurs. However, the mechanism of DNA synthesis, although beginning to be experimentally approached, is not understood. As has already been pointed out, it may be dependent even in normal cells on protein or ribonucleic acid metabolism; and in bacteriophage it is probably dependent on such metabolism by the host cell. The nature of the initial step of radiation damage remains to be determined. On the basis of bacteriophage inactivation, it has been suggested that the DNA model, or template, on which the new molecules are thought to be formed, has been altered in such a way as to make its reduplication impossible. The temporary inhibition of DNA synthesis may lead to abnormal DNA formation and this is perhaps related to the killing of cells and to mutation, but in what exact manner is not known.

61. So far, the syntheses of ribonucleic acid and proteins and lipids in bulk do not appear to be consistently impaired by radiation and may even be enhanced, but these compounds are very complex and their study in bulk form, the manner in which it has mostly been carried out so far, cannot be regarded as adequate. Proteins and RNA, bound to the chromosomes and other nuclear and cytoplasmic structures, are probably very complex and each fraction should be studied independently.[144] This will only become possible, however, when more is known about the chemical composition of cellular structures and when refined analytical procedures are available.

62. The inhibition of *induced protein synthesis* in micro-organisms has usually been found to be resistant to radiations, except in the case of hydrogenlyase in E. Coli.[146] In mammals, a few cases of induced synthesis of enzymes are known: the tryptophane peroxidase activity of rat liver can be increased if the animal is injected with large amounts of tryptophane. This process is inhibited by radiations, but this inhibition only becomes apparent after two or three days.[150] However, if tryptophane is *not* given to the animal, an *increased* activity of the peroxidase during the first few hours after irradiation can be observed, but this increase does not occur in adrenalectomised rats and is therefore due to a secondary adrenal stimulation.[151,152] There are therefore two conflicting mechanisms which have opposed effects. It has furthermore been shown that the occurrence of infection in irradiated mammals can be related to an impaired synthesis of *antibodies* if irradiation takes place before the injection of the antigen;[146,147,148,149] this is not necessarily due to the depletion of antibody-forming cells, but

might be related to the inhibition of the *induced synthesis* of a specific protein, a complex process generally considered to be related to the metabolism of ribonucleic acid, but which is not understood. The complete process of immunological response (the sequence of events between the invasion of the organism by an antigen and the synthesis of a new specified antibody) is also not properly understood and the cells which are concerned are just beginning to be identified. The process of induced synthesis is believed to be related to ribonucleic acid metabolism, and in micro-organisms it is quite sensitive to U.V. light absorbed by their constituents which affects the synthesis not only of the new proteins but also of ribonucleic acid.[153]

*Effects on transport mechanisms in the cell membrane*

63. Enzymatic systems at the surface of the cell membrane take a prominent part in the active transport of metabolites through the cell membrane,[154] but, although cell permeability has often been said to be affected after irradiation,[155,156] few critical experiments have been performed. It has been shown, for instance, that lethal irradiations and still higher dosages have often led to a leak of potassium ions into the medium; this has been proved in erythrocytes, in muscle but not in liver.[157] Similar phenomena, if existing in nerve cells, could be a basis for explaining some of the nervous symptoms of irradiation. Surface mechanisms can be affected in yeasts by U.V. light 365 mμ, without apparently producing other effects than delaying mitosis; these surface lesions cause considerable loss in potassium.[158]

64. The loss of small organic molecules like adenosine triphosphate has been shown to occur from irradiated micro-organisms,[159] and techniques of tissue culture will make it possible to establish whether such behaviour applies also to mammalian cells. In mammals, it is known that amino acids and other small molecules (taurine for instance) are released in the blood stream and urine,[160,161] and this might be the result of impaired permeability.

65. The exact significance of these various biochemical effects is difficult to discuss because our present knowledge of the sequence of biochemical mechanisms taking place in a normal cell and their interrelationship is still very fragmentary.

## IV. Cytological effects

66. In order to explain the biological effects of radiation, cytologists have tried for the last half century to identify abnormal cell structures.

*Nucleus*

67. *In the cell nucleus,* the most conspicuous damage is in the *chromosomes,* which are very sensitive and frequently grossly altered; irradiation as low as 25 r or even less is sufficient to induce chromosome aberrations in embryonic nerve cells[162] or in many plant tissues.[163,164]

68. Irradiation causes the breakage of chromosomes, which probably occurs during exposure; this is followed by normal or abnormal recombination of the broken ends; but these may remain separate. As not only the molecular integrity but also the order of the genes on the chromosomes is important, this damage may lead to genetical effects simulating mutations. Point mutations are molecular alterations of genes usually not accompanied by visible aberrations, and they may perhaps concern only a very few sub-units (nucleotides) of genetical material;[165,166] however, a point mutation could occur at the point of breakage and reunion of the chromosome and in this case the damage would be visible. Two types of mechanisms for chromosomes breakage appear to be possible;[86] the first would be the result of the breaking of weak ionic bonds, the second the rupture of stronger covalent bonds. In the first case, restitution is possible in the absence of external energy sources; in the second, energy of respiratory origin is necessary. This interpretation is by no way definitive; it is the one which best fits the present experimental data, but its simplicity is obviously a reflection of our ignorance of the over-all molecular structure of chromosomes and of the dynamic mechanisms of chromosome function. It is presumed that ionization must take place in the gene itself or in its immediate vicinity to cause a mutation.

69. Less defined damage, making the chromosomes stick to each other, is also observed; the result of this stickiness is, as is often also the case for well-defined abberations, an uneven distribution of chromosomes between the daughter cells, which affects the process of mitosis or the survival of the cells.[162,167] Staining abnormalities of the nucleus have frequently been observed.[70,168]

70. New techniques have only recently been developed for mammals, making possible in them the identification of all the chromosomes in a sufficient number of cells for the quantitative study of aberrations, which would lead to the establishment of dose effect relationships in men. Observations of this kind will be extremely laborious and one cannot expect much information before many competent observers have been trained.

71. The morphology as well as the number of *nucleoli* (small nuclear spherules characterized by their high content of ribonucleic acid) may be altered in mammalian cells.[169] The total cellular volume may increase as a result of irradiation, as the volume of the nucleus often does; the nucleoli may become swollen, fragmented or vacuolated.[167,170] The precise function of the nucleoli in normal cells is far from completely known, but it may be related to such diverse processes as cell differentiation, protein synthesis and coenzyme synthesis, and their obvious relationship with the chromosomes in many instances make these organelles of prominent interest for the proper functioning of the cell.[171]

*Cytoplasm*

72. Nuclear swelling is often accompanied by cytoplasmic swelling, and giant cells are often observed after irradiation of micro-organisms as well as of mammalian cells.[172] The fact that the dry weight or total nitrogen increases at the same time indicates that many synthetic reactions have not been interrupted. Swelling of cells (or elongation of bacteria) appears to be the result of an impaired cytoplasmic cleavage.[173,174,175,176,179] This cellular swelling has often been the basis of a misinterpretation: many references to the *stimulation of growth* of irradiated organisms can be cited. Actually, as in the case of seedlings, this is merely the result of the elongation of non-dividing cells:[176,177,178] the inhibition of one process (cell division) may result in the increase of available energy or building blocks for other reactions, thus merely shifting one steady state to another. The energy of radiation and its random distribution is such that the chances of obtaining deleterious reactions appear greater than those for specifically removing inhibitory processes, another logical mechanism by which stimulation could be explained. Effects of radiation should always be thoroughly analysed before they can be assumed to be useful to the irradiated subject.

73. The cell cytoplasm is known to contain a variety of particular structures, the exact identity of which has not yet thoroughly been worked out.[180]

74. *Mitochondria* are the largest of cellular particles; they contain most of the enzymes and coenzymes responsible for cellular respiration which release the major part of energy used in biochemical reactions; they also have important functions in lipid metabolism.[192] They have been observed to swell or show abnormal staining in irradiated spleen cells,[181,182,183] a finding which has been supported by biochemical evidence (inhibition of oxidative phosphorylation).[184,185] If, after irradiation, the behaviour of the various biochemical functions which are attributed to mitochondria were compared, it should be possible to draw a consistent picture of their alterations;[185] unfortunately the experiments have seldom been carried out in comparable conditions.

75. The following have been described:

(*a*) An inhibition of respiration and phosphorylations chiefly in thymus and spleen; the phosphorylation processes appear to be more sensitive than respiration.[184,186,187]

(*b*) An increase of spleen adenosine-triphosphatase which seems to be independent, at least initially, of the inhibition of phosphorylation.[186]

(*c*) An altered lipid metabolism characterized chiefly by an increased synthesis of the phospholipids of the liver;[188] however in spleen and thymus it is slightly lower or remains normal. It must be emphasized, however, that lipid synthesis may not necessarily be linked to mitochondrial integrity, as suggested by a number of experiments.[189,190,191]

76. Thus, the different reactions to radiation of three different mitochondrial functions do not appear to respond identically. This raises the problem of the identity of the mitochondria performing all these three functions. Much better controlled work, where several properties of the same particles are investigated in identical conditions, could help to solve this important problem, and radiations could perhaps in this instance be useful as an analytical tool: the site of lipid metabolism could be a radioresistant type of mitochondrion.

77. It must finally be kept in mind that respiratory processes appear, as in yeast, to be controlled by nuclear or cytoplasmic factors;[193] the latter may or may not be identical with the cytoplasmic particles carrying the respiratory enzymes themselves. An alteration of these controlling mechanisms could very well be the origin of late radiation effects on these functions.

78. *Microsomes* form another class of smaller, cytoplasmic structures organized in a reticulum, as seen by the electron microscope.[194,195] They have a strong affinity for basic dyes, a condition which is strikingly augmented in tissues undergoing differentiation and actively synthesizing protein; in the course of these processes, ribonucleic acid, chemically related to the desoxyribonucleic acids constituting the nuclear genes, undoubtedly plays an important part. There does appear to be a functional relationship between microsomes and nucleoli, but its nature is not understood. These particles are at present considered to be the major site of protein synthesis.[171]

79. Surprisingly, electron microscopy has not been much used for the study of the structure of the irradiated cytoplasmic reticulum and the scanty observations so far performed in the thyroid and in the testes have not revealed any damage to this reticulum.[196]

80. If the microsomes are considered from a dynamic point of view and the cellular functions to which they are related are studied, several conclusions can be tentatively reached.

81. In general, *protein synthesis* does not appear to be impaired immediately after irradiation,[198] and it is, on the contrary, often enhanced; however, this increased activity is often followed by a depression, as in the case of the synthesis of the protein moiety of hemoglobin.[197,199] This bimodal response to radiation, often found for protein synthesis, makes it difficult to interpret the variations of the serum proteins[200] in irradiated animals where a very complex picture is often obtained and when the many results available are difficult to compare on account of different methods and timing of the experiments.

82. The inhibition of the *induced synthesis* of tryptophane oxidase and antibodies are perhaps also related to microsome activity.[150]

83. *Cholesterol synthesis* is also related to the integrity of microsomes[201] and is often enhanced after irradiation; when it is inhibited as in spleen, this only becomes apparent after twenty-four hours.[97]

84. In most cases, the effects of radiation on microsome function probably do not become expressed immediately after irradiation. It will not be possible to understand these late effects until the fundamental facts about protein synthesis and their relation to nuclear activity are known. Experiments on enucleated unicellular organisms have shown that the nucleus has a definite but remote control over the cytoplasmic ribonucleoproteins;[171] the irradiation of non-nucleated cytoplasm in the amoeba has shown that at least ultra-violet light affects cytoplasmic ribonucleoproteins quite rapidly.[202]

85. *Lysosomes* form a type of cellular particle chiefly studied in liver; they are intermediate in size between microsomes and mitochondria;[180] they are characterized by a high content of iron and by their association with several enzymes like desoxyribonuclease II, ribonuclease, cathespin, glucuronidase, and acid phosphatase. As the activity of the first three of these enzymes has been found to increase in tissue homogenates or in the blood stream after irradiation,[203,204,205,206,207] it could be suggested that this is a result of damage to the lysosomes; critical experiments in which enzymes are assayed simultaneously in an irradiated animal might prove this hypothesis. In the case of cathepsin, the increased activity can be related to the disappearance after irradiation of an enzyme inhibitor normally present in the blood.[207,208]

86. *Chloroplasts,*[209,212] the chlorophyl-containing cytoplasmic particles of plant cells, and *kinetosomes,*[210] the particles related to flagella in protozoa, are both endowed with genetic continuity; this gives to these structures great theoretical importance. If the speed of multiplication of these structures can be reduced to a greater extent than that of cell division, one can expect to find that some of the daughter cells have completely lost them. The reverse could also be true, and recent work on moderately irradiated grasshopper testes[196] has shown in the electron microscope the appearance of supernumerary tail filaments and centrosomes, probably related to the kinetosomes of protozoa. These observations have led their authors to an interesting theory of radiation damage based on the synergistic action of non-specific molecular displacements leading to the formation of abnormal

structures.[196] Extensive work on irradiated plant cells has led to the demonstration that the activity of several enzymes bound to the chloroplasts were altered.[211]

## V. Biological effects

87. The effects on homogeneous populations of cells will be considered first, and then those on complex organisms.

### *Homogeneous cell populations*

88. Cell populations such as micro-organisms, protozoa, unicellular algae, cultures and surviving suspensions of cells from multicellular organisms like fibroblasts, bone marrow cells, gametes and certain cancerous cells have been extensively studied.[1,213,214,215,217,218] Recent techniques make possible the culture in liquid media of almost any type of mammalian cell;[177,178] these cells are capable, *in vitro*, of forming organized structures recalling the original tissue they come from,[216] which should be of great value in studying problems of cellular organizations and in understanding multicellular organisms. These cell populations have been irradiated in rather comparable conditions, and they have been shown to react in very similar ways.

89. When *fundamental properties* of the cells such as survival, *cell multiplication* or mitosis, *increase in dry weight, differentiation* of non-mature cell types, cell *movements*, or *permeability* of the cell membranes are studied, one can usually describe a *common pattern of reaction to radiation.*

90. On the other hand, cells performing *specialized functions* may react to radiation in a specific manner related to this function. In *multicellular* organisms, important *interactions between the different tissues* have also to be considered.

*Mitosis* (i.e., cell division)

91. Cells are rarely killed immediately, but usually die after having attempted division or after having undergone one or several divisions. Mitosis itself is interfered with and is usually *delayed*, if irradiation happens early enough in the mitotic cycle. This has been examined most elegantly by direct observation on hanging drop preparations of neuroblasts from grasshopper embryos.[167] These experiments have shown the existence of a very critical stage of cell division during the period when the chromosomes condense as visible threads and when both the nuclear membrane and nucleolus disappear. Irradiation *before* this critical stage usually makes the whole process stop for a duration depending on dosage; *after* it has passed this stage, the mitotic events do not appear to be interfered with if dosages are small. It is remarkable that, if applied at the right moment before the critical period, dosages as small as 8 or 16 rad will delay the progression of mitosis in this type of cell. These observations are essentially similar to the previous analyses on fibroblast cultures;[220,221] they also fit rather well with the experiments on irradiated gametes of the sea-urchins, where cleavage of the fertilized embryos obtained by the conjugation of irradiated gametes (either or both of which have been irradiated) is also delayed, if irradiation occurs before early prophase in this case.[222] If irradiation occurs afterwards, it is the subsequent cleavage which is slowed down. This general picture of mitotic delay may be subject to some alteration when different types of cells are considered; less direct methods of observation may have led to a different timing of the critical period in other cells.[219,221] Also, in each cell type, although the general course of mitosis is quite similar, the duration of each phase and sometimes the exact denomination of the stage considered may vary to a considerable extent, which makes exact comparisons very difficult.

92. The exact cause of the inhibition of mitotic division is not known. It has been suggested that it is related to the inhibition of DNA synthesis[214,223] which occurs frequently — but some instances where cell division is inhibited with apparently normal DNA metabolism will force us to reconsider this view.[224] DNA synthesis, as stated previously, is a complex process; it is perhaps associated with chromosomal protein[225] or RNA synthesis,[138] of which next to nothing is known. It has been suggested on the other hand that an interference of radiation with the oxido-reduction of sulfhydryl compounds known to occur during cell divisions[228,229,230] might also be one cause of its inhibition; inhibition of mechanisms of cytoplasmic cleavage[226] or of spindle formation[227] are other plausible hypotheses.

*Mutations*

93. It has been stated earlier that cells which do not die after several divisions are said to recover. This statement is very imprecise, because all that is known is that these cells *look* as if they had recovered. However, in certain instances although they continue to have a quite normal appearance, they have undergone *mutation.* These changes have been observed most clearly in bacteria, moulds, and other unicellular autotrophic or heterotrophic organisms; and very recently, the studies of cultures of isolated mammalian cells have suggested that such mutant forms also exist amongst the survivors.[231] These mutations are characterized by the fact that the surviving cell as well as *most of its descendants* have been affected in a way which makes them *permanently* incapable of performing some biochemical reaction. If this biochemical reaction (for instance, the formation of an essential building block) is necessary for the cell to grow and multiply, the mutation will lead to the arrest of growth and multiplication, and finally the cells will die, if this essential building block is not provided in the culture medium. It is believed that *there is a period of time following irradiation during which the process of mutation is not fully established.*[232,233,234,235] What takes place during this time is not known—but it is possible, at least in the case of ultra-violet irradiation of micro-organisms, that the expression of damage depends on the synthesis of some protein. Although this time-lag gives the possibility of interfering with mutagenesis[234,236]—a subject which will be discussed more thoroughly in another section—it is generally accepted that this damage *once fully established cannot be reversed by non-genetical processes.* In addition to induced mutants there are always a certain number of *spontaneous* ones, which arise in the absence of any added external agents.

94. *Back mutation* (reverse mutation), the apparent reversal of the previous mutation and the evolution from dependency to independence of some specific metabolite, may occur spontaneously or by irradiation of the mutant; apparently there is what could be called a true recovery of the cell or at least of that part of the cell which had first been altered.[237] However, the spontaneous phenomenon has a small probability of occurring and the process of back mutation, *unless it could be directed,* is not a practical recovery process.

95. Other mutagenic agents (lower energy radiation like ultra-violet light,[238] many toxic compounds and chemical analogues to normal building blocks)[239,240] are all useful in helping to clarify the mechanism of mutations. Chemical analogues, for instance, compete with normal building blocks and may often replace them in important macromolecules like nucleic acids, sometimes preventing their reduplication or their normal functioning. Comparison of ultra-violet lights of different wavelengths will indicate which of them is most effective and enables the nature of the chemical groups absorbing the energy to be determined. The use of these agents is of very great importance in elucidating the mechanism, not only of mutation, but also of chromosome breakage and of mitosis, which they are capable of disturbing.[239]

96. Genes presumably control the biochemical mechanisms (many of which are located in the cytoplasm) responsible for producing enzymes or other specific cellular constituents.[241] It is possible to imagine that, as a result of irradiation, the block in the reaction chain between gene and enzyme-forming system could occur in some intermediate *cytoplasmic* structure. If this structure is one which, like the chromosomes and the genes they carry, has to reproduce itself at each mitosis in order that each daughter cell be identical to its parents, and if damage has rendered the reduplication of the original structure impossible, one will obtain a *cytoplasmic mutation*. Nothing much is known about these, but the induction in yeasts of respiratory deficient strains by poisons or radiation and the demonstration that this deficiency is not necessarily of nuclear origin, indicates the existence of heritable cytoplasmic characters.[193,242]

*Movement*

97. *Cell mobility* can be stopped by irradiation, but usually very high dosages are needed for such an effect. Irradiation of spermatozoa[244] may result in the loss of motion, probably as a consequence of the inhibition of phosphorylation;[243] this causes them to become infertile, but the dosages are much larger than the ones required to delay cleavage of the fertilized egg. Nothing specific is known of the effects of radiation on the cellular migrations which occur in the developing embryo. On the other hand, radiation is known to inhibit phagocytosis in mammalian polymorphonuclear white blood cells,[245] but phagocytosis is a complex phenomenon and this effect is not necessarily due to the inhibition of movements. Alterations of cytoplasmic or nuclear movements inside living cells might also give useful indications, but so far their quantitative measurement is difficult.

*Membrane phenomena and ionic equilibria*

98. The statement frequently made that radiation alters the cell permeability needs to be specified. The exchange of inorganic or organic molecules and ions between cells and their natural environment is a very complex process, because many substances have to be concentrated inside the cell against a concentration gradient, a process which requires energy,[154] and inhibition of permeability could result from the inhibition of energy-forming systems. This is the case for $K^+$ or carbohydrates; in the case of the latter, complex enzymatic systems, located on the cellular membrane, have been described, and it would furthermore not be surprising that this organized structure be upset by radiation as are other patterns of cellular organization.

99. It has been shown in many cases that potassium leaks out of many irradiated cells like erythrocytes,[246,247,248] and cardiac muscle,[250] but not out of liver or kidney,[251] or striated muscle.[249]

100. The entry of glucose or amino acids into cells is also dependent on surface enzymes, and it should be clarified whether an inhibition of these systems might affect secondarily synthetic or energy-forming mechanisms. In micro-organisms (*E.Coli*, yeasts), it is known that the induced synthesis of many enzymes is not inhibited by X-rays[252] for doses which completely arrest cell multiplication, which indicates that the inductor substrates are still capable of penetrating into the cells. However, quantitative studies have not been performed. On the other hand, it has been proved that in similar organisms (*E.Coli*) irradiation leads to the diffusion of many nucleotides[159] into the outside medium, as well as of potassium, which has already been discussed (paragraph 63).

101. In mammals, it has been found that when glucose is injected under the skin immediately after irradiation, its entrance into the blood stream is slowed down.[253] The passage of metabolites from the hypodermal region into the blood capillaries could be a more complex phenomenon, because it involves the passing of the molecule through an organized tissue. The same applies to the inhibition of the intestinal absorption of glucose, which is diminished three to six days after total body irradiation in rats. However, in this case the inhibition is accompanied by important cytological damage.[254] The case of the barrier separating the eye from the blood stream[255] as well as many others[156] have also been studied with similar results.

*Cell death*

102. Irradiated cells die either immediately (i.e., during irradiation) or after a certain delay; in the former case, much higher dosages are needed, and death can be attributed to a general denaturation of cellular constituents. Many conflicting results on cell death have appeared in the literature; this can be accounted for by the difficulty in defining cell death: in micro-organisms, for instance, death has been defined as the inability to form visible colonies on agar plates. Furthermore, the primary cause of cellular death may differ from one system to another, and it is not necessarily unique; any of the cytochemical, biochemical, physiological or genetical effects of radiation so far discussed could each take part in killing the cell. A mutation in a micro-organism leading to the inability to form an essential building block will be "lethal" *only* in the case where the culture medium does not contain this substance.

103. Delayed death of dividing cells occurs after one or several cellular divisions have taken place,[220,256,257] and it may often be linked to chromosome damage,[258] but it could also be due to nutritional or other deficiencies, such as occur in a non-dividing population. Delayed death is caused by much more specific damage than immediate death, and its study is thus of far greater interest. The doses required for obtaining delayed death may be different not only for cells of different species,[1] but also for closely related cells such as different strains of the same bacterial species.[259]

104. Recent experiments on *cultures* originating from different single mammalian cells have shown a very similar sensitivity;[231] this probably results from the fact that in these abnormal conditions cells undergo relatively

rapid division, whereas in the whole organism this process may be extremely slow and may differ from one tissue to another. When penetrating radiations are used, it can be assumed that each cell of an irradiated population receives the same amount of radiation. In an average-sized mammalian cell, submitted to an irradiation of 1 r, several hundreds of ionizations occur, and the probability of a structure being damaged will depend on several factors, including its size and the radiosensitivity of its constituent molecules *in vivo*. It has been calculated that 100 r to a mammalian cell nucleus produce 100-200 hits into the DNA; 1,000 r to a bacterium will produce of the order of 5 to 20 direct hits in the DNA alone, and every radical which might reach the DNA could damage another molecule.[69] Alterations of DNA could be one cause of late cellular death, but other cellular constituents are also damaged. It can be shown that some cells die while others recover and apparently behave again like normal ones. This probably results from differences in the distribution of the energy to "critical" and to less "critical" molecules and it has to be remembered that it is the remaining physiological activity of each cell constituent which will determine the final biological effect.

*Effects on viruses and K particles in Paramecia*

105. Radiation effects on such specialized biological systems may at first appear to be out of place in a general survey as this one, aiming at understanding radiation hazards to man. However, these systems are very closely related to chromosomes (and presumably the genes they carry) and to many cytoplasmic particles; they consist of nucleoprotein, and the mechanism by which viruses reproduce autocatalytically offers the best model at present available for the study of the reduplication of cellular nucleoproteins. Viruses are very important in radiobiology, because they can be studied both as chemical entities *in vitro* and they can be irradiated independently of the cells they multiply in. Bacterial viruses (bacteriophage),[260,261] some of the animal viruses and the cytoplasmic K particle of *Paramecia*[262] are desoxyribonucleoproteins, like the bulk of the chromosomes; plant viruses and some animal viruses are ribonucleoproteins, others are desoxyribonucleoproteins.

106. Bacterial viruses are the ones most attention has been paid to, and the following fundamental facts have been discovered and have in some cases been confirmed using other viruses.

107. Ionizing or ultraviolet radiation applied *in vivo* or *in vitro inactivates them, i.e. interferes with the possibility of their being self-duplicated inside the cell.*[260,261,262]

108. For certain strains, non-irradiated bacteriophages are capable of growing in bacteria heavily irradiated by X-rays or ultraviolet radiation, indicating very clearly that *the self-duplicating structure itself* has to be affected and that the bacteria remain capable of supporting phage multiplication.[263,264]

109. If the conditions of infection are such that there are *several* ultraviolet inactivated bacteriophage per cell, for certain strains of bacteriophage, the intact parts of each virus can *recombine* into a complete new unit, which is again capable of duplication (this is called *multiplicity reactivation*).[265] This is a crude and probably quite inaccurate way of explaining a complex mechanism of which little is known. This type of reactivation has also been described for X-rays.[266]

110. Experiments like these may have very general implications for the understanding of damage and of recovery processes taking place in cells of more complex organisms and therefore should be vigorously encouraged.

*Effects on lysogenic cells*

111. Certain types of bacteriophages invade their host but do not multiply in the usual way; on the contrary, they appear to become integrated into the bacterial desoxyribonucleoprotein and thus reduplicate simultaneously with the bacterial nuclear material without causing any apparent trouble to the cell. However, extremely low dosages of irradiation as well as a variety of other agents induce the transformation of this "prophage" to a virulent bacteriophage, which will multiply and finally lyse the infected cell.[267] In certain strains of lysogenic bacteria, a dosage of 0.1 r may give a measurable induction, and the linearity of the dose-response curve for this "genetic" effect has been demonstrated down to such low dosages.[37,100] What characterizes induction is that it takes place in almost 100 per cent of lysogenic cells, whereas mutation only takes place in a small number.

112. Experiments on infected micro-organisms have also shown that a virus is capable of becoming integrated into the genetic material of the host and of *transducing* some genetic characters from one genetic type of host to another.[160,268] It is not unlikely that processes similar to bacterial transformation by DNA or to transduction involving the transfer of genetic material from one type of cell to another, also exist in mammals. If such phenomena were discovered, *directed reversed mutations might become possible in mammals.*

*Differentiating cell populations*

*Embryonic development*

113. Gametes arise from the differentiation of stem cells, the oogonia or spermatogonia, which takes place in the gonads. This differentiation (oogenesis or spermatogenesis) is a process during which the double genetic equipment (*diploid*) existing in the stem cells as well as in the somatic cells is halved evenly through the complex process of *meiosis* to give daughter cells, which will produce gametes containing only one gene of each kind (*haploid*). Fertilization will result in the fusion of the parent nuclei, and the usual diploid number of the somatic cells is thus obtained.

*Irradiation of gametes*

114. We have seen that when either of the gametes is irradiated, the first cleavage of the fertilized egg is delayed; if the embryo is then left to develop, the cleavage divisions usually proceed apparently quite normally up to the blastula stage. However, embryonic development usually comes to a permanent stop before the completion of blastulation or during early gastrulation; this is one of the numerous examples of delayed death.[269] The fundamental biological situation is that gastrulation is the first stage of development during which *cellular differentiation* occurs: this process is preceded by a striking increase in the metabolism of ribonucleic acid (both in the cytoplasm and nucleolus), as is the case in most biological processes where intense protein synthesis and differentiation is taking place.[270] Furthermore, during gastrulation important cellular movements lead to the formation of three different cellular layers which ultimately become organized in tissues

and organs. Some of the cells in certain layers are capable of *inducing* specific differentiation processes in others. There is not just a change in the "geographical" relationship of the cells as a result of these movements, but their apparent uniformity up to the stage of the blastula is lost; this is demonstrated by the fact that the *nuclei* lose the general potentialities they had until then.[271]

115. The cause of the death of embryos obtained from oocytes fertilized with irradiated sperm appears certainly to be related to *nuclear damage:* the sperm cell contains only very little cytoplasm, and the damage can remain hidden, as it may do in mutations, over many cellular generations. Cell divisions appear to be blocked as a result of incomplete fusion of the maternal chromosomes with the abnormal ones of male origin, a situation leading eventually to abnormality and uneven distribution of chromosomes between daughter cells.[269,272,273,274,275] It is important to notice that the process of cell division becomes inhibited at a stage of development where the genetic material is presumed to initiate differentiation. If, however, the fusion of the abnormal paternal chromosomes with the normal maternal ones is completely prevented (which can be done by using *higher* dosages of radiation), a situation arises where the abnormal nucleus is eliminated, and in this case an *apparently normal* embryo will develop if the species studied are capable of parthenogenetic development.[269,272,275] This is one example, amongst others, where dosage-effect relationships appear to be non-linear and even paradoxical; *higher* dosage producing *less* final damage than lower ones. The explanation is that complex mechanisms of development, secondary to the initial damage to the chromatin are observed; this damage, however, is probably related in a simple way to the amount of irradiation received. A similar paradoxical situation may be found in the experimental inductions in the embryo of certain abnormalities such as microphthalmia[273] and this can be logically explained by the existence of some competition with other lesions at higher dosage.

116. In the wasp *Habrobracon*[276] and in silk worm[277] the reverse situation is possible, and the fusion of a normal sperm cell with a highly irradiated egg cell may lead to an androgenic embryo (containing only its *father's* chromatin). Experiments such as this point again to the very important role of radiation damage to the cell nucleus. Nuclear damage (genetic) is probably also responsible for the various forms of abortion or of malformations of offspring born of parents, one or both of which have been irradiated. In this case, the development of the embryo ceases at some stage of organogenesis, sometimes even after birth. However, as different *stages of gametogenesis* have different radiosensitivities, one expects to have a different probability of abnormal offspring when mating occurs at different times after irradiation.[278] The longer the time lapse before conception, the smaller the probability of abnormal development, because it has been found that the earlier stages are the least sensitive ones, at least in mice.[25,278] With slight irradiation, development may in many cases proceed and this will result in more or less dramatic expressions of genetic damage visible in the offspring.

*Irradiation after fertilization*

117. If irradiation is given at different *stages of embryonic development,* the inhibition of cell division and differentiation and cell death may cause the development to be either completely or partially stopped. In the mouse, the pattern of response to irradiation (200 r) of the embryo is the following: irradiation of the mother after fertilization but during the pre-implantation period leads to a high incidence of prenatal death; however, the survivors have very few major abnormalities; this means that only the slightly affected embryos survive. In contrast, if irradiation occurs after the embryo is implanted in utero, during the period of organogenesis, death usually occurs only after birth—but it is much less frequent; on the other hand, there is a very marked increase of malformations of the embryo. During early embryonic development (if irradiation takes place during the formation of the neural folds), malformations may occur in the eyes, brain and medulla but also in the kidney and liver. Irradiation at a slightly later stage of organogenesis gives rise chiefly to abnormalities of the skeleton of various types. There appear to be short critical periods of development during which certain types of abnormalities arise with very great frequency.[279]

118. The exact mechanism of all these effects, which are all possible in humans, is far from being well understood on account of our ignorance of many important facts concerning embryonic development, such as the nature of *induction* (interaction between neighbouring tissues), the cause of *morphogenetic movements* or the nature of *genetic expression,* that is, the mechanism by which one single cell is capable of becoming differentiated into a multitude of daughter cells performing a variety of functions.

*Dosage-effect relationships*

119. These have been studied in certain cases, and for most bone abnormalities they have been found to be of the *sigmoid type.*[280] In the case of the decreased weight of the foetus at birth, the dosage relationship is *linear,*[280] and litter size appears to fall off logarithmically with dosage to the gametes.[281] A constant finding is that a higher dose not only increases the incidence but also the degree of malformation and the length of the sensitive period during which a specific response can be induced.[280] It has been shown that a dose as small as 25 r to the mouse embryo has led to the induction of minor but nevertheless well defined abnormalities. It is difficult at present to know how such small doses could affect human embryos, but it can be expected that very minute malformations of the brain, which could perhaps not be detected in experimental animals, will result in some kind of psychological disorders. Responses to lower dosages still could probably be detected if a greater number of animals and more refined tests were used. The case of leukemia, also believed to be inducible by irradiation of the human embryo,[282] is discussed in detail in chapter V and annex G.

*Adult organisms*

*Differentiation*

120. Some undifferentiated cells are carried on into the adult organisms and these stem cells go on differentiating throughout life: the white blood cells are formed in the bone marrow and in the lymphatic tissues (lymph nodes and spleen and other organs). The lymphatic tissues are considered to be of major importance in antibody formation. The red blood cells originate from bone marrow and during embryonic life from spleen and liver. In rodents, myelopoesis and erythropoiesis continue in spleen during adult life, but not in man. This is one of many physiological differences it is essential not to overlook when one transposes the results from experimental animals to man.

121. Adult organisms contain other tissues *continuously regenerating* from stem cells, such as epithelia (skin, gut, etc.) or bone; finally there are tissues in which *few cell divisions* take place (liver, kidneys, pancreas, brain, or conjunctive tissue).

122. As in the case of isolated cells, experimental evidence points to the *particular radiosensitivity not only of rapidly dividing cells, but also of the embryonic or stem cells which are still due to undergo cellular differentiation.*[41] This can be shown when one observes the survival or the cytological alterations of these cells. The mature lymphocyte, however, which does not belong to either of these classes is an exception to this rule; its great sensitivity to radiations[283,284] is not well understood but may be related in some way to the fact that the nucleus is surrounded by unusually little cytoplasm which may diminish spontaneous recovery mechanisms or to the fact that it is a cell with a very short life-expectancy. It is also sensitive to many other stimuli. The situation is different from that in the spermatozoon, whose haploid nucleus plays an important role both in cell division and in differentiation processes which do not occur in the case of the lymphocyte, whose diploid nucleus may be more resistant than the sperm nucleus.

*Mutations in multicellular organisms*

123. Genetic mutations are found when gametes or the cells they originate from have survived irradiation and undergo fertilization.[285,286]

124. Many mutations are not lethal, and genetic abnormality of one of the gametes is believed to be the cause of many forms of congenital malformations: in this case, embryonic development is only very locally inhibited, and this leads to abnormalities such as harelip, cleft palate, spina bifida or the many deficiencies of the nervous system like congenital blindness, deafness or mental deficiencies. Hereditary diseases due to well defined biochemical deficiencies are also known to occur in mammals, and in a few instances they have been quite thoroughly analysed: in man the missing enzyme has sometimes been identified, as in galactosemia[288] and in phenylpyruvic oligophrenia[287], a form of mental deficiency related to abnormal phenylalanine metabolism.

*Mutations in somatic cells*

125. Mutations in somatic cells will affect the lineage of these cells but will not be carried to the offspring. These mutations have been shown to take place at a frequency of the same order as that found in the germ cells before meiosis (gonia)[25,289,290,291] and they have been found to occur in irradiated tissue culture; such mutations might play an important part in the determination of malignant growths.

126. It is very probable that the mechanism of mutation in higher organisms is very similar to that in micro-organisms; and the importance of fundamental studies in bacteriophage, microbial or fruit-fly genetics is that they enable us to get answers much more rapidly and in much better defined environmental conditions than can be hoped for in the case of the higher animals. Tissue culture, which is complex in the case of these organisms, may become of primary importance for the study of genetical mechanisms in mammalian cells, since such studies have become possible by culturing isolated mammalian cells in the same way as micro-organisms; mutations have been induced in such cultured cells.[292,231] Many somatic effects may have their origin in such mutations or in chromosome damage of non-germinal cells either as a result of death or loss of specific cell functions.

*Carcinogenesis and other somatic effects*

127. These effects, as well as their possible genetic origin, are discussed in chapter V and in annex G.

## VI. Variables in radiation effects

*Physiological conditions*

128. Physiological conditions may vary in many ways and this can influence radiation responses.[41]

129. *During cell division (mitosis and meiosis)* there are different phases of radiosensitivity which one has attempted, not too successfully so far, to link to the different phases of new chromosome formation and nucleic acid synthesis which occur during these events. The survival of cells, the incidence of mutation and the alterations of chromosomes all undergo striking changes in radiation response, depending on the stage of the division cycle during which the organisms are irradiated, but it is difficult to generalize as to which is the critical stage since it can vary from one effect, or from one organism, to another.[227,293,294]

130. The induction of abnormalities or the lethal effect in developing embryos after irradiation of immature gametes of either sex, is strongly dependent on the stage of gametogenesis during which irradiation takes place. The first *meiotic* division is the period when it is possible to induce the greatest number of dominant lethals in the mouse oocyte.[278] In the case of the male, spermatogonia are the most sensitive and it seems that the degeneration occurs during the interphase or the first prophase following irradiation. The period of greatest sensitivity for various effects induced during embryonic development need not be identical.

131. *The age of cells and organisms* may affect their radiosensitivity: in an aged *bacterial suspension,* when the cells have reached their stationary phase, they become less sensitive to radiation;[295] but what is usually called an old culture is simply an "undernourished" one which has ceased to divide because the stationary phase only begins when some nutrient begins to be deficient; modern continuous cultures in media constantly renewed. By means of the chemostat might help to demonstrate whether aging occurs in micro-organisms or cellular suspensions of dividing cells of more complex organisms. The possibility of aging would exist if the daughter cells were not identical; and such a condition would arise if cytoplasmic material endowed with genetic continuity were not distributed evenly between daughter cells. It is probable that in aged cultures the radioresistance is greater because the bacteria have stopped dividing.

132. In the case of *higher organisms,* there is usually a great sensitivity during foetal life and the $LD_{50}$ is less than half that of the adult, and, as has been already shown, the type of lesion depends on the time of embryonic development during which the radiation is delivered. In certain strains of mice, 200 r on the ninth day of gestation is 100 per cent lethal; on the tenth day, twice this dosage is required and after birth greater dosages still are needed. The sensitivity continues to decrease until adult life is reached: the $LD_{50}$ is 500 r at forty days and reaches 670 r at 140 days for $CAF_1$

mice.[296,297,298] The sensitivity then remains very constant up to the last months of life—when it again increases sharply. A similar pattern of response exists in rats;[299] *Drosophila*[300] and birds,[301] on the other hand, have a much more constant radiosensitivity throughout their adult life.

133. These variations of resistance with age may be due to changes in mitotic rate (there are no divisions of somatic cells in *Drosophila*) or to changes in metabolic activity of different tissues, or to the fact that foetal tissues are undergoing active differentiation, or because the recovery processes of the aged cells have become inefficient.

134. *Nutritional and other physiological conditions.* Starvation of micro-organisms may render them more resistant, as seen in paragraph 131, but in other instances, or in reference to other types of effects, they can become more sensitive: fermentation by yeasts cultivated in a medium poor in ammonium salts is inhibited by doses which do not affect the same process when these nutrients are normal.[302]

135. There are few data on the effects of nutritional conditions on the radiosensitivity of the mammal, although a certain number of radiation effects concerning adrenal metabolism (weight, ascorbic acid, cholesterol) have the same sensitivity after one or seven days fasting.[303]

136. *Other conditions:* Anaemia apparently renders mice more sensitive to radiation, as is shown by the lower $LD_{50}$ of certain anaemic strains. Exercise, on the other hand, does not seem to have much effect in mice.[304] It is possible, however, that in human populations, undernourishment and strain may affect the recovery processes.

137. *Oxygen tension.* The irradiation of water solutions in the presence of oxygen results in the formation of $D_2H^0$ radicals, in addition to $H^0$ and $OH^0$. This radical could also be formed *in vivo.* This would explain that when the *oxygen tension is diminished,* a lower response to irradiation occurs;[305] this is true for the survival of mammals,[306,307] and of birds,[308] for certain mutations[309,311] but not all,[310] for chromosome damage,[312] for various effects on embryonic development[313,280] and for certain biochemical reactions dependent on oxygen. Chemical metabolites or poisons whose presence in tissues reduces the oxygen tension may have similar effect. Lowering the oxygen tension may reduce the response to irradiation by a factor of 3 to 5 in the case of high energy radiation having a low ionizing density (X and $\gamma$ rays, fast neutrons); when the oxygen tension is increased, these effects are not enhanced, which indicates that in air the oxygen tension is sufficient for the maximum effect. In the case of the densely ionizing $\alpha$ particles or slow neutrons, there is no oxygen effect.[305]

### *Comparative radiosensitivity of living organisms*

138. When the survival rates after irradiation of different types of living organisms are compared, the sensitivities are found to vary very widely.[314] Mammals appear to be the most sensitive of all classes of organisms and doses able to kill 50 per cent of animals in thirty days ($LD_{50/30}$) range from about 200 rad for the guinea pig to 900 rad for the rat, the best estimate for man being 400 ± 100 rad. Cold blooded animals have an $LD_{50/30}$ which can rise to 3,000 r for the triton and perhaps 20,000 r for the snail. Bacteria and other micro-organisms cannot be compared on exactly the same basis, but it often takes as much as 100,000 r or sometimes much more to prevent 50 per cent of the organisms of many species from developing colonies, and certain protozoa may need more than 300,000 r to kill them.

139. Various factors may explain these differences. In cold blooded animals, either low *metabolic rates* or low cell division rates imply that radiation damage will take longer to develop; but this will not hold true for micro-organisms, which divide much faster than mammalian cells and resist much higher doses.

140. There may also be varying *oxygen tensions* in different organisms which could account for different radiosensitivities.

141. In the same species, organisms of different *genetic strains* may vary in radiosensitivity to lethal effects. This has frequently been observed in micro-organisms but it holds true also for mammals, where different strains of mice have different $LD_{50/30}$.[318,319] It has also been shown that similar genes in different species of *Drosophila* may mutate at rates which can differ by a factor as high as 2.[236,315,316] It has furthermore been shown that the frequency of production of developmental abnormalities may depend very much on the genetic strain: in Balb.C mice, certain malformations of the spine occur in 100 per cent of animals irradiated with 200 r during the 8th ½ day of gestation, whereas in the hybrid (C57×NB) $F_1$ no such malformations occur.[317] *For practical purposes, this means that observations obtained from one human population do not necessarily apply to a genetically different population.*

142. In some organisms such as adult insects where no cell divisions take place, one expects, and finds, a higher radioresistance; but in this case the gonads, where cell divisions do take place, appear also to be rather radioresistant; on the other hand, we have seen that embryonic cells may be very sensitive,[320] as in grasshoppers.

143. The presence of natural radioprotectors may be yet another factor: some organisms like insects are known to have a higher concentration of aminoacids (which are fair radioprotectors) in their body fluids. The degree of oxygenation of the tissues should also be taken into consideration.[320]

144. Finally, the number of sets of genes (*ploïdy*) has certainly something to do with radiosensitivity, as has been demonstrated for yeast and certain other micro-organisms, in which diploïd strains (containing two sets of genes) are more resistant than haploid ones (containing only one set).[320,321] Not only the number of sets of genes, but the number of chromosomes and their length appear to be important; the greater their number or the shorter their length, the more resistant the organisms seem to be. This holds true at least in the case of the plants which have been studied in this respect.[322]

145. Many of these suggestions are mere working hypotheses and nothing systematic has ever been done to find out about these different factors. Work in this direction may lead to the discovery of better ways of protection.

### *Adaptation to radiation*

146. Little is known about the possibilities of organisms becoming adapted to radiation; the following suggestions may however be made.

147. Increase in catalase (an enzyme destroying hydrogen peroxide and possibly neutralizing other peroxides) in algae from the Bikini area has led to the hypothesis that this might be the result of some adaptive enzymatic processes induced by the unusual amount of peroxide detectable in the sea water.[323]

148. *Selection* might be expected to lead, in certain populations of mixed species, to the predominance of the most resistant strain. Furthermore, it is quite conceivable that irradiation itself induces a mutation which increases or decreases the radiosensitivity of an originally homogeneous population of cells. However, work done on *Drosophila*[236] and yeasts[324] does not indicate that breeding in a high radiation background leads to the appearance of more resistant genes. The UV irradiation of E Coli B, on the other hand, has selected a small number of radioresistant mutants (B/r)[250] occurring in normal cultures as a result of spontaneous mutations with the rate of about $1 \times 10^{-5}$ mutations per bacterium per generation; one would expect that under chronic irradiation one could select this strain to some extent.

149. Tumours have often been claimed to become radioresistant when treated with X-rays; it is however difficult at present to give any sound explanation for such a behaviour; adaptation of the cells has been given as one reason[325,326,327,329] but it is difficult to dismiss the fact that the oxygen tension may decrease as a result of pathologic changes in the blood vessels and that the polyploidy of the tumour cells may enhance their radioresistance.

150. Another possible interpretation is that tumour cells may become incapable of further cell division *in vivo*, although when cultured they can resume division. Recent experiments tend to indicate that small dosages of X-rays (25 r) to embryonic mice makes them somewhat more resistant to exposure to X-rays during their adult life; this is however true only for females, the males appearing on the contrary to be adversely affected.[328] This apparent beneficial effect of low doses of X-rays on females is compensated by the fact that the number of litters they were able to bear fell from 5 for the control to 0.5 for the 80 r group; furthermore the number of young per litter was also greatly reduced —it may therefore be the fact of not bearing offspring which is responsible for the increase in life-expectancy.[330]

151. The study of the biology of species living in regions of high natural radioactivity may lead to some information concerning this problem. However, such work, although it may lead quite rapidly to definite ideas concerning the behaviour of short lived organisms or to the identification of pathological symptoms in man, will need to be carried on over many years or decades for the reactions of humans to such conditions to be understood. The mechanism of possible changes in these populations will need to be worked out in the laboratory where genetic strains as well as experimental conditions can be accurately controlled.

152. In certain experiments, the conclusion has been drawn of the favourable effect of small doses of radiation ("biopositive influence", "stimulating effect") both from external and internal sources.[331,332,333] However, further analysis usually explains this as a consequence of pathologically shifted functional equilibrium, where one biological function, taken in isolation, may appear to be stimulated. Also, the possibility of stimulating the initial stages of plant development and growth, followed by higher crop yield, is reported with various contradictory results.[334,335,336]

### *Secondary effects*

153. One important problem is to know whether irradiation applied to one site of a cell or organism can induce an effect in another part.

#### *Nuclear cytoplasmic relationships at the cellular level*

154. Such secondary effects can be expected on account of the close physiological relationship between the different cellular organelles. It is known that if the normal isolated nucleus of an amoeba is put into the irradiated cytoplasm of another amoeba that had previously been enucleated, mitosis is inhibited in the reconstituted amoeba at cytoplasmic dosages only three times those producing the same effect in a normal organism.[337] It has also been shown that unspecific chromosome damage can be induced in an intact frog oocyte nucleus introduced in the irradiated cytoplasm of another oocyte[338] and ultra violet irradiation of the cytoplasm of the giant unicellular *Acetabularia Mediterranea* induces very rapidly some cytochemical alterations in the nucleolus which had been shielded during irradiation (this last effect is hardly apparent in the case of X-rays).[339] However, nuclear damage to *Acetabularia* is also demonstrated if only the nucleus is irradiated. In the course of experiment on eggs of *Drosophila*, the much greater sensitivity of the nucleus when directly irradiated is evident: it takes much more energy to kill the offspring by irradiating the cytoplasm of the egg alone than by irradiating the nucleus;[340] the same holds true for attempts to induce chromosome damage by micro-irradiating other parts of the cell.[341] Primary nuclear damage appears to play a prominent role in processes where nuclear activity is important as in cell division, mutations or many lethal effects. However, this does not mean that the cytoplasm does not participate in radiation damage. In some cells where no division occurs, cytoplasmic processes may become efficiently inhibited; this is the case of non-nucleated cytoplasms of *Amoeba* and *Acetabularia* which survive for shorter periods than if they contain a nucleus:[202,342,343] In this case, the role of the nucleus could be associated with some repair processes which cannot take place as efficiently in its absence, perhaps on account of the fact that the synthesis of cytoplasmic ribonucleic acid becomes seriously impaired in cytoplasm which has been deprived of its nucleus for some time.[171]

#### *Peroxide formation in irradiated cells*

155. One of the possible agents for these secondary effects could be organic or other peroxides arising during irradiation. It has been found that bone marrow cells incubated *in vitro* produce peroxides when the cells originate from an irradiated rabbit.[344] The significance of this finding is difficult to understand on account of the fact that many tissues (although not bone marrow) from non-irradiated rabbits also produce peroxides *in vitro*. Not much is known of the effects these peroxides might have on other cellular populations. It has, however, been demonstrated that many lysogenic bacteria show a diminished response when put in the presence of catalase (catalase reactivation after U.V. and X irradiation).[345] Another argument for the formation of peroxides in irradiated organisms is that even with small dosages (17,000 r) to yeasts grown in anaerobiosis, these organisms synthesize catalase or peroxidase when kept in

anaerobiosis, a condition during which they normally only have traces of the enzymes.[346] The synthesis of new enzymes is believed to be induced by peroxides formed during irradiation.

156. Radiation is also capable of inducing the formation of peroxides outside the cells, and irradiation by X or U.V. rays of organic culture media is mutagenic for the bacteria which are cultured afterwards; the effect can be prevented by catalase.[347]

*Multicellular organisms*

157. It has been found repeatedly that the *nucleic acid metabolism* of a carcinoma is temporarily decreased as a result of irradiation of the animal bearing it, although it had been completely shielded during the irradiation.[348,349] It has also been demonstrated that tumours originating from non-irradiated thymus cells can develop if these cells are grafted on a totally irradiated host whose thymus had previously been removed;[350] damage (by radiation or other means) or removal of the thyroid may lead to pituitary cancer.[351] No final explanation of effects of this type can be given; the first mentioned could be due to diffusible organic peroxides produced during irradiation and very small quantities of peroxides have been found in irradiated mice.[352]

158. On the other hand, normal regulatory processes located in the irradiated part of the animal can certainly be affected: hormonal effects, which are dealt with in chapter V, must be considered.[353] Stimulation of the pituitary as a result of thyroid disfunction is probably the cause of the pituitary tumour mentioned above (paragraph 157). *The exact relationships between hormones and biochemical processes in normal organisms should be known to understand many effects of radiation in the mammal.*

## VII. Alterations of radiation effects by foreign agents

### *Protection*

159. *Protecting agents* are those whose *presence during irradiation* decreases the response of an organism to radiation. Many experiments reported earlier (paragraphs 38, 42 to 47) constitute a basis for finding chemicals capable of protecting living organisms against radiations. However, our ideas on the mechanisms of protection *in vivo* are often conflicting, for the simple reason that the fundamental processes of radiobiology are not understood.

160. The idea of protecting organisms against radiations arose about a decade ago, as a result of the discovery of the indirect nature of radiation effects on dilute solutions. However, as stated earlier, it is very much doubted at present whether effects of radiation on organisms necessarily occur through indirect mechanisms. It can furthermore be expected that the relative contribution of direct and indirect mechanisms will vary for different biological effects and in each case the possibility of protection may thus be different.[355,350,358]

161. There are many possible ways by which radiation damage might be diminished: (*a*) loading the organism with chemicals capable of reacting with $H^0$, $OH^0$, and $O_2H^0$ radicals may divert these from reacting with important cellular constituents; (*b*) protecting agents could also act by covering the sensitive site of cell constituents, and this type of mechanism could be operative both for direct and indirect effects;[357] (ch) all agents capable of decreasing the intracellular oxygen tension can be expected to afford protection against direct or indirect effects which are oxygen dependent;[354] (*d*) finally, a protector might conceivably give more chemical stability to a macromolecule and favour the rejoining of broken bonds or divert energy from it. It is, however, at present very difficult to choose between any of these possibilities.

162. Very many experiments have been performed, very many chemicals have been tested and many effects have been found susceptible of a certain amount of protection.

163. The *survival* of unicellular and multicellular organisms have been quite considerably increased by the use of various agents. *SH* and *amino reagents* (cysteine, cysteamine or cystamine, glutathione) or the methyl derivative, methionine, as well as thiourea have been used successfully on micro-organisms and mammals.[355,356,358] Very similar possibilities have been found with S-2-aminoethylisothiuronium . Br . HBr (AET)[118] which is less toxic and may thus be used in many mammals, including monkeys and dogs.[359] As far as is known, there have been no attempts to use this compound in man. Further analysis has shown that at neutral pH a rearrangement of the AET to guanidine form occurred, so that the effective compound was 2-mercaptoethylguanidine hydrobromide (MEG).[360]

164. These protecting agents appear to have greater efficiency in promoting recovery processes rather than in preventing the initial damage observed: this is most striking in the case of the white blood cells and of the metabolism of spleen nucleic acid which seem to follow a similar pattern of response.[361]

165. The *number of chromosome aberrations*[161,362,367,368,369] and in some instances the *number of mutations*[118] have also been reduced when similar protective agents were used during irradiation. Successful experiments on plant cells have been reported, but cysteine does not reduce chromosome aberrations in mouse thymus,[363] although nucleic acid integrity does appear to be protected by thiourea or cysteamine[366] in the same organ. In *Drosophila,* however, and in micro-organisms, mutations have not so far responded to the protective action of cysteine or cysteamine.[364] In micro-organisms a protective action probably exists, but it is often difficult to interpret the experiments because increased survival as a result of protection could lead to an enhanced opportunity for a mutation to become expressed.[118]

166. These agents have in common the properties of having an amino-group and a sulfur atom (which often is in the form of a sulfhydryl group) and both these are believed to be important.[370] However, they can act independently because many amines are also found to be satisfactory protectors in the absence of a sulfhydryl, and a sulfhydryl group alone may be efficient in some instances.[370,371,372] It has often been suggested that the sulfhydryl group decreases the intra-cellular oxygen tension and this has been found to be the case in few living systems protected with cysteine or cysteamine.[129]

167. Many other agents have been used with a varying degree of success and the mechanism of action of some of these does seem to be dependent on the decrease of cellular oxygen, as in the case of the protection of micro-organisms with hydrosulfite.[20] A certain number of natural metabolites (succinate, glucose, alcohol) have protecting properties in a few instances, probably by consuming the cellular oxygen in the course of their

normal enzymatic oxidation.[118] Anoxia can also be obtained with a certain number of drugs like morphine which depress the respiratory centres; in that case a protecting effect is also found.[373] Cyanide, a strong inhibitor of respiratory enzymes, has been found to be an efficient protector of mice, although it would tend to increase the intracellular tension of oxygen.[374] On the other hand, seeds irradiated in its presence show a greater mutation rate when it is used in low concentrations, but a smaller one when the concentration is increased.[375] However, in these conditions an increased number of chromosome breakages is observed.[376]

168. It is not clear at present to what extent the protection is complete, because although damage is not lethal it may well be present and only become apparent at a later stage. It has been shown that rats, protected during irradiation, develop a large number of tumours;[377,378,379,380] these might have developed in the non-protected animals had they lived, as in the case of mutations in micro-organisms; and it is difficult to know if the primary events of induction of cancer have or have not been diminished. Nothing much is known on the protection against other late damage or against the early aging of irradiated organisms.

169. Protecting agents are much less efficient in the case of alpha rays or neutrons.[381,382] As was seen (paragraph 37) in these cases reduction of the oxygen tension is not expected to have any effect.

*Sensitization*

170. Radiosensitizing agents have been used in cancer therapy, but the fundamental aspects of sensitization are certainly much less known than in those in the case of protection. There are a few instances of enhanced reactions to irradiation in the course of *in vitro* experiments,[383] but these are not at present susceptible to application *in vivo*. It has, for instance, been shown that the oxidation of ferrous sulfate by X-rays is enhanced in the presence of various alcohols or of benzene.

171. As a result of the systematic study of many chemicals, it has been found that *synkavit,*[384] a derivative of vitamin K, increases the radiation induced mitotic inhibition in chick fibroblasts cultured *in vitro;* this effect was carried on in the absence of synkavit for several generations; and if rats are treated with the compound before irradiation their mortality is increased. Synkavit is also capable of increasing the permanent regression after irradiation of experimental tumours in the rat or of cancer in man. All that is known about the mechanism of action of this agent is that it becomes concentrated in the tumour as compared to the other tissues and that in tissue cultures its effect can be abolished by guanosine; this may indicate some interference with nucleic acid metabolism. If one increases the oxygen tension of tumours where it is usually low, one increases their radiosensitivity, a finding which has proved to be useful in cancer therapy.[385]

172. It is not known to what extent natural radiosensitizers might accumulate during certain steps of normal metabolic processes and thus alter the radiosensitivity.

*Recovery*

173. When organisms are irradiated, many processes, inhibited at first, recover. The synthesis of desoxyribonucleic acid is often decreased immediately after irradiation, but only temporarily; other biochemical effects which appear later are also temporary and display apparent recovery. In irradiated mammals, bone marrow and gonads can recover at the expense of the surviving cells which multiply and repopulate these organs, but permanent damage, leading for instance to more rapid aging, to an increased radiosensitivity or to the development of cancer, may have been established.

174. The lapse of time existing between irradiation and the biological expression of the primary damage, gives an opportunity of preventing the development of the lesion or of enhancing the spontaneous recovery processes.

175. *Recovery agents* are those which are effective when given *after irradiation.* Various methods for promoting the recovery of irradiated organisms have been described and can roughly be classified into two groups:

176. (*a*) *Those whose object is to destroy some intermediate compound* before the damage is definitively established: as in the *photorestoration* of a great number of effects of ultra-violet light,[386,388] the *catalase restoration* of lysogenic bacteria treated with ultra-violet light[346] or, in one instance, the effects of X-rays.[387] The first of these processes, in the case of ultra-violet irradiated bacteriophage is only possible if illumination takes place in the presence of extracts of normal bacteria; the second appears to lead to the destruction of organic peroxides formed during irradiation.

177. Restoration achieved in some instances by cooling or heating the irradiated cells[388] may inhibit the expression of injury before it is definitively established but none of these mechanisms is properly understood.

178. (*b*) *Those whose object is to replace a damaged compound or cell.* The provision of nutrients to micro-organisms which have lost the capacity of synthesizing them could be considered as one possible mechanism of recovery; recovery is however only apparent, because the fundamental damage has not been removed.

179. True recovery would depend on the possibility of replacing the damaged molecules or cells by non-irradiated ones. Experiments on bacterial transformations or on genetic recombinations in micro-organisms have shown that it is possible to control some alteration of their genetic characters. The mechanisms of the greater radioresistance of diploid compared with haploid cells may well have their origin in closely related mechanisms. On these grounds, the use of intact desoxyribonucleic acid to replace the irradiated compound inside the chromosome becomes a possibility. One successful experiment of saving ultra-violet irradiated Salmonella with intact DNA has been reported.[389]

180. It is possible to replace whole cell populations of irradiated animals and thus promote their survival; this can be done by injecting intact bone marrow from a non-irradiated donor into the circulation of a lethally irradiated one. This type of experiment was at first performed as a consequence of the demonstration that the death incidence of mice was considerably decreased when hematopoietic organs (like bone marrow of the hind limb, spleen or liver) are shielded during irradiation. Bone marrow injections have since proved to be successful in dogs, hamsters, monkeys.[391] Only tissues containing cells capable of forming granulocytes (mostly polymorphonuclear white blood cells), red blood cells or platelets are capable of this activity. These cellular suspensions are effective in preventing acute death from X or $\gamma$ rays but apparently death caused by neutrons is much more difficult to prevent.[390,391,392,393]

181. As a result of injected bone marrow, the blood cells and platelets tend to reach normal values again, the weight of the body, of the thymus and spleen increases and immunological defence which had disappeared also becomes functional again. However, many of the lesions caused by radiation are not diminished after bone marrow injection: the greying of hair is not influenced and the fertility of gametes is not restored,[395] tumours develop with greater frequency in protected or parabiotic animals[396,397,398] and the normal life-expectancy of the animal remains decreased.[394] All these facts seem to demonstrate that only acute death has been prevented by the graft.

182. Important immunological problems are brought up by such experiments as they were in the case of the first blood transfusions: it is well known that mammals are only able to accept definitively grafts from subjects belonging to the same genetic strains (isologous grafts). For instance, one has known for a long time that grafts from one human being to another (homologous grafts) are usually eliminated rather rapidly, as in the case of skin grafts; this is also the case when grafts are made between different species of animals like rats and mice (heterologous grafts). This incompatibility originates from the fact that mammals possess immunological defence mechanisms which make them synthesize new antibodies to any foreign protein entering their blood circulation. However, it has been found that the immunological response of mammals is strongly inhibited in the days following total body irradiation, and in these circumstances both homologous grafts (from other strains of mice) and heterologous grafts (from rats) of bone marrow are capable of saving lethally irradiated mice. Cells of the donor animal have been characterized in the receptor animal by specific genetical or immunological identification;[390,399] and the repopulation of the myeloid and of the lymphoid tissue has been demonstrated. In the case of heterologous grafting of thymus tissue from rats into irradiated mice, the cells appear at first to be exclusively of rat origin but the later appearance of an agglutination reaction with specific mouse antisera indicates that thymus cells of mouse origin may be recovering.[400]

183. The survival of the animals injected with bone marrow becomes, however, dangerously compromised after a certain time, because, whether homologous or heterologous grafts are used, the incompatibility between these and the cells from the receptor animals reappears. The discussion has arisen as to whether the recovered cells from the irradiated organisms are again able to synthesize antibodies against the injected cells or whether these are making antibodies against the cells of the irradiated host.[401,402]

184. There have been recent attempts to stimulate bone marrow regeneration. It has been shown that alkoxyglycerols obtained from bone marrow, as well as some of their derivates, stimulate the white blood cells counts of patients irradiated for therapeutic purposes; this increase seems to concern the neutrophil polymorphonuclears and has also a beneficial effect on the platelet count.[403] It has also been found that the bactericidal properties of the blood serum were diminished in irradiated rats; this could be due to a loss of properdin, presumably a natural non-specific antibody. Treatment of these animals with a fraction from serum rich in properdin appears to increase the survival.[404,405]

185. Experiments on cell transfer have been made in attempts to replace leukemic cells, which can be destroyed by high dosages of irradiation, by normal marrow tissue with the hope of preventing further development of leukemia. Experiments performed on mice have shown that such a treatment is capable of increasing considerably the survival time of experimental leukemic mice.[406] One such attempt is now being made in a case of human leukemia.

186. The multiplication of donor cells in the irradiated host has unquestionably been established; however, this does not necessarily exclude a possible effect of subcellular fractions. The idea of the possible recovery capacity of bone marrow or spleen nucleoproteins was put forward a few years ago but was later abandoned on the ground that a small number of intact cells were present in the fractions injected.[407] It is, however, not possible at present to exclude the possibility that sub-cellular fractions do play a role in these recovery phenomena and, on account of the tremendous importance of proving or disproving this hypothesis, both for fundamental and applied purposes, work on the biological activity of nucleoproteins in normal or irradiated mammals is of great interest and should certainly be very actively pursued.

187. It will probably become possible to enhance similar recovery processes in human beings, but this *will* certainly require a much better understanding of immunological processes and of interactions between cellular populations before it becomes a reality.

## VIII. Conclusions

188. Radiobiology has certainly made great headway within the last fifteen years. It has had, like cancer research, strong governmental support in many countries, and both these aspects of medicine have the common feature that *many* cellular mechanisms appear to be simultaneously concerned. This is why effects of radiation are as diverse as are cellular functions. The visible damage will probably depend on which particular mechanism is most sensitive at the time of irradiation, on its relative importance to the over-all economy of the cell and on the possible interference of other less damaged processes. Mutations, carcinogenesis, and the inhibition of mitotic activities, of cellular differentiation and of immunological processes, to name but a few examples of radiation damage, affect extremely complex cellular mechanisms, which, despite the efforts of many able scientists, remain one of the most provocative challenges. It thus becomes vital, if effects of radiation are to be understood and possibly prevented, that the functioning of normal cells and the organization of cellular populations be known. Radiobiology is not a science in itself; it is but an applied science and it rests entirely on our knowledge of the great principles of biology which cannot be studied independently of one another. The understanding of some aspects may at times progress more rapidly than that of others, but in the long run all these have to be integrated into one harmonious picture. The problem is not merely to push forward the study of genetics or of carcinogenesis, because it is obvious that these problems are dependent on most other aspects of cell physiology. Our ignorance of fundamental biology (taken in its widest possible sense) is undoubtedly the major factor limiting our understanding of radiation effects on man.

1. Lea, D. E., *Actions of radiations on living cells,* Cambridge Univ. Press, 1946.
2. Pollard, E., A. Buzzell, C. Jeffreys, F. Forro, Arch. Bioch. Bioph. *33,* 9-21 (1951).
3. Alexander, P., *Advances in Radiobiology,* p. 8, Ed. by Hevesy, Forssberg and Abbatt, Oliver and Boyd, Edinburgh and London (1956).
4. Bacq, Z. M., P. Alexander, *Principes de Radiobiologie,* Sciences et Lettres, Liège, p. 59 (1955).
5. Zimmer, K. G., Acta Radiologica *46,* 595-602 (1956).
6. Blan, M., K. Altenburg, Annal der Physik *12,* 315 (1923).
7. Dessauer, F., Zschr. Physik *12,* 38 (1923).
8. Dale, W. M., *Modern Trends in Radiation Biochemistry* in *Actions chimiques et biochimiques des radiations,* Ed. by Haissinsky, Masson, Paris (1955).
9. Lebedinsky, A. V., Proc. Internat. Conf. Peaceful Uses of Atomic Energy *11,* 7-24, United Nations (1956).
10. Meissel, M. N., Proc. Internat. Conf. Peaceful Uses of Atomic Energy *11,* 227-243, United Nations (1956).
11. Rheinberg, S. A., Vest. rentg. radiol. (Moskva) No. 5, 3-10 (1955).
12. Zirkle, R. E., *Radiation Biology,* Ed. by Hollaender, Vol. I, pp. 315-350, McGraw Hill (1954).
13. Kirby-Smith, J. S., C. W. Sheppard, D. L. Craig, *Radiobiology Symposium 1954,* pp. 262-264, Ed. by Bacq and Alexander, Butterworth, London (1955).
14. Storer, J. B., P. S. Harris, J. E. Furchner, W. H. Langham, Rad. Research *6,* 188-288 (1957).
15. Bacq, Z. M., P. Alexander, *op. cit.* ref. 4, p. 96.
16. Lea, D. E., *op. cit.* ref. 1, p. 72.
17. Fano, U. *Radiation Biology,* Ed. by Hollaender, Vol. I, p. 123, McGraw Hill (1954).
18. Atwood, K. C., and A. Norman, Proc. Nat. Ac. Sci. U.S. *35,* 696-709 (1949).
19. Zirkle, R. E., C. A. Tobias, Arch. Biochem. and Biophys. *47,* 282-306 (1953).
20. Hollaender, A., and G. E. Stapleton, Proc. Internat. Conf. Peaceful Uses of Atomic Energy, *11,* 311-314, United Nations (1956).
21. Latarjet, R., Rev. Canad. Biol. *5,* 9-47 (1946).
22. Latarjet, R., *The nature of virus multiplication,* Cambridge Univ. Press, pp. 173-193 (1953).
23. Latarjet, R., et B. Ephrussi, C. R. Acad. Sci., Paris, *229,* 306-308 (1949).
24. Puck, T. T., and P. I. Marcus, J. Exp. Med. *103,* 653 (1956).
25. Muller, H. J., *Radiation Biology,* Ed. by Hollaender, Vol. I, pp. 475-626, McGraw Hill (1954); and UN document A/AC.82/G/R.58/Annex I.
26. Russell, W. L., Bull. of Atom. Scientists *12,* No. 1 (1956).
27. Muller, H. J., *op. cit.* ref. 25, p. 481.
28. Court-Brown, W. M. and R. Doll, *Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondilitis,* H.M. Stationery Office, London (1957); UN document A/AC.82/G/R.105.
29. Lewis, E. B., Science *152,* 965-972 (1957).
30. Muller, H. J., J. Genet. *40,* 1-66 (1940).
31. Kaufmann, B. P., Cold Spring Harbor Symposium *9,* 82-92 (1941).
32. Lea, D. E., *op. cit.* ref. 1, p. 147.
33. Auerbach, R., Nature *177,* 574 (1956).
34. Sax, K., Genetics *25,* 41-68 (1940).
35. Wolff, Sh., and H. E. Luippold, *Progress in Radiobiology,* pp. 217-221, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
36. Fano, U., *op. cit.* ref. 17, p. 135.
37. Duplan, J. F., H. Marcovitch, UN document A/AC.82/G/R.16/Add.1.
38. Marcovitch, H., Nature *174,* 796-797 (1955).
39. Lea, D. E., *op. cit.* ref. 1, p. 227.
40. Goldfeder, A., G. E. Clarke, Radiation Res. *7,* 318, Abstr. 51 (1957).
41. Patt, H. M., A. M. Brues, *Radiation Biology,* Vol. I, pp. 919-958, Ed. by Hollaender, McGraw Hill (1954).
42. Stearner, S. P., Amer. J. Roentg. Rad. Therap., *65,* 265-271 (1951).
43. Stearner, S. P., Amer. J. Roentg. Rad. Therap. *65,* 272-276 (1951).
44. Hershey, A. D., M. D. Kamen, J. W. Kennedy, H. Gest, J. Gen. Physiol., *34,* 305-319 (1951).
45. Stent, G., and C. R. Fuerst, J. Gen. Physiol. *38,* 441 (1955).
46. Mazia, D., and G. Blumenthal, Proc. Nat. Acad. Sci. U.S. *40,* 521-527 (1954).
47. Steffensen, D., Proc. Nat. Acad. Sci. U.S. *41,* 155-160 (1955).
48. Steffensen, D., Genetics *42,* 239-252 (1957).
49. Odell, T. T., and A. C. Upton, Acta Haematol, *14,* 291-293 (1955).
50. Moutinho de Oliveira, M., M. T. Cabral, Portug. Acta Biol. Ser. A, *4,* 297-314 (1955), Chem. Abstr. *50,* 101955 (1956).
51. Lefort, M., in *Actions chimiques et biologiques des radiations,* Ed. by Haissinsky, Masson, Paris, pp. 95-204 (1955).
52. Dainton, F. S., *Progress in Radiobiology,* p. xix, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
53. Lea, D. E., Brit. J. Radiol., Suppl. 1, p. 59 (1947).
54. Franck, J., R. Platzman, *Radiation Biology,* Vol. I, p. 246, Ed. by Hollaender, McGraw Hill (1954).
55. Alexander, P., Personal communication (1957)
56. Bacq, Z. M., P. Alexander, *op. cit.* ref. 4, p. 131.
57. Lefort, M., *op. cit.* ref. 51, p. 162.
58. Stein, G., and J. Weiss, J. Chem. Soc., 3265 (1951).
59. Dale, W. M., *op. cit.* ref. 8, p. 219.
60. Bacq, Z. M. and P. Alexander, *op. cit.* ref. 4, p. 146.
61. Whitcher, S. L., Naturwiss. *39,* 450 (1952).
62. Lefort, M., *op. cit.* ref. 51, p. 161.
63. Swallow, A. J., *Progress in Radiobiology,* pp. 317-323, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
64. Barron, E. S. G., Ph. Johnson, Rad. Res. *5,* 290-302 (1956).

65. Barron, E. S. G., *Radiation Biology,* Vol. I, pp. 283-314, Ed. by Hollaender, McGraw Hill (1954).
66. Bacq, Z. M. and P. Alexander, *op. cit.* ref. 4, p. 171 and p. 181.
67. Davison, P. F., B. E. Conway and J. A. V. Butler, Progr. Bioph. and Bioph. Chem. *4,* 148-220 (1954).
68. Ephrussi-Taylor H., R. Latarjet, Bioch., Bioph. Acta *16,* 183-197 (1955).
69. Guild, W. R., Radiation Res. *7,* 320, Abstract 55 (1957).
70. Errera, M., *Effets biologiques des radiations — Actions biochimiques*—in *Protoplasmatologia,* Ed. by Weber and Heilbrunn, Springerverlag, Vienna, p. 105 (1957).
71. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 156.
72. Alexander, P., and A. Charlesby, J. Polym. Sci. *23,* 355-375 (1957).
73. Alexander, P., M. Fox, K. A. Stacey, D. Rosen, Nature *178,* 846-849 (1956).
74. Kaplan, R. W., Naturwiss. *42,* 466-467 (1955).
75. Collinson, E., F. S. Dainton, B. Holmes, Nature *165,* 267 (1950).
76. Alper, T., *Radiobiology Symposium 1954,* pp. 39-45, Ed. by Bacq and Alexander, Butterworth, London (1955).
77. Ebert, M., Personal communication (1957).
78. Forssberg, A., Nature *159,* 308 (1947).
79. Schoenberd, M. D., R. E. Brook, J. J. Hall, H. Schneiderman, Personal communication (1950).
80. Bacq, Z. M., P. Alexander, *op. cit.* ref. 4, p. 171.
81. Dale, W. M., *op. cit.* ref. 8, p. 223.
82. Pollard, E. C., W. R. Guild, F. Hutchinson and R. B. Setlow, Adv. Biophys. and Biophysic. Chem. *5,* 72-108 (1955).
83. Gordy, W., Proc. Nat. Acad. Sci. U.S. *41,* 983 (1955).
84. Fairbanks, A. J., Radiation Res. *7,* 314, Abstract 42 (1957).
85. Zimmer, K. G., L. A. Ehrenberg, Strahlender, *103,* 3-15 (1957).
86. Charlesby, A., Nature *171,* 167 (1953).
87. Franck, J., R. Platzman, *op. cit.* ref. 54, pp. 231-253.
88. Mazia, D., and G. Blumenthal, Proc. Nat. Acad. Sc. U.S. *34,* 328-336.
89. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 60.
90. Dale, W. M., *Ionizing radiation and cell metabolism,* Ciba Foundation Sympos., p. 26 Churchill, London (1956).
91. Lea, D. E., *op. cit.* ref. 1, p. 108.
92. Setlow, R. B., and B. Doyle, Arch. Bioch. Bioph. *46,* 46 (1953).
93. Alexander, P., Radiation Res. *6,* 653 (1957).
94. Alexander, P., D. Toms, J. Polymer Sci. *12,* 343 (1956).
95. Hutchinson, F., Rad. Res. *5,* 483, Abstract 47 (1956).
96. Gray, J. H., Brit. J. Radiol. *26,* 609 (1953).
97. Bacq, Z. M. and P. Alexander, *op. cit.* ref. 4, pp. 361-401.
98. Hewitt, H. B., and J. Read, Brit. J. Radiol. *23,* 416-423 (1950).
99. Gray, L. H., Acta Radiol. *41,* 63-83 (1954).
100. Errera, M., *op. cit.* ref. 70, p. 187.
101. Johnson, G. R. A., G. Stein and J. Weiss, Science *114,* 412 (1951).
102. Alexander, P., and M. Fox, Trans. Farad. Soc. *50,* 605 (1954).
103. Loiseleur, J., and R. Latarjet, Bull. Soc. Chim. Biol. *24,* 172 (1942).
104. Lefort, M., *op. cit.* ref. 51, p. 200.
105. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 178.
106. Marcovitch, H., Ann. Inst. Past. *90,* 458-481 (1956).
107. Scholes, G., J. Weiss, C. M. Wheeler, Nature *178,* 157 (1956).
108. Ekert, B., and R. Monier, Ann. Inst. Past. *92,* 556-558 (1957).
109. Loiseleur, J., and M. Sauvage, C. R. Acad. Sci. Paris *237,* 204 (1953).
110. Anderson, R. S., Brit. J. Radiol. *27,* 65 (1954).
111. Alper, T., Brit. J. Radiol. *27,* 50 (1954).
112. Latarjet, R., Ciba Foundation Sympos. on *Ionizing radiation and cell metabolism,* pp. 275-308 Churchill, London (1956).
113. Errera, M. Cold Spring Harbor Sympos. *12,* 60 (1947).
114. Errera, M., *op. cit.* ref. 70, p. 107.
115. Scholes, G., and J. Weiss, *Progress in Radiobiology,* pp. 93-104, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
116. Conway, B. E., Nature, *173,* 579-581 (1954).
117. Dale, W. M., Biochem. J. *36,* 80 (1942).
118. Hollaender, A., and G. E. Stapleton, *Ionizing radiation and cell metabolism,* Ciba Foundation Sympos., pp. 120-139 Churchill, London (1956).
119. Barron, E. S. G., S. Dickman, J. A. Muntz and T. S. Singer, J. Gen. Physiol. *32,* 537 (1949).
120. Doherty, G. D., Fed. Proc. *11* (Part 1), 35 (1952).
121. Dale, W. M., Bioch. J. *34,* 1367 (1940).
122. Dale, W. M., Bioch. J. *36,* 80 (1942).
123. Gray, L. H., Brit. Med. Bull. *4,* 11 (1946-47).
124. Eldjarn, L., and A. Pihl, *Progress in Radiobiology,* p. 249, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
125. Littman, F. E., E. M. Carr, J. K. Claus, Science *125,* 737-738 (1957).
126. Errera, M., *op. cit.* ref. 70.
127. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 384.
128. Hollaender, A., and G. E. Stapleton, Physiol. Rev. *33,* 77 (1953).
129. Gray, L. H., *Progress in Radiobiology,* pp. 267-278, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
130. Ginoza, W., and A. Norman, Nature *179,* 520-521 (1957).
131. Meissel, M. N., *op. cit.* ref. 10, p. 227.
132. Graevskii, E. Y., L. I. Korchak, Doklad. Akad. Nauk SSSR *102,* 939 (1955).
133. Meissel, M. N., *op. cit.* ref. 10, p. 230.
134. Cherez, E., Klin. Woch. *34,* 95-98 (1956).
135. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 303.

136. Drew, R. M., Rad. Res. *3*, 116-120 (1955).
137. Butler, J. A. V., Rad. Res. *4*, 20-32 (1956).
138. Volkin, E., and I. Astrachan, Virology *2*, 149-161 (1956).
139. Burton, K., Bioch. J. *61*, 473-483 (1955).
140. Hershey, A. D., and N. E. Melechen, Virology *3*, 207 (1957).
141. Errera, M., *op. cit.* ref. 70, p. 33 and p. 175.
142. Meissel, M. N., *op. cit.* ref. 10, p. 236.
143. Almeida, A. B., and F. G. Sherman, J. Cell. Comp. Physiol. *44*, 333-334 (1954).
144. Errera, M., *op. cit.* ref. 70, pp. 109, 128, 140, 171.
145. Lebedinsky, A. V., *op. cit.* ref. 9, p. 17.
146. Pigalyev, I. A., Proc. Int. Conf. Peaceful Uses of Atom. En., *11*, 80-87, United Nations (1956).
147. Gaude, G., and J. Coursaget, Proc. Int. Conf. Peaceful-Uses of Atom. En., *11*, 169-174, United Nations (1956).
148. Taliaferro, W. H., and L. G. Taliaferro, J. Immunol. *66*, 181-212 (1950).
149. Taliaferro, W. H., and L. G. Taliaferro, J. Infect. Disease *99*, 109-128 (1956).
150. Gros, Ch., G. P. Talwar, J. Coursaget, Bull. Soc. Chim. Biol. *36*, 1569-1580 (1955).
151. Thompson, J. F., and E. T. Mikuta, Proc. Soc. Exp. Biol. Med. *85*, 29-32 (1954).
152. Bacq, Z. M., Personal communication (1957).
153. Errera, M., *op. cit.* ref. 70, p. 85.
154. Rothstein, A., *Protoplasmatologia, 2*, E 4, Ed. by Weber and Heilbrunn, Springerverlag, Vienna (1954).
155. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 300 and p. 334.
156. Lebedinsky, A. V., *op. cit.* ref. 9, p. 22.
157. Errera, M., *op. cit.* ref. 70, p. 66.
158. Bruce, A. K., J. Gen. Physiol., *41*, 693 (1958).
159. Billen, D., B. L. Strehler, G. E. Stapleton, E. Brigham, Arch. Bioch. Bioph. *43*, 1-10 (1953).
160. Kay, R. E., S. C. Early, C. Entenman, Rad. Res. *6*, 98-109 (1957).
161. Williams, C. M., G. M. Krise, D. R. Anderson, R. M. Dowben, Rad. Res. *7*, 176-183 (1957).
162. Carlson, J. G., N. G. Harrington, Rad. Res., *1*, 491, Abstr. 13 (1954).
163. Catcheside, D. G., Adv. in Genet. *2*, 271-358 (1948).
164. Kaufman, B. P., *Radiation Biology*, Vol. I, pp. 627-711, Ed. by Hollaender, McGraw Hill (1954).
165. Benzer, S., *The Chemical Basis of Heredity*, pp. 70-93, Ed. by W. D. McElroy and B. Glass, John Hopkins Press, Baltimore (1957).
166. Demerec, M., Cold Spring Harbor Symp. *21*, 113-121 (1956).
167. Carlson, J. G. *Radiation Biology*, Vol. I, pp. 763-824, Ed. by Hollaender, McGraw Hill (1954).
168. Meissel, M. N., and V. A. Sondak, Dokl. Akad. Nauk SSSR., *105*, No. 6 (1955).
169. Sherer, E., D. Ringelb, Strahlenther. *90*, 41-52 (1954).
170. Errera, M., *op. cit.* ref. 70, p. 173.
171. Brachet, J., *Biochemical Cytology*, Acad. Press (1957).
172. Bloom, M. A., *Histopathology of irradiation from external and internal sources*, McGraw Hill (1948).
173. Klein, G., and A. Forssberg, Exp. Cell. Res. *6*, 211-220 (1954).
174. Klein, G., and A. Forssberg, Exp. Cell. Res. *6*, 480-497 (1954).
175. Reinberg, S. A., Klin. Med. (Moskva), *34*, 3-5 (1956).
176. Moutschen, J., Z. M. Bacq, A. Herve, Experientia *12*, 314-315 (1956).
177. Puck, T. T., and H. W. Fischer, J. Exp. Med. *104*, 427-434 (1956).
178. Puck, T. T., and H. W. Fischer, J. Exp. Med. *104*, 613 (1956).
179. Meissel, M. N., *op. cit.* ref. 10, p. 229.
180. De Duve, C., and J. Berthet, Int. Rev. Cytol. *3*, 225-276 (1954).
181. Sherer, E., Strahlenther. *99*, 230 (1956).
182. Sherer, E., and E. Stolle, Strahlenther. *93*, 317-320 (1954).
183. Sherer, E., and D. Ringelb, Strahlenther. *90*, 34-40 (1953).
184. Van Bekkum, D. W., Bioch. Bioph. Act. *16*, 437-438 (1955).
185. Van Bekkum, D. W., *Ionizing radiations and cell metabolism*, Ciba Foundation Symp. 77-91 Churchill, London (1956).
186. Potter, R. L., and F. H. Bethel, Fed. Proc. *11*, 270 (1952).
187. Ord, M. G., and L. A. Stocken, Brit. J. Radiol. *28*, 279-282 (1955).
188. Chevallier, A., C. Burg, *Radiobiology Symposium 1954*, pp. 1-25, Ed. by Bacq and Alexander, Butterworth, London (1955).
189. Errera, M., *op. cit.* ref. 70, pp. 70-74.
190. Popjak, G., and A. Tietz, Bioch. J. *60*, 147-155 (1955).
191. Popjak, G., and A. Tietz, Bioch. J. *60*, 155-165 (1955).
192. Kennedy, E. P., and A. Lehninger, *Phosphorous Metabolism*, Ed. by W. D. McElroy and B. Glass, Baltimore, Vol. II, pp. 253-281 (1952).
193. Ephrussi, B., *Nucleocytoplasmic relations in microorganisms*, Oxford (1953).
194. Palade, G. E., *Enzymes, Units of Biological Structure and Function*, Acad. Press, pp. 185-215 (1956).
195. Palade, G. E., and P. Siekevitz, J. Biol. and Bioch. Cytol. *2*, 171-198 (1956).
196. Tahmisian, Th., and R. L. Devine, Personal communication (1956).
197. Richmond, D. E., K. I. Altman, K. Salomon, J. Biol. Chem. *190*, 817-825 (1951).
198. Errera, M., *op. cit.* ref. 70, pp. 74-91.
199. Nizet, A., S. Lambert, Z. M. Bacq, A. Herve, Arch. Int. Physiol. *62*, 129-131 (1954).
200. Ord, M. G., and L. A. Stocken, Physiol. Rev. *33*, 356-386 (1953).
201. Cornatzer, W. E., J. P. Davison, O. D. Engelstad, C. Simonson, Rad. Res. *1*, 546-550 (1954).
202. Skreb, Y., and M. Errera, Exp. Cell. Res. *12*, 649-656 (1957).

203. Kowlessar, O. D., K. I. Altman, L. H. Hempelmann, Arch. Bioch. Bioph. *52,* 362 (1954).
204. Kowlessar, O. D., K. I. Altman, L. H. Hempelmann, Arch. Bioch. Bioph. *54,* 355 (1955).
205. Okada, S., E. R. Gordon, R. King, L. H. Hempelmann, Arch. Bioch. Bioph. *70,* 469-476 (1957).
206. Goutier-Pirotte, M., Bioph. Bioch. Act. 22, 396-399, (1956); and UN document A/AC.82/G/R.3.
207. Feinstein, R. N., and J. C. Ballin, Proc. Soc. Exp. Biol. Med. *53,* 6-10 (1953).
208. Ballin, J. C., and R. N. Feinstein, Feder. Proc. *11,* 184 (1952).
209. Rhoades, M. M., Cold Spring Harbor Sympos. *11,* 202-207 (1946).
210. Lwoff, A., Sympos. CNRS, *Unités biologiques douées de continuité génétique* Paris (1936).
211. Sissakian, N. M., Proc. Internat. Conf. Peaceful Uses of Atomic Energy *11,* pp. 248-255, United Nations (1956).
212. Lesley, J. W., and M. M. Lesley, Genetics *41,* 575-588 (1956).
213. Hollaender, A. (Ed.), *Radiation Biology,* McGraw Hill (1954).
214. Errera, M., Ann. Soc. Sci. Med. Nat., Brussels, *5,* 65 (1951).
215. Sparrow, A. H., and F. Forro, Ann. Rev. Nucl. Sci. *3,* 339-368 (1953).
216. Moscona, A., Proc. Nat. Acad. Sci. U.S., *43,* 184-194 (1957).
217. Meissel, M. N., T. M. Kondrateva, K. N. Emelyanov, Dokl. Akad. Nauk SSSR *81,* No. 6 (1951).
218. Ivanitckaya, A. F., Dokl. Akad. Nauk SSSR *110,* 978-981 (1956).
219. Gaulden, M. E., M. Nix, J. Moshman, J. Cell. Comp. Phys. *41,* 451 (1953).
220. Spear, F. G., Brit. Med. Bull. *4,* 2 (1946-1947).
221. Mayer, E., Tab. Biol. *19,* 237 (1939).
222. Henshaw, P. S., Am. J. Roentg. Rad. Ther. *43,* 899 (1940).
223. Errera, M., *op. cit.* ref. 70, p. 167.
224. Gaulden, M. E., Abstr. Genet. Soc. Amer., Genetics *41,* 645 (1956).
225. Bloch, D. P., and G. C. Goodman, J. Biol. Bioph. Chem. *1,* 17-28 (1955).
226. Deering, R. A., and R. B. Setlow, Science *126,* 397 (1957).
227. Sparrow, A. H., Ann. N.Y. Ac. Sci. *51,* 1508 (1951).
228. Gonzales, E. L., and E. S. G. Barron, Bioph. Bioch. Acta *19,* 425 (1956).
229. Rapkine, L., J. Chim. Phys. *34,* 137 (1938).
230. Stern, H., Science *124,* 1292 (1956).
231. Puck, Th. T., Radiation Res. *7,* 444, Abstr. 100 (1957).
232. Demerec, M., and R. Latarjet, Cold Spring Harbor Sympos. *9,* 38-56 (1947).
233. Witkin, E., Cold Spring Harbor Sympos. *21,* 123-140 (1956).
234. Lüning, K. G., and B. Hannerz, Hereditas *43,* 549 (1957) and UN document A/AC.82/G/R.174.
235. Baker, W. K., and E. von Halle, J. Cell. Comp. Physiol. *45,* Suppl. 2, 299-307 (1955).
236. Lüning, K. G., and S. Jonsson, UN document A/AC.82/G/R.69.
237. Giles, N. H., Brookhaven Sympos. on Biol. *8,* 103-125 (1955).
238. Swanson, C. P., and L. J. Stadler, *Radiation Biology,* Vol. II, pp. 249-284, Ed. by Hollaender, McGraw Hill (1955).
239. Hemmerly, J., and M. Demerec, Cancer Res. Suppl. 3, 69-75 (1955).
240. Novick, A., Brookhaven Symp. on Biol. *8,* 201-216 (1955).
241. Suskind, S. R., *Chemical Basis of Heredity,* Ed. by W. D. McElroy and B. Glass, John Hopkins Press, Baltimore (1957).
242. Nanney, D. L., in *Chemical Basis of Heredity,* pp. 134-166, Ed. by W. D. McElroy and B. Glass, John Hopkins Press, Baltimore (1957).
243. Kanazir, D., and M. Errera, Bioch. Bioph. Acta *16,* 198-202 (1955).
244. Evans, T., J. C. Slaughter, E. P. Little, G. Failla, Radiobiol. *39,* 663-680 (1942).
245. Hiramatsu, H., and T. Okamoto, UN document A/AC.82/G/R.63, para. 12.
246. Maizel, M., J. Physiol. *112,* 59-89 (1951).
247. Sheppard, C. W., and M. Steward, Fed. Proc. *10,* 125 (1951).
248. Sheppard, C. W., and M. Steward, J. Cell. Comp. Physiol. Suppl. 2, 188-215 (1952).
249. Wilde, W. S., and C. W. Sheppard, Proc. Soc. Exp. Biol. Med. *88,* 249-253 (1955).
250. Coons, J. M., L. E. Ellinwood and J. E. Wilson, Fed. Proc. *14,* 329 (1955).
251. Denson, J. R., E. J. Gray, J. L. Gray, F. J. Herbert, J. T. Tew, H. Jensen, Proc. Exp. Biol. Med. *22,* 707-711 (1953).
252. Baron, L. S., S. Spiegelman, H. Quastler, J. Gen. Physiol. *36,* 631-641 (1953).
253. Loureau-Pitres, M., Ark. Kemi. *7,* 211-223 (1954).
254. Detrick, L. P., H. C. Upham, D. Highly, V. Debley, T. J. Haley, Rad. Res. *2,* 483-489 (1955).
255. Kiselev, P. N., and P. A. Buzini, Vest. rentg. radiol. (Moskva) No. 5, 17-26 (1955).
256. Lasnitzki, I., Brit. J. Radiol. *16,* 61 (1943).
257. Lasnitzki, I., Brit. J. Radiol. *16,* 137 (1943).
258. Carlson, J. G., *op. cit.* ref. 167, p. 804.
259. Witkin, E. M., Proc. Nat. Ac. Sci. U.S. *32,* 59 (1946).
260. Luria, S. E., in *Radiation Biology,* Vol. II, pp. 333-364, Ed. by Hollaender, McGraw Hill (1955).
261. Pollard, E. C., *The physics of viruses,* Academic Press (1953).
262. Sonneborn, T. M., *Proc. 9th Intern. Congr. Genet. Caryologia,* Suppl. pp. 307-325 (1953).
263. Labaw, L. W., V. M. Mosley, R. R. Wyckoff, J. Bact. *65,* 330-336 (1953).
264. Cheever, F. S., and L. W. Smith, Fed. Proc. *14,* 459 (1955).
265. Luria, S. E., and R. Dulbecco, Genetics *34,* 93-125 (1949).
266. Watson, J. D., Genetics *33,* 633 (1948).
267. Lwoff, A., Lysogeny *17,* 269-337 (1953).
268. Zinder, N. D., and J. Lederberg, J. Bact. *64,* 679-699 (1952).

269. Dalcq, A., and S. Simon, Protoplasma *14,* 497 (1932).
270. Brachet, J., *Embryologie Chimique,* Desoer (Liège) and Masson (Paris) (1945).
271. King, Th. J., and R. Briggs, Cold Spring Harbor Symp. *21,* 271-290 (1956).
272. Muller, H. J., *Radiation Biology,* Vol. I, pp. 351-473, Ed. by Hollaender, McGraw Hill (1954).
273. Russell, W. L., *Radiation Biology,* Vol. I, pp. 825-859, Ed. by Hollaender, McGraw Hill (1954).
274. Hertwig, O., Arch. Mikroskop. Anat. Entwicklungsmech. *82* (II), 1-63 (1913).
275. Hertwig, P., Zschr. indukt. Abstamm. Vererbungslehre *17,* 254-261 (1917).
276. Whiting, A. R., Genetics *35,* 139 (1950).
277. Astaurov, B. L., Zhur. Obshchei Biol. *8,* 421 (1947).
278. Russell, L. B. and W. L. Russell, *Progress in Radiobiology,* pp. 187-192, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
279. Russell, L. B., *Radiation Biology,* Vol. I, pp. 861-918, Ed. by Hollaender, McGraw Hill (1954).
280. Russell, L. B., *op. cit.* ref. 279, pp. 904, 905 and 907.
281. Snell, G. D., J. Exp. Zool. *65,* 421-441 (1933).
282. Stewart, A., J. Webb, D. Giles and D. Hewitt, Lancet *2,* 447 (1956).
283. Wakabayashi, M., and F. Kawamura, UN document A/AC.82/G/R.43.
284. Tsuzuki, M., UN document A/AC.82/G/R.4.
285. Auerbach, R., Nature, *179,* 725-727 (1957).
286. Welshom, W. J., and W. L. Russell, Proc. Nat. Ac. Sci. U.S. *43,* 608 (1957).
287. Fruton, J. S., and S. Simmons, *General Biochemistry,* Wiley, p. 732 (1953).
288. Kalckar, H. M., Science *125,* 105 (1957).
289. Russell, L. B., and M. H. Major, Genetics *36,* 621 (1952).
290. Russell, L. B., and M. H. Major, Genetics *42,* 161-175 (1957).
291. Naville, B., Dissertation Zurich (1955), UN document A/AC.82/G/R.27.
292. Puck, T. T., P. I. Marcus and S. J. Ciecciura, J. Exp. Med. *103,* 273-284 (1956).
293. Giese, A. C., Quart. Rev. Biol. *22,* 253-282 (1947).
294. Errera, M., *op. cit.* ref. 70, pp. 165-168.
295. Stapleton, G. E., Ann. N.Y. Ac. Sci. *59,* 604-618 (1955).
296. Patt, H. M., and A. M. Brues, *op. cit.* ref. 41, p. 932.
297. Sacher, G. A., Science *125,* 1039-1040 (1957).
298. Kohn, H. I., and R. F. Kallman, Science *124,* 1078 (1956).
299. Hursh, J. B., and G. Cassarett, Personal communication (1955).
300. Baxter, R. C., and L. W. Tuttle, Radiat. Res. *7,* 303, Abstr. 14 (1957).
301. Patt. H. M., and A. M. Brues, *op. cit.* ref. 41, p. 933.
302. Sherman, F. G., Experientia *8,* 429-431 (1952).
303. Nims, L. F., and J. L. Geisselsoder, Rad. Res. *5,* 58-64 (1956).
304. Smith, F., L. and W. W. Smith, Am. J. Physiol. *165,* 662 (1951).
305. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, pp. 263-275.
306. Dowdy, A. H., L. R. Bennett, S. M. Chastain, Radiology *55,* 879-885 (1950).
307. Stender, H. S., and T. Hornykiewytsch, Naturwiss. *10b,* 32-34 (1955).
308. Stearner, S. Ph., E. J. B. Christian, A. M. Brues, Am. J. Physiol. *176,* 455-460 (1954).
309. Russell, L. B., M. H. Major, Genetics *38,* 687-688 (1953).
310. Hollaender, A., W. K. Baker, E. H. Anderson, Cold Spring Harbor Symp. *16,* 315-326 (1951).
311. Baker, W. K., Brookhaven Symp. Biol. *8,* 191-200 (1955).
312. Giles, N. H., *Radiation Biology,* Vol. I, pp. 713-761, Ed. by Hollaender, McGraw Hill (1954).
313. Russell, L. B., W. L. Russell and M. H. Major, Anat. Rec. *111,* 455 (1951).
314. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, pp. 276-285.
315. Timofeeff Ressovsky, N.W., Biol. Zentralblatt *52,* 468-476 (1932).
316. Lefèvre, G. J., Genetics *40,* 374-387 (1955).
317. Russell, L. B., *op. cit.* ref. 279, p. 907.
318. Kohn, H. I., and R. F. Kallman, Rad. Res. *6,* 329-332 (1957).
319. Grahn, D., and K. F. Hamilton, Genetics *42,* 189-198 (1957).
320. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 282.
321. See Annex H.
322. Sparrow, A. H., Science *118,* 697-698 (1953).
323. Blinks, L. R., J. Cell. Comp. Physiol. *39,* Suppl. 2, 11 (1952).
324. Welch, G. P., Personal communication (1957).
325. Brues, A. M., Adv. Canc. Res. *2,* 190 (1954).
326. Windholz, F., Radiology *48,* 398 (1947).
327. Glucksmann, A., Brit. J. Radiol. *25,* 38 (1952).
328. Rugh, R., and J. Wolff, Rad. Res. *7,* 462, Abstr. 149 (1957).
329. Dittrich, W., G. Höhne, G. Schubert, *Progress in Radiobiology,* pp. 381-385, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
330. Stadler, J., Gowen, J. W., Abstr. Genet. Soc. Amer.; Genet. *42,* 398 (1957).
331. Stoklasa, I., I. Penkava, *Biologie des Radiums und der radioaktiven Elemente,* Berlin (1932).
332. Lorenz, E., J. Nat. Canc. Inst. *15,* 1049 (1955).
333. Vlasyuk, P. A., *Tracer Elements,* Publ. Acad. Sci. Latv. SSR, p. 95 (1955).
334. Johnson, E., Plant Physiol. *23,* 544 (1948).
335. Granhall, I., L. Ehrenberg, Botan. Notiser *2,* 155 (1953).
336. Kuzin, A. M., Proc. Intern. Conf. Peaceful Uses of Atomic Energy *12,* p. 149, United Nations (1956).
337. Ord, M. J., and J. F. Danielli, J. Gen. Physiol. *39,* 29-37 (1956).
338. Duryee, W. R., J. Nat. Canc. Inst. *10,* 735-796 (1949).
339. Errera, M., F. Vanderhaeghe, Exp. Cell. Res. *13,* 1-10 (1957).
340. Ulrich, H., Nature, *42,* 468 (1955).
341. Zirckle, R. E., and W. Bloom, Science *117,* 487-493 (1953).

342. Bacq, Z. M., F. Vanderhaeghe, J. Lamblon, M. Errera and A. Herve, Exp. Cell. Res. *12,* 639-648 (1957).
343. Mazia, D., and H. Hirshfield, Exp. Cell. Res. 2, 58-72 (1951).
344. Bernheim, F., A. Ottolenghi and K. M. Wilbur, Rad. Res. *4,* 132-138 (1956).
345. Latarjet, R., and L. R. Caldas, J. Gen. Physiol. *35,* 455-470 (1955).
346. Sels, J., and H. Chantrenne, Personal communication (1957).
347. Stone, R. S., O. Wyss, F. Haas, Proc. Nat. Acad. Sci. US *33,* 59 (1947).
348. Ahlström, L. H., H. von Euler, G. Hevesy, Ark. Kemi. *19* (13), 16 (1945).
349. Kuzin, A. M., and E. V. Budilova, Dokl. Akad. Nauk SSSR *91,* 1183 (1953).
350. Kaplan, H. S., W. H. Carnes, M. B. Brown, B. B. Hirsh, Cancer Res. *16,* 422-436 (1956).
351. Furth, J., Recent Progr. in Horm. Res. *11,* 221-249 (1955).
352. Horgan, V. J., and J. St. L. Philpot, *Radiobiology Symposium 1954,* pp. 26-29, Ed. by Bacq and Alexander, Butterworth, London (1955).
353. Lebedinsky, A. V., *op. cit.* ref. 9, p. 17.
354. Gray, L. H., Nature *179,* 991-994 (1957).
355. Patt, H., Physiol. Rev. *33,* 35-76 (1953).
356. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, pp. 61, 84, 361.
357. Eldjarn, L., and A. Pihl, J. Biol. Chem. *223,* 341-352 (1956).
358. Bond, V. P., and E. P. Cronkite, Annual Rev. Physiol. *19,* 299-328 (1957).
359. Crouch, B. G., R. R. Overman, Science *125,* 1092 (1957).
360. Doherty, D. G., R. Shapira, T. W. McKinley, Biology Division Annual Informal Meeting ORNL, Abstr. 10 (1957).
361. Bacq, Z. M., and P. Alexander, *op. cit.* ref. 4, p. 392.
362. Mikaelsen, K., Exp. Cell. Res. *8,* 400-403 (1955).
363. Devik, F., Brit. J. Radiol. *27,* 481-484 (1956).
364. Höhne, G. H., H. A. Kunkel, R. Struckerman, Naturwiss. *42,* 491-492 (1955).
365. Limperos, G., and W. A. Mosher, Amer. J. Roentgenol. *63,* 691-700 (1950).
366. Gros, C., P. Mandel, J. Rodesh, C. R. Ac. Sci. Paris *236,* 2010 (1953).
367. Riley, H. P., Amer. J. Bot. *42,* 765-769 (1955).
368. Wolff, S., H. E. Luippold, Science *122,* 231 (1955).
369. Hollaender, A., R. F. Kimball, Nature *177,* 726-730 (1956).
370. Bacq, Z. M., and . Alexander, *op. cit.* ref. 4, p. 376.
371. Hagen, V. Chem. Abstr. *50,* 15662 (1956).
372. Hagen, V., Chem. Abstr. *50,* 15671 (1956).
373. Kahn, J. B. Jr., Proc. Soc. Exp. Biol. Med. *78,* 486 (1951).
374. Herve, A., and Z. M. Bacq, C. R. Soc. Biol. *143,* 881 and 1158 (1949).
375. D'Amato, F., and A. Gustafsson, Hereditas *34,* 181-192 (1948).
376. Mikaelsen, K., Proc. Nat. Acad. Sci. U.S. *40,* 171-178 (1954).
377. Maisin, J., P. Maldague, A. Dunjić, H. Maisin, Progress in Radiobiology, pp. 463-467, Ed. by Mitchell, Holmes and Smith, Oliver and Boyd, Edinburgh and London (1955).
378. Kaplan, H. S., J. Nat. Canc. Inst. *13,* 185 (1952).
379. Kaplan, H. S., J. Nat. Canc. Inst. *14,* 303 (1953).
380. Meeuwissen, D. J. and M. Brucer, Nature *179,* 201-202 (1957).
381. Forssberg, A., and N. Nybom, Physiologia Plantarum *6,* 78 (1953).
382. Patt, H. M., J. W. Clark, H. Vogel, Proc. Soc. Exp. Biol. Med. *84,* 189-193 (1953).
383. Lefort, M., *op. cit.* ref. 51, p. 141.
384. Mitchell, J. S., *Radiobiology Symposium 1954,* pp. 170-193, Ed. by Bacq and Alexander, Butterworth, London (1955).
385. Gray, L. H., A. D. Conger, M. Ebert, S. Hornsey, O. C. Scott, Brit. J. Radiol. *26,* 638 (1953).
386. Dulbecco, R., *Radiation Biology,* Vol. II, pp. 455-486, Ed. by Hollaender, McGraw Hill (1955).
387. Miletić, B., C.R. Acad. Sci., Paris, *238,* 1541-1542 (1954).
388. Errera, M., *op. cit.* ref. 70, p. 195.
389. Kanazir, D., (in press).
390. Barnes, D. W. H., and J. F. Loutit, Ciba Foundation Symp. on *Ionizing Radiation and Cell Metabolism,* pp. 140-160 Churchill, London (1956).
391. Congdon, C. C., *Progress in Hematology* (in press).
392. Duplan, J. F., C. R. Soc. Biol. *150,* 949-951 (1956).
393. Comsa, J., and Ch. M. Gros, Fortschr. Geb. Roentgenstr. *85,* 274-281 (1956).
394. Cole, L. J., P. C. Nowell, M. E. Ellis, J. Nat. Can. Inst. *17,* 433-445 (1956).
395. Habermayer, J. G., L. J. Cole, H. N. Stolan, Radiat. Res. *7,* 462, Abstr. 147 (1957).
396. Brecher, G., E. P. Cronkite, J. H. Peers, J. Nat. Canc. Inst. *14,* 159 (1953).
397. Finerty, J. C., R. T. Binhammer, M. Schneider, and A. P. Cunningham, J. Nat. Canc. Inst. *14,* 149 (1953).
398. Binhammer, R. T., J. C. Finerty, M. Schneider, A. W. P. Cunningham, Rad. Res. *6,* 339-348 (1957).
399. Makinodan, T., Proc. Soc. Exp. Biol. Med. *92,* 174-179 (1956).
400. Urso, I., N. Gengozian, C. C. Congdon, Radiat. Res. 7, 457, Abstr. 135 (1957).
401. Van Bekkum, D. W., Radiat. Res. *7,* 458, Abstr. 137 (1957).
402. Lengerova, A., Cesk. Biol. (Praha) *7,* 230 (1958).
403. Brohult, A., *Advances in Radiobiology,* pp. 241-247, Ed. by Hevesy, Forssberg and Abbatt, Oliver and Boyd, Edinburgh and London (1956).
404. Pillemer, L., Blum, L., Lipow, I. H., Ross, O. A., Todd, E. W., and Wardlaw, A. C., Science *120,* 279-285 (1954).
405. Strond, A. N., Brues, A. M., Summers, M. M., J. Nat. Canc. Inst. *15,* 1109-1123 (1955).
406. Barnes, D. W. H., M. J. Corps, J. F. Loutit, F. E. Neal, Brit. Med. J. *2,* 626 (1956).
407. Cole, L. J., and M. E. Ellis, Cancer Res. *14,* 738-744 (1954).

## Annex G

# MAMMALIAN SOMATIC EFFECTS

TABLE OF CONTENTS


*Paragraphs*

I. SHORTENING OF THE LIFE SPAN IN EXPERIMENTAL ANIMALS

The experimental effect of single doses on short-term survival.. 1

The acute $LD_{50}$ ..... 8

Acute effects in single organs..... 9

Recovery from whole-body exposure ..... 10

The experimental effect of single doses on long-term survival... 11

The experimental effect of chronic exposure on long-term survival ..... 14

*Article: "Shortening of life by chronic irradiation: the experimental facts"*, by R. H. MOLE

II. LIFE SHORTENING EFFECTS IN MAN..... 16

III. CANCER IN MAN

Leukemia in man..... 27

Atom bomb survivors in Hiroshima..... 28

*Article: "Leukemia in Hiroshima City Atomic survivors"*, by NIEL WALD ..... 33

Leukemia in radiologists ..... 34

Leukemia in children ..... 35

Leukemia after X-ray therapy for ankylosing spondylitis.... 40

Theoretical considerations for estimation of radiation hazards 47

REFERENCES

## I. Shortening of the life-span in experimental animals

### *The experimental effect of single doses on short-term survival*

1. The short and long-term effects of whole-body exposure to a single dose of radiation have been studied in a variety of mammals. When "survival time" (duration of life after exposure) is studied as a function of radiation dose, the results with all species have shown fundamental similarities that may be illustrated here with the data of a hypothetical experiment.

2. The plan and results of the hypothetical experiment are shown in table I and figure 1. The animals were young adult males, 100 days old on irradiation. They were of a species with a relatively short life span of 2½ years. Slightly different results would be obtained with females. Greater effects per unit of radiation dose would be obtained with immature animals or with sick animals.

3. The mortality-time curve (figure 1) illustrates three major periods:

(*a*) The acute period lasting about one month, for which the $LD_{50}$ is 600 rem;

(*b*) The intermediate period whose duration of 1.5-2 years depends on the radiation dose, and during which practically no deaths occur;

(*c*) The terminal period during which the population dies out rapidly.

4. Long-term somatic effects develop during the intermediate period and some of them become "limiting factors" for survival in the terminal period. The complete quietude of the intermediate period indicated in figure 1 is therefore misleading—the intermediate period is, in fact, a period of increasing morbidity. The rate of increase may be slow or fast, depending on the radiation dose and also on various biological factors, many of which are predetermined genetically.

5. The long-term decrease in life-span, illustrated in figure 1, is dealt with quantitatively in the sixth column ("Days") of table I. The decrease is not proportional to the acute mortality (column 4). The decrease can also be expressed as a percentage of the normal life span (column 7), which in the present experiment was 900 days. It is useful to express life-shortening in per cent of normal life span for purposes of comparing results of experiments involving species that differ in life-span.

Table I. Hypothetical experiment

The animals (males, 100 days old) received a single whole-body exposure on experiment-day 0. The table records the doses given to the various groups, and the resulting changes in their median life-spans.

| *Group* | *Radiation dose rem* | *Number of live animals* | | *Median survival time of animals alive on day 30 days* | *Long-term decrease in life-span* | |
|---|---|---|---|---|---|---|
| | | *Day 0* | *Day 30* | | *Days*[a] | *Per cent of control*[b] |
| 1..... | 0 | 100 | 100 | 800 | — | — |
| 2..... | 300 | 100 | 100 | 710 | 90 | 10 |
| 3..... | 500 | 100 | 82 | 650 | 150 | 17 |
| 4..... | 600 | 100 | 50 | 600 | 200 | 21 |
| 5..... | 700 | 100 | 11 | 530 | 270 | 30 |
| 6..... | 800 | 100 | 0 | — | — | — |

[a] The difference between the datum for group 1 (800 days) and the data for other groups in column 5 (median survival time).
[b] The life span of the controls (group 1) was 900 days.

6. The dependence of biological effect on radiation dose is illustrated in figure 2. In the case of acute mortality (deaths within thirty days of exposure calculated from table I, column 4), the dose-effect curve shows a threshold—the first deaths occur somewhere between 300 and 500 rem. In the case of the long-term decrease in life-span (per cent of normal life-span) the course of the curve as drawn does not show a threshold and indicates that even at the smallest radiation doses there is some decrease in life-span (see paragraph 11).

7. Biological effects not only depend on radiation dose but also on dose rate. In the hypothetical experiment, the animals received a single dose at 50 rem/min. The same results would have been obtained with dose rates of 5 or 500 rem/min. Below 5 rem/min., however, the effect per unit dose diminishes. In the case of acute mortality, it does so relatively rapidly. It may do so quite differently in the case of the various kinds of late injuries, including those shortening the life-span.

### *The acute $LD_{50}$*

8. Recent determinations of the acute $LD_{50}$ (single, whole-body exposure) for mature mammals are given in table II. Values for immature and senescent animals would be lower than those tabulated. It has been pointed

Table II. Acute x- and gamma-ray $LD_{50}$ of mature mammals[a]

| *Species* | *$LD_{50}$ (rads)* | *Number of determinations* |
|---|---|---|
| Swine..... | 190–310 | 4 |
| Goat..... | 240 | 1 |
| Dog..... | 240–320 | 6 |
| Man..... | 300 (?) | 0 |
| Guinea pig..... | 380–490 | 3 |
| Monkey..... | 520 | 1 |
| Mouse..... | 520–670 | 7 |
| Hamster..... | 590–800 | 3 |
| Rabbit..... | 680–750 | 3 |
| Rat..... | 790–820 | 2 |

[a] The original reports are listed in reference 1. All doses are estimates for the middle-longitudinal axis of the animal under conditions of approximately homogeneous soft tissue dose distribution. The dose rates ranged from 5–60 rads/min. The $LD_{50}$ is that dose killing half the animals within 30 days of exposure. Almost all of the deaths occur within three weeks.

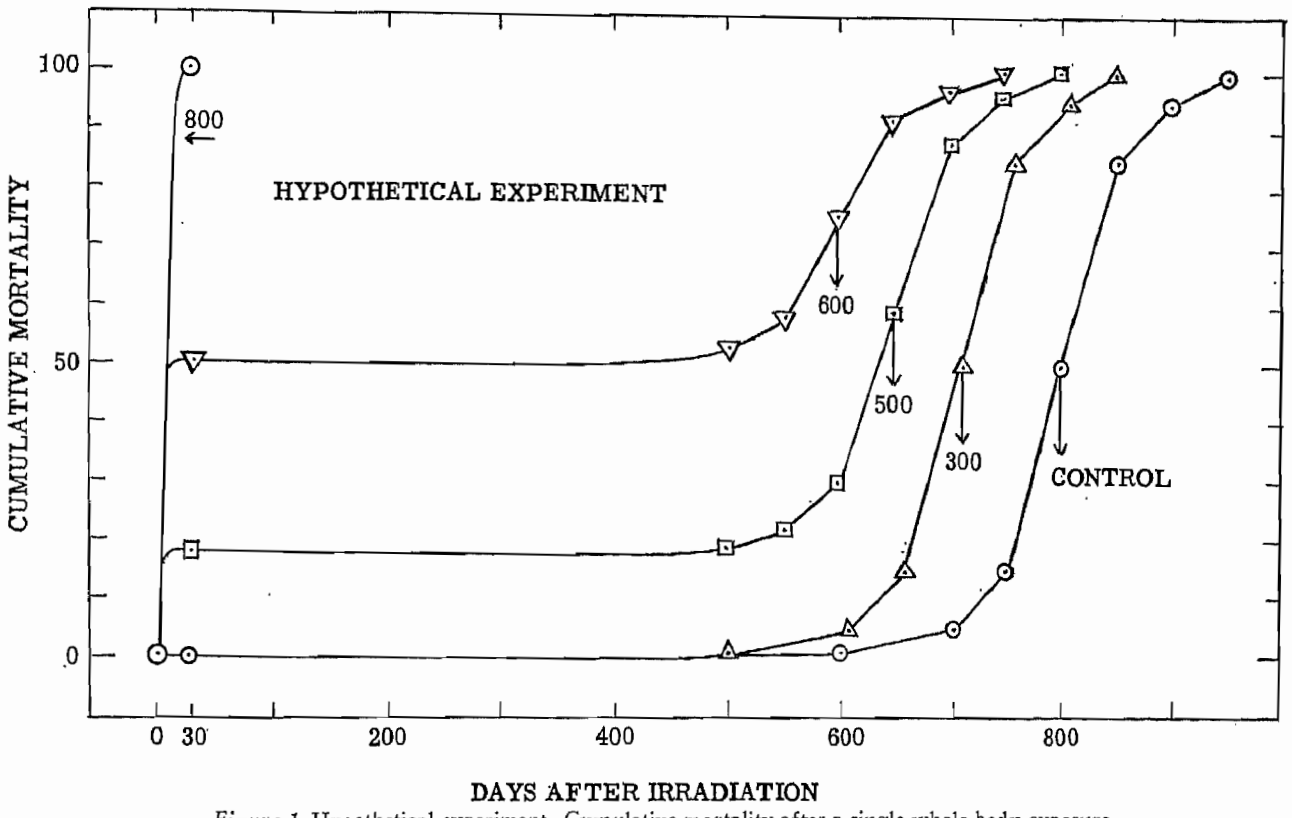



*Figure 1.* Hypothetical experiment—Cumulative mortality after a single whole-body exposure. The dose in rem is specified for each curve.

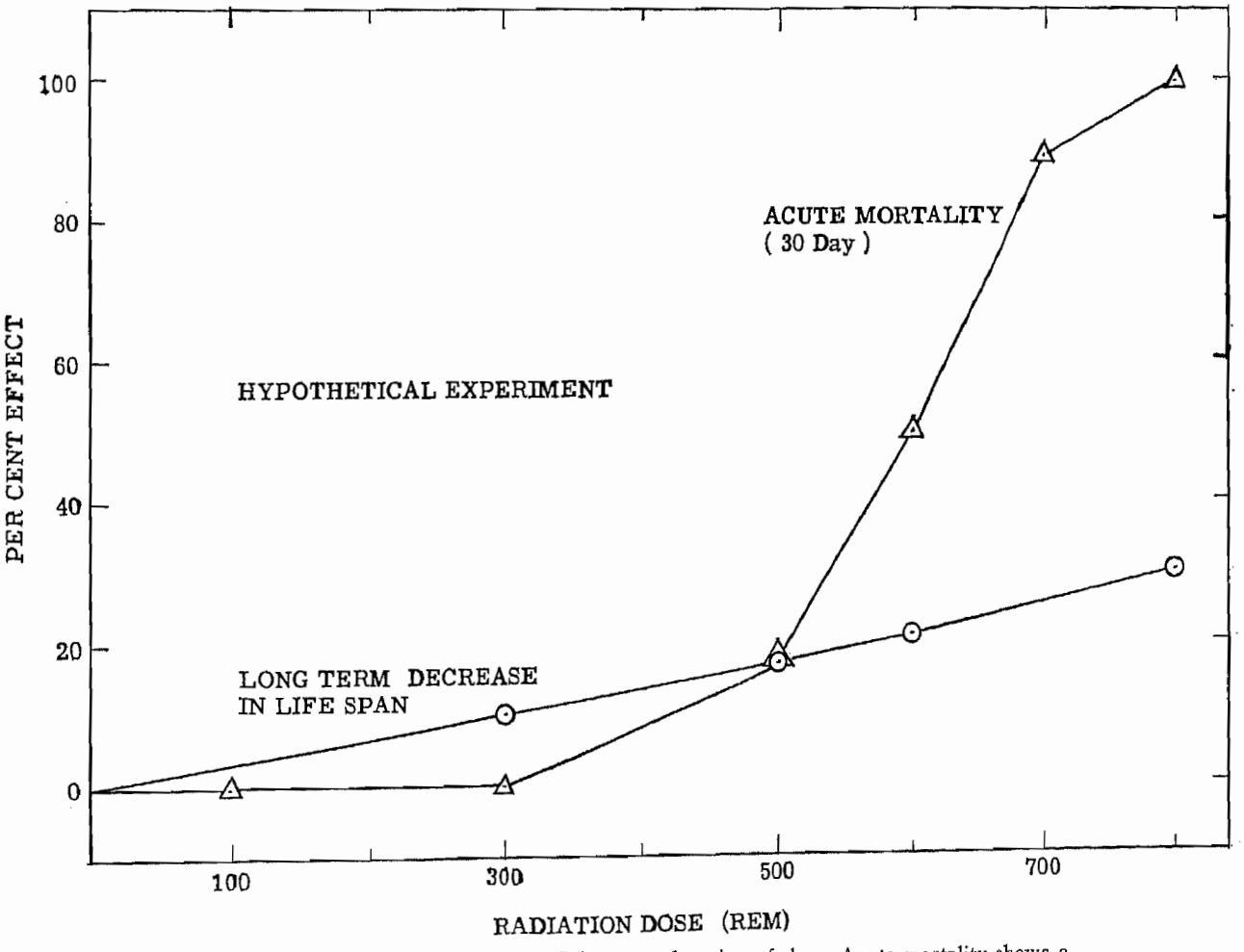



*Figure 2.* Hypothetical experiment—Effect as a function of dose. Acute mortality shows a threshold whereas long term decrease in life-span does not.

out[1] that the values fall into two groups. Those for the "larger" mammals are in the range 200-300 rem; those for the "smaller" mammals are in the range 400-800 rem. The only monkey listed (M. mulatta) falls into the "small" animal class. The estimate for man is close to the determinations for the guinea pig and dog, suggesting that studies with these species may be of special importance. It is to be noted, however, that the figure for man is speculative.

*Acute effects in single organs*

9. A very great number of somatic effects have been described that occur within hours, days, or several weeks of irradiation. Doses as low as 5 rem, for example, have a measurable although brief effect on the mitotic index of the skin of mice.[2] In the range from approximately 25 to 200 rem, simple *quantitative* relations between somatic effect and radiation dose have been demonstrated in such organs as the lymph node, spleen, thymus, testis, and intestine,[3] using both microscopic and gross methods of examination (e.g., weighing). In these examples, restitution occurs relatively quickly, during the course of some days or weeks, and often seems complete.

*Recovery from whole-body exposure*

10. When two or more exposures instead of one are employed, some restitution occurs during the interval(s) between them. One method to study the rate of restitution is to give a non-lethal dose on day 0 and to determine the $LD_{50}$ on various days thereafter. Suppose that the $LD_{50}$ of unirradiated animals is 600 rem. Furthermore, suppose that after 300 rem on day 0 the $LD_{50}$ is:

(*a*) 300 rem on day 1;
(*b*) 450 rem on day 2;
(*c*) 600 rem on day 8;
(*d*) 600 rem on day 20.

It may be concluded therefore that acute recovery from 300 rem was complete by day 8, since by then the $LD_{50}$ had returned to "normal", and half-complete by day 2. Experiments of this type (table III) have shown that the rate of recovery depends on genetic factors, and therefore varies with the strain and species of animal.[4] The rate also depends on the magnitude of the dose—large doses may, so to speak, inhibit the recovery process *per se*.

TABLE III. TIME FOR 50 PER CENT RECOVERY FROM A SINGLE WHOLE-BODY EXPOSURE TO X-RAYS[a]

| *Animal* | *Number of strains* | *X-ray dose (rem)* | *50 per cent recovery time (days)* |
|---|---|---|---|
| *Mouse* | | | |
| Young | 1 | 260 | 7.4 |
| Adult | 6 | 200–400 | 1.6–3.0 |
| Adult | 1 | 600 | 12.0 |
| *Rat* | 2 | 310 | 4.9 and 8.5 |
| *Hamster* | 1 | 320 | 6.1 |
| *Monkey (M. mulatta)* | 1 | 260 | 4.8 |

[a] Recovery measured under the particular conditions described in paragraph 10. The original reports are listed in reference 4.

*The experimental effect of single doses on long-term survival*

11. Data on life-shortening in mice and rats after a single whole-body exposure to X- or gamma-rays at the time of puberty or young adulthood are summarized in figure 3.[5] The radiation dose is expressed as a percentage of the acute $LD_{50}$, e.g., a dose of 300 rem is called 50 per cent if the acute $LD_{50}$ is 600 rem. In the various experiments, the $LD_{50}$ (in r) varied from 500 to 800 r. The curve fitted to the points in figure 3 is on the assumption that life-shortening is directly proportional to dose. For mice and rats it appears that life is shortened by about 10 per cent following a "25 per cent dose". The curve drawn through the points in figure 3 runs straight to the origin, indicating that radiation decreases the life-span no matter how small the dose may be. It is to be noted that the figure only suggests this conclusion, but does not prove it.

12. The data in figure 3 are based on exposure in youth or early adulthood. Comparable data for exposure during middle age or old age are not available.

13. It is known from clinical as well as laboratory evidence that partial-body exposure decreases the life-span much less than whole-body exposure (when the effects of roughly similar doses in rads are compared). There is a paucity of information, however, concerning the quantitative dependence of the life-span on (*a*) the region or organ irradiated and (*b*) the absorbed dose. The data from an experiment of this type are given in table IV.[6] More information of this kind is needed.

TABLE IV. DECREASE IN LIFE-SPAN—PARTIAL AND WHOLE-BODY X-RAY EXPOSURE COMPARED IN THE MOUSE[a]

| *Region exposed* | *Dose (rem)* | *Median survival time after exposure (days)* | *Significantly different from control ($P \leq .05$)* |
|---|---|---|---|
| Control | 0 | 676 | — |
| Entire animal | 530 | 582 | Yes |
| Entire chest | 720 | 646 | No |
| One-half chest | 570 | 654 | No |
| *and* caudal | 1140 | 591 | Yes |
| 2cm. of trunk | 1700 | 525 | Yes |

[a] Female mice, 170 days old when irradiated. With the doses employed there were no acute deaths. Data from reference 6.

*The experimental effect of chronic exposure on long-term survival*

14. The experimental literature on the shortening of life by chronic exposure to radiation, and its bearing on the maximum permissible dose for man, are discussed in the article by R. H. Mole,[7] presented in its entirety following paragraph 15. Among other details, the report considers whether a threshold dose exists below which the life-span is unaffected. The report finds the evidence equivocal. A significant conclusion might be established for animals if very great numbers of them were used in such experiments. The report points out, however, that even if such a conclusion were established, its application to the human case would require a theoretical basis to justify such an extrapolation. Such justification is lacking at present.

15. Of the experimental groups referred to in paragraph 14, two (mouse, guinea pig) that received less than 1 rem per week lived a greater total number of days than their respective controls. In a more recent experiment[8] with Sprague-Dawley male rats exposed throughout

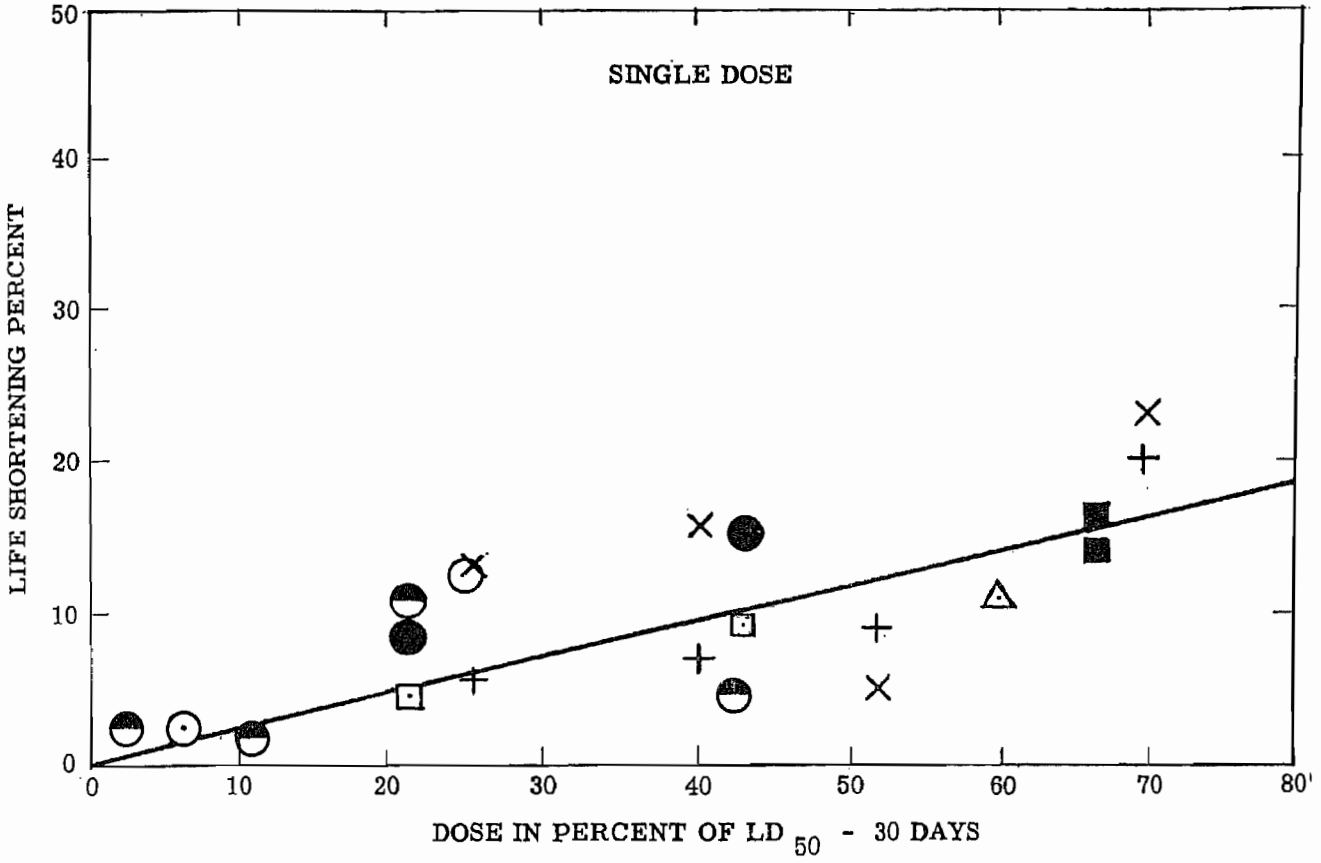



*Figure 3.* Life shortening (percentage) in mice and rats after a single, whole-body exposure to X- or gamma-rays. The dose is expressed as a percentage of the acute $LD_{50}$. The figure is taken from reference 5 where the original reports are listed.

adult life to 0.8 r/day of $Co^{60}$ gamma-rays, the median survival times were as follows:

| *Temperature of environment* | *Survival time (days)* | |
|---|---|---|
| | *Control* | *Irradiated* |
| 5° C..... | 240 | 305 |
| 25° C..... | 460 | 600 |

Although there were only twenty-two animals per group, the differences between the irradiated and control groups were consistent throughout the course of the experiment.

## Shortening of life by chronic irradiation: the experimental facts* by R. H. Mole

*Medical Research Council Radiobiological Research Unit*
*Atomic Energy Research Establishment*
*Harwell, Berks., England*

It is probably true to say that more is known of the biological effects of radiation than of any other environmental hazard except bacteria. Certainly the chronic toxicity of no chemical substance has been investigated as thoroughly as the chronic toxicity of whole-body irradiation by penetrating gamma-rays or fast neutrons. The incentive has been obvious: the very large industrial hazard during the war-time development of the atom bomb, and afterwards the increasingly widespread risk associated with the remarkable development of atomic energy as a source of industrial power and of a unique series of military weapons. Chronic toxicity experiments in the strict sense must cover the whole life-span of the experimental animal and thus take years to carry out, even with the relatively short-lived laboratory mouse. The results of war-time work in the United States have become generally accessible in the past few years[1-5] and work carried out in this laboratory is just beginning to be published.[6] A brief survey of the experimental results relating to shortening of the life-span may provide a few facts in a field of current general interest and perhaps raise the academic question of how the results of chronic toxicity experiments, as such, may be generalized—a question which needs an answer before they may be used to help solve the practical problem of setting safe limits to the environmental exposure of man to irradiation.

### *Experimental methods*

Daily irradiation has been given to animals in a variety of ways, for details of which the original reports should be consulted.[1-7] The more important experimental features are summarized in table I. There are two important differences between the experimental arrangements of Henshaw *et al.*[3] and Evans[2] on one hand, and those of Lorenz *et al.*[4] and of this laboratory on the other. In the first two sets of experiments, the animals had to be transferred individually each day from their living cages to the irradiation boxes and back again, and each daily dose of radiation was given in a few minutes. In the second two sets of experiments, the animals were irradiated in their living cages, undisturbed by additional handling with its accompanying traumatic effects, and the daily dose of radiation was spread over 8-24 hours. In general, the experimental animals were examined

*UN document A/AC.82/G/R.115; also published in Nature *180*, 456-460, 1957. For table I, figures 1 and 2, and bibliography referred to in this article, see immediately following the article.

daily and the time of death noted. Post-mortem examinations to determine tumour incidence and the cause of death were usually made, but the experimental reports differ very greatly in the detail with which these findings are given. For this reason, and since shortening of life-span is often considered the most sensitive experimental index of the toxicity of chronic irradiation, survival-time is the only experimental end-point considered here.

*Results and their interpretation*

By chronic irradiation is meant daily irradiation five, six or seven days a week at dose-levels which allow survival for at least six months. All the experiments on chronic irradiation for the duration of life which have ever been carried out, so far as is known, are referred to in table I and, where possible, shown in figure 1. The duration of life of an irradiated group of animals has been expressed as a proportion of its corresponding control and plotted against the weekly dose of radiation on a logarithmic scale. The results from this laboratory are shown in black symbols. They provide the first direct experimental comparison between gamma-rays and fast neutrons for chronic irradiation, where the dose of fast neutrons was measured in terms of energy absorbed in tissue. The relative biological efficiency factor for the fast neutrons used as compared with cobalt gamma-rays was 13.

This factor has been applied to the other two fast-neutron experiments, where the fast-neutron dose was measured in arbitrary units and where a somewhat uncertain conversion factor (table I) has to be used for estimating the tissue dose. In this way the results of all the experiments with fast neutrons as well as those with gamma-rays from other laboratories have been plotted, using open symbols, together with our own results in figure 1. The agreement, when mice were used as experimental animals, is remarkable, and suggests, in spite of the various uncertainties in the comparisons, that chronic irradiation shortens the life of mice in a reproducible manner.

It should be noted that there are eight experimental points at weekly doses of less than 10 r. or its equivalent in neutrons, and that the duration of life in none of these experimental groups was significantly different ($P \geq 0.05$) from its control.

The experimental results have been put down as they were obtained. More sophisticated analyses of some of these results have been made elsewhere.[1,5,6,9,10] The purpose of such analyses has usually been to find some regularity in the results which would allow extrapolations to daily doses smaller than, and to species other than, those used experimentally.

*Curve fitting*

Three curves have been fitted to the mouse data and are shown in figure 1.

(1) The straight line which provided the relative biological efficiency factor of 13 from our second experiment (Neary *et al.*, II, table I) is clearly a good fit to its results, and is also reasonably close to the only experimental group in our first experiment with a markedly decreased survival-time. The simplest interpretation of such a linear relation is that there is a threshold of between 1 and 2 r. daily below which no shortening of a mouse's life will be produced by daily irradiation. This may be considered confirmed by the repeated experimental failure to find a demonstrable shortening at weekly doses of less than 10 r. (see above). Considering the nature of the data, it would be difficult to have a clearer experimental demonstration of the existence of a threshold.

(2) The biologist, almost as a reflex, attempts to fit a Gaussian curve to quantitative data. Such a curve is shown as a dashed line in figure 1, and clearly fits all the experimental data very well. The meaning of the fit at weekly doses of less than 10 r., where none of the points differs significantly from the base line, is less clear.

(3) Boche (1946, 1954)[1] suggested that shortening of life-span was proportional to the total accumulated dose,

$$t - t_0 = kdt$$

where t and $t_0$ were the mean life-spans of irradiated and control animals, d was the daily dose of radiation and k was a constant. This curve ($k = -0.04$ for gamma-rays) is shown in figure 1 as a dotted line, which also fits all the experimental points very well.

Curves 1 and 2 are empirical; curve 3 has some claim to a theoretical basis, the idea that the bigger the total dose of radiation the bigger the effect, that is, the shorter the mean life-span. For daily exposures which kill in less than six months, however, the converse is found to be true.[4,9,11] This is not as paradoxical as it may seem once the importance of recovery processes is appreciated; but it makes data on the effects of high daily dose (on shortening of life by much more than 50 per cent) of little value in helping to decide which is the best of several curves, each purporting to describe the effect of low daily doses.

Curves 2 and 3 are clearly so close together that over the experimentally determined range they cannot be distinguished. (The possibility that this algebraic similarity has a much wider biological significance is being investigated.) Each curve appears to fit all the points better than the straight line of curve 1, but this may be a spurious consequence of experimental uncertainties. In two experiments the exact conversion factor from arbitrary units of fast neutrons to rads is unkown (see above) and factors numerically different from those used (table I) but just as plausible (see literature) would make the fit look less good. There seems to be no intrinsic reason why different mouse strains *should* behave identically and the curvilinear arrangement of the experimental points may merely reflect differences of strain and of dose.

Each of the second two formulations indicates that there is no absolute threshold for shortening of life by chronic irradiation. The apparent threshold suggested by curve 1 may be thought of either as an absolute or as an effective threshold, depending on whether shortening of life is considered in proportional or absolute terms. If time is necessary for the effects of daily irradiation to show themselves, and if this time is longer the lower the daily dose, then an effective threshold *must* be reached at a dose-level which takes longer than the life-span to produce its effect. If so, each species would be expected to have its own threshold, and the longer the natural life-span the lower this would be. The only relevant experimental data are those of Lorenz *et al.*[3] on chronic irradiation of guinea pigs and these are included in figure 1. The effect of 1.1 r daily was possibly greater than in mice (though still not significantly different from its control) and the apparent threshold possibly a little less. The difference in life-span between mice and guinea pigs is probably not large enough to decide the point, and in an event there are no confirmatory data for guinea pigs as there are for mice.

The data for guinea pigs do show that species differences occur. Boche[1] suggested on, admittedly tenuous evidence, that the constant k (curve 3) is $\alpha t_0$, where $\alpha$ is the same for all mammals. If this were true, the mouse data should not agree so well, since $t_0$ for the different mouse strains differed. If the mean mouse $t_0$ is 600 days, $\alpha = 7 \times 10^{-5}$ (rather different from Boche's own estimate), and this has been used to construct the theoretical curve for guinea pigs ($\alpha t_0 = -0.09$ curve 3, figure 1); the fit to the experimental points is poor.

*Nature of the experimental material*

In any event, too much should not be read into the results because of the nature of the experimental material. First, the results have all been expressed in terms of mean survival-times. This is really a rather unsatisfactory parameter to use, as may be seen from figure 2, which illustrates the shape of the mortality curve of normal control female CBA mice. The shape of the human mortality curve in the more materially advanced human civilizations is similar, but that of mice with a high spontaneous incidence of leukemia may be very different.[4,12] The mean survival-time and its statistics are markedly affected by the occasional early deaths and no great precision in mean survival-time can be expected. A small decrease in mean survival-time could occur either because of a small increase in the frequency of earlier deaths or because of a small reduction in life-span of the upper two quartiles. In fact, an analysis of cause of death in relation to duration of life is imperative in order to see whether irradiation decreases life-span by increasing the frequency of particular causes of death which kill earlier than the average, or merely by making all causes of death kill at an earlier age.[6]

Second, the nature of a chronic toxicity experiment usually, if not invariably, makes it impossible to randomize treatments and to ensure that the only difference between experimental groups is the treatment being investigated. For example, if animals are arranged at different distances from a source of radiation, the animals will occupy different parts of a room for their whole lives and it will be impossible to be sure that environmental temperature, humidity, degree of air movement and other relevant factors possibly not even thought of are exactly the same for each different dose-group. Thus the differences in, say, mean survival-time between different groups, will be due to the differences in radiation-level plus any other relevant environmental differences. This is not just a theoretical point. Differences of the order of 5 per cent in the mean survival-time of female CBA mice have been found during the past few years not only between different "lots" of controls but also between two sets of randomly chosen controls kept, so far as could be, in the same environment but some 20 feet away from each other.[6] The apparent increase in survival-time at the lowest daily dose used by Lorenz *et al.*[4] (figure 1) may well be due to the fact that the animals at this dose-level were kept without air conditioning in a different room from all the other groups, including the controls. Such variability is to be expected by the biologist, but it should also enjoy caution in extrapolation of the results of analysis of intrinsically inexact data.

Replication on a sufficiently large scale, though often completely impractical, could overcome this particular difficulty. In fact, however, replication is almost completely lacking from the experiments listed in table I. The logic of experimentation is that experiments are repeated and give the same result. Yet with the exception of a still unfinished investigation,[10] no one concerned with duration-of-life irradiation experiments has ever repeated his experiment even once—for which there are perhaps understandable reasons. The nearest to repetition so far has been the two experiments carried out in this laboratory,[6,13] where although the same mouse strain was used the radiation doses were different. From this point of view the value of figure 1 is to demonstrate that an experiment has been done, that is, that the same result has been obtained several times over.

Lastly, it should be pointed out that in all the experiments considered here irradiation has been for the duration of life. This may not be the most appropriate experiment to carry out. Recent,[6,14,15] as well as older,[4,16] evidence has shown that, in some circumstances at least, not all radiation is of equal value, the first of a series of daily doses having proportionately greater effects in shortening life and inducing leukemia than the later daily doses. This is presumably one aspect of the time factor; time is needed for the effects of irradiation to develop to the point where biological damage can be detected,[11,14,17] and/or the reactivity of the biological object may change with age.[11] But if the phenomenon is true of weekly doses of less than 50 r., which has not yet been demonstrated, formulae which give equal weight to each of a series of doses as Boche's, cannot be properly extrapolated. Further, if at relatively high daily doses much of the radiation is wasted, so far as producing an effect is concerned,[11] then an observed linearity of response against total dose (curve 3, figure 1) may imply a decreasing ability of radiation to harm as the daily dose decreased.

There has also been very little work yet on the problem of whether the effect of chronic irradiation is altered by changing the distribution in time of, say, a constant weekly dose. The data of table I and figure 1 suggest that it matters little whether a daily dose is given in a few minutes or spread out over many hours; but other as yet uncompleted observations[14,17] suggest that the delayed effects of irradiation may depend as much on the way the irradiation is given as on the total dose. In these experiments there was no wasted radiation: on the contrary, as much time as possible was allowed for the full development of any damage that radiation may have caused. Such experiments may give a relation between shortening of life and dose of radiation very different from those shown in figure 1, and indeed this might well be anticipated by anyone aware of the normal complexity of biological phenomena. Dose-response curves should not be extrapolated without fully realizing the nature of the experimental material on which they are founded.

*Possibilities of extrapolation*

It should first be emphasized how unusual it is to pay any attention to the ends of a biological dose-response curve. Normally, the aim of the biologist is to work in the middle ranges and, if irregularities appear at the ends, this is regarded as just to be expected, not necessarily deserving investigation.

The current maximum permissible level of radiation for occupational exposure of man, 0.3 r. weekly (Recommendations of the International Commission on Radiological Protection), is indicated in figure 1. Extrapolation suggests that this dose-level would shorten the lives of mice by nil, 0.02 or 0.2 per cent, depending on which of the three curves described earlier is taken to be

correct. As already shown, the experimental data on chronic irradiation at low doses are not sufficiently exact to distinguish between the curves, and the adequacy of fit at high levels of irradiation seems quite irrelevant. Thus the value of any attempt at extrapolation must depend on whether there is some theoretical reason for preferring one mathematical form to another. When this question is settled, there is the additional problem of extrapolating from one species to another.

One principle of selection often used nowadays in general discussion on radiation as it affects mankind, and at first sight self-evidently sound, is to take the most pessimistic assumption suggested by experiment or theory for the relation between dose and effect. Lorenz[8] used a very similar criterion when discussing the effects of daily irradiation on the difficult tissues and organs of different species. He concluded that man should be considered to be as sensitive as that species of animal found experimentally to be the most sensitive. Clearly this is no absolute criterion; as the range of species examined is widened, the apparent sensitivity of man must decrease. A consistent use of this criterion would involve denying the possibility of chemotherapy, or of selective killing by pesticides. It does not seem realistic to maximize pessimism as a means of choosing the best dose-response curve.

The most plausible reason for thinking that species differences among mammals in their reactions to irradiation are likely to be smaller than in their reactions to chemical agents is that the penetration of radiation into cells is not affected by the series of permeability barriers which every chemical agent has to pass before reaching the site of its action.[18] The uniformity of the acutely killing dose for all mammals gives supporting evidence. However, the chronic toxicity of radiation would be expected to depend on a balance between the continuing damage produced by the radiation and the ability of the irradiated animal to keep pace with the damage by repair. The ability to repair and its rate must depend on many of the structural and metabolic features which distinguish strains and species, and, for this reason, strain and species differences in the dose-response curves for chronic irradiation might be expected. Some of the experimental facts can best be understood in this way.[6]

An alternative view is to assume that the chronic toxicity of radiation is due to processes where repair of damage does not occur, like genetic mutation. It may then be plausibly argued that the genetic material of all mammals is very similar, both physically and chemically, and that therefore dose-response curves will in general be the same for all species. Such a view would suggest that damage should be proportional to total dose, as in Boche's formula (curve 3, figure 1), and would be consistent with the somatic mutation theory of carcinogenesis and the fact of carcinogenesis by ionizing radiation. But there are difficulties in the way of equating damage and total dose, as already suggested, and really very little evidence in support of the mutation theory of carcinogenesis. The theory is an easy one to accept; but even with the most recent advances in technique its testing seems almost impossible to envisage. However, in the experimental animal there is no simple relation between carcinogenesis and dose of radiation, and for mouse leukemia there is good evidence of the great importance of an indirect mechanism.[19] Moreover, the experimental evidence suggests that radiation shortens life apart from inducing cancer, and this is not easy to understand in terms of mutation.

If the results of animal experiments are to be carried over to man, there must either be very good evidence that all mammals behave alike, or sufficient human evidence of similarity with experimental animals to inspire confidence in the process of filling the human gaps from animal experience. It will at least be generally agreed that experimental dose-response relations which cannot satisfactorily account for all experimental results are scarcely worth applying to the human case. In the absence of a satisfactory theory, it seems pointless to expend the enormous experimental effort required to define the relation between daily dose and life-span for mean survival-times of 95 per cent and more of the control: it is only in this region that extrapolation to man is of any particular interest.

I would like to thank my colleagues for allowing me to make use of unpublished material.

TABLE I.

*Of preceding paper by R. H. Mole*

| *Reference* | *Source and type of irradiation G=Gamma rays N=fast neutrons* | | *Unit of dose (conversion factor to rads)* | *Details of irradiation exposure* | | *Symbol used in Fig. 1* | *Experimental animal* | | | | *Method of reporting survival-time* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Days/ week* | *Duration of daily dose* | | *Mouse strain* | *Age at start of irradiation (days)* | *Control life-span from start of irradiation (days)* | *No. of animals used* | |
| Henshaw *et al* (ref. 3)..... | $^{182}$Ta Graphite reactor | G N | r. r. (2.0) | 6 6 | minutes minutes | ▽ △ | $CF^1$ (females only) | ? | 440 | 820 | Median[a] |
| Evans (ref. 2)..... | Cyclotron | N | N (2.5) | 5 | minutes | □ | $CF^1$ Swiss | 28–42 | 420 475 | 500 | Median[b] |
| Lorenz *et al.* (ref. 4)..... | Radium | G | r. | 7 | 8 hr. | ○ | $LAF^1$ | 52–85 | 703 | 240 | Mean |
| Neary *et al.* I (ref. 6)..... | Graphite reactor | N | rad | 6–7 | 16–24 hr. | ■ | *CBA* | 75–95 | 780 | 500 | Mean[c] |
| Neary *et al.* II (ref. 13) ... | Graphite reactor | N | rad | 7 | 16–24 hr. | ▲ | *CBA* | 45–75 | 818 | 320 | Mean[c] |
| | $^{60}$Co | G | r. | 7 | 24 hr. | ● | *CBA* | | | | |
| Thompson *et al.* (ref. 16).. | $^{60}$Co | G | r. | 7 | 24 hr. | + | Rats (Sprague-Dawley, females only) | 90–120 | 585 | 42+ | Mean |
| Lorenz *et al* (ref. 4)..... | Radium | G | r. | 7 | 8 hr. | × | Guinea pigs (hybrid) | 137–196 | 1,372 | 112 | Mean |

[a] Mean survival times calculated from data provided by Hollaender and Stapleton (1948, personal communication) have been used in fig. 1.

[b] Mean survival-time of the two strains combined were also reported and have been used in fig. 1 because standard errors were also given. However, irradiation stopped when 8–30 per cent of an experimental group was still alive, so that the mean survival times include variable proportions of radiation-free time.

[c] There were real sex differences in control life-span and possibly also in the effects of irradiation. The data have been pooled to make them comparable with those of the other authors.

The data of Henshaw (ref. 7) have not been included because the mean life-span of his controls was less than a year. The data of Boche (ref. 1) have not been included for a variety of reasons: his monkeys had tuberculosis, his mice salmonellosis; the dogs and rabbits were irradiated in small numbers and irradiation stopped after two years, long before the end of the natural life-span; irradiation of the rats also ceased after two years when 16–36 per cent of the lower level and control groups were still alive and were killed, which prevents estimation of mean survival-times.

Evans's X-ray data (ref. 2) have not been included because mean survival-times were not given. The control life-span was not given by Hagen and Simmons (ref. 5). In each of Sacher's (ref. 5) and Mole's (ref. 11) experiments with daily X-irradiation of mice, one experimental group survived about seven months; they are omitted because no groups surviving longer are available and because the relative biological efficiency for X- to gamma-rays for chronic irradiation is not known.


BIBLIOGRAPHY FOR PRECEDING PAPER BY R. H. MOLE

1. Boche, R. D. (1946), cited by him in "Biological Effects of External Radiation" (edit. H. A. Blair), NNES VI-2 (McGraw-Hill, New York, 1954).
2. Evans, T. C., Nucleonics, *4*, 2 (1949).
3. Henshaw, P. S., Riley, E. F., and Stapleton, G. E., Radiology, *49*, 349 (1947).
4. Lorenz, E., Jacobson, L. O., Heston, W. E., Shimkin, M., Eschenbrenner, A. B., Deringer, Margaret K., Doniger, Jane, and Schweisthal, R., in "Biological Effects of External X- and Gamma-Radiation" (edit. R. E. Zirkle), NNES IV-22B (McGraw-Hill, New York, 1954).
5. Sacher, G., *J. Nat. Cancer Inst., 15*, 1125 (1955).
6. Neary, G. J., Munson, R. J., and Mole, R. H., "Chronic Irradiation of Mice by Fast Neutrons" (Pergamon Press, London, 1957). In the press.
7. Henshaw, P. S., J. Nat. Cancer Inst., *4*, 513 (1944).
8. Lorenz, E., in "Biological Effects of External X- and Gamma-Radiation" (edit. R. E. Zirkle, NNES IV-22B (McGraw-Hill, New York, 1954).
9. Blair, H. S., "Peaceful Uses of Atomic Energy", *11*, 118 (United Nations, New York, 1956).
10. Sacher, G., *Radiology*, 67, 250 (1956).
11. Mole, R. H., *J. Nat. Cancer Inst., 15*, 907 (1955).
12. Sampford, M. R., *Biometrics, 8*, 13 and 307 (1952).
13. Neary, G. J., Munson, R. J., Hulse, E. V., and Mole, R. H. (unpublished observations).
14. Mole, R. H., in "Progress in Radiobiology", edit. J. S. Mitchell, B. E. Holmes and C. L. Smith (Oliver and Boyd, Edinburgh, 1956).
15. Mole, R. H., *Brit. J. Radiology, 30*, 40 (1957).
16. Thompson, J. F., Tourtellotte, W. W., Carttar, M. S., Cox, R. S., Jr., and Wilson, J. E., *Amer. J. Roentgenology, 69*, 830 (1953).
17. Mole, R. H., Proc. VI Int. Haematology Congress, Boston (in the press).
18. Mole, R. H., *Brit. J. Radiology, 26*, 234 (1953).
19. Kaplan, H. S., Carnes, W. H., Brown, M. B., and Hirsch, B. B., *Cancer Research, 16*, 422 (1956).


## II. LIFE SHORTENING EFFECTS IN MAN

16. Data were examined relating to the mortality of medical specialists in order to learn if those exposed to X-rays had a shortened life-span. In one extensive analysis,[9] utilizing the mortality data for specialists 35-74 years of age who died during 1938-1942, the *mortality ratio* was calculated for each specialty. The mortality ratio is the ratio of the number of deaths observed to the number that specialty would experience if subject to the specific death rate calculated for all physicians. These mortality ratios are given in parentheses in the last column of table V. It is seen, first, that specialists have a lower mortality than physicians in general; the specialist mortality ratio is only 0.78. Secondly, the various specialties appear to have different mortality ratios, from 0.99 to 0.62.

17. The mortality ratios of the various specialties were recalculated,[10] using the death rate for all special-

ists instead of all physicians (table V). The ranking of the mortality ratios by this method agreed with that of paragraph 16. Eight specialties had mortality ratios greater than unity, but in no case was the difference statistically significant.

18. The extent to which repeated small exposures to X-rays shorten the life of man is a matter of speculation. In the past, radiologists were so exposed, but from the mortality statistics it cannot be demonstrated that the life-span of this group of medical specialists has been shortened relative to that of other medical specialists[11] although this has been suggested.[12] It is known, however, that the incidence of leukemia is increased in these men.

## III. Cancer in man

19. It is generally agreed that the incidence of cancer* in man can be increased by exposure to ionizing radiation. Quantitative data will be considered relating the incidence rate of cancer to radiation dose and to time after exposure. For introduction, the method of calculating the incidence rate and the influence of certain variables on it will be discussed briefly.

20. The prevalence of cancer may be defined as the number of cases per unit of population at a specified time, e.g. 15 cases per 10,000 on January 15.

21. The cancer incidence rate $R$ may be defined as the number of new cases per unit of time and population occurring during a specified interval of time, e.g., 5 per 10,000 per annum. Alternatively, it may be said that an estimate of the probability that an individual in the population will acquire a cancer equals 5/10,000 or $5 \times 10^{-4}$ per annum. $R$ is an important statistic in the calculations to be made below.

22. The total effect of exposing a population to radiation is estimated in terms of the total number of cases, $N_x$, induced per unit of population. If the rate after exposure is constant at $R$, and if prior to exposure it was constantly $R_o$, then $(R-R_o)$ is the number of extra

* Cancer is a generic term and, as used here, includes leukemia and all forms of so-called neoplastic or malignant disease.

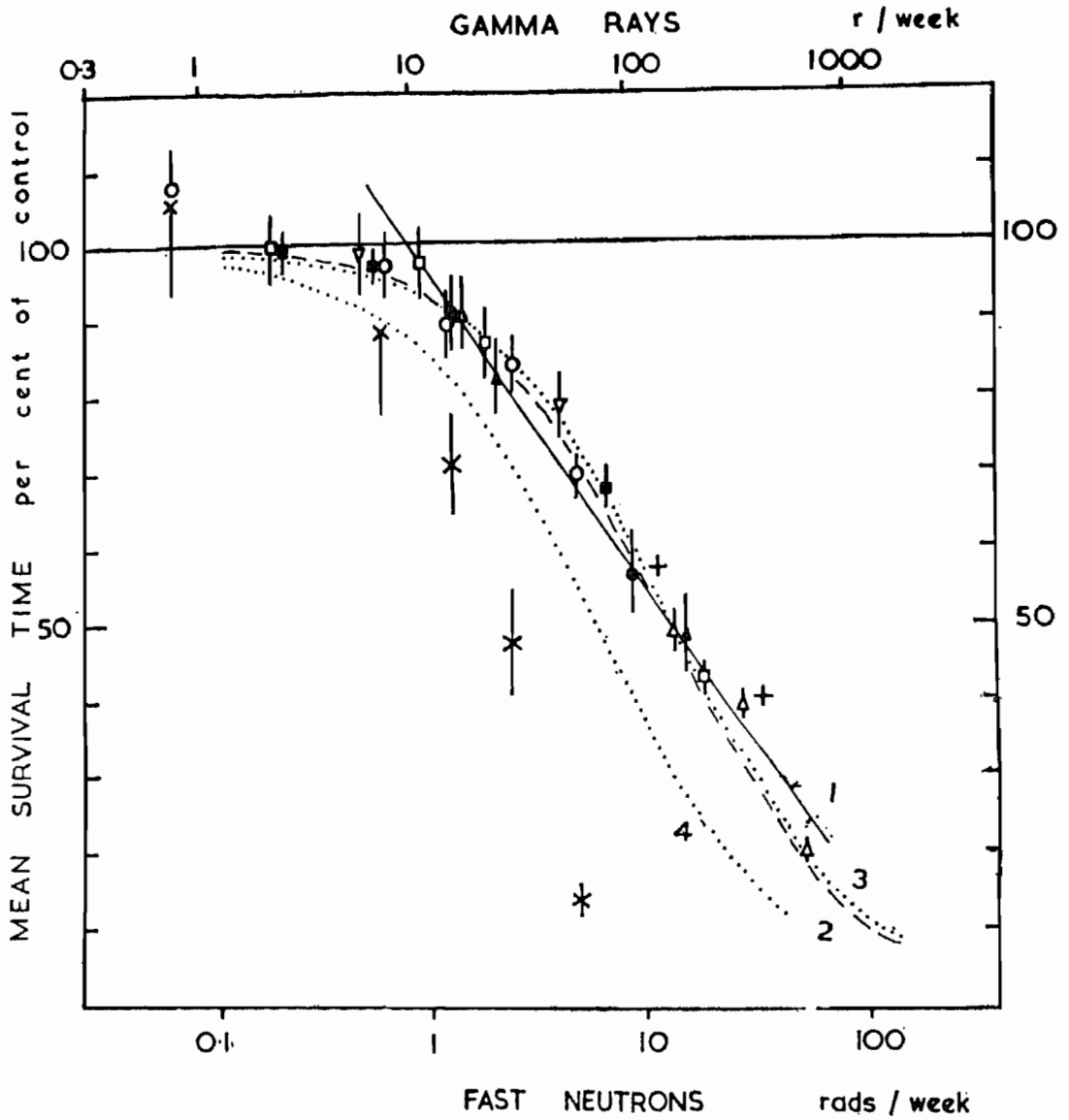



*Figure 1* (of preceding paper by R. H. Mole). Mean survival-time (per cent of control) and weekly dose of radiation (logarithmic scale).
The symbols are given in table 1. The curves are numbered as in the text, where they are discussed. The gamma and neutron scales are in the ratio 13:1 (see text).

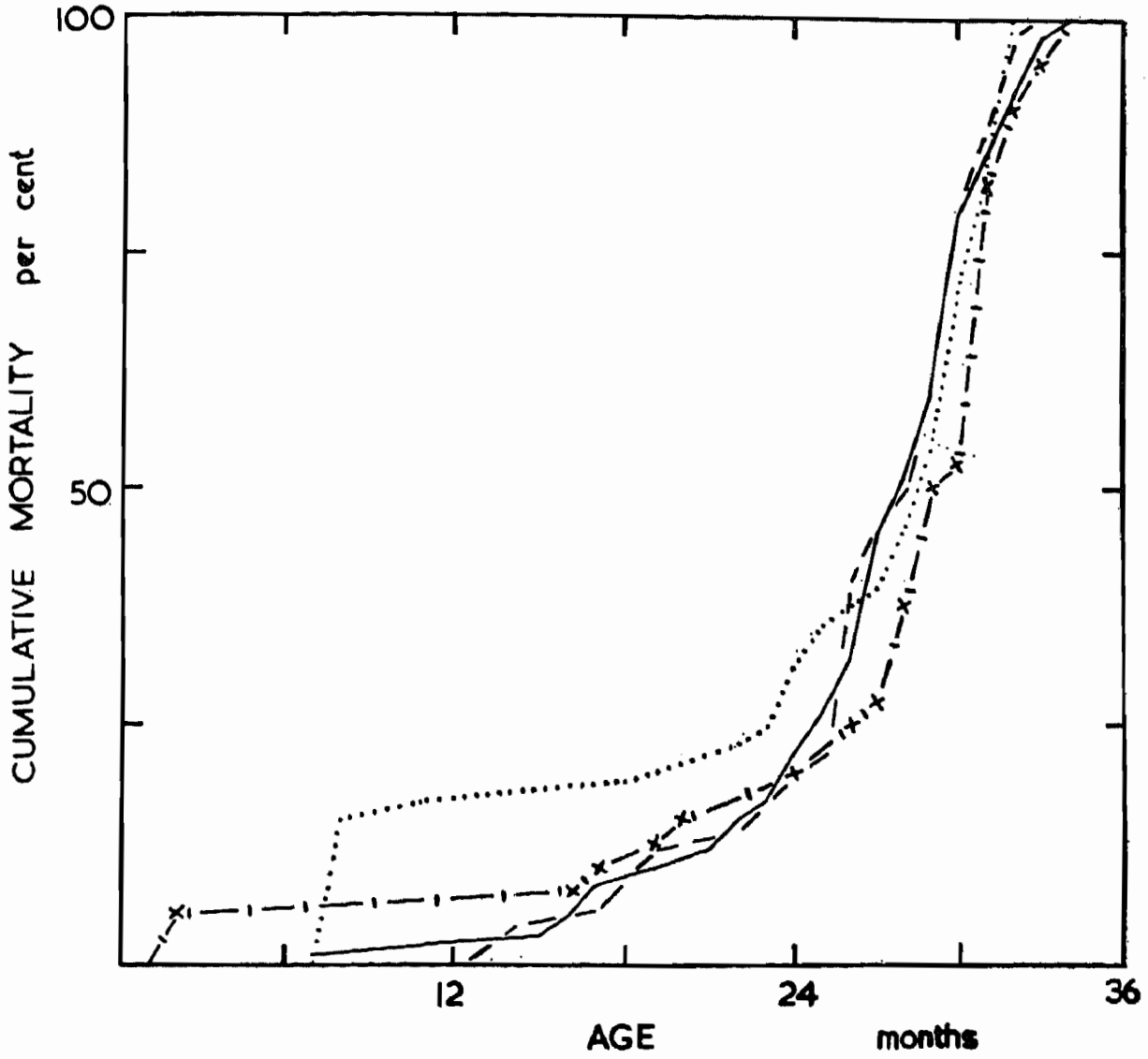



*Figure 2* (of preceding paper by R. H. Mole). Cumulative mortality of female CBA mice (four different control groups 1951-54). All times plotted from same starting age of 70 days.

TABLE V. MORTALITY RATIO (ALL CAUSES OF DEATH) FOR MEDICAL SPECIALISTS

| *Rank* | *Specialty* | *Observed deaths* | *Expected deaths* | *Mortality ratio*[a] |
|---|---|---|---|---|
| 1. | Tuberculosis | 43 | 34.2 | 1.26 (0.99) |
| 2. | Dermatology | 60 (58)[b] | 47.8 | 1.25 (0.98) |
| 3. | Roentgenology and radiology | 96 (91)[b] | 82.4 | 1.16 (0.90) |
| 4. | Anesthesiology | 17 | – | – (0.88) |
| 5. | Orthopedic surgery, proctology, urology and industrial surgery | 199 | 179.1 | 1.11 (0.86) |
| 6. | Neurology and psychiatry | 142 | 133.0 | 1.07 (0.83) |
| 7. | Public health | 99 | 94.3 | 1.05 (0.83) |
| 8. | Surgery | 360 | 346.7 | 1.04 (0.81) |
| 9. | Obstetrics and gynecology | 112 | 116.3 | 0.96 (0.75) |
| 10. | Eye, ear, nose and throat | 502 | 523.4 | 0.96 (0.75) |
| 11. | Internal medicine and pediatrics | 378 | 423.6 | 0.89 (0.69) |
| 12. | Pathology and bacteriology | 38 | 48.1 | 0.79 (0.62)[c] |
| | ALL | 2,046 | | 1.00 (0.78) |

[a] The ratio of (*observed deaths in a specialty at ages 25 to 74 years*) to (*expected deaths on the basis of age specific death rates for all specialists, 1938–1942*). The ratios were calculated from data made available by Dr. M. Spiegelman. The figures in parentheses are the published[9] mortality ratios for specialists based on the age specific death rates for all physicians (instead of all specialists) at ages 35 to 74 (2,046 deaths). Note that the ranking of the mortality ratios is the same for both methods of calculation.

[b] Omitting deaths from leukemia.

[c] Pathology only.

cases per unit of population per annum. In a period of $T$ years,

$$N_x = (R - R_0)T \qquad (1)$$

Although simple in principle, the use of equation (1) is somewhat difficult in practice. First, $R$ is not a constant, but varies with times. In general, exposure is followed by an initial period during which few if any radiation-induced cases occur. The duration of the initial period may be shorter after large doses than after smaller ones. Thereafter, depending on the particular cancer studied and the nature of the population, there will be a second period during which the vast majority of radiation-induced cases occur. This period might last for five years or for twenty-five. We are now only in the process of learning what the duration of such periods may be. Secondly, precise values of $R_0$ may not be available. In the case of some kinds of cancer there is some evidence that $R_0$ is changing relatively rapidly (e.g. leukemia). For these, it would be necessary to estimate the changes in $R_0$ as a function of time independently of the changes in $R$. Thirdly, the numbers of radiation-induced cases actually dealt with are very small, as will be seen below.

23. Having obtained a method for estimating $N_x$, it becomes feasible to investigate how $N_x$ depends on the dose of radiation, $D$. Is $N_x$, for example, a simple linear function of $D$, is it a non-linear function or is there a threshold dose below which radiation is without effect? Before attacking such a problem, it is important to note that the same dose may result from a single exposure, multiple exposures, or a long period of continuous exposure. Such differences in dosage may lead to major differences in the end results and therefore must be explicitly dealt with when making comparisons or extrapolations.

24. It is worth special note that the factor of time has entered the problem in more than one way. In equation (1) paragraph 22, there is the term $T$, often referred to as *period at risk*. In paragraph 23, the role of time in dosage is considered; this may be referred to as *period under exposure*. The period under exposure may last for only a minute and thus be an insignificant fraction of the years at risk. On the other hand, in the case of long-lived isotopes, for example, the period under exposure may be a matter of many years and thus partially or even completely overlap the period at risk.

25. Constitutional factors are known to influence the production of cancer in man. These include race, age, sex, nutrition and other environmental and genetic influences. All of these factors have to be taken into account in discussing the production of cancer in man through exposure to ionizing radiation, especially when comparing the effects in one group with those in another.

26. The total of all human data that can be used for the quantitative analysis of cancer-induction by radiation is meagre. For example, only sixty-eight cases of leukemia are involved in the Hiroshima data of table VII. It is important that full use be made of such data while at the same time recognizing and giving due weight to their limitations. In the case of the calculations, extrapolations and applications that follow, the reader is urged to note the simplifying assumptions that may have entered into the analyses, especially in regard to the following items:

(a) *Absorbed dose.* In what organ is the absorbed dose to be determined? If the dose is not uniform throughout the organ, how shall it be averaged or otherwise expressed? Should the integral absorbed dose be considered?

(b) *Temporal factors.* What allowance, if any, should be made for multiple or continuous exposure? Is each successive year at risk of equal significance?

(c) *Constitutional factors.* What is the nature of the irradiated population with respect to age, general health, genetic constitution, etc.?

(d) *Dose-effect curve.* Is there a threshold? Is the effect a linear or some other function of dose? Can a factor be determined that will relate $N_x$ to $D$?

### *Leukemia in man*

27. Demographic data relating the incidence of leukemia to radiation exposure come from four population groups whose exposures were either a hazard of war or profession, or were incurred during diagnostic and therapeutic medical procedures.

### *Atom bomb survivors in Hiroshima*

28. The most recent information on the incidence of leukemia in the Japanese survivors of the 1945 atomic bomb is given in a report which is reproduced in paragraph 33 below. From the condensed summary in table VI of the Hiroshima data, it is seen that the incidence of leukemia in the population exposed at 0-1,499 metres from the hypocentre has been twenty times greater than in the population exposed at 1,500 metres and beyond. Thus at the end of 1957, $N$ (0-1,499 m.) = 5570; $N$ (> 1,499 m.) = 280. $N$ is the total number of cases per million persons present at the time of the explosion. Taking the cases at 1,500 metres and beyond as a crude estimate of the natural incidence of leukemia, the number of cases $N_x$ due to radiation may be estimated as 5,570 — 280 = 5,290, or in round numbers 5,300 per million.

TABLE VI. LEUKEMIA IN SURVIVORS AT HIROSHIMA, 1948–1957[a]

| | | *Number of cases*[b] | |
|---|---|---|---|
| | | *Distance (metres) from hypocentre* | |
| *Period of onset* | *Total* | *0–1,499* | *1,500 and beyond* |
| 1948–49 | 12 | 8 | 4 |
| 1950–51 | 20 | 18 | 2 |
| 1952–53 | 23 | 16 | 7 |
| 1954–55 | 14 | 9 | 5 |
| 1956–57 | 11 | 5 | 6 |
| TOTAL: 1948–57 | 80 | 56 | 24 |
| N (cases per $10^6$) | 835 | 5,570 | 280 |
| R (average of cases per year per $10^6$) | 84 | 557 | 28 |

[a] Data from reference 13. The full report from which these and the data of table VII were taken is given below.

[b] 10,051 persons were exposed at 0–1,499 metres; 85,768 were exposed at 1,500 metres and beyond.

29. The data in table VI indicate that the biennial rate of leukemia in the heavily exposed population reached its maximum in 1950-1951 and has been declining since then. If this tendency continues, practically all cases of radiation-induced leukemia probably will have occurred by 1960, within fifteen years of exposure, so that at lease 80 per cent of them may be said to have occurred already, within ten years of exposure. In these circumstances, the annual rate of leukemia taken by itself is not

TABLE VII. LEUKEMIA INCIDENCE FOR 1950–57 AFTER EXPOSURE AT HIROSHIMA[a]

| Zone | Distance from hypocentre (metres) | Dose (rem) | Persons exposed | L (Cases of leukemia) | $\sqrt{L}$ | N[b] (total cases per $10^6$) | $N_x$ (Radiation-induced cases per $10^6$) | $N_x$/rem | $P_L$ ($N_x/10^6$/year/rem) |
|---|---|---|---|---|---|---|---|---|---|
| A | under 1,000 | 1,300 | 1,241 | 15 | 3.9 | 12,087 ± 3,143 | 11,814 | 9.1 | $1.14 \times 10^{-6}$ |
| B | 1,000–1,499 | 500 | 8,810 | 33 | 5.7 | 3,746 ± 647 | 3,473 | 6.9 | $0.86 \times 10^{-6}$ |
| C | 1,500–1,999 | 50[c] | 20,113 | 8 | 2.8 | 398 ± 139 | 125 | 2.5 | $0.31 \times 10^{-6}$ |
| D | 2,000–2,999 | 2 | 32,692 | 3 | 1.7 | 92 ± 52 | −181 | −90 | $-11 \times 10^{-6}$ |
| E | over 3,000 | 0 | 32,963 | 9 | 3.0 | 273 ± 91 | Control | — | — |

[a] Based on data in reference 13. Prior to 1950 the number of cases may be understated rather seriously.

[b] The standard error is taken as $N(\sqrt{V}\,L/L)$.

[c] It has been noted [15, 16] that almost all cases of leukemia in this zone occurred in patients who had severe radiation complaints, indicating that their doses were greater than 50 rem.

a good index of the total radiation effect; it is the total number of case $N_x$ that should be employed as such a measure.

30. Considering the exposed population by itself, the segment that was closer to the hypocentre has had the greater incidence of leukemia. However, the quantitative relation between *leukemia incidence in Hiroshima* and *radiation dose* is not yet known. Before such a relation can be formulated it will be necessary to have better estimates of the *absorbed dose in rem* than have been available hitherto. The estimates must be made both for the various dose zones in which the population was distributed, and, also, for every individual case of leukemia, taking into account both its position within the zone and the shielding immediately around it. Such work is under way.

31. None the less, using such data as were available, estimates have been made of the potency of this bomb radiation in causing leukemia.[14] The exposed populations of Hiroshima and Nagasaki were considered to have been exposed in a number of zones for each of which a mean dose was assumed. The extra probability of leukemia occurring in an exposed person per rem and per year elapsed after exposure was then calculated for the population of each zone:

$$P_L = \frac{\text{average extra number of new cases per year (1948–1955)}}{\text{number of persons exposed} \times \text{dose (rem)}}$$

In zones A (1,300 rem), B (500 rem), and C (50 rem), the values of $P_L$ were calculated to be 0.9, 0.7, and $0.7 \times 10^{-6}$, respectively. This finding was taken to support the suggestion that the extra leukemia incidence is directly proportional to radiation dose, and conversely, to argue against the existence of a threshold for leukemia induction.

32. $P_L$ might be used in estimating $N_x$, the total number of extra cases of leukemia that follow a dose of radiation. The average value of $P_L$ in paragraph 31 is $0.8 \times 10^{-6}$ based on statistics for the years in which the leukemia rate is considered to be maximal. Taking 15 years to be the entire period of leukemia production (period at risk), the total number of cases (per individual exposed per rem) $= 15 \times 0.8 \times 10^{-6} = 12 \times 10^{-6}$. On this basis if each of a million persons receives 1 rem, a total of 12 extra cases of leukemia will eventually develop.

33. It is of interest to apply the above method to the latest data on leukemia incidence in Hiroshima, using the same zoning system and estimates of dose (table VII). Contrary to previous findings, the present findings indicate that $P_L$ decreases markedly as the dose falls, that therefore leukemia incidence is not a linear function of dose, and that a threshold for leukemia induction might occur. In fact, according to table VII a dose of 2 rem is associated with a decreased leukemia rate. It is to be emphasized again, however, that the estimates of dose employed in the present and previous analyses are much too uncertain to permit drawing conclusions relative to the vital points in question. The calculations are made only to illustrate how variable the results may be when inadequate data are utilized.

## LEUKEMIA IN HIROSHIMA CITY ATOMIC BOMB SURVIVORS* by

NIEL WALD†

*Atomic Bomb Casualty Commission*
*Hiroshima, Japan*

It has become generally accepted that an increased incidence of leukemia follows the acute or chronic exposure of various experimental animals and of man to ionizing radiation.[1] Recently an attempt has been made to establish a quantitative relation between the probability of radiation-induced leukemia and the unit-dose of radiation received, on the basis of data from studies of various groups of radiation-exposed human beings.[2]

The survivors of the atomic bombings in Hiroshima and Nagasaki, Japan, comprise two such groups. Reports concerning the occurrence of leukemia in these populations over a period through June 1956 have been published at intervals by various staff members[3] of the Atomic Bomb Casualty Commission.[4] In addition, an unpublished compilation of certain specific detailed information requested by the British Medical Research Council was prepared in September 1955.[5] An analysis of these data appeared in a publication of the Medical Research Council[6] and a portion was also published in a report of the National Research Council.[7]

Since that time a review has been made of all the leukemia cases known to the Atomic Bomb Casualty Commission, and a master list has been compiled. Some of the cases on the September 1955 listing have been dropped for various reasons, and many cases have been added. No detailed official report has been published recently in the hope that more adequate dosimetry data might become available. This wish is nearing fulfilment because of the joint initiation of a large programme of

* Science *127*, 699-700, 1958, for table 1 and bibliography referred to in this article, see immediately following the article.

† Present address: University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pa.

dosimetry studies in 1955 by the Atomic Bomb Casualty Commission and a group of interested organizations including the Atomic Energy Commission's Division of Biology and Medicine, the National Academy of Sciences — National Research Council, the U.S. Air Force School of Aviation Medicine, Los Alamos Scientific Laboratory, and Oak Ridge National Laboratory. The programme is designed to make possible the assignment of a specific neutron or gamma ray dose or both in rads to the record of each survivor in the Atomic Bomb Casualty Commission's files for whom sufficient pertinent information is available.

A detailed interim report on leukemia in the Hiroshima atomic bomb survivors is presently being prepared by various staff members of the Atomic Bomb Casualty Commission and the National Research Council. It will include the best currently available dosimetry information resulting from the afore-mentioned collaborative effort. However, because of the present interest in data pertinent to radiation leukemogenesis and the desirability of making available current information obtained by the Atomic Bomb Casualty Commission, table I, summarizing results of the leukemia survey in Hiroshima as of December 1957, is presented at this time.

Certain limitations of these data should be pointed out. The programme was initiated in 1947 but the present level of intensity of effort was not achieved until about 1950. Therefore, while it may be assumed that the numbers of cases shown for the years 1950 through 1956 are fairly accurate, the numbers that arose in the preceding years may be understated rather seriously. With respect to 1957, it is probable that additional cases remain to be discovered with onset in that year.

The denominators of the incidence rates are estimates, subject to errors of presently unknown magnitude. The 3 June 1953 Residential Census of Hiroshima was conducted by the Hiroshima Census Bureau and was presumably of a reasonable degree of accuracy. The categorization by distance from the hypocentre was made on the basis of Atomic Bomb Casualty Commission investigations of 50.8 per cent of the males and 44.6 per cent of the females who reported themselves exposed to the bomb. However, it was found that 3.1 per cent of those reportedly exposed were in fact not in the city at the exact time of the bombing.

Apart from the uncertainties regarding the population on 3 June 1953, it may be incorrect to assume that migration in and out of the city during the period from 1950 to the present was the same for persons exposed in different distance categories. However, despite the current lack of pertinent information, the simple expedient of multiplying the June 1953 population values by eight to obtain estimates of person-years at risk has been adopted since the census date is roughly near the midpoint of the interval under study. This procedure seems reasonable at present, although the magnitude of any resultant error is hard to estimate.

In addition to the above-mentioned points, which have to do with the intrinsic accuracy of the data presented, a further caution should be strongly emphasized. The uncertainties involved in inferring radiation dose from distance alone are too large to support conclusions beyond the previously reported qualitative one that those survivors who received large doses of radiation—that is, who were within 1,500 metres of the hypocentre, had a significantly higher incidence of leukemia than those beyond that distance, who received relatively little or none.[3] The relationship of incidence to distance as presented in table I cannot be given a more quantitative interpretation because there are too many variables, as yet unresolved, which cannot be ignored.

TABLE I.
*Of preceding paper by Niel Wald*
LEUKEMIA IN HIROSHIMA ATOMIC BOMB SURVIVORS WHO WERE RESIDENTS OF HIROSHIMA CITY AT THE TIME OF DIAGNOSIS (DIAGNOSES VERIFIED BY THE ATOMIC BOMB CASUALTY COMMISSION)

| *Year of Onset* | *Total* | *Distance from hypocentre (metres)* | | | | |
|---|---|---|---|---|---|---|
| | | *Under 1,000* | *1,000–1,499* | *1,500–1,999* | *2,000–2,999* | *Over 3,000* |
| 1945 | | | | | | |
| 1946 | | | | | | |
| 1947 | 3 | | 1 | | 2 | |
| 1948 | 7 | 2 | 4 | | 1 | |
| 1949 | 5 | 1 | 1 | 1 | 1 | 1 |
| 1950 | 9 | 3 | 5 | | | 1 |
| 1951 | 11 | 3 | 7 | 1 | | |
| 1952 | 11 | 3 | 5 | 1 | | 2 |
| 1953 | 12 | 2 | 6 | 2 | 1 | 1 |
| 1954 | 6 | 2 | 2 | 1 | 1 | |
| 1955 | 8 | 1 | 4 | 2 | | 1 |
| 1956 | 6 | | 1 | 1 | 1 | 3 |
| 1957 | 5 | 1 | 3 | | | 1 |
| TOTAL | 83 | 18 | 39 | 9 | 7 | 10 |
| Estimated population[a] | 95,819 | 1,241 | 8,810 | 20,113 | 32,692 | 32,963 |
| Number of cases with onset in 1950–1957 | 68 | 15 | 33 | 8 | 3 | 9 |
| Estimated person-years at risk | 766,552 | 9,928 | 70,480 | 160,904 | 261,536 | 263,704 |
| Annual incidence of leukemia per 100,000 | 8.9 | 151.1 | 46.8 | 5.0 | 1.1 | 3.4 |

[a] Based on Hiroshima Census Bureau's Daytime Population Census of Hiroshima City, 3, June 1953.

For example, the presently available estimates of the air dose in Hiroshima have a large uncertainty, the magnitude of which is itself not yet definite. Also, experimental dosimetry studies at Oak Ridge National Laboratory emphasize the need for detailed information, such as is being collected by the Atomic Bomb Casualty Commission, concerning the shielding situation of any particular survivor at any distance. It is conceivable that the radiation received within a light frame house (the most common shielding situation) may vary from an amount almost equalling the outside air dose to one equal to the outside air dose attenuated by perhaps a factor of two, depending on the position of the person in the house.

In determining the relationship of radiation exposure to the incidence of leukemia, such detailed data must be examined not only for each leukemic survivor, but also for enough of the population at risk to permit calculation of statistically significant incidence rates. Until this information becomes available from the dosimetry programme, it is premature to attempt precise quantitation of dose-effect relationships in radiation leukemogenesis on the basis of the Hiroshima and Nagasaki radiation-populations.[8]


BIBLIOGRAPHY FOR PRECEDING PAPER BY NIEL WALD

1. J. Furth and E. Lorenz, *Radiation Biology* (McGraw-Hill, New York, 1954), vol. 1, pt. 2.
2. E. B. Lewis, *Science 125,* 965 (1957).
3. J. H. Folley, W. Borges, T. Yamawaki, *Am. J. Med. 13,* 311 (1952); R. D. Lange, W. C. Moloney, T. Yamawaki, *Blood 9,* 574 (1954); W. C. Moloney, and M. A. Kastenbaum, *Science 121,* 308 (1955); N. Wald, *Acta Haematol. Jap. 20,* 152 (1957); N. Wald *et al.,* "Proc. Intern. Soc. Hematol., 6th Intern. Congr. Boston, 1956" (Grune and Stratton, New York, in press).
4. The Atomic Bomb Casualty Commission is a field agency of the National Academy of Sciences—National Research Council, operated with funds supplied by the U.S. Atomic Energy Commission.
5. "Listing of Leukaemia Cases in Hiroshima and Nagasaki" (Atomic Bomb Casualty Commission, Hiroshima, Japan, Sept. 1955).
6. "The Hazards to Man of Nuclear and Allied Radiations" (*Med. Research Council (Brit.) Cmd. 9780*) (H. M. Stationery Office, London, 1956), appendix A.
7. "Report of the Committee on Pathologic Effects of Atomic Radiation" *Natl. Acad. Sci.—Natl. Research Council, Publ. No. 452* (Washington, D.C., 1956). appendix I.
8. Grateful acknowledgement is made for the biostatistical assistance of Mr. Seymour Jablon, National Research Council, and also for the aid of Dr. Lowell Woodbury, head of the Biostatistics Department of the Atomic Bomb Casualty Commission, and his staff. Appreciation is also expressed for the help of Dr. Robert M. Heyssel, who provided the hematological data for 1957, and for the co-operation of the physicians of both the Atomic Bomb Casualty Commission and the city of Hiroshima, who make the long-term Hiroshima leukaemia study possible.


*Leukemia in radiologists*

34. The most recent estimate of the leukemia death rate for United States radiologists (ages 35 to 74 years) is based on the data of 1938-1952, inclusive.[14] During this period there were 17 deaths, corresponding to an average annual rate of 610 per million. The rate observed in the population at large (corrected for age distribution) was 121 per million.

*Leukemia in children*

35. Two reports have associated leukemia in children with previous X-ray exposure during infancy or the prenatal period. In the first,[17] a study was made of 1,700 United States children treated during infancy for a condition known as enlargement of the thymus gland. The untreated siblings of the irradiated children served as controls. There were 17 cases of cancer, including 7 of leukemia in the irradiated group; there were 5 cases of cancer, but none of leukemia in the control group (tables VIII and IX).

TABLE VIII. EXPECTED AND OBSERVED RATES FOR CANCER[a]

| | *Treated children* | | *Untreated siblings* | |
|---|---|---|---|---|
| | *Expected* | *Observed* | *Expected* | *Observed* |
| All cancers | 2.6 | 17 (?19) | 2.7 | 5 |
| Leukemia | .6 | 7 (? 8) | .6 | 0 |
| Thyroid cancer | .08 | 6 | .08 | 0 |

[a] Data from reference 17.

TABLE IX. DISTRIBUTION OF NEOPLASIA ACCORDING TO AMOUNT OF RADIATION[a]

| | *Under 200 r.* | *Over 200 r.* | *Unknown* |
|---|---|---|---|
| Number treated | 604 | 804 | 313 |
| Cases of leukemia | 2 | 5 | (?1) |
| Other cancers | 0 | 4 | 0 |
| Carcinoma of thyroid | 0 | 6 | 0 |
| Adenoma of thyroid | 0 | 6 | 3 |

[a] Data from reference 17.

36. In a British study[18] of the history of 547 mothers whose children had died before the age of ten from leukemia and other cancers, it was found that 85 of the mothers (15.5 per cent) reported that they had had diagnostic abdominal radiography involving the foetus during the relevant pregnancy. In a comparison series of 547 mothers with healthy and living children only 45 (8.3 per cent) reported radiologic exposure during the relevant pregnancy (table X).

TABLE X. LEUKEMIA AND CANCER INCIDENCE IN OFFSPRING RELATED TO X-RAY EXAMINATIONS IN THEIR MOTHERS DURING THE RELEVANT PREGNANCY[a]

| *Type of cancer in child* | *Number of cases* | *Number of mothers and foetuses exposed to* | |
|---|---|---|---|
| | | *Abdominal examination* | *Examination of other parts of body* |
| 1. Leukemia | 269 | 42 | 25 |
| Controls (living) | 269 | 24 | 23 |
| 2. Other cancers | 278 | 43 | 33 |
| Controls (living) | 278 | 21 | 32 |
| 3. Total cancer | 547 | 85 | 58 |
| Total control | 547 | 45 | 55 |

[a] Data from reference 18.

37. The suggestion has been made that a proportion of the leukemias and cancers in the first group, namely

7.2 per cent, may have been caused by the exposure during intrauterine life of the patients in question. However, radiological examination of other parts of the body was not correlated with increased cancer incidence.

38. The data indicate a correlation between leukemia and other cancers in childhood and irradiation of the foetus, although alternative possibilities cannot be excluded. It is possible that some mothers who give birth to leukemic children might be in greater need for diagnostic X-ray service during pregnancy and that in the present cases leukemia or cancer may have resulted independently of exposure sustained during intrauterine life.

39. In any event, the clinical indications for the X-ray examinations of the mothers of these particular children are not known, nor is information available on the types of examinations performed and on the actual doses of X-ray received by the mothers and the foetuses. Additional data and final evaluations of their significance are known to be in course of publication (British Medical Journal).

*Leukemia after X-ray therapy for ankylosing spondylitis*

40. A dependence of the incidence of leukemia on radiation exposure has been demonstrated in a study of 13,352 cases of ankylosing spondylitis treated during 1935-1954 at 82 radiotherapy centres in Great Britain.[19] In this series, 28 patients were certified to have died of leukemia and 12 of aplastic anemia, as of 31 December 1955. The numbers of expected deaths were 2.9 for leukemia and 0.3 for aplastic anemia. (The over-all death rate per million persons for leukemia in England and Wales has been as follows: 21 in 1935, 34 in 1945, 49 in 1954). A thorough study of the series led to the following tabulation of cases with blood disease:

| *Group* | *Males* | *Females* |
|---|---|---|
| Leukemia (A) | 35 | 1 |
| Probable leukemia (B) | 5 | 0 |
| Aplastic anemia | 4 | 0 |
| Undecided | 2 | 2 |

41. To study the distribution of cytological types, all available cases of leukemia in patients with ankylosing spondylitis, both treated and untreated were tabulated:

| | *X-ray treated series* per cent | *Untreated series* per cent |
|---|---|---|
| Lymphatic leukemia | 3 (8) | 3 (38) |
| Myeloid leukemia | 31 (78) | 4 (50) |
| Monocytic leukemia | 6 (15) | 1 (13) |
| Type unspecified | 9 | 0 |

There is a relative deficiency of the lymphatic type of leukemia among the X-ray treated cases, and the difference between the two series was found to be just significant ($P = 0.05$).

42. Only male cases of leukemia and "probable leukemia" (groups A and B) were available in adequate numbers for further statistical analysis. After a single course of treatment, the evidence of 10 cases indicated that leukemia occurred within 5 years. When all cases were considered, i.e. those receiving multiple courses over a period of years as well as those receiving a single course in a month or so, it was noted that leukemia was diagnosed within 5 years of the last treatment in 35 of 37 cases.

43. The radiological treatment of ankylosing spondylitis usually consisted of irradiating the spine and the region of the sacroiliac joints. In some cases other regions were also treated. Most (7,215) of the patients in the present series received only one course of treatment, but some (1,119) received as many as four courses over a period of years. Preparatory to examining the relation between leukemia incidence and radiation dose elaborate studies were made so that for each course of treatment in each case there could be determined:

(*a*) *The spinal dose:* the mean dose to the spinal marrow, based on the average of 3 points (upper sacral, mid-dorsal, mid-cervical).

(*b*) *The integral dose:* the integral dose to the whole body.

The distribution of doses in the entire population of 11,287 men was estimated from the doses of a randomly drawn sample of 1,878 men. The dose of each leukemia case was determined individually. For multiple courses of treatment due allowance was made for the years at risk at each dose level. Dose-classes were then established (e.g., 250—499 rem, 500—749 rem), and the crude incidence of leukemia determined in each class. In addition, the standardized incidence of leukemia was determined, i.e., the incidence standardized for age.

44. In studying the dose-effect relationship, the following assumptions were made:

(*a*) The significant parameter of dose is the mean dose to the spinal marrow. (The spinal marrow was always irradiated; the amount of irradiated extra-spinal marrow was variable.)

(*b*) There is an absolute waiting period of one year after exposure during which no cases occur. Thereafter, each year at risk has equal weight. (The authors considered this to be an over-simplification, but used it as a practical method of dealing with the many cases that had received multiple courses of treatment).

(*c*) Fractionation of dose did not diminish its effectiveness.

(*d*) The probability of inducing leukemia is directly proportional to the number of man-years at risk. The number of man-years at risk equals the product of (number of individuals given a particular dose) × (mean years since exposure—1).

(*e*) Constitutional factors may predetermine a greater radiosensitivity in this population, but no allowance can be made for it.

45. Results from these studies are summarized in table XI and figure 4. It is clear that the incidence of

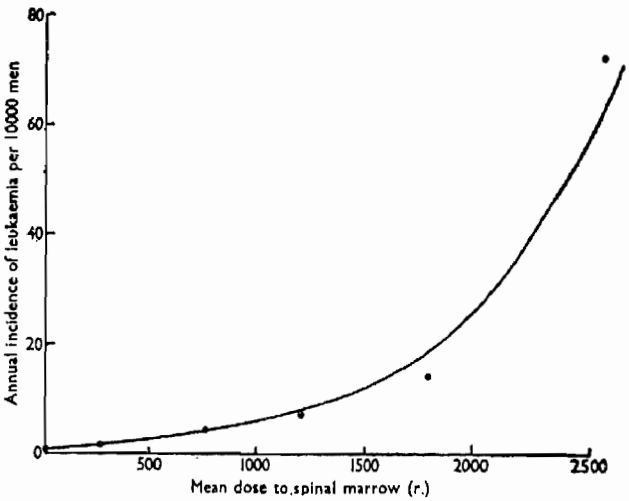



*Figure 4.* The incidence of leukemia, standardized for age, in relation to the mean dose of radiation to the spinal marrow: all male patients in the study series and 'A' and 'B' cases of leukemia, excluding co-existent cases. (Figure 4 is Figure 1 in the original reference 19.)

leukemia increases with radiation dose and that the relation between them is not linear. The curve through the points in figure 4 is drawn to reach the control rate at zero dose without indicating a threshold for the induction of leukemia. It should be noted, however, that only one case of leukemia received a dose of less than 400 rem and that this case had lymphatic leukemia and had had large doses of extra-spinal irradiation. Therefore the course of the curve between this dose and zero must be regarded as practically undetermined. The slope of the curve between 750 and 1,250 rem appears to be relatively constant and is equal to about 0.6 new cases per year per $10^6$ men per rem to spinal marrow.

46. The data for the limited group of patients that received irradiation to the spinal axis only are given in table XII. In this group, 18 patients developed leukemia. Analysis of these data[20] suggested a threshold of 54 rem by one method and of 130 rem by another. These estimates, however, are subject to great uncertainty owing to the small number of cases in the series and the lack of data for the range in question. Statistical analysis indicated that the threshold might lie anywhere between 0 and 460 rem. The slope of the dose-effect curve was about the same as that given in paragraph 45.

*Theoretical considerations for estimation of radiation hazards*

47. The quantitative statement of a radiation hazard involves the precise relation between the total number of radiation-induced cases $N_x$ and the radiation dose $D$, throughout an extended range of dosage. At present, such a statement cannot be satisfactorily made for any kind of human cancer. For certain purposes, however, a very crude estimate may be better than none at all and two methods have been proposed with this end in mind.

48. The first method assumes (1) that *all* cancer is caused by ionizing radiation and (2) that the annual cancer rate is directly proportional to the annual radiation dose. The total cancer incidence rate $R$ in the United States, for instance, is now about 2,800 cases per annum per million population. The annual background radiation dose rate is about 0.1 rem, and the dose rate from other sources is perhaps another 0.1 rem. The average annual dose rate per individual is thus about 0.2 rem. The potency factor $k$ is, therefore,

$$k = \frac{2800}{0.2} = 14 \times 10^3, \qquad (2)$$

i.e., 1 rem will produce a total of 14,000 new cancer cases when a population of one million has been exposed. Such a figure appears to be absurdly large. It has been suggested that such a calculation applies only to certain kinds of cancer but not to others. There appears to be no scientific basis for such a selection, however.

TABLE XI.[a] THE NUMBERS OF PATIENTS WHO DEVELOPED LEUKEMIA, AND THE CRUDE AND STANDARDIZED INCIDENCE RATES: AFTER DIFFERENT MEAN DOSES OF THERAPEUTIC RADIATION TO THE SPINAL MARROW: MALE 'A' AND 'B' CASES, EXCLUDING CO-EXISTENT CASES

| | *Mean dose to spinal marrow (r.)* | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *0*[b] | *Less than 250* | *250–499* | *500–749* | *750–999* | *1,000–1,249* | *1,250–1,499* | *1,500–1,749* | *1,750–1,999* | *2,000–2,249* | *2,250–2,499* | *2,500–2,749* | *2,750 or more* | *All doses* |
| *No. of men developing leukemia* | | | | | | | | | | | | | | |
| 'A' cases | — | 1 | 2 | 6 | 3 | 7 | 2 | 3 | 1 | 2 | 3 | 1 | 1 | 32 |
| 'A' and 'B' cases | — | 1 | 3 | 6 | 4 | 8 | 3 | 3 | 1 | 2 | 4 | 1 | 1 | 37 |
| *Crude incidence per* 10,000 *men per year* | | | | | | | | | | | | | | |
| 'A' and 'B' cases | 0·49 | 2·16 | | 4·59 | | 6·99 | | 12·18 | | | | 63·65 | | 5·98 |
| *Standardized incidence per* 10,000 *men per year* | | | | | | | | | | | | | | |
| 'A' and 'B' cases | 0·49 | 1·98 | | 4·66 | | 7·21 | | 14·44 | | | | 72·16 | | 5·98 |

[a] This table was table 19 in the original reference.[19]

[b] The rate given for 'zero' therapeutic dose is the corresponding rate among men of the same age-distribution and observed over the same period, calculated from the mortality from leukemia experienced by the whole male population of Britain.

TABLE XII.[a] THE INCIDENCE OF LEUKEMIA AFTER DIFFERENT MEAN DOSES OF THERAPEUTIC RADIATION TO THE SPINAL MARROW: MALE 'A' AND 'B' CASES GIVEN ONLY SPINAL IRRADIATION, EXCLUDING CO-EXISTENT CASES

| | *Mean dose to spinal marrow (r.)* | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *0* | *Less than 250* | *250–499* | *500–749* | *750–999* | *1,000–1,249* | *1,250–1,499* | *1,500–1,749* | *1,750–1,999* | *2,000 or more*[b] | *All doses* |
| No. of man-years at risk following exposure to dose | — | 5,404 | 7,673 | 6,573 | 8,262 | 7,411 | 2,782 | 897 | 566 | 679 | 40,247 |
| *No. of men developing leukemia* | | | | | | | | | | | |
| 'A' cases | — | 0 | 2 | 4 | 3 | 4 | 0 | 2 | 1 | 1 | 17 |
| 'A' and 'B' cases | — | 0 | 2 | 4 | 3 | 5 | 0 | 2 | 1 | 1 | 18 |
| *Crude incidence per 10,000 men per year* | | | | | | | | | | | |
| 'A' and 'B' cases | 0·49 | 1·53 | | 4·72 | | 6·75[c] | | 8·12[d] | | | 4·47 |
| *Standardized incidence per 10,000 men per year* | | | | | | | | | | | |
| 'A' and 'B' cases | 0·49 | 1·44 | | 4·83 | | 6·82[c] | | 8·70[d] | | | 4·47 |

[a] This table was table 20 in the original reference.[19]

[b] Average dose, 2,290 r.

[c] For the group receiving 1,000–1,499 r. the crude incidence is 4·91; standardized incidence 5·06.
For the group receiving 1,000–1,749 r. the crude incidence is 6·31; standardized incidence 6·82.

[d] For the group receiving 1,500 r. or more the crude incidence is 18·68; standardized incidence 19·86.
For the group receiving 1,750 r. or more the crude incidence is 16·07; standardized incidence 16·82.

49. The second method uses the results of the British study of leukemia incidence in a radiation-treated population, discussed above. (The data for Hiroshima have not been used owing to the uncertain dosimetry.) To compensate for the paucity of data, a number of assumptions are made in the following analysis:

(*a*) The significant parameter of dose is the mean dose to the entire red marrow. In uniform whole-body exposure, the doses to the entire red marrow and the spinal marrow are the same. When only the spinal marrow is irradiated, the mean dose to the entire red marrow is probably about 40 per cent of the spinal dose.

(*b*) The total number of years at risk is 15, and each year has equal weight. This assumption was arrived at from the following considerations. The mean period of observation in the British study was 5 years; this would set a lower limit for all types of cases. Those 10 cases of leukemia that received only one course of treatment all occurred within 5 years of that treatment. For the population exposed at Hiroshima the cancer rate began falling after 8 years, and a complete period at risk of 15 years has been suggested. The maximum duration of the period at risk cannot be greater than the duration of life after exposure. In the case of a population of children, this could be 65 years, in the case of the usual mixed population, the average would be about 35 years.

(*c*) Fractionation or protraction of dose does not diminish its effectiveness.

(*d*) Constitutional factors may be neglected.

(*e*) Cancer production is a linear function of radiation dose. Linearity has been assumed primarily for purposes of simplicity. In the case of the British data for doses below 1,300 rem, a linear relation provides a fairly accurate fit.

(*f*) There may or may not be a threshold dose. The two possibilities of threshold and no-threshold have been retained because of the very great differences they engender.

50. The potency factor $k$, equal to $N_x/D$, can now be calculated. For a single exposure of the entire red marrow to 1 rem, the average annual leukemia rate is estimated to be 1.5 cases per million persons exposed. If the total number of years at risk is assumed to be 15, $k$ is equal to $1.5 \times 15$, or approximately 20 cases per million exposed per rem. These calculations are based on observations following single large exposures. However, under conditions of prolonged exposure at lower dose rates, the period of risk may be longer. In the calculations of chapters V and VII where a *maximum* estimate is wanted, the period at risk is assumed to equal the average remaining life-time of the exposed population (35 years). The value of $k$ has therefore been taken as 52 cases per million per rem in the calculations in paragraph 128 of annex D and in paragraph 61 of chapter V of this report.

51. The use of $k$ to predict the number of cases of leukemia depends on the magnitude of the threshold. If there is no threshold, $N_x$ is equal to the product of $k$, $D$, and the number of persons exposed. If a threshold is assumed, there will be no cases in persons who have received less than that dose.

52. Besides the alternative possibilities of a linear relation with or without a threshold, it is possible that a non-linear relationship may exist, as has been found, for example, in the case of many chromosome abnormalities.[21] As noted in paragraph 45 and illustrated in figure 4, the incidence of leukemia in the British study was a curvilinear function of dose, not a linear one. A curve providing a good fit to these data is obtained when leukemia incidence is considered to be proportional to the square of the radiation dose. In general, curves of this type predict a finite incidence of leukemia at small doses. However, this incidence may be very much lower than that predicted by a linear function based on all of the same data.

53. The methods used above to estimate the risk of leukemia after radiation exposure are of general use. They may be applied both to other cancers and also to non-cancerous lesions such as occur in the eye (cataract), the skin and in the bones. Their use is contingent upon the availability of adequate statistical estimates of the incidence of the disease in question related to the radiation doses received by the population at risk. It may be noted that such methods do not depend on detailed knowledge of how the radiation induces the lesion within the cell, e.g. by somatic mutation or some other alleged or hypothetical mechanism. At present, adequate statistical data are not available for bone tumours or for tumours of other organs to make such estimates of risk. However, it is known that pertinent studies are under way for bone tumours in man that are caused by radioactive substances.

## References


1. Bond, V., and J. S. Robertson, Annual Review of Nuclear Science *7*, 135-162, 1957.
2. Knowlton, N. P., and L. H. Hempelmann, Journal of Cellular and Comparative Physiology *33*, 73, 1949.
3. Conard, R. A., Radiation Research *5*, 167-188, 1956.
   De Bruyn, P. P. H., and M. M. Tornova-Svehlik, Radiation Research *6*, 573-584, 1957.
   Kallman, R. F., and H. I. Kohn, Radiation Research *3*, 77-87, 1955.
   Kohn, H. I., and R. F. Kallman, British Journal of Radiology *27*, 586-591, 1954.
   Patt, H. M., M. E. Blackford, and R. L. Straube, Proceedings of the Society for Experimental Biology and Medicine *80*, 92-97, 1952.
   Oakberg, E. F., Radiation Research *2*, 369-391, 1955.
   Trowell, O. A., Journal of Pathology and Bacteriology *64*, 687-704, 1952.
   Schrek, R., Radiology *46*, 395-410, 1946.
   Storer, J. B., P. S. Harris, J. E. Furchner, and W. H. Langham, Radiation Research *6*, 188-288, 1957.
   Patt, H. M., Annals of the New York Academy of Sciences *59*, Art. 4, 649-664, 1955.
4. Kohn, H. I. and R. F. Kallman, Radiation Research *7*, 85-97, 1957.
5. Blair, H. A., Collected data pertaining to shortening of life span by ionizing radiation, available as University of Rochester Report UR-442, 1956. See also: Blair, H. A., Proc. Internat. Conf. Peaceful Uses of Atomic Energy *11*, 118-120. United Nations 1956.
6. Communicated by R. F. Kallman and H. I. Kohn, 1958.
7. Mole, R. H., UN document A/AC.82/G/R.115. Also published in Nature *180*, 456-460, 1957.
8. Carlson, L. D., W. J. Scheyer, and B. H. Jackson, Radiation Research *7*, 190-197, 1957.

9. Dublin, L. I., and M. Spiegelman, Journal of the American Medical Association *137*, 1519-1524, 1948.
0. Communicated by G. A. Sacher, 1957.
1. Seltser, R., and P. E. Sartwell, Journal of the American Medical Association *166*, 585-587, 1958.
2. Warren, S., Journal of the American Medical Association *162*, 464-468, 1956.
3. Wald, N., Science *127*, 699-700, 1958.
4. Lewis, E. B., Science *125*, 965-972, 1957.
5. Hempelmann, L. H., in Hearings before the special subcommittee on radiation of the joint committee on atomic energy, Congress of the United States, Part 1; 989, 1957. UN document A/AC.82/G/R.130.
16. Pathologic Effects of Atomic Radiation. Report of the Committee of the National Academy of Sciences National Research Council, Washington, D. C., 1956. Appendix I, pp. 1-13. Un document A/AC.-82/G/R.11.
17. Simpson, C. L., and L. H. Hempelmann, Cancer *10*, 42-56, 1957.
18. Stewart, A., J. Webb, D. Giles and D. Hewitt, Lancet *ii*, 447, 1956.
19. Court-Brown, W. M., and R. Doll, Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis, Medical Research Council, Special Report Series No. 295. London, H.M.S.O., 1957, See also UN document A/AC.82/G/R.105.
20. Court-Brown, W. M., and R. Doll, Lancet *4*, Jan. 1958.
21. Lea, D. E., Actions of radiations on living cells, Cambridge University Press, 1946.

## Annex H

# THE GENETIC EFFECTS OF RADIATION

TABLE OF CONTENTS


*Paragraphs*

I. MUTATION ..... 1

1. THE MECHANICS OF MUTATION

The gene ..... 1
Gene mutations ..... 2
Chromosome breaks ..... 4
The hereditary material ..... 6
Linearity of dose-mutation curve ..... 10
Mechanism of mutation ..... 12
Other possibilities of interference between irradiation and its effects at the cellular level ..... 14
Comparison between natural and radiation-induced mutations 16
Detection of mutation ..... 19

2. MUTATION RATES

Natural mutation rates ..... 23
Natural mutation rates in man ..... 29
Radiation-induced mutation rates ..... 39
Radiation-induced mutation rates in man ..... 46

3. THE REPRESENTATIVE DOUBLING DOSE ..... 62

Estimates of the representative doubling dose for human genes ..... 63

4. ESTIMATES OF TOTAL RATE OF RADIATION-INDUCED MUTATIONS IN THE GENOME OF MAN ..... 74

II. THE GENETIC CONSEQUENCES OF IRRADIATION

1. THE CONNEXION BETWEEN MUTATION AND GENETIC DAMAGE: SELECTION ..... 75

2. APPROACHES TO QUANTITATIVE ASSESSMENT OF THE GENETIC CONSEQUENCES OF IRRADIATION OF HUMAN POPULATIONS.... 80

3. THE CURRENT SOCIAL BURDEN OF GENETIC ORIGIN IN HUMAN POPULATIONS, ITS CONNEXION WITH MUTATION AND RADIATION EXPOSURE ..... 87
Specific traits ..... 88
Biometrical characters ..... 95
Fertility ..... 104
Pool of recessive mutants..... 106

*Table*

I. Measured or calculated values of natural mutation rates in man
II. Measured or calculated values of natural mutation rates at single loci of organisms other than man
III. Measured or calculated values of total natural mutation rates for classes of loci in organisms other than man
IV. Rates of radiation-induced mutations at single loci in organisms other than man
V. Total rates of radiation-induced mutations in classes of loci in organisms other than man
VI. Surveys of human populations for purposes of radiation genetics
VII. Content of DNA in various types of cells
VIII. Calculated doubling doses in organisms other than man
IX. Comparison of approaches to quantitative assessment of mutational damage
X. Some over-all estimates of social burden

XI. List of specific traits, with estimated incidences: Category I

(*a*) Autosomal dominant traits

(*b*) Autosomal recessive traits

(*c*) Sex-linked recessive traits

(*d*) Summary of traits of Category I

XII. List of specific traits, with estimated incidence: Category II

XIII. List of specific traits, with estimated incidences: Category III

XIV. Dominant conditions identified in the Northern Ireland population but not included in Categories I and II for the reasons stated

XV. Classes of biometrical character

REFERENCES

APPENDIX

Table XVI. Calculated consequences of changes in the parameters governing birth-weight distribution

# I. MUTATION

## 1. The mechanics of mutation

### *The gene*

1. The conventional concept of the gene has been that of a functional hereditary unit. In recent years this concept has required a more precise definition, since sensitive tests of allelism have indicated that a single functional gene may be separable into component elements by recombination and so shown to be capable of many pseudoallelic differences.[1,2] Single mutational events which modify or prevent the action of the functional unit may affect different large or small parts of this unit.[3] During the same period, it is notable that features of the genetics of natural populations have indicated the extent to which individual functional genes can be involved in larger complexes and lack complete autonomy.[4] Possibly the most striking manifestation of this is at present in *Salmonella typhimurium,* in which it appears possible that there are integrated linear sequences of adjacent gene-structures responsible for whole sequences of biochemical operations, assembly-line fashion.[5]

### *Gene mutations*

2. Take in its widest sense, mutation means any change of the genetical constitution not due to recombination, ranging from whole genomes to alleles. Often mutation is used in a more restricted sense, viz. as change of the action of some specific gene. This is commonly referred to as point mutation, which, however, may be a misleading term, as it is known, especially from the work on *Drosophila* by Dubinin and others,[6,7] that a change of the position of a gene may change its habit of action. Moreover, the idea of a point mutation, as distinct from a deletion or rearrangement, was formerly based upon the smallest unit of structure microscopically visible. Because recent structural analysis of the gene has seemed to penetrate almost as far as the much smaller ultimate units of its physico-chemical structure, believed to be the single nucleotides, it has already been suggested that the term "point mutation" be reserved for mutational events involving only one such unit.[8] Such ideas do not by themselves affect the distinction between intragenic and intergenic mutations[9] and may, indeed, clarify these; for example, it remains possible that further investigations of genes and chromosomes[10] will lead to a distinction between a structural backbone and separate attached genes. There is no doubt that advances in this field will eventually add greatly to the refinement of current ideas concerning all aspects of mutation.

3. In man, the primary genetic concern is with all transmissible hereditary changes which simulate the change to a new allele. These are perhaps best grouped together under the term "apparent gene mutations", whatever their structural nature. However, other forms of genetic damage require consideration in connexion both with somatic effects and with the requirement that mutations must survive transmission through the germ cells if they are to be observed. These latter forms include both gene mutations and chromosome structural changes in somatic cells, which may well have a sensitivity to the radiation-induced process quite similar to that of germ line cells.[10a] Mutations and chromosome changes in these cells could bring about consequences, recognizable for the organism as serious somatic effects, ranging from death or incapacity of cells fulfiling vital specialized functions to unrestricted proliferation.

### *Chromosome breaks*

4. It remains a major question to what extent chromosomal or other genetic effects may be responsible for cell death or damage in somatic or germinal tissues of man.[11] Visible chromosomal alterations resulting from irradiation have been studied in cytologically favourable material, principally of plants and of insects. They commonly arise through one or more chromosome breaks in the cell rejoining in some new configuration. A frequent result is dominant lethality through loss of substantial chromosome parts or interference with cell division. In spite of the difficulties of objective numerical scoring of cytological phenomena, many quantitative investigations have been made upon them:[12] it has been shown that the more densely ionizing radiations are relatively more effective in producing them[12,13] and that the numbers observed or recovered can be considerably affected by various post-irradiation treatments if these are applied sufficiently early.[12,14] In this way, recent work has suggested that there are some breaks at ionic bindings, which reheal very rapidly, and others at co-valent bonds, which heal more slowly,[14] as well as two separate effects of radiation, one in causing the breaks and the other in affecting the rejoining mechanism.[14] The effects of oxygen, both at the time of irradiation and during the subsequent rejoining process, have played an important and controversial part in this advance.[15] It would be of interest to learn to what extent investigation of post-irradiation modifiers of the rejoining process showed biochemical relationships parallel to those observed with modifiers of the cell lethality induced by irradiation.

5. Many investigations have connected ploidy with radiation resistance in unicellular organisms, especially the extensive work of Mortimer and his colleagues on yeast;[16] and this, together with the increased RBE of the more densely ionizing radiations, has led to the idea that much radiation-induced cell lethality has its origin in dominant genetic changes. Certain cases are, however, known in which this is not true; instead, lethality results from an imbalance or block in metabolism (as in very heavily irradiated Habrobacon eggs,[17]) or a generalized failure of the mitotic process hardly to be ascribed to individual processes of the break-rejoin type. On the basis of a two-hit killing curve for mammalian tissue culture cells of various ploidies, Puck has recently argued that radiation-induced death in these is chromosomal in origin;[18,19a] cytological evidence will perhaps be required before such a conclusion can be considered as finally established. However, the reduction in growth rate observed by Puck *et al.* in colonies derived from diploid mammalian tissue culture cells which had survived X-irradiation already provides *prima facie* evidence that even at doses of the order of 100 r, most surviving cells have suffered dominant deleterious changes.[18,19a] Moreover, Bender has recently demonstrated a rather high sensitivity of tissue culture cells derived from human kidney to chromatid breaks induced by X-rays.[19]

### *The hereditary material*

6. Recent years have remarkably advanced the knowledge of genetic material and of the role played in it by desoxyribonucleic acid (DNA). Indirect evidence from

different sources has long led cellular physiologists to believe that DNA, in close association with protein, forms part of genes and chromosomes; this has included the relative DNA content of haploid and diploid cells of various tissues of an organism,[20] cytochemical evidence, including the almost complete restriction of the presence of DNA to the cell nucleus and the association of DNA synthesis with cell division.[21] More recently, a very close association has been demonstrated between the assimilation of radioactive tracers incorporated in DNA, and chromosome division.[10] In addition, other evidence has inclined many geneticists to believe that DNA may be the actual material whose configuration constitutes genetic information; this evidence includes:

(*a*) The transformation of hereditary characters of cells of *Pneumococcus*[22] and *Haemophilus*[24] bacteria by application of solutions of pure DNA.

(*b*) The role played by DNA in the growth and heredity of the coliphages of the T series.[25,26]

(*c*) Indications from current work that increased mutation in microbial systems occurs under conditions of deficiency for an essential constituent of DNA such as thymine, or in presence of a competitive analogue of a constituent, such as bromouracil.[27]

All such phenomena carry the promise of new lines of investigation of the mechanisms of gene mutation.

7. Concurrent investigations have remarkably advanced understanding of the chemistry and structure of DNA, particularly the X-ray diffraction studies of Wilkins *et al.*[28] and the complementary biochemical relationships uncovered by Chargaff and others,[29] leading to the remarkable double helical structure proposed by Crick and Watson,[30] so suggestive of the exact replicative process required for the transmission of hereditary characters, and already so productive of fresh ideas concerning the mechanics of mutation.

8. While none of these arguments is alone conclusive, and while it is recognized that the genetic material of cells of higher organisms is organized into very substantial stainable structures, which must be more complex physically and chemically than the fine DNA fibrils visible only under the electron microscope,[21] nonetheless very many geneticists believe that the ultimate carrier of genetic information is likely to be the arrangement of nucleotides in DNA.

9. In that event, total radiation-induced mutation rates, in the widest sense of change of the hereditary information, might be expected to be quantitatively correlated with the DNA content of the cells of the germ plasm together with the biochemical operations which construct and maintain DNA. It at least seems reasonable that when comparisons of mutation rates between different species or physiological conditions are made, parallel DNA comparisons should be kept in mind. The DNA contents of some relevant types of cell are listed in table VII. Most kinds of cell nuclei contain enough DNA to form a structural molecule of great length which could only be packed inside the nucleus by much folding. This has given rise to the recent suggestion, now appearing on purely structural grounds, that the chromosome may consist of a multi-stranded structure.[10] If the structure turned out to be, say, a proteinaceous backbone with attached DNA molecules as side arms forming the genes (a possibility which is not excluded), the distinction between inter- and intragenic mutations could eventually come to have a very real physical basis, and the two kinds of mutation could differ in mechanisms.

### *Linearity of dose-mutation curve*

10. The experimental justification for speaking of radiation-induced mutation rates at low doses rests upon *Drosophila* data, in which the linearity of the dose-mutation curve, when it is investigated under sufficiently rigorous conditions, has been confirmed down to X-ray doses of 25 rad for irradiation of spermatozoa by the painstaking work of Stern and his collaborators,[31-33] following earlier experimenters.[34-36] Muller[37] has recently argued cogently that there is no point in pressing the test of linearity below 5 rad, and has indicated that this limit could be reached in *Drosophila* by techniques at present available. Many geneticists would agree with the implication of the cited passage, that linearity can already be safely accepted, without the enormous labour involved in its extension to still lower doses—at least in the absence of a definite proposed basis for expecting a non-linearity. However, it must be borne in mind that linearity has not been tested in this range of doses for spermatogonial irradiation. In the case of irradiation of these cells it is still difficult to conceive *a priori* of a non-linearity at low dose, followed by a linear portion of the curve at medium or high exposures. However, Oakberg[38] has shown that some classes of spermatogonial cells of the mouse are very sensitive to the lethal effects of low doses (5 rad — 100 rad) of gamma-radiation. If these same classes were to turn out also to be unusually sensitive to the induction of mutations by radiation, the curve of recovered mutations as a function of dose might turn out to be linear in the range of moderate doses, but to have considerably higher slope in the very low dose range where an appreciable proportion of the cells surviving irradiation belonged to the sensitive group.

11. The Committee has been informed of current experiments upon mice which will enable the linearity of the dose-mutation curve for irradiation of spermatogonia, oögonia and oöcytes to be checked down to 37.5 rad.[39] Attention must, however, again be drawn to the dependence of the whole quantitative assessment of genetic effects of low doses upon an assumed linearity and for irradiation of a particular type of cell in a dose-range not experimentally investigated.

### *Mechanism of mutation*

12. Many attempts have been made to affect the process of induced mutation after its initiation by exposure to ionizing radiation. Some of these have been successful to a greater or lesser degree,[40-44] and this fact is of cardinal importance as demonstrating at least the possibility of interference between the irradiation and its principal genetic consequence. Unfortunately, in many of these cases the precise genetic nature of the mutational event is not known; association with chromosome breakage or rejoining may therefore be suspected. Moreover, many of the experiments refer to microbial material, in which it is possible that the gene structures are far more exposed and more easily able to be reached and affected by external agents than are the mammalian chromosomes. Nevertheless, it is a hopeful sign that recent experiments reported to the Committee have extended the demonstration of post-irradiation interference to a well-known class of apparent gene mutations, the sex-linked recessive lethals of *Drosophila*.[45] These experiments seem to show that a finite interval of at least some tens

of minutes exists in *Drosophila* before "fixation" of radiation-induced mutations.

13. In connexion with any possibility of ultimate practical use of chemical or other modifiers of induced mutations, it is well to remember that, in many populations, the largest man-made exposures of the gonads occur through comparatively large doses delivered relatively infrequently in the course of medical work at controlled times. The possibilities of modifying the mutational effects of radiation should be considered in the light of the more general discussion of modifiers of radiation effects in chapter IV and annex F of this report.

*Other possibilities of interference between irradiation and its effects at the cellular level*

14. Interference with and control of genetic consequences of irradiation does not end with the completion of the mutational process. However, to look further requires that the completed mutations be detectable. The number of conditions in which carriers of unexpressed deleterious genes can be detected has recently increased greatly;[46,47] this trend is closely associated with advances in general biochemical and immunological genetics, and it is to be hoped that Governments will foster and encourage its progress. A second field closely related to this and other aspects of the present subject is that of human chromosomal cytology. We are indeed a long way removed from the beautiful situation which prevails in *Diptera* where giant salivary gland chromosomes can be studied in minute detail; nevertheless recent technical advances in the field have been considerable[48,49] and can give us great hopes of progress. Such advances may bring about radical changes in human genetics and especially human radiation genetics.

15. Other radical possibilities for dealing with radiation-induced mutation, besides the cumbersome and often painful process of selection, beyond question exist. An example which must be considered, in the light of technological advance, is that of the natural or controlled transfer of genetic characters. This phenomenon is well-established in microbial materials,[50] although usually but not always with very low frequency,[51] and as an eventual aid in the elimination of harmful genes or their consequences it cannot be entirely dismissed as speculation.

*Comparison between natural and radiation-induced mutations*

16. There has been a widespread belief among geneticists, based largely upon the classical work of Stadler in corn[52] that radiation produces in general a different type of mutant allele from those which occur naturally—more extreme, less likely to be reversible, more frequently a loss of function. However, Stadler's work may not be entirely typical even of plant material.[188] Muller has recently reviewed the evidence against existence of such a distinction.[9] Certainly, both the mechanism of production and the distribution among loci of radiation-induced and natural mutations differ;[53] there is also some indication of small differences in the proportions of mutation to the different alleles at a single locus.[54] Minute one-hit deletions do occur under the action of radiation,[55] and some radiation-induced point mutations in *Drosophila* may be associated with breaks or structural changes near them.[56] Moreover, evidence in *Drosophila* is against any appreciable correlation between natural mutation rate and radiation-induced mutability where either individual genes,[57] strains,[58] or physiological conditions[59] result in altered natural rates. Very little correlation is also found between radiation-induced mutability and the natural rate in the sample of thirty biochemical back-mutations examined by Glover.[58] However, the wide variations in the ratio of radiation-induced to natural mutability found both in the work of Glover on bacteria and in extensive work on plants[60] do not seem to be correlated with the type or severity of the forward or back-mutation involved, and it is generally accepted that the ratio of visibles to lethals is much the same for natural and radiation-induced mutations in *Drosophila*, although no explicit study of this point has been made. Moreover, a very detailed investigation by Giles[61] of purple-adenine and other mutants in *Neurospora* has shown no evidence for a qualitative or quantitative difference between radiation-induced and spontaneous mutations at the same locus. The evidence of Stadler primarily relates to the compound *A* locus; consequently, a possible explanation is that *A* has a very low sensitivity to radiation-induced point mutation. It is therefore reasonable to accept as a tentative assumption that spontaneous and radiation-induced mutations are qualitatively similar; wide differences in the two mutation processes exist but are functions of individual loci, and are not appreciably correlated with the type or severity of effect exerted by the mutant allele.

17. In connection with this problem, attention may be drawn to certain organisms such as *Aspergillus*,[62] bacteria,[63] and coliphage,[64-66] in which very sensitive tests of allelism are possible: tests which may be calculated[51] in some cases to be adequate for resolution of recombination distances corresponding to one nucleotide pair if genes are primarily constituted of DNA. Such investigations might eventually shed much light on the real magnitude of the structures disturbed by various types of mutational event of different origin, and indirectly on the "quality" of mutations caused by different agents. Unfortunately, all the above organisms are microbial and not necessarily representative of the larger chromosomes of higher organisms.

18. In man, little information yet exists concerning the relative sensitivities of genes to specific mutagens. However, a notable beginning has been made upon the problem by Penrose,[67,198] who has analysed the mean parental age at birth of propositi showing various conditions, and correlated these shifts with hypotheses as to the principal kinetically different classes of mutagens, such as natural radiation (expected to raise both mean paternal and maternal ages by an equal small increment), copy-error (expected to raise mean paternal age somewhat), or chemical mutagens (which might under some circumstances raise the mean maternal age in such a way that incidence increased more than linearily with age). Thus the prospect already exists of the analysis of human genes in terms of sensitivities to different kinds of mutagen.

*Detection of mutation*

19. An apparent gene mutation can be detected if it results in a new allele which differs so much in its action from the original one that it can be scored by appropriate methods. There exist different alleles (isoalleles) whose phenotypic effects cannot at present be distinguished but which may differ in other respects as, for example, mutability.[68] Studies of natural and induced mutations are restricted to those which can be distinguished pheno-

typically, and measurements of their frequency will consequently be minimum figures for the total mutation rates of the genes concerned.

20. In *Drosophila* as well as in mice the rate of visible mutations at specific loci has been studied after matings of the stock to be tested with animals of the opposite sex containing the marker genes whose mutation frequency is to be examined. By this method the visibles scored include both those which are recessive lethals in homozygous condition and those which are homozygous viable, provided only that they are visible and viable as heterozygotes with the allele in the marker stock.[189] As reported by Russell,[69] six out of twenty-one tested mutants induced in spermatogonia of mice were lethal, seven were semi-lethals and eight were viable. The corresponding data from Alexander's[70] test of mutations in spermatogonia in *Drosophila* yielded three lethals, one semi-lethal and four viable. Excluding rare heterozygotes combining a recessive viable visible with a recessive lethal visible, what could be scored in any corresponding study in man might be only those recessive visibles not rendered unscorable by their association with recessive lethals. Supposing the same relationship between viable and lethal visibles as in mice, one might easily underestimate the total mutation rates of genes in man by a factor of two or three.

21. In estimating mutation rates it must also be borne in mind that the same phenotypic effect need not mean a genetically identical condition. In man, as in many other organisms, several different genotypes may exist which give rise to indistinguishable phenotypic expressions. In the case of man one must think of classes of genes each causing a similar effect, rather than of specific single genes. The number of genes in each such class may vary considerably, causing a strong variation between the observed rates of natural mutations in the various classes. Thus in man, because test breeding cannot be used to pin down an alteration to a specific locus, a mutation rate is always in fact measured for the whole class of genes giving rise to one altered condition, recognizable trait, or clinical entity.

22. In recent years many important studies of the mutational process have been made in unicellular organisms. There are, however, several major problems in the measurement of gene mutation rates in single cell material, including a lag between application of radiation or other mutagenic agent and the observable expression of mutations which enables them to be counted; this lag can be due to various factors, segregational or physiological.[71] Furthermore, there is always a possible effect of non-mutant cells upon the survival of mutants during tests.[72] A different problem, peculiar to back-mutations, is the difficulty of distinguishing apparent back-mutation at the same locus from suppressor or modifier effect. For this problem, which is related rather closely to the important question of the reversibility or otherwise of radiation-induced as compared to spontaneous mutations, there are great advantages to microbial material in which both kinds of forward and reverse mutations have been and are being explored. Both radiation-induced and spontaneous mutation rates have been measured with relatively high precision in unicellular organisms, especially bacteria, under a variety of conditions;[73,74] it is to be hoped that the techniques and methods developed will yield equally valuable results when applied to the clones of mammalian tissue-culture cells now available.

## 2. Mutation rates*

### *Natural mutation rates*

23. The basic difficulty in any quantitative study of natural mutation rates is to obtain large enough numbers, for these rates are low (tables I, II) and cannot of course, be raised artificially for purposes of study. Consequently, investigation has been confined to organisms which can be handled or are present in rather large numbers, such as bacteria, *Drosophila,* and humans. The limit to the information on natural mutation rates which can be derived from the very extensive and careful control observations in mice, in the work both of Carter, Lyon and Philips[76] and of Russell[69,70] illustrates the difficulty. Because chromosome structural changes occur naturally at much lower frequencies even than apparent gene mutations[77,80,164] and the study of rates has been confined almost entirely to the latter events, only these will be considered here. In man, individual cases, once found, can be followed up with relative ease even in large populations, because the family and individual are indentifiable by name, etc. As a result, it is possible that more information about natural mutation rates for single phenotypic entities exists for man than for any other organism. In man, however, as in other organisms, the basic problem of small numbers governs consideration of the field.

### *The rate and variation of natural mutations in experimental organisms*

24. In other organisms than man, it has been possible by experiment and test breeding to examine more closely the variations in natural mutation rates as well as the absolute magnitudes. The general ranges of the latter do not vary very widely (table II).

### *Physiological variations*

25. As noted above in another context, physiological variables affecting natural mutation rates of individual loci have been examined in bacteria by Novick and Szilard[78] who concluded that the number of mutations increased as a function of chronological time rather than cell division. This may, however, not be generally true:[79] moreover, the genetic material of bacteria may not be entirely representative of that of higher organisms. Moreover, the general lack of systematic variation of doubling dose among species of widely different generation times, militates against any assumed dependence of number of natural mutations upon chronological time.

26. Work on physiological variables in *Drosophila* has been carried out in relation to mutation at classes of loci, such as the recessive lethals, rather than at single loci. Differences between natural strains[174] and between sexes[80] and dependence upon age[80] have been established for a number of organisms. These variations in natural mutability are not known to be correlated with variations in the radiation-induced rates.

* Strictly, the term mutation rate refers to the rate of occurrence of mutational events and not to the frequency of mutant gametes among tested gametes, although it is also commonly used to refer to this latter measure. The distinction must, however, be borne in mind in certain situations: for example, if it is desired to compare true natural mutation rates estimated for free living unicellular forms of life with the frequencies of appearance of mutant gametes in higher organisms, since the latter do not directly reflect the rates of occurrence of mutational events in the germ line cells (see table II).

*Variations between loci*

27. The difficulty, even in *Drosophila,* of obtaining enough data to document significant variations in natural mutation rates between loci other than exceptional unstable genes further underlines the basic problem of numbers in the investigation of natural mutation rates. Variation between loci, and in certain cases between isoalleles at the same locus is, however, well-known in this organism.[68] It has been far more extensively documented in the bacteria, at least for back-mutations; the rates of these vary from $10^{-5}$ to the lower limit of detection near $10^{-10}$: they are correlated with mutability by radiation to only a very small extent.[53]

28. In extreme cases variations between loci may originate in genes which are themselves unstable or confer instability upon others. Where mutator genes affect all or a large part of the genome, they may in addition be partially responsible for variations in spontaneous mutability between strains. Again, such genetic modifications of spontaneous mutation rates is not known to be correlated with change in radiation-induced rates.

*Natural mutation rates in man*

29. Penrose, Neel and others have tabulated a number of calculated rates for single clinical entities in man (see table I). In examining these values, it is necessary to bear in mind the limitations of the data and of the methods of calculation by which they are obtained.

*Direct methods: autosomal dominants and sex-linked recessives (table I)*

30. In the case of clear-cut autosomal dominant visible entities, the mutation rate is in principle directly estimated by observation of propositi whose parents and other close relatives are normal. The various technical difficulties such as failures of ascertainment and occurrence of phenocopies, degree of penetrance, and the proportion of cases not due directly to fresh mutation have been discussed in the literature.[81,82] The experimentally ideal dominant visible combining full penetrance, complete ascertainability and responsibility for total sterility would be of reduced value, since it could not be proved directly to be genetic in origin. Moreover, in practice studies are commonly made upon the natural mutation rates in those populations where they are known to be highest, simply in order to obtain enough documented cases to make the results statistically significant. It is therefore questionable whether the observed rates are representative. They cluster around $10^{-5}$ per gamete in a distribution which is rather skew. If a population of $10^7$ is surveyed during five years for an ideal condition, observable during thirty years, it already constitutes a considerable labour, and yet significant results are unlikely to be obtained unless the mutation rate exceeds $10^{-6}$. In practice, no such ideal conditions exist. It is very probable that some of the well-documented human mutations[88] have much lower frequencies. Perhaps the possibility should be faced that the sample of spontaneous mutation rates which have been measured in man is not representative, and that the true centre of gravity of the rates for this group of entities lies at or below $10^{-6}$ rather than near $10^{-5}$ per gamete. This encourages the suspicion that among the autosomal recessive visibles for which rates have been calculated indirectly, more than hitherto suspected might show heterozygous advantage. There is need for Governments to foster extension of the scope of existing methods, especially to conditions which are rare or of weak or irregular expression.

*Indirect methods: autosomal recessives (table I)*

31. The mutation rate for autosomal visible recessives is calculated indirectly, by a process originally due to Haldane.[84] The observed number of propositi, together with an estimated selective disadvantage in the homozygote, is used to calculate the rate of disappearance of the mutant alleles concerned from the population, and a balancing rate of forward mutation is inferred from an assumption of genetic equilibrium. The uncertainties concerning possible existence of small selective effects in the heterozygote and of large departures from equilibrium render extremely uncertain the values obtained in this way: indeed, perhaps the most notable use of such figures has been to deduce *a priori* expectation of heterosis from a few "unreasonably high" calculated mutation rates, although most of them lie in the same order of magnitude as those for dominant entities (see table I).

*Lower limit to detection of recessives*

32. An autosomal recessive with a selective disadvantage of only 1 per cent in the heterozygote, in a population whose coefficient of inbreeding was 0.01 per cent, would, if its mutation rate were $10^{-6}$, show up phenotypically in no more than about 1 in $10^8$ of the population. Even if the condition were fully penetrant, a mutation rate would be very difficult to estimate. Such genes, if their natural mutation frequencies were in the range of $10^{-7}$, could hardly be observed at all. There is therefore reason to believe that the best documented sample of recessives for which indirect estimates of mutation rate are available may be unrepresentative. If this is because they show very slight heterozygous advantage, the mutation rates calculated for them are also too high; but then there is a fallacy in the converse argument, that because many of these turn out upon investigation to be heterotic, most human mutant alleles are so.

*Consanguineous marriages*

33. The study of consanguineous marriages does not lead to estimates of natural mutation rates but to estimates of the numbers of recessive alleles present in populations. In principle, these marriages constitute a test-breeding for the presence of recessive alleles through the associated degree of homozygosity ($\frac{1}{16}$ for first cousins) which they bring about. It may, however, be questioned whether a truly comparable control group can ever be obtained, although internal controls by comparison of different degrees of consanguinity are usually available. The limited number of studies made show as yet no very consistent picture. Of them, those by Sutter and Tabah[85,86] and by Schull[100] are the most extensive, and that by Böök[87] the most intensive. Morton, Crow and Muller,[88] by an ingenious argument, have shown how to present the over-all reduction in viability, which is observed in three of the surveys, in the form of an equivalent number of alleles which would be lethal if homozygous, or lethal equivalents, carried per head of population. From the surveys analysed by them they conclude that 3-5 lethal equivalents acting before maturity were present per individual in the population, a figure with which the survey reported by Schull is in satisfactory agreement. Unfortunately, the intensive examination carried out by Böök shows an entirely different picture of viability, although in a very small sample; the total deaths, including prenatal and up to age 30, in Böök's sample, were almost identical in the cousin marriages and the controls.

34. The content of deleterious recessive genes of a population, whether expressed in lethal equivalents or otherwise, is an important parameter indicative of its genetic state. It is also a valuable standard of comparison for actual or postulated mutation rates. There is, however, another possible use for it. Comparison can be made of the total recessives in lethal equivalents, derived from vital statistics only, with intensive investigation of all the known recessive lethals present, such as that undertaken by Böök. (Ideally, the total reduction in viability and fertility up to the second generation beyond the cousin marriages should be employed, (see paragraph 113 below) and the intensive examination should cover all known recessive conditions.) In this way it might be possible to obtain some idea of what proportion of recessive damage is covered by the known effects, and what proportion remains unknown: a factor of great importance to our confidence in any estimates or predictions, based as they must be upon current limited knowledge. This possibility is discussed in more detail in paragraph 113.

35. It is clear that improved recording of such consanguineous marriages, in maternity hospitals or centres of vital statistics, would be of great value and should be encouraged by Governments if they wish to be aware of the general state of genetic well-being of their peoples.

36. The Committee has been informed of large-scale current or planned surveys of consanguineous marriages both in Japan, where the frequency of these is high, and, as regards vital statistics, in Canada.[89,90]

37. It has, unfortunately, not been possible so far to establish total natural mutation rates in man for very large classes of genes, such as that formed by the sex-linked recessive lethals of *Drosophila*. Such large classes, if they could be investigated upon a firm genetic basis, might more easily provide adequate numbers for reliable statistical analysis than can be obtained from the laborious search for specific rare conditions. In this connexion, it is of interest that Lejeune and Turpin[91] have recently attempted to interpret the decrease of sex-ratio at birth with age of either parent in terms of a mutational hypothesis. There is, however, no certainty that the secondary sex-ratio does decrease with the age of the mother,[186] and the combined data upon irradiated and aged fathers appears at present to involve contradictions. Since there does appear to be a decrease in sex-ratio with age of the father,[186,187] it seems a reasonable possibility that mutations to sex-limited detrimental autosomal dominants are concerned and that they are due to natural irradiation or other non-cumulative, time-independent causative agents (Penrose's Class I,[97] see paragraph 18 above). It would evidently be of great value if clear-cut interpretations could be established in some other mammal, such as the mouse, since secondary sex-ratio data are widely recorded in large populations, although not always in a form suitable for genetical analysis, and they are relatively free from the ambiguities of fine diagnostic distinctions. The possible interpretation of sex-ratio data is further discussed in paragraph 64 below.

*Mutator and unstable genes*

38. In any consideration of variations in spontaneous mutation rates, the evidence of mutator genes and unstable genes, well-established in corn, in *Drosophila* and in bacteria,[92] must be borne in mind, together with the fact that these commonly do not affect the rate of induction of mutations by irradiation. Minor effects of this kind might be more common than are supposed and could perhaps give rise to some variations in natural mutation rates between human populations. If that were so, these in turn could be expected not to give rise to any corresponding variation in radiation-induced rates. Although variations in frequencies of appearance of mutant phenotypes between different human populations are well known to occur,[93] they have been inadequately documented, especially for dominant conditions. In the case of recessives they are usually attributed to past selective differences, although it is conceivable that genetic drift also plays a part.[94]

*Radiation-induced mutation rates*

39. Radiation-induced gene mutations have not yet been observed with certainty in man, and so no quantitative dose-mutation relation exists for the genes responsible for any specific clinical entity. In consequence, quantitative assessments of the mutational affects of the irradiation of human populations must rely at present upon tenuous arguments and upon extrapolations which are often of uncertain validity. In any event they depend upon the well-established results of the investigation of radiation-induced mutation in other organisms.

*Magnitude and variation of radiation-induced mutation rates in organisms other than man*

40. Since the field of mutational radiation genetics was opened by Muller in 1927,[95] it has been established in all the many organisms tested that ionizing radiations can induce apparent gene mutations: hence the same is believed true of man. X-ray induced mutation rates have been measured for a large number of single loci, especially in *Drosophila*. Both the range and average of such rates are known for a wide variety of individual visible markers through measurements made under very carefully controlled conditions, and so also is the total rate for certain large classes of markers such as the sex-linked recessives of *Drosophila*. A number of rates observed in experimental species are listed in tables III, IV and V.

41. In mammals, the most extensive investigation of the X-ray induction of mutations at single loci so far carried out is that for mice,[69,75,76,96] in which the rates at seven autosomal recessive visible loci have been investigated in spermatogonia; the average of these rates is found to be about fifteen times the average for a comparable group of loci in *Drosophila*.[70]

42. Extensive research has been conducted upon the variation in sensitivity to radiation-induced mutation with physiological condition. In the male it has now been established that the mutability is low in spermatogonia, rises to a peak during the time of formation of spermatids, falls to a second minimum in immature spermatozoa, and then rises up to the time of ejaculation, both in *Drosophila*[97,98] and the mouse.[99] In the female *Drosophila*, the öogonia show a mutability similar to that of spermatogonia while late öocytes are very mutable.[37,100] The subject has recently been reviewed by Glass.[100] *Drosophila* is also the only organism for which extensive determinations exist of the relative rates of mutations in different selective and other classes, either at single loci or summed over large parts of the genome.[101,102]

43. Muller[103] has pointed out that evidence in *Drosophila* indicates that mutation rates in somatic and gonial

cells are about equal. Extension of this principle to other species[104] and eventually to man might make possible very informative conclusions from investigations on somatic mutation rates *in vivo* in man.

44. Calculations have been made by Haldane[105] and others concerning the practicability of observing not single locus rates but total rates over a large part of the genome in a mammal such as the mouse. Such an experiment upon the very large scale necessary might be of considerable value at this juncture in the process of extrapolation to man; it would, however, involve the expenditure of a great many scarce mouse-geneticist-years. The Committee has been informed of the existence of a pilot experiment on these lines.[106]

45. The concept of genes as finite structures of different sizes which carry hereditary information largely in the form of different arrangements of nucleotides in DNA has recently made possible one particularly interesting interspecies comparison concerning induced mutations.[107,108] There is evidence that in mice the total rate of induction of recessive lethal mutations in sperm is higher than the corresponding rate in *Drosophila* by a factor of about 20.[107] The same is true for the rate of mutation per locus averaged over several different loci, and in addition there is a similar difference of about twenty-fold in the same direction in the DNA content per nucleus. This suggests that perhaps mouse genes are not more numerous but are larger than *Drosophila* genes —that the extra DNA has gone into building genes that are bigger and more complex rather than more numerous. The possible application of such an idea to man, an organism in which mutational events cannot in general even be assigned to definite loci by test crosses, but which has a DNA content per nucleus similar to that in the mouse, might lead one to expect rather high mutation rates, both spontaneous and induced, when measured "per clinical entity", as well as all the complexities and peculiarities of large multiple allelic series, of which a notable example has been uncovered by Dunn in the t-alleles of the mouse.[109] Penrose[93] has already drawn attention to the possibility of some unusually complex genes in the X chromosome of man, in connexion with very high observed natural mutation rates.

### *Radiation-induced mutation rates in man*

#### *Surveys of radiation-induced gene mutations in man*

46. Whatever approach is adopted to the problem of radiation-induced mutation rates, the gonad doses received both by control and by experimental groups will have to be known.

47. In principle, the simplest method to obtain a quantitative relation between dose and radiation-induced gene mutations in man is to make a comparative survey of the progeny of an irradiated ("experimental") and a comparable un-irradiated ("control") population. Those surveys published so far are concerned only with the first generation born of irradiated parents. However, it is easy to show that, as human matings cannot be controlled, examination of the first generation provides more information in itself than examination of subsequent generations.

48. In the last analysis, all the observed quantities come down to variations in frequency, and therefore:

(*a*) All studies must be accompanied by the examination of a control sample presumably issued from genetic stock identical to that of the irradiated sample. This condition greatly restricts the value of the results published so far.

(*b*) All the results obtained are subject to an inevitable sampling error which necessitates the collection of a very large amount of data.

A number of quantitative characters, such as birth-weight, size and various anthropometric measurements, as well as statistical data, such as neo-natal mortality, have been suggested and examined. Unfortunately, the precise genetic component in these variables is not known; on the contrary, they are known to be dependent upon factors which are economic (standard of living), demographic (age of parents, order of birth, etc.) and sociological (medical care).

49. The characters that can be utilized may be grouped in two categories, according to whether they are connected with dominant (or sex-linked) visible mutations or with dominant (or sex-linked) lethal mutations. The detection of visible dominants is carried out in practice by the observation of malformations at birth. It is in fact reasonable to assume that an increase in the frequency of dominant mutations associated with visible effects would manifest itself to some unknown extent as an increase in frequency of malformations. The same would be true of visible sex-linked recessives in boys born to irradiated women. Lethal mutations may be revealed in four ways:

(*a*) Increase in frequency of miscarriages (virtually impossible to determine with certainty);

(*b*) Increase in frequency of still-births (much more feasible but subject to the demographic considerations mentioned in connexion with neo-natal mortality);

(*c*)Reduction in fertility, or even sterility (virtually impossible to measure in man);

(*d*) Disturbance in the ratio of the sexes at birth (deviation in the sex-ratio, an easily observable criterion).

50. The various studies which may be taken into account at the present time are listed, together with pertinent results, in table VI. Given the very uneven quality of the data presented by the various authors, and the particular way in which they were arranged by each of them, it is impossible to add together the figures from the separate surveys. In general, none of the investigations makes a definitive demonstration of a genetic phenomenon. Only the decrease in the sex-ratio, which is found in the three studies of irradiated mothers, seems to be acceptably established as a reality. Although no one of these studies concerning sex-ratio yields statistically significant results by itself, the fact that all three deviate in the same direction gives some confidence concerning the reality of the effect. Although several of the studies to date raise the possibility of an increase in congenital malformations among the offspring of irradiated persons, the findings in this regard are much less consistent than those concerning the sex-ratio. In this connexion, it must constantly be borne in mind that where many comparisons are being drawn between two groups, on the basis of chance alone one in twenty of these comparisons will yield differences exceeding the 5 per cent level of significance. Further observations regarding the possibility of an increase in congenital defect or early death are highly desirable.

51. In summary, it seems possible, although only with great difficulty, to distinguish a detrimental effect of irradiation on the first generation issuing from irradiated parents. The possibility of firm demonstration and

measurement of this phenomenon suggest that all these studies be extended on the largest scale possible, wherever practicable surveys can be made with a reasonable probability of yielding positive significant results in a comparison with adequate controls.

52. In view of this possibility of future surveys of the progeny of irradiated persons, it seems worthwhile to indicate the criteria which determine the value or "resolving power" of any such study. In brief, five points must be considered:

(*a*) The dose to the parents of the individuals under study;

(*b*) The number of individuals whose parents have been so exposed;

(*c*) The number of characteristics of genetic significance to be recorded;

(*d*) The manner in which information on these characteristics is collected;

(*e*) The availability of a suitable control group.

53. To illustrate the manner in which (*a*) and (*b*) may be taken into consideration, a particularly simple hypoethetical case has been selected, that of the detection of an ideal autosomal dominant visible allele causing complete sterility:

Suppose the gene concerned to mutate at a rate m per gamete in the control population and at an increased rate fm per gamete in the irradiated population. If the doubling dose for the mutational step concerned is $D_2$ rad and the mean genetically significant exposure *per parent* of the irradiated group is D rad, then

$$f - 1 = D/D_2$$

If P progeny of the irradiated group and Q of the unirradiated are examined with complete ascertainment for the visible allele, the numbers expected to be observed are respectively 2mfP and 2mQ. The observed difference in rate between the two groups is $\Delta = 2m(f - 1)$ and has an approximate variance due to the limited sample size of

$$\sigma_\Delta^2 = 2m(f/P + 1/Q)$$

In consequence, even if no other sources of error are considered,

$$\chi^2 \Rightarrow \frac{\Delta^2}{\sigma_\Delta^2} = \frac{2m(f-1)^2}{(f/P + 1/Q)}$$

If we require that $\chi^2 \geqslant 4$ for a significant increase of mutation rate in the irradiated group to be established, and denote $\chi^2/4$ by R, then for a significant increase in mutation rate at a single locus,

$$R = \frac{m}{2}(f-1)^2 \Big/ (f/P + 1/Q) \geqslant 1$$

In terms of D and $D_2$

$$R = \frac{m}{2}(D/D_2)^2 \Big/ \left(\frac{1 + D/D_2}{P} + 1/Q\right)$$

For example, in the study of Neel and Schull,[111] the progeny of irradiated parents numbered $3.3 \times 10^4$ and the progeny of control parents, $3.2 \times 10^4$, while the average excess radiation exposure to the combined parents of the former group is about 17 rad. Because of the known heterogeneity of exposures, R for any single locus must be computed by adding together the calculated R values for the various exposure classes, which add up to $2.3 \times 10^{-2}$ on the assumption that the representative doubling dose is 30 rad. With respect to the possibility of significant findings based on mutation at *any one locus,* then this study (and any other study to date) is far below the level of significance.

54. Where multiple traits are involved in the inquiry, the power of the study is a function of the precise number of traits under consideration. For example, if one were to make the over-simplified assumption that mutation at any one of 100 loci resulted in completely penetrant, dominant mutations responsible for congenital defect, assuming independence in the expression of mutation at these loci, the calculated resolving power of the previously mentioned study becomes 2.3, and the failure to observe a significant effect of radiation on the frequency of congenital malformations in the aforementioned study might indicate that the assumed doubling dose was too low.

55. The sex-ratio is one of the more conveniently studied indicators of possible genetic damage. Information on this point is relatively easy to collect and has a high degree of objectivity. The calculations corresponding to those of paragraph 53 are relatively simple and proceed as follows:

Suppose a group of mothers receive gonad doses averaging $D_m$ prior to conception of children, and suppose the irradiation causes a shift in the secondary sex-ratio s which is linear with the dose

$$\Delta s_m = k_m D_m$$

Suppose $P_m$ progeny of these mothers are examined, the variance in the determination of the sex-ratio of the progeny of the group, due to limited sample size, will be

$$\sigma^2 = \frac{s(1-s)}{P_m}$$

Since s is always approximately ½, this may be written

$$\sigma_\Delta^2 = \frac{1}{4P_m}$$

If such a group is compared with $Q_m$ progeny of a control group the variance of the observed difference is

$$\sigma_\Delta^2 \frac{1}{4P_m} + \frac{1}{4Q_m}$$

and the significance of the observations is determined by

$$\chi^2 = 4k_m^2 D_m^2 \Big/ \left(\frac{1}{P_m} + \frac{1}{Q_m}\right)$$

If we require $\chi^2 \geqslant 4$ before the shift can be considered significant, then

$$R_m = k_m^2 D_m^2 \Big/ \left(\frac{1}{P_m} + \frac{1}{Q_m}\right) \geqslant 1$$

Similar formulae can be derived for comparison of the progeny of irradiated fathers with controls, where

$$R_f = k_f^2 D_f^2 \Big/ \left(\frac{1}{P_f} + \frac{1}{Q_f}\right)$$

A number of completed surveys, irrespective of the significance of their results, all show decreases in s when the mother is irradiated from which values of k of the order of $-1 \times 10^{-4}$/rad can be derived. If this figure is adopted for purposes of calculation, then

$$R_m = 10^{-8} D_m^2 \Big/ \left(\frac{1}{P_m} + \frac{1}{Q_m}\right)$$

On the basis of the present limited information, values of $R_f$ have been calculated using a similar numerical value of k but of opposite sign

$$R_f = 10^{-8} D_f^2 \Big/ \left(\frac{1}{P_f} + \frac{1}{Q_f}\right)$$

Clearly, if $k_f$ and $k_m$ do in fact differ in sign, then significant results may occasionally be obtained by the comparison of progeny of irradiated mothers with those of irradiated fathers, even where neither group differs significantly from the controls. On the basis of the numerical values adopted here, the same condition upon significance would then become

$$R_{f,m} = 10^{-8} \left(D_f + D_m\right)^2 \Big/ \left(\frac{1}{P_f} + \frac{1}{P_m}\right)$$

where $P_f$ is the number of progeny of irradiated fathers examined and $P_m$ is the number of progeny of irradiated mothers examined. The resolving power of comparisons with controls of progeny both of whose parents have been exposed will, under these circumstances, involve $D_f - D_m$ and be relatively poor if the doses to the two parents are quite similar. If $k_f$ and $k_m$ were to have the same sign, the situation would be reversed. By way of a numerical example, the data of Turpin and Lejeune[117,118,165] may be considered. In this study, $P_m$ is 136 and $Q_m$ is 236. For the purposes of this calculation, $D_m$ and $D_f$ will both be set at 450 rads. Then $R_m$ may be calculated to be 0.175. The calculated $R_f$ for the same data is 0.52. In passing, it might be noted that because of the many somatic factors thought to influence sex-ratio, one would as a matter of principle have more confidence in the genetic origin of a sex-ratio change among the offspring of irradiated fathers than among offspring of irradiated mothers.

56. That comparisons of the progeny of irradiated and non-irradiated groups must be carried out on rather a large scale, if there is to be any prospect that they will yield significant positive results, is emphasized by the high proportion of non-significant results obtained in the completed surveys of table VI. Moreover, they may require rigorous and complex analyses of controls,[111] and therefore involve considerable effort of a very specialized kind. While negative results on a sufficient scale can be of great value in excluding the most alarming possibilities,[111] only positive ones will suffice for a quantitative relation between dose and mutation frequency. In this connexion, a survey of the high radiation area of Kerala[112,195] appears to have a potentially somewhat greater resolving power than any previously made, if an equally intensive investigation over a ten-year period is assumed.

57. At its first session, this Committee requested advice from the World Health Organization about the possibility of setting up a standard of recognition for one or more clearly recognizable medical conditions thought to be largely or solely genetic in origin. In their discussions of this, the geneticists of the study group which framed the reply of WHO made clear that they strongly questioned the feasibility of using a single condition as an indicator of the mutation level in large populations.[113] Their feeling appeared to be based in part on the manifold uncertainties which exist concerning almost every single likely indicator condition,[110] and in part upon the belief that reliability of results in this field depends upon intensive study of every case. The study group recommended that simultaneous investigations always be carried out on several conditions.[113] Indeed, the sense of the document cited is such as to cast some doubt upon the practicability of such surveys, in view of the associated difficulties of obtaining sufficiently large numbers. It does not, however, rule out large-scale survey plans if the urgency of the situation warrants them. Moreover, if the objective were to survey one population serially in time so as to be able only to establish limits of possible relative increases in the mutation rate, without any interpretation as to cause, some of the difficulties might diminish.[110] One such difficulty seem to lie in combining the intensive examination of cases, which is the classical approach of human genetics, with the extensive survey of very large populations which is required if adequate numbers are to be obtained for studies of mutation rates at or near the spontaneous rate in man. This difficulty is emphasized by the sharp limit of about $3 \times 10^6$ set in discussion upon the size of human population which can be covered by an institute conducting epidemiological surveys of the classical type (see also ref. 11).

58. The difficulties of comparative surveys of high resolving power have led Penrose[93] to propose a modified approach, by which a given class of mutant propositi would first be collected from a large population heterogeneous in radiation exposure as well as in other respects, and only then would personal histories, including radiation histories of the parents, be compiled for the propositi and a comparable control group. The method is a powerful one for the wider field of general human genetics, since it can serve as a basis for quantitative investigations of other mutagens than radiation. As applied to the radiation problem, this same possibility of alternative and perhaps unknown causes complicates the choice of a legitimate control group. Moreover, the burden of work is in part thrown into a sphere where rather considerable difficulty also prevails: the quantitative compilation of individual histories of irradiation.[114] In order to obtain a quantitative dose-effect relation from a survey of this type, it is necessary to know not only the incidence of the condition under investigation in the general population, but also the general incidence in that population of individuals having similar radiation exposures to those of various classes of propositi. Many features of the approach are exemplified by the recent work of Steward *et al.*[115] on a somatic radiation problem.

*Possible aids in extrapolation of radiation-induced mutation rates from other species to man*

59. In view of the difficulties of a formal human radiation genetics, it is necessary to consider possible ways in which radiation-induced mutation rates can be measured in systems closer to the *in vivo* germ cells of man. In this connexion a new field of work has been opened by the ability of Puck and his collaborators to grow colonies of tissue-culture cells, the majority of which are viable and able singly to give rise to fresh colo-

nies[121,122] The well-developed methods of microbial genetics can in principle now be applied to such cultures both for natural and radiation-induced mutations, although certain features are believed by many workers still to limit the applicability of the material to this problem:

(*a*) Tissue-culture cells usually need a more complex medium than the whole organism from which they originate.

(*b*) Well-established lines tend to be poly- or aneuploid. They resemble both each other and the malignant HeLa strain, with which Puck first developed his techniques. In certain types of radiation experiment, this difficulty may be circumvented, as in the work of Bender,[10] who used tissue-culture cells very recently derived from human kidney (within four transfers) in a cytological study of induced chromosome breaks. But the repeated propagation of lines of stable diploids from single cells appears to be a prerequisite for systematic studies of gene mutation in human tissue-culture.

(*c*) Some workers in the field doubt whether any line of normal (i.e. non-malignant) cells has really been successfully propagated as such (but see Puck).[18,121,122,104]

(*d*) It is not yet known what is the exact relevance of studies on the mutational behaviour of somatic cells *in vitro* to that of mammalian germ cells *in vivo*.

Points (*b*) and (*c*) can perhaps be circumvented in part by applying the technique to cultures derived as freshly as possible from normal tissues. However, a difficulty of principle remains: the tissue-culture cell is a free living organism, whereas the ancestral tissue cell is part of an organism so that its growth, division and differentiation are subject to the developmental controls of that organism. In view of the close connexion of all, and especially the genetic, effects of radiation upon the cell with the process of cell division, some initial caution in interpretation is undoubtedly required. Nevertheless, the future role to be played by the tissue-culture methods in the making of comparisons between species so as to provide a basis for extrapolating from the known *in vivo* mutation rates or rates of occurrence of gross structural changes, does not seem open to doubt.

60. There is some evidence[103,104] that the frequencies of radiation-induced mutations in somatic cells is similar to that in gonial cells. If this correlation could be extended to the variation between species, attempts to measure induced and/or natural mutation rates in human somatic cells *in vivo* might provide information of great value as a guide in estimating mutation rates in human genes.

*Continued need of research in fundamental genetics*

61. It cannot be too strongly emphasized that there is little basis either for planning or for interpreting *ad hoc* radiation genetic surveys in man, or for making calculations concerning radiation-genetic effects in man, except the great volume of fundamental research upon other organisms which has been carried out for its intrinsic interest alone, and directed wholly as a contribution to human understanding. This foundation must be extended and strengthened, and must not be weakened in the interests of the applied superstructure.

### 3. The representative doubling dose

62. Provided that the dose-mutation rate relation has a linear form

$$m = m_0 + kD$$

the relative increase of mutation rate per unit dose is readily expressed by the ratio $k/m_0$. Another convenient parameter to use is the reciprocal of this ratio, $m_0/k$, which is the radiation dose required to produce a number of mutations equal to those occurring naturally, or the "doubling dose" ($D_2$). For a whole series of mutations $m_i$ whose effects sum up or are collectively observed $\sum_i m_i = \sum_i m_{0i} + D\sum_i k_i$

and one can define a mean $D_2$ as $\frac{\sum_i m_{0i}}{\sum_i k_i} = \overline{D}_2$.

This procedure can be used to estimate a $\overline{D}_2$ for as representative a group of human genes as possible. It is not necessary to know how many genes are involved or of what kinds, provided that they can reasonably be assumed to be a representative sample and provided that there is assumed to be no correlation between $D_{2i}$, $k_i$ or $m_{0i}$ and the degree or kind of manifestation. The representative $\overline{D}_2$ should then express the dose-effect relation for any set of radiation-induced mutational events in so far as this itself depends upon a sufficiently representative sample of human genes: usually the sets will be of a kind in which the mutations at a very large number of loci are summed, both in calculating and in making use of $\overline{D}_2$.

*Estimates of the representative doubling dose for human genes*

*General levels in other species*

63. It has been pointed out[145,150] that a number of doubling doses calculated for different species cluster around the range 30-60 rad (table VIII). However, the significance of this fact for present purposes is limited by several considerations:

(1) The majority of the experimental radiation exposures concerned were of gametic cells. Where irradiation of gonial cells is concerned, it is true that the best estimate that can at present be made for a group of genes in the mouse (the only mammal so far investigated) is of the order of 30 rad, but this must be compared, for instance, with values for *Drosophila* ranging up to 400 rad (see table VIII).

(2) No satisfactory interpretation of the observed concurrence or range of values exists, and consequently any empirical extrapolation to man would have to rest upon an unsure basis.

(3) The lack of correlation of observed doubling doses with life-span can be interpreted as an indication that mutation at a constant rate in chronological time is not the dominant factor in determining the natural rates in the experimental species. But man is so much longer-lived than the experimental organisms that in his case an appreciable fraction of natural mutations is already quite likely to result from time-independent causes such as irradiation from natural sources. (See Penrose[140] for a preliminary investigation of this point).

*Sex ratio*

64. Observations have been made of a shift of the sex-ratio in the progeny of irradiated mothers (see paragraphs 50, 55). In a first attempt to make use of the available data, Lejeune and Turpin[120] have proposed a comparison between the effect of irradiation and the

effect of aging. These authors have calculated a significant decrease of the sex-ratio with the aging of the mother alone, the partial regression coefficient being $-3.36 \times 10^{-4}$ for an aging of five years. Taking a value of $-6 \times 10^{-5}$ for one rad as an estimate of the decrease of the sex-ratio following irradiation of the mother (table VI), and assuming that both decreases are related to the same extent to newly arising sex-limited detrimental mutations, they have proposed a doubling dose of

$$\frac{-3.36 \times 10^{-4} \times 6}{-6 \times 10^{-5}} \doteqdot 30 \text{ rad} \Big/ \begin{matrix}\text{From age 0} \\ \text{to age 30 years.}\end{matrix}$$

Unfortunately, as these authors themselves recognize, such a calculation cannot be considered as legitimate before many problems have been solved. The needs include:

(1) A good estimate of the gonad dose effectively received by the mothers;

(2) A better estimate of the decrease of the sex-ratio with irradiation, including a test of linearity of the relationship between these quantities, which is implicit in all current calculations concerning sex-ratio;

(3) An explanation of the apparent contrast between the sex-ratio's decrease with the father's aging[186,187] and the possible *increase* observed after acute irradiation of the father's gonads;[111,124]

(4) The study of other variates such as birth rank[186] which might interact with the real effect of the aging of the mother.

65. Only some preliminary data relevant to the problem of irradiation of the father are available, but these indicate that a sex-ratio decrease after chronic irradiation may perhaps have occurred in man[120] and in the mouse.[126] The latter body of data, although not significant at the 5 per cent level, yields at face value a representative doubling dose in satisfactory agreement with other data for this species.

66. In summary, while the possibility exists in principle of deriving a representative doubling dose by comparing the changes in secondary sex-ratio when parents either age or are irradiated, the relevant phenomena are, at present, not sufficiently well established either quantitatively or qualitatively for this procedure to be reliable. Yet relevant surveys of the secondary sex-ratio are more readily and widely carried out in human populations than are others which must depend upon finer diagnostic distinctions. Consequently, more extensive quantitative data concerning comparable irradiated and non-irradiated human populations should continue to be sought. In particular, it may be worth attempting to search for a decrease of sex-ratio among the progeny of not too heavily irradiated human males; the conclusion of such a test might go far to determine the utility of the parameter in considerations relevant to the human genetic radiation hazard.

67. It is not at present certain, even in *Drosophila*, whether the postulated genetic causes of shifts in the sex-ratio play the quantitative roles expected of them; and data of this kind are needed. It is also possible that further investigations upon experimental animals, especially among the progeny of male mice irradiated at low doses, together with similar observations upon irradiated female mice, may show that in both cases a doubling dose can be derived from sex-ratio shifts which is of the same magnitude as that calculated from purely mutational experiment. Establishment of such facts would greatly strengthen interpretation of corresponding observations upon man.

68. Although today it is not possible to assign any definite confidence to the use of the sex-ratio as an indication of mutation rates, it must be borne in mind that the parameter, even if not totally satisfactory, is the only one easily surveyed in entire populations, and that it represents the "cheapest" genetic trend available to research workers in terms of technical effort expended in surveys.

*Induction of leukemia*

69. A reasonable probability now exists that, in an intermediate dose range, the radiation-induced incidence of leukemia is a linear function of the exposure of the bone marrow, whatever the manner of delivery of the dose. Upon this hypothesis, it has been calculated that 30-50 rad mean exposure of the red marrow might suffice to double the natural incidence of leukemia among an adult group.[127]

70. Leukemia certainly involves a transmissible hereditary change in the tissue cells concerned, a "mutation" in the widest sense of the word. Whether the process of its induction in somatic cells corresponds qualitatively or quantitatively in any way to the process of apparent gene mutation as it is normally thought of in germ cells is extremely doubtful. Nevertheless, it is not entirely excluded from providing an indication of the relative sensitivity of human cells to natural and radiation-induced genetic changes. The indication must, however, be regarded with great reserve: even if the most helpful possibility eventually proved true, and leukemogenesis were primarily a process of somatic gene mutation, a single very atypical gene in a somatic cell might be responsible, and might be entirely unrepresentative of transmissible germ-line mutations.

*Survey of Japanese cities*

71. Although the results were negative, the extensive observations of Neel and Schull[111] in Nagasaki and Hiroshima provide some evidence of a lower limit for the representative doubling dose for human genes, at least for the dominant mutations which would have been observed by these authors. A difficulty of the type of survey conducted by Neel and Schull must be mentioned here: in order to obtain significant data, it is necessary to continue collection of it for some considerable time. Among a population who have been subjected to heterogeneous, heavy exposure, there may perhaps be some infertility of a progressive kind selectively induced among the most heavily exposed groups. In that event, incipient positive results may be masked by later data collected in the attempt to make the observations more significant. It is possible that the significance of the observations made in this kind of survey, because of its scale, complexity and uniqueness, can only be evaluated adequately by the authors. It therefore seems reasonable to accept the opinion of Neel and Schull that their negative results make it improbable that the representative doubling dose for human genes irradiated in gonial cells lies below 10 rad.

*The natural exposure*

72. The representative doubling dose for human genes undergoing chronic irradiation cannot be less than the

genetically significant exposure of natural origin. In most areas this is about 3 rad per generation. In exceptional areas, the natural radiation may contribute so heavily to the natural mutation rate that the observed representative doubling dose would be increased.*

*Current best estimates*

73. Not one of the arguments in paragraphs 63-71 gives a reliable estimate of the representative doubling dose, yet each depends upon a different, independent set of unproven ideas. This Committee recognizes a need, in our existing state of knowledge, to make use of every available source of information, however tenuous. It considers that the separate arguments and repeated independent observations of small changes, in spite of the statistical limitations upon their significance, provide a reasonable indication when taken together; the representative doubling dose for human genes irradiated in pregametic cells is likely to lie between 10 and 100 rad. There is supplementary evidence that it cannot be less than 3 rad. The Committee notes that the value 30 rad is compatible with the whole of the probable range cited, within a factor of about 3: it therefore has a certain degree of utility for purposes of calculation wherever a "most probable" value of the representative doubling dose is required.

### 4. Estimates of total rate of radiation-induced mutations in the genome of man

74. Because radiation-induced mutation has not yet been observed with certainty in man, it is not possible to give a satisfactory estimate of total induced mutation rate: indeed, this is hard enough even in *Drosophila*.[108] Nevertheless, it could be hoped that the total rate might bear some relation to total genetic material: such a hope has recently been supported by the only available comparison, that between calculated total induced recessive lethal rates and DNA contents in the mouse[107] and *Drosophila*.† The DNA content of human cells is about 6/5 that of mouse cells, according to Vendrely.[20] Hence, upon the stated hypothesis, it might be expected that roughly one recessive lethal per 250 rad would be induced in human sperm by irradiation. Again by analogy with both the mouse and *Drosophila*, which behave alike, it might be expected that in spermatogonia only about one quarter as many gene mutations would occur. However, in *Drosophila* it has been estimated that the total rate of mutation to appreciably deleterious alleles is about four times the recessive lethal rate.[108] In the assumptions made so far, it has been possible to rely upon common quantitative behaviour of two diverse species. But the induced mutation rates for single loci of mice, as well as the total recessive lethal rate, are greater than those of *Drosophila* by a factor of 20, corresponding approximately to the ratio of DNA contents per cell. This has suggested that perhaps the individual genes of the mouse are not more numerous but are larger and more complex than those of *Drosophila*. In turn, the ratio of total to recessive lethal mutations might be very greatly affected. That this is perhaps not so is suggested by comparison of the induced mutations at sets of visible recessive loci in the two organisms. In both cases, some two-thirds of the experimentally induced mutations have been found upon investigation to be lethal. The similarity could be a property peculiar to visible loci; but it at least suggests that the ratio of total to recessive lethal mutation rates may be the same for these two and possibly other species. If the *Drosophila* ratio is applied to man on these tenuous grounds, a total induced rate of appreciably deleterious mutations of about one for every 250 rad applied to the gonial cells is suggested. It will be clear to the reader that based as it is upon so many tenuous hypotheses, this figure, must be regarded with the very greatest reserve. In particular, it applies only to the sum of oligogenes with individually detectable effects and neglects the polygenes involved in quantitative inheritance, an especially serious omission for organisms which may have considerably larger and more complex genes than *Drosophila*, and may therefore be relatively much more liable to small changes giving rise to many isoalleles even at known loci.

## II. THE GENETIC CONSEQUENCES OF IRRADIATION

### 1. The connexion between mutation and genetic damage: Selection

75. The fate of a mutant allele newly introduced into a population is determined by selection. Hence the connexion between mutation and the genetic damage due to it depends primarily upon the selective properties of the mutant alleles concerned and, in particular, upon the degree of dominance or recessivity of these. Our ignorance of the relevant facts in man is very complete and urgently requires rectification.

76. It is useful to precede inquiry into the action of the selective process upon mutant alleles by an inquiry as to the origin of genetic variation in natural populations and its connexion with fitness. The question is an old one, especially in connexion with plant material, where the great extent of natural genetic variation was early observed, and where breeding experiments early gave rise to the controversial notion of "hybrid vigour". However, much of the agronomic literature is primarily concerned with the externally applied criterion of "yield" rather than with fitness. Moreover, natural populations of plants differ decisively from those of animals in the aspects of genetic structure which are of immediate concern here.

77. What may be called the classical view of the adaptive norm of a natural population supposes the optimal allele to be homozygous at most loci: this situation of maximum fitness is disturbed by mutation, continually restored by selection: rarely, due to chance, to change in external conditions in time or space, or to change in other parts of the genotype, a mutant allele will prove itself advantageous, displace the former predominant allele at the same locus, and become the new wild-type allele (see review in ref. 130). In recent years this view has been increasingly strongly challenged

* The parameter of biological interest is, of course, the ratio of the spontaneous mutation rate to the induced mutation rate per unit dose. In man the spontaneous and induced components of the natural rate cannot be separated, and it is convenient to define the representative doubling dose in terms of the total natural rate. However, in situations such as that described here, the distinction between the spontaneous and natural rate becomes of importance and must be maintained.

† A figure for the total rate of induced recessive lethals has also been given for yeast by the careful work of Magni.[128] It appears at first sight to disagree with the hypothesis put forward here, because of the exceptionally low DNA content of the yeast cell (table VII). However, yeast is known to possess a relatively extensive non-chromosomal genetic apparatus.[129] It has therefore not been used here for comparison.

by some,[130] especially in connexion with the accumulation of extensive evidence concerning the prevalence and the superiority in many respects of structural heterozygotes in natural populations of *Drosophila*,[131,132] a finding which is itself, however, compatible with the classical view of genic homozygosity as the adaptive norm. It has also been argued on more general grounds[133] that heterozygosity is the adaptive norm at most loci and that heterozygotes are in fact intrinsically better able to adapt themselves and maintain their own stability in the face of changing environmental conditions. A recent experiment by Wallace[134] seems to indicate that even random unselected radiation-induced heterozygosity in general confers an advantage, at least upon individuals otherwise homozygous for certain pairs of arbitrarily chosen chromosomes in laboratory populations of *Drosophila*.

78. These two views lead to different general expectations concerning the consequences of mutation. On the first, most mutants alleles will contribute to the limited degree of heterozygosity, will be harmful, and will require to be eliminated, diminishing the fitness of the population. On the second, mutational events, although the majority of them will still be harmful and will require to be eliminated, will scarcely affect the great degree of heterozygosity already existing, and will diminish the existing reproductive fitness to only a correspondingly small extent. However, this is a consequence of the fact that since the mating of diploid heterozygotes produces some homozygotes, on the second hypothesis the population must pay for its built-in adaptability and plasticity by a permanently reduced fitness due to these.

79. Unfortunately, while evidence now exists for the second view of natural populations of *Drosophila*, this particular organism has certain features (principally chromosomal inversions) which bestow upon it a special capacity for carrying structural heterozygotes, together with all the consequences which may flow from this capacity; these features include the absence of crossing-over in the male,[135–137] coupled with a mechanism for eliminating undesirable products of cross-over between structurally different chromosomes from the egg in the female.[138] There is no reason to suppose man to possess either this particular structural mechanism or an optimal degree of genetic heterozygosity, although the possibility is not excluded that equivalent mechanisms may be found. Hence the Committee is compelled to assume that the general genetic structure of human populations corresponds more closely to the classical model in so far as this relates to known genes having individually detectable effects. There is, however, no basis in our present limited state of knowledge for deciding whether the genes responsible for quantitative inheritance do or do not maintain themselves by overdominance in so far as they affect the over-all fitness. It must be emphasized that upon all the hypotheses discussed here, the great majority of radiation-induced mutations will be to alleles which are in the first instance harmful and unlikely to be retained in the population.

### 2. Approaches to quantitative assessment of the genetic consequences of irradiation of human populations

80. On the classical basis, the irradiation of human populations is expected to result in mutations to alleles whose expressions are harmful and lead to their elimination: the expressions of these alleles also contribute to the genetic component of human ills.

81. As yet, nothing is known of the rate of induction by radiation of the mutations responsible for any specific condition in man. In consequence, the discussion which follows will be restricted to broad categories of effects. Only by such a grouping together of the consequences of mutation at a large group of loci can a representative rate of induction of mutations per gene, or a representative doubling dose, be applied: these are the only two parameters expressing a dose-effect relation so far available.

82. It is natural, in applying the results of an experimental science, to try to use a synthetic approach, assessing an effect from the accumulated knowledge of various causes. In the present instance, this means attempting to assess the magnitude of the social consequences of increased mutation by using mutation frequencies per rad at particular loci to build up a combined estimate from the effects of induced mutation at all loci. To use this method, let the total mutation rate to the set of alleles responsible for any specific condition denoted by i be $k_iD$, where D is the genetically significant dose of radiation to the population. By a theorem originally due to Haldane[84] there must on the average be $k_iD$ subsequent eliminations of the mutant alleles through differential failure of reproduction. These are often referred to as genetic deaths, although they may take place through phenomena such as very early abortions, which are of no social significance, as well as through more or less severe disabilities or even premature death. Suppose a fraction $p_i$ are eliminated by socially serious expressions and think of $p_i$ as including some weighting factor whereby such qualitatively diverse end-results as death, physical disability, mental deficiency, etc. may somehow be quantitatively compared. Then the contribution to the social burden is $k_ip_iD$ and the whole contribution of the dose D to the future social burden is $\sum_i k_ip_iD$ over all such specific conditions. The above argument continues to hold whether the mutation involved is to an allele which from the selective point of view is conditionally or unconditionally deleterious, although if the mutant allele is only conditionally deleterious then (*a*) it cannot be eliminated in those situations in which it is selectively favourable, and (*b*) the total elimination rate at any one time may greatly exceed the mutation rate, because the increased fertility of carriers under the selectively favourable conditions increases the gene frequency. If the natural mutation rate $m_i$ is known, then $k_i$ can be re-expressed in terms of the doubling dose $D_{2i}$ by $k_iD_{2i} = m_i$ and for all mutations or a large class of them a mean doubling dose $\overline{D}_2$ can be defined by the equation $k\overline{D}_2 = m$ where $k = \sum_i k_i$ $m = \sum_i m_i$. It is unfortunate that in man we do not know any individual $k_i$ or $D_{2i}$. Still more unfortunately, the fractions eliminated by socially serious expressions, $p_i$, are unknown and may depend upon rather small positive or negative fertility differentials in those who carry the mutant allele without expressing it, if they greatly out-number those in whom it is expressed. Nor can a mean $p_i$ be estimated for mutant human alleles. As a result, the synthetic approach leads to an estimate in such terms that it cannot as yet be satisfactorily related to the social consequences.

83. There is an alternative formulation of the problem by an analytic approach, based upon analysis of the

present social burden in terms of naturally occurring hereditary defects. In this, it is asked, (*a*) what is the social burden $b_i$ due to a given condition denoted by i, whose occurrence is related to the presence of adverse genes? (*b*) Of the genetic burden $b_i$, what fraction $f_i$ is due to recurrent mutation? (*c*) By what fraction $g_i$ will this be increased immediately or in the future by a given fractional change $c_i$ in the natural mutation rate $m_i$? If the change $c_i$ is caused by a genetically significant dose D to the population,

$$c_i m_i = k_i D \text{ or } c_i = D/D_{2i}$$

For all conditions or a large class of them the total genetic burden may be written $b = \sum_i b_i$, that due to recurrent mutation $fb = \sum_i f_i b_i$ and that due to a given dose D as $\sum_i g_i f_i b_i$. If it is assumed that $g_i = c_i$, this may be written as

$$D \sum_i \frac{f_i b_i}{D_{2i}}$$

It may be assumed that $b_i$ and $f_i$ are independent of $D_{2i}$. Then the increased burden may be written

$D/\overline{D}_2 \quad \sum_i f_i b_i$ which may be written $(D/\overline{D}_2)\ f\ b$

where $f = \sum_i f_i b_i \ / \sum_i b_i$

That is, the genetic burden due to a given dose equals

$$\frac{\text{given dose}}{\text{doubling dose}} \times \begin{pmatrix}\text{part of genetic burden}\\ \text{maintained by recurrent}\\ \text{mutation}\end{pmatrix}$$

The relation between induced mutation rate and exposure enters here only through the representative doubling dose. In the present state of knowledge, the analytic approach is more certain than the synthetic approach, because the relation between induced mutation rate and exposure enters only through the representative doubling dose.

84. Even supposing the necessary quantitative relations between mutation rate and dose or radiation exposure to be known, calculation of the social consequences still requires knowledge of one of the sets of parameters, $p_i$ or $f_i$, dependent upon selective behaviour of the mutant alleles. The two approaches are compared from this point of view in table IX. It will be seen that, under conditions in which mutation contributes a large part of the social burden, $f_i$ is relatively well known but $p_i$ is not. Moreover, there is some reason to believe that most heterozygous carriers of individually detectable, socially deleterious recessive alleles are slightly less fertile than average.[88,182,188] If this is true, most $f_i$ are known but most $p_i$ are not. It is concluded that, for most purposes, the analytic approach starting from the current social consequences of unfavourable alleles is to be preferred to the alternative method at the present stage of knowledge.

85. Certain assumptions are implicit but not stated in the analytic approach to the problem adopted here:

First, it has been assumed that the genetic component of the social burden is directly related to the expressed effects of unfavourable alleles. However, the actual social burden realized in a population will be modified by environmental factors such as the extent of care devoted to those affected. For this reason, the actual social burden resulting from a given genetic situation may be heaviest in those countries having the best medical care of the afflicted.

Second, the genetic component of today's social burden has been assumed to be related to the present natural rate of occurrence of mutations and to present selective conditions. Certainly this assumption is not true —the number and distribution of recessive alleles is determined by a long history of past mutation rates and past conditions of selection—yet with our present limited knowledge of the distant past and future no alternative assumption seems to present a possible basis of calculation. A number of considerations indicate that the errors involved may not be too serious:

(*a*) Because of recent improvements in medical care the present genetic burden may be below equilibrium with today's rates of elimination of undesirable alleles, so that the effects of a given increase in mutation rates are underestimated. On the other hand, further improvements in medical care are likely in the future to reduce the socially serious effects of mutations. This process cannot by itself affect the influence of mutation upon the Darwinian fitness of the population, but may affect the future social burden due to present mutations if it occurs without a corresponding effect upon the rates of elimination of the socially deleterious alleles. If this elimination takes place largely through rather trivial effects in heterozygous or other carriers of unexpressed alleles, alleviation of the expressions in grossly affected individuals might be accomplished with little influence upon the process of elimination. We would then have overestimated the future social burden from present mutations. Thus the two sources of error due to improving medical care act in opposite senses.

(*b*) In spite of changes in diet and living conditions of all kinds, there is no reason to suppose that natural mutation rates have changed very greatly; for example, chondrodystrophy, which, in man, is largely a dominant disease, has been prevalent at a low frequency since ancient times.[189] Selection has, by contrast, certainly undergone great changes. This fact is relevant to the recommendation, contained in the report of a WHO study group submitted to this Committee,[11] that research be initiated upon selection in primitive communities while the opportunity to do this still exists.[11] But many of the specific detectable conditions with which we shall be concerned here either arise from dominant alleles, and hence do not in general persist for so many generations as recessives, or else they confer a reduction in selective fitness which has not yet been greatly modified by advances in medical practice. The working assumption may therefore be not too greatly in error for the broad categories of effects to be considered. In point of fact, the effect of improved living conditions and improved medical care is far from obvious. Penrose[140] has pointed out that, besides preserving less fit individuals, this change may in recent years have removed the selective advantage of alleles which confer a degree of protection against an infectious disease in the heterozygote while being grossly deleterious in the homozygote: the classical example is sickle cell anaemia.[141] How many such situations exist is debatable. However, the consequences of improved medical care could be called eugenic rather than dysgenic in such cases. It must also be borne in mind that the total potential intensity of selection in populations has, at least in recent years, not been changing anything like as rapidly as the qualitative basis of it.[142,143] It may be observed here that the possible dys-

genic effect of future improvements in social and medical care is limited by the fact that no more deleterious mutant alleles can be saved for later generations than arise by mutation; moreover, a subsequent withdrawal of improved medical care by some social catastrophe will not cause more losses than would have occurred anyway had it never been present. Only the distribution in time will be altered. Thus, in a constant population, the dysgenic effect of a changing selection does not increase the total number of seriously affected individuals but by contrast, the dysgenic effect of increased mutation does increase the total number of seriously affected individuals. Finally, it has been assumed that radiation-induced mutations and spontaneous mutations are qualitatively similar: that there is no correlation between $D_{21}$ and the degree or kind of manifestation ($f_1$, $b_1$, $p_1$) of a given mutation. This assumption has been discussed in another section and is acceptable to the Committee.

86. On the basis of the above arguments, the Committee considers:

(*a*) That the most satisfactory assessment of the genetic consequences of irradiation of human populations which can be attempted at the present time must be based on the present social burden due to hereditary conditions. Because it must employ the representative doubling dose, it must be restricted to rather broad categories of effects;

(*b*) That the sources of error in an assessment of this kind may not be too serious;

(*c*) That two principal sources of error are related to the extent to which selection changes in the transition from a technologically primitive to a technologically advanced environment and to the extent to which alleles responsible for socially serious conditions may confer small favourable differentials of fertility in the heterozygous, impenetrant or other "carrier" states. Both require to be investigated.

### 3. The current social burden of genetic origin in human populations, its connexion with mutation and radiation exposure

87. In order to make use of the representative doubling dose discussed earlier, there will be considered here only broad categories of damage, each of which may be caused by mutation at any one of many loci, such as the sums of specific clinical conditions or traits within various genetic categories, or biometrical characters such as intelligence, life-span or birthweight, each likely to be dependent upon many genes, or fertility.

#### *Specific traits*

88. For the present purpose, the available information concerning the incidence in man of specific diseases or disabilities of genetic origin is severely limited. Only very few sizeable populations have been surveyed, notably in Denmark,[139] Michigan, U.S.A. and Northern Ireland.[144] Moreover, good quantitative data are only available for clear-cut traits or disorders, and, even here, the genetic interpretation of the facts is almost never straightforward.[110] In the past, various estimates have been made of the frequencies of such specific traits, but the basis of the estimates has not always been clear. Sometimes it has been uncertain whether the trait frequencies referred to were those at birth or in the whole population. The latter estimate would always be expected to be lower, particularly if the trait was severe in its effects. Independent over-all estimates, both in the literature and in reports to this Committee, seem to be in reasonable superficial agreement with each other and are summarized in table X; each of these implies consideration of one or another category out of a total of some 500 clear-cut disorders or traits.[139] However, it has seldom been specified which traits are included and which excluded in them.

89. In order to formulate, upon a precise basis, over-all estimates to which a representative doubling dose can reasonably be applied, the Committee has made use in the present report of a single, definite list of traits and their estimated frequencies of appearance in a single population, namely that compiled by Stevenson[144] for the population of Northern Ireland. In so doing, it is recognized that the frequencies of specific traits will be different in other populations, so that some listed here may not occur at all, and others not in the present list will be prevalent. Nevertheless, such comparisons as can be made of the population frequencies of traits in different parts of Europe, North America and Japan suggest that, while the contributions of individual traits to the total may differ considerably in different populations, the totals, and their division into principal categories, will not vary appreciably so long as present methods of detection are employed.

90. The list of traits compiled by Stevenson has been broken down into separate categories in the following manner, which differs somewhat from that used in the original compilation.[144]

*Category I (table XI (a)-(b)):* Category I includes traits determined by single, harmful mutant alleles. The majority of these are dominant with a high degree of penetrance, but some are autosomal recessive and a few are sex-linked. Most are not recognizable in the affected person at birth. It seems reasonable to assume that in respect of these traits there is no significant selective pressure in either direction against apparently unaffected carriers of the mutant alleles, although this cannot be proved in our present state of knowledge. It would therefore be expected that the ultimate consequence of an increase in mutation rate at each or all of these loci would be a direct effect upon trait frequency. About 110 different mutations are required to explain these traits. No doubt some similar, but separately identifiable, traits are determined by alternative alleles. Of these mutant alleles about 72 are dominant, 30 autosomal recessive and 8 sex-linked recessive. The estimated total of live-born affected is 1.1 per cent.

*Category II (table XII)*: Category II includes a considerable number of traits mostly detectable at birth. A proportion of them sometimes determines intra-uterine death, but this fraction of these conditions is ignored in the present context. Maternal health and intra-uterine environment appear to play a considerable part in determining whether and to what degree they are expressed. Their familial patterns in a community seldom satisfy the criteria of a single mutant expression. In all there is a familial concentration of cases greater than would occur by chance. In some, the family pattern approaches some of the criteria of those included in category I, and it will be clear to the reader that arbitrary decisions have had to be made. The estimated total of live born affected is 1.0 per cent.

*Category III (table XIII (a)-(b))*: Category III comprises two unequal classes of traits. The first and smaller proportion (category III (*a*); table XIII (*a*)) consists of traits which appear to follow closely the ex-

pected family patterns of a single recessive mutant genes, but show a frequency too high to be explained on a basis of mutation pressure alone, unless it is assumed that mutation occurs many times more frequently at the relevant loci than at those loci giving rise to dominant mutations in man or than in the general range of all types of mutation in experimental animals. In the data for Northern Ireland[144] and elsewhere in the United Kingdom, only fibrocystic disease of the pancreas and deaf mutism clearly fall into this category, although other conditions well-known elsewhere such as sickle cell anaemia and thalassemia also belong to it. It is possible, although neither provable or disprovable at present, that the gene frequencies in these conditions are maintained mainly by relative selective advantage in the heterozygous carriers. In deaf mutism several independent mutants contribute to the trait frequency. The two conditions together determine about 37 per cent of the total frequency of recessive traits at birth in the population studied by Stevenson (*loc. cit.*) and have a combined frequency of 0.09 per cent of all live births. The second and larger proportion (category III (b); table XIII (*b*)) of category III is difficult to define and limit. Six examples of serious, "constitutional," diseases are listed in the table, but it is difficult to know where to draw the line thereafter. In different communities the frequencies will vary considerably. It is impossible to estimate frequencies without making some arbitrary decisions as to what will be included; as an example, admission to hospital might be made a criterion. Furthermore, the frequencies depend on the ages to which people live in populations, as in the cases of diabetes and the primary presenile psychoses. Finally, there are environmental factors of importance which vary in different populations. In sum, at least 1.5 per cent of those liveborn will suffer from one or another of this group of disorders.

91. It must be emphasized that the list of traits, trait frequencies and categories outlined above and in tables XI-XIII:

(*a*) Represents only tangible or detectable genetic damage, which in principle, although in practice with great difficulty only, can be assessed by "counting heads";

(*b*) Includes only defects of such severity as to be at least very inconvenient to their possessors;

(*c*) Is certainly an incomplete list, even of such conditions;

(*d*) Ignores maternal/foetal incompatibility and mongolism; in the latter the genetical component appears to be weak, and in the former the relative frequency of the alleles, which is the most important factor in determining proportions of affected infants, would probably not be affected appreciably by increased mutation rates;

(*e*) Excludes a group of individually rare or mild traits which mostly appear to be determined by simple, irregular, dominant genes and are listed in table XIV. Nevertheless, the list gives rise to the expectation that some 4 per cent of the liveborn suffer or will suffer from defects predominantly of genetic origin. Certain comments are pertinent to this estimate:

(1) Any present over-all estimate of total genetic damage must of necessity be minimal. However, even though more sophisticated methods of detection can be expected to increase the present estimates, it is unlikely that in the near future more than a very small number of new specific traits will be discovered, relative to the total so far known. (See also paragraph 104 below.)

(2) The present estimates refer to those born alive. In addition, approximately another ¼ to ½ per cent of foetuses alive after the twenty-eighth week of pregnancy are born dead mainly by reason of detectable developmental defects which may be of genetic origin.

(3) In about half of the affected liveborn, the defect will be detectable at or soon after birth, but in the other half the expression of the genotype will only be apparent in later childhood or in adult life.

92. The division of the 4 per cent affected live-births into categories as outlined above may be summarized as follows:

Category I: About 1 per cent of defects due to single mutants of classical type (majority not recognizable at birth);

Category II: About 1 per cent showing no consistent familial pattern compatible with a simple genetic hypothesis and often having an environmental component in their aetiology (majority recognizable at birth);

Category III: About 1.6 per cent either (*a*) show trait frequencies too high to be maintained by mutation pressure, or (*b*) determine constitutional illnesses whose frequency is also unexpectedly high in relation to their severity.

This division into categories is of great importance for predicting the results of increased exposures of populations to ionizing radiations. The supply of recognizably disadvantageous mutant alleles in a population may be maintained either by recurrent mutations balanced by selection or by selective advantage among individuals in whom the disadvantage is not expressed; that is, by a balance between opposing selective forces. A reasonably small increase in mutation rate cannot be expected to affect greatly the pattern of gene elimination and so should cause at equilibrium an equal fractional increase in the genetic damage due to alleles maintained in the first manner (corresponding to traits in category I above, together with an unknown fraction of those in categories II and III), but a much smaller increase in the genetic damage due to alleles mentioned in the second manner (corresponding to an unknown fraction of the traits in categories II and III above). It follows that permanent exposure of a population to an extra genetically significant dose D per generation may be expected eventually to give rise to an increase in the incidence of live births who are or will be affected of between $D/\overline{D}_2$ per cent and $4D/\overline{D}_2$ per cent where $D_2$ is the representative dose. If the increased irradiation were to occur in only one generation to a population of fixed breeding size P, it follows, by a principle of detailed balancing, that the calculated total number of affected live births is expected to lie between

$$\frac{D}{\overline{D}_2} \times \frac{P}{100} \text{ and } \frac{D}{\overline{D}_2} \times \frac{4P}{100}$$

93. It must be borne in mind that the mutant alleles concerned in the above estimates range all the way from severe dominant to true recessive, and the time during which the genetic damage either climbs to equilibrium or completes its expression after exposure of a single generation varies in turn from one or two to many tens of generations. Thus, in the case of irradiation of the present population, the damage may well become expressed under social and technological conditions which

cannot even be imagined today, and which may grossly affect the relation between gene elimination and its social consequences. Some geneticists therefore question the utility of assessment of a hazard so far in the future.[145]

94. In conclusion, it must be emphasized that even for this most tangible kind of genetic damage, far more work is needed on family studies, on sib-correlations, incidence in consanguineous marriages, twin studies etc., so as to establish more accurately the genetic nature of the traits listed here and other conditions. If Governments wish to know the genetic health of their peoples it will be necessary for them to support the necessary work. It has been argued that, at present, populations under review by single institutes of human genetics cannot conveniently exceed $3 \times 10^6$.[11] However, the problems related to both the scale and scope of such work involve questions of general medical education and co-operation as well as legal and administrative aspects which merit the attention both of Governments and public health authorities. For example, a number of human geneticists feel that the present *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death* is inadequate in its present scope and form for scientific purposes in the classification of congenital conditions.

### *Biometrical characters*

95. Many important characteristics of man, among which specific mention must be made of intelligence, lifespan and birthweight, vary continuously in natural populations about some mean which is often close to a selectively optimal value. Where this is true, selection may act on the phenotype quite largely by reducing the variance, rather than by shifting the mean; to that extent, it is normalizing or stabilizing selection.[148] Such quantitative variation is often influenced by many genes in combination whose separate effects cannot be distinguished, in contrast to those exhibiting specific qualitative effects and discussed above. These genes can only be studied statistically, principally through that part of the variance of the character for which they are responsible. This variance may be of considerable importance as a social burden or loss of population fitness. Discussion of the consequences of possible shifts in the mean of such characters will be deferred to paragraph 99 below.

96. The genetic component of the variance has been tentatively estimated in the case of birthweight by Penrose and by Robson as some 40 per cent,[149,185] half of it associated with maternal genotype, and in the case of intelligence as ½, or perhaps as high as ¾.[150] In each of these cases, the more extreme phenotypes of the distribution are observed to be associated with a loss in viability or reproductive fitness and with social burden. Thus on the basis of Penrose's[149] and Karn and Penrose's[151] work it can be estimated (see appendix) that the genetic component of this variance was associated with the occurrence of some 1.6 per cent of stillbirths and neo-natal deaths among males. Mather[152] has calculated that on an intelligence quotient scale normalized to mean 100 and standard deviation 15, 2.3 per cent of children will fall below intelligence quotient 70, and a doubling of the heritable component of variance, assuming no shift in the mean, would increase this number by a factor which may lie between 2.2 and 2.9; this calculation depends upon the assumption of a Gaussian distribution of the measured variable at the tails of the distribution, where the assumption is itself least sure and confers greatest uncertainty. Mather's calculation is a useful guide to the upper limit of the social burden expected to be conferred by radiation-induced genetic changes in the variance of intelligence (but see footnote to paragraph 102 below).

### *Relationship of genetic component of variance to mutation*

97. The relationships of selection, genetic variability and mutation in a character of relatively low selective importance (bristle number) have been studied by several authors in *Drosophila*. In particular, Clayton and Robertson[153] have been able to show that the natural additive genetic variance in an outbred population, from which their experimental flies were originally drawn, exceeded the spontaneous increase in genetic variance per generation by a factor of 1,000, and observations by Paxman (quoted by Mather[157,196]) support this conclusion. By comparing irradiated and unirradiated populations, Clayton and Robertson further showed that some $10^5$r would have been needed to produce an increment equal to the natural variance. With selective neutrality such a genetic variance in the natural population is perfectly compatible with an established equilibrium between mutation and a degree of inbreeding due to limited effective population size. For a character of greater selective importance the genetic variance displayed by the population would exceed the increment per generation by a correspondingly smaller factor. Haldane[154] has pointed out that, in the cited case of birthweight, selection removes 10 per cent of the observable variation per generation. If this selection makes no distinction between variation of genetic and of environmental origin, it poses the question: How is the genetic component of variance maintained?

98. Robertson[155] has recently discussed the theoretical consequences of selection for optimal central phenotype. It appears that this process cannot of itself maintain genetic variability, even though heterozygotes have intermediate values of the character (see Fisher[156]). The genetic variation must therefore be maintained either by the selective advantage, in some circumstances, of the heterozygotes as such (i.e., the majority of the genes are individually heterotic) or by mutation. Lerner[138] has argued for expecting heterosis among genes of this kind, his argument being based partly upon an anticipation of improved buffering or canalization in the developmental processes of heterozygotes and partly upon experimental evidence (of which, however, a considerable fraction is drawn from *Drosophila*) and general experience of inbreeding. Paxman[157,196] has, on the other hand, failed to find evidence of such heterosis, despite a search for it. Thus evidence of the necessary heterosis is by no means conclusive and further data are much needed. At the same time, the high rate of selective elimination does not seem compatible with replacement by mutation at the low rates observed in experiment. This difficulty may well, however, be less than it seems, because where many genes of similar effect contribute to the variation of a character, only a portion of the total genetic variability present in the population is manifest as variation actually observable by difference among the phenotypes of the individuals. In a polygenic system, alleles at different loci can exert their actions in opposite directions and thus balance out one another's effects, so that some of the variation lies hidden as balanced differences within the genotypes of the individuals.[197] The proportion of the total variability so hidden increases directly with the

number of genes in the system, and it may go up even higher if the genes are linked. The hidden variability is released by recombination of the genes which balance one another, to become exposed as phenotypic differences, and this rather than mutation is the immediate source of replenishment of the observable variation eliminated by natural selection. Ultimately replenishment must depend on mutation; but, by virtue of the reservoir of hidden variability, the accumulation of new variation from mutation need balance loss through selection only in the long term. Thus the rate of selective elimination observed at any given time need not provide a reliable indication of the rate at which new variation is arising by mutation. Furthermore, the selective elimination of any fraction of the observable variation represents the loss of a much smaller fraction of the total genetic variability. Thus with birthweight, 10 per cent of the observable variation is eliminated in each generation, but this loss could represent as low a fraction as 1 per cent of the total genetic variability for this character in the population if it depended on the simultaneous action of no more than 10 polygenes. Mutational increments quite low in relation to the total variability might thus suffice to maintain the plygenic variation of a character against the erosion of selection. This is a matter on which more data are needed; but pending their appearance it would seem conservative to suppose that $\frac{1}{10}$ of the genetic variability of most quantitative characters is the greatest fraction which it is necessary to envisage as replenished by mutation in each generation, and the fraction may indeed generally be very much smaller than this. The Committee emphasizes, however, that there is at present no satisfactory experimental basis for determining whether this fraction is large or small even in experimental species, much less in man. Clearly, further data are much needed in this whole area.

*Shifts in mean values of metrical characters*

99. Besides contributing to the variance of a metrical character, genetic factors may impose a social burden by affecting the position of its mean. Three quantities must be considered: the population mean, the selective optimum and the social optimum. The three may all differ, as is illustrated in table XV for the characters mentioned in paragraph 95.

100. The great majority of well-studied single-locus mutants in experimental organisms are hypomorphic;[159,160] that is, they appear to lead to a reduction in the function or character most immediately affected. There is good *a priori* reason to expect this, as random interference with a complex machine will more often be destructive than constructive. In consequence it might be expected that most mutations and mutant alleles would act so as to diminish the population mean relative to the selective optimum. However, it must be questioned whether there are sufficient grounds for extrapolating this view to polygenes affecting quantitative characters. Provided that the changes are not so large that they excessively disrupt the organism's general control of the developmental channels concerned, is it not just as reasonable to suppose that a particular organ of social import—for example, the brain—may in fact benefit from hypomorphic changes in most other organs, due to a compensating diversion of resources, so that many such changes would be hypermorphic for it? Among the characters of table XV, it is of interest that the facts concerning birthweight[161] fit the classical expectation, but that those concerning intelligence[161] possibly do not.

101. In the case of birthweight, it can be calculated (see appendix) that the difference by which Karn and Penrose observed the selective optimum to exceed the population mean in males is associated with 0.4 times as many deaths at or near birth as the total variance and about 0.7 times as many as the estimated genetic component of variance. What proportion of this deviation is genetic in origin is not known, but it is clear from the arguments outlined above that recurrent mutation could easily be the principal cause; if so, continued application of a doubling dose to every generation might eventually bring about an increased incidence of some 1.2 per cent in the deaths at or near birth. This selection acts so as to diminish the difference between the mean and the selective optimum by about 7 per cent per generation.[154] If it does not distinguish between genetic and environmental components of the difference, the genetic effects of an altered mutation rate upon the mean must be expected to be spread over some ten generations, and any shift to a new equilibrium value will take a comparable period of time.

102. The case of intelligence is somewhat different. Here the social optimum lies far away from the selective optimum, and it is not simple even to decide what must be computed to assess the social implications of a given change. Moreover, the genetic picture is complicated by a high degree of phenotypic assortative mating.[158] For the purposes of this report Mather's calculations[152] based on United Kingdom figures have been available. Mather based his calculations concerning the effect of increased variance upon an unchanged mean but he also considered a situation in which increased mutation was associated also with a falling mean, such that the effects mediated through mean and variance were roughly comparable in magnitude. However, there is no indication in the figures at present available for the United Kingdom that the population mean lies below the selective optimum; this gives rise to a presumption that increased mutation might not depress the mean appreciably. It seems important to try to find out if this situation is true and, if so, whether it is peculiar to the somewhat special demographic situation in the United Kingdom or is more general, since it raises a question as to how such a position might arise and be maintained.[158] In the meantime, it seems premature to attempt here any assessment of the expected effects of increased mutation rate upon mean intelligence. The social consequence of hereditary shifts in intelligence probably occur mainly as a result of shift in the numbers at the extremes of the I.Q. distribution (of which only changes at the lower end are numerically cited in para. 96 above);* a change in variance will in any event affect these more markedly than an equal change in the mean. Part of the difficulty in discussing shifts of the mean intelligence as measured by intelligence quotient may lie in the need to consider small intelligence quotient differences; it is possible that present tests of intelligence are not sufficiently well-developed and free from bias associated with other variables to serve as suitable material for close quantitative analysis. The problem of further progress in this field may thus depend upon developments in pure human biology. In any

* An increase in variance without change in mean also causes an increase in the classes of highest I.Q. upon which it has been claimed that much of human progress depends. Any judgement concerning the relative value of this increase is a social one; it has therefore not been computed here and no attempt has been made in this report to offset its value against the social burden represented by a calculated increase in the numbers of individuals with I.Q. <70. It must be borne in mind that there is some reason to believe that the distribution of variance due to new mutations would not be symmetrical, and that most of the increase would be in the direction of lowered intelligence.

over-all discussion of intelligence, it is necessary to bear in mind that it is affected not only as a biometrical character by many genes with small interacting effects, but by known specific loci, radiation-induced mutations at which will almost always cause serious harm to any individual in whom the mutant alleles are expressed.

103. In the case of the life-span, the data of Russell[162] on the progeny of male mice irradiated by fast neutrons suggest the existence of the kind of effect which would be expected from classical hypomorphic mutations; that is, the occurrence of radiation-induced mutations to a series of weakly dominant alleles which collectively cause a shortening of the life span. However, the magnitude of any corresponding effect which might be expected in man is entirely unknown. It might seem at first sight as if increased variance in life span would confer little or no increased social burden, but be selectively neutral as long as it affected only groups beyond the age of child-bearing. However, if the mechanism of shortening were related to an effective contraction of time-span of the physiological processes, the reproductive period might be adversely affected, and the selective optimum for life-span might then be very long. It is essential that the work of Russell be confirmed and extended in order to have an adequate experimental basis in other organisms for consideration of the possible implications for man. Russell's experiments are in line with effects observed in irradiated mammalian tissue culture cells and other organisms, among which the survivors frequently carry slightly deleterious dominant alleles,[18,194] as well as with observed correlations between the life-spans of related individuals suggestive of genetic influences.[163]

*Fertility*

104. The most direct expression of the effect of undesirable mutations is through the net reproduction per generation or fertility differentials. Penrose[93] has suggested that, in man, some 50 per cent of the zygotes of each generation fail to contribute to the next one by reproduction, and has suggested, by analogy with other metrical characters, that some half of this might be of genetic origin. Penrose also points out that, on the same analogy, much of the infertility might well be due to the presence of conditionally deleterious alleles which are not primarily maintained by mutation and are essentially unaffected by changes in mutation rate. However, one may compare such a rate of elimination with an estimate of the total rate of mutation to unconditionally deleterious alleles such as was derived in paragraph 74 above.

105. Applying a representative doubling dose of 30 rad to the estimate of paragraph 74, the natural rate of mutation to deleterious alleles would amount to some $\frac{1}{8}$ (i.e., approximately 30/250) per haploid gamete or $\frac{1}{4}$ per diploid zygote. At equilibrium, these could be eliminated by $\frac{1}{4}$ of zygotes failing to reproduce. These estimates of mutation are therefore consistent with that of Penrose concerning fertility, and with the assumption of genetic equilibrium, which suggests the possibility that at present $\frac{1}{4}$ of all zygotes fail to contribute to the next generation because of the presence of deleterious alleles maintained by recurrent mutation. Taking this to be an upper estimate, indefinite application of a doubling dose to each generation might eventually extend the fraction of non-contributing zygotes from $\frac{1}{2}$ to $\frac{3}{4}$ and require a doubling of average family size for a previously constant population to maintain itself. This appears to be well within human capacity. If it be further supposed that the mixture of dominants and recessives concerned has an average persistence in the population of 10-100 generations, then exposure of one generation to 10 or 100 times the doubling dose would impose the equivalent of the same load for a period of 10 or 100 generations. Such doses are of the magnitude 300-3000 rad, and in a range which is such as to render further considerations of genetic problems redundant. It therefore seems probable that the human race has ample breeding capacity to survive the genetic consequences of any foreseeable radiation exposure.

*Pool of recessive mutants*

106. Examination of the offspring of consanguineous marriages can give information concerning the total of deleterious recessive mutant alleles in a population, and Morton, Crow and Muller[88] have recently shown how the results of statistical surveys of this kind can be expressed in the form of a number of lethal equivalents per member of the population. In the absence of a figure operationally equivalent to the total number of genes per individual, this information does not relate directly to the social burden upon the population nor, without assuming an average dominance, can it be related to the natural mutation rate. The number of lethal equivalents per head is, however, in its own right, a most important parameter describing the genetic state of a population, derivable from a purely demographic type of information. Governments would do well to investigate it in their populations.

107. It is also possible in principle to compare the number of lethal equivalents, derived from vital statistical information, with the number of recessive deleterious genes found in the direct intensive surveys of smaller numbers of consanguineous marriages. Ideally, such studies should cover the whole period during which identical alleles are together and so liable to give rise to an effect through homozygosity; thus not only the number and viability but also the fertility of the progeny of consanguineous marriages should be investigated; a preliminary study of this kind has been initiated by Fraser.[193] Such a comparison could be of great importance as indicating what fraction of the total recessive deleterious pool we know about, through recognizable specific effects. At the present time the evidence of both kinds is very scanty. By direct examination of a north Swedish population, Böök has estimated that about three recessive deleterious genes are carried per individual.[87] However, using the criteria of Stevenson, this figure would be only 0.8-1.7.[144] Stevenson, himself, in a somewhat smaller sample, has found 0.5-0.9.[144] It is not possible to estimate accurately what is the reproductive fitness of the afflicted individuals, relative to the general population, but it is reasonable to suppose that the average would lie between 20 per cent and 80 per cent. Probably, therefore, the best direct intensive investigations today show up about 0.2-0.8 post-natal lethal equivalents per individual in the general population. Following Morton, Crow and Muller's analysis of the work of Sutter and Tabah,[85,86] but excluding stillbirths and neo-natal deaths, it is likely that a total of some 2-2.8 post-natal lethal equivalents per individual are present in their population. This suggests that present recognition encompasses somewhere between 7 per cent and 40 per cent of the total deleterious recessive damage which arises. These numerical figures reflect the strictness of the particular criterion employed by Stevenson in his use of the term "recessive".

108. The specific genetic conditions whose incidence is reported by Stevenson are divided into dominant and

recessive conditions; a most striking feature of the data is that the total incidence of rare dominant conditions exceeds that of recessives by a factor of 10. If a correction is applied for those recessive conditions not at present recognized, using the figures derived in the preceding paragraph, the ratio of total incidence of recessive conditions to total incidence of dominant conditions shifts from 0.1 to between 0.25 and 1.4 and the total incidence is increased by a factor of between 1.2 and 2.3. The calculation is now relatively insensitive to the exact criterion of recessivity employed, provided that it is the same throughout. It perhaps serves to give some idea of the limits of confidence which can be placed upon current estimates of the genetic social burden due to specific recognizable conditions.

109. It is of some interest to compare the ratio of the observed rates of elimination of deleterious recessive and dominant alleles, corrected as in the previous paragraph, with that to be expected from equilibrium with forward mutations. In mice, the ratio of recessive to dominant lethals occurring naturally appears to be about 2.5:1 or 3:1.[107,164] (It is very different for *Drosophila*, perhaps as low as 0.1:1, but if *Drosophila* has much less complex genes than mouse or man, it may be a poor guide.) If the ratio of natural rates is similar in man and mouse, the corrected ratio of elimination rates, between 0.5:1 and 2.8:1, is in reasonable agreement with it, but suggests that the recessive alleles might, if anything, tend to be on the average slightly deleterious rather than advantageous in the heterozygous state.

TABLE I. MEASURED OR CALCULATED VALUES OF NATURAL MUTATION RATES IN MAN[111, 169]

| Trait studied | Mutants per tested gamete |
|---|---|
| *Autosomal dominants (direct observation)* | |
| Epiloia | $8 \times 10^{-6}$ |
| Achondroplasia | $45 \times 10^{-6}$ |
| Aniridia | $5 \times 10^{-6}$ |
| Retinoblastoma | $4–23 \times 10^{-6}$ |
| Partial albinism with deafness | $4 \times 10^{-6}$ |
| Microphthalmos | $5 \times 10^{-6}$ |
| Neurofibromatosis | $1.3–2.5 \times 10^{-4}$ |
| Average of 7 loci | $4 \times 10^{-5}$ |
| *Rare dominant* | |
| Porcupine | $<10^{-9}$ [a] |
| *Sex-linked recessives (direct)* | |
| Hemophilia | $3 \times 10^{-5}$ |
| Duchenne's type muscular dystrophy | $4–10 \times 10^{-5}$ |
| *Autosomal recessives (indirect)* | |
| Albinism | $2.8 \times 10^{-5}$ |
| Ichthyosis congenita | $1.1 \times 10^{-5}$ |
| Total colour blindness | $2.8 \times 10^{-5}$ |
| Infantile amaurotic idiocy | $1.1 \times 10^{-5}$ |
| Amyotonia congenita | $2.0 \times 10^{-5}$ |
| True microcephaly | $4.9 \times 10^{-5}$ |
| Phenylketonuria | $2.5 \times 10^{-5}$ |
| Average of 7 loci | $2.4 \times 10^{-5}$ |

[a] Very rough estimate: see ref. 83.

TABLE II. MEASURED OR CALCULATED VALUES OF NATURAL MUTATION RATES AT SINGLE LOCI OF ORGANISMS OTHER THAN MAN

| Mutants studied | Mutants per tested gamete | |
|---|---|---|
| *D. melanogaster* | | |
| Average for 9 sex-linked recessive visibles in XXY female | $3 \times 10^{-5}$ [a] | Muller, Valencia and Valencia[171] |
| Average for 4 autosomal recessive visibles in Oregon-R females | $2.5 \times 10^{-6}$ | Glass and Ritterhof[172] |
| Average for 4 autosomal recessive visibles in Oregon-R males | $4.5 \times 10^{-5}$ | Glass and Ritterhof[172] |
| Average for about 12 sex-linked recessive visibles in Oregon-R females | $2.4 \times 10^{-6}$ | Glass and Ritterhof[172] |
| White eye | $0.7–3.7 \times 10^{-5}$ | Bonnier and Lüning[173] |
| 8 sex-linked recessive visibles in mutable Florida stock | $3 \times 10^{-5}$ | Demerec[174] |
| *Mice* | | |
| Average of 7 autosomal recessive visibles in male | ca. $7 \times 10^{-6}$ | Russell[76], Carter *et al.*[75] |
| *Bacteria* | | |
| Average of about 30 biochemical back-mutations | $4.5 \times 10^{-9}$ | Glover in Demerec *et al.*[53] |
| Range of above | $10^{-11}$ to $4 \times 10^{-8}$ | Glover in Demerec *et al.*[53] |

[a] But approximately $5 \times 10^{-6}$ if allowance is made for the fact that the rate of sex-linked recessive lethals was abnormally high in this experiment. *Drosophila* rates vary very widely with stage of life, cell-development, etc.

TABLE III. MEASURED OR CALCULATED VALUES OF TOTAL NATURAL MUTATION RATES FOR CLASSES OF LOCI IN ORGANISMS OTHER THAN MAN

| Class of mutants studied | Mutants per tested gamete | |
|---|---|---|
| *D. melanogaster* | | |
| Sex-linked recessive lethals: | | |
| young sperm | $1.0 \times 10^{-3}$ | Spencer and Stern[32]; Uphoff and Stern[31] |
| aged sperm | $2.0 \times 10^{-3}$ | Caspari and Stern[33]; Uphoff and Stern[31] |
| range for various wild type stocks | $0.7–11 \times 10^{-3}$ | Demerec[174] |
| mutable Florida stock | $1.1 \times 10^{-2}$ | Demerec[174] |
| XXY females | $7.0 \times 10^{-3}$ | Muller *et al.*[171] |
| | $1.8 \times 10^{-3}$ | Muller[108] |

TABLE IV. RATES OF RADIATION-INDUCED MUTATIONS AT SINGLE LOCI IN ORGANISMS OTHER THAN MAN

| Loci studied | Mutations/locus/r | Source |
|---|---|---|
| *D. melanogaster* | | |
| Average of 9 recessive visible autosomals in oocytes, oogonia | $1.4 \times 10^{-8}$ | Muller, Valencia and Valencia[171] |
| Average of 9 recessive visible autosomals: | | |
| spermatogonia | $1.5 \times 10^{-8}$ | Alexander[70] |
| mature sperm | $6 \times 10^{-8}$ | Alexander[70] |
| mature sperm | $4.4 \times 10^{-8}$ | Patterson[175] |
| mature sperm | $5.2 \times 10^{-8}$ | Demerec[176] |
| White eye mature sperm | $0.8–1.2 \times 10^{-7}$ | Bonnier and Lüning[173] |
| *D. virilis* | | |
| Average of 7 sex-linked recessive visibles: | | |
| mature sperm | $7.6 \times 10^{-8}$ | Girvin[177] |
| *E. coli* | | |
| Average of about 30 biochemical back-mutations | $2.7 \times 10^{-10}$ | Glover in Demerec *et al.*[53] |
| *Mice* | | |
| Average of 7 recessive visible autosomals: | | |
| spermatogonia | $2.5 \times 10^{-7}$ | Russell[76] |

TABLE V. TOTAL RATES OF RADIATION-INDUCED MUTATIONS IN CLASSES OF LOCI IN ORGANISMS OTHER THAN MAN

| | Mutations/r | |
|---|---|---|
| *D. melanogaster* | | |
| Sex-linked recessive lethals in | | |
| aged sperm | $2.3 \times 10^{-5}$ | Uphoff and Stern |
| young sperm | $2.8 \times 10^{-5}$ | Uphoff and Stern |

TABLE VI. SURVEYS OF HUMAN POPULATIONS FOR PURPOSES OF RADIATION GENETICS

| Experiment | Reference | Number of irradiated parents | Dose range in rads | Results: Abortions Irrad. | Abortions Control | Still-births Irrad. | Still-births Control | Congenital malformations[a] (live births) Irrad. | Congenital malformations[a] (live births) Control | Sex-ratio (live births) Irrad. | Sex-ratio (live births) Control | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Survey of pregnancies in Hiroshima and Nagasaki | Neel and Schull[111] | approx. 27,000 ♀ | 8–200 | | | 546 | 408 | 300 | 294 | regression lines based upon several doses: for raw data see Ref. 111, Chapter VII. | | Observations include sex-ratio, frequency of stillbirths and neonatal deaths, birthweight, occurrence of congenital malformations, and, for a random 30% sample reexamined at age 9 months, certain bodily measurements and the occurrence of additional malformations not apparent at birth. |
| | | approx. 14,000 ♂ | 8–200 | | | 33,181 | 31,559 | 33,527 | 31,904 | | | Non-significant decrease in sex-ratio $k = -5.5 \times 10^{-5}$/rad for irradiated mothers: among earlier births[123] k was $-8 \times 10^{-5}$ and significant. Slight non-significant increase for irradiated fathers in earlier births[123]. |
| Survey of offspring of French patients | Turpin, Lejeune and Rethore[117, 165] | 289 ♂ | 4–450[b] | 47 | 46 | 8 | 7 | 9 | 8 | 225 | 358 | Diminution of sex-ratio for irradiated mothers significant compared to irradiated fathers ($\chi^2 = 4.2$), not significant compared to controls. k between $6 \times 10^{-5}$/rad and $12 \times 10^{-5}$/rad. |
| | | | | 452 | 742 | 405 | 696 | 405 | 696 | 405 | 696 | |
| | | 97 ♀ | 40–450[b] | 26 | 18 | 7 | 5 | 5 | 1 | 63 | 130 | No account taken of age and parity. Inquiry by questionnaire. |
| | | | | 162 | 254 | 136 | 236 | 136 | 236 | 136 | 236 | |
| Follow-up on progeny of women treated for sterility | Kaplan[119] | 311 ♀ | ca. 60 | 91 | | 2 | | 3 | | 191 | | No control as yet. Very low sex-ratio significantly different from 0.515, $k \backsim -8 \times 10^{-4}$/rad. |
| | | | | 513 | | 513 | | 513 | | 409 | | |
| Surveys of children of American radiologists | Crow[166] | 654 ♂ | Unknown accumulation of many small doses | Abortions and Still-births Irrad.: 274 | Control: 215 | | | | | | | No data on malformations or sex-ratio. Inquiry by questionnaire. |
| | | | | 1,653 | 1,348 | | | | | | | |
| | Macht and Lawrence[126] | 5,461 ♂ | | 766 | 548 | 328 | 216 | 2,090 | 1,766 | | | Non-significant increase in still-births and abortions. |
| | | | | 5,461 | 4,484 | 5,461 | 4,484 | 4,127 | 3,390 | | | Significant increase in malformations ($\chi^2 = 6.7$) includes many very slight malformations or other diseases, but remains significant if restricted to cardiac malformations only. Inquiry by questionnaire. |

[a] Earlier literature surveys by Maurer[168] and by Murphy and Goldstein[167] respectively revealed $\frac{7}{229}$ and $\frac{7}{417}$ malformations among mothers who had received heavy doses, but without controls.

[b] Taking the gonad dose to be 1/3 the skin dose.

TABLE VII. CONTENT OF DNA IN VARIOUS TYPES OF CELLS[20a]

| Organism and cell types | | gm DNA-phosphorus per cell | gm DNA per cell |
|---|---|---|---|
| Bacteria | *B. lact. aerog.* | $2 \times 10^{-15}$ | |
| | *E. coli* | $2.3 \times 10^{-15}$ | |
| | (compare T2 bacteriophage | | $3 \times 10^{-16}$ per particle) |
| Microbes | *Penicillium* | | $1.5 \times 10^{-13}$ per spore |
| | *Aspergillus* | | $1.9 \times 10^{-12}$ per spore |
| | Yeast | | $6.2 \times 10^{-15}$ |
| *Drosophila* | Salivary glands ♂ | $2.6 \times 10^{-11}$ | |
| | ♀ | $2.8 \times 10^{-11}$ | |
| | Diploid cells (limb) | | $1.7 \times 10^{-13}$ |
| Rat | Diploid cells | $0.6–1.0 \times 10^{-12}$ | |
| Mouse | Submaxillary glands (diploid) | $0.7–1.4 \times 10^{-12}$ | |
| Man | B.M. | $8.7 \times 10^{-13}$ | |
| | Leukocytes | $8.6 \times 10^{-13}$ | |
| | RBC | $7.0 \times 10^{-13}$ | |
| | Liver | $1.0 \times 10^{-13}$ | |
| | Kidney | $8.7 \times 10^{-13}$ | |

[a] For a further extensive table, see ref. 21.

TABLE VIII. CALCULATED DOUBLING DOSES IN ORGANISMS OTHER THAN MAN[178]

| Organism | Loci | Conditions of irradiated cell | Doubling dose (rad) | Ref. |
|---|---|---|---|---|
| *Zea mays* | 4 recessive visibles | Pollen | 28 | 179 |
| *Oenothera*, *Prunus* | Self-incompatibility | Pollen | 60 | 180, 181 |
| *Drosophila* | Sex-linked lethals | spermatozoa | 50 | 31–33 |
| | | aged spermatozoa | 140 | 31–33 |
| | | oöcytes and oögonia | 390 | 171 |
| Mouse | 7 recessive autosomal visibles | spermatogonia | 30 | 76, 69, 75 |
| | Dominant lethals | through spermiogenesis except time of peak sensitivity | <50 | 164 |
| | Sex-ratio[a] | spermatogonia | 50 | 125 |

[a] Approximate calculation for natural rate corresponding to age of mice used in 76, 69, 75.

TABLE IX. COMPARISON OF APPROACHES TO QUANTITATIVE ASSESSMENT OF MUTATIONAL DAMAGE

| Fertility of carriers of the unexpressed mutant allele | Knowledge of $p_i$ | Knowledge of $f_i$ | Relative effect of mutation upon frequency of condition |
|---|---|---|---|
| Higher than average | $p_i = 1$ | Small but unknown | Small |
| Lower than average | Small but unknown | $f_i = 1$ | Large |

TABLE X. SOME OVER-ALL ESTIMATES OF SOCIAL BURDEN

| Author | Class of traits | Incidence: In population | Incidence: At birth |
|---|---|---|---|
| *Stevenson*[144] | Rare heterozygotes | $1.36 \times 10^{-2}$ | $1.9 \times 10^{-2}$ |
| | Rare homozygotes | $1.0 \times 10^{-3}$ | $2.1 \times 10^{-3}$ |
| | Rare sex-linked | $1.6 \times 10^{-4}$ | $4 \times 10^{-4}$ |
| | Common traits of hard interpretation | $1.0 \times 10^{-2}$ | $1.5 \times 10^{-2}$ |
| | TOTAL | $2.7 \times 10^{-2}$ | $3.6 \times 10^{-2}$ |
| *U.S.A. Panel*[145] | Tangible defects of genetic origin (1/2 total) | | $2 \times 10^{-2}$ |
| *Kemp*[139, 191] | Physical malformations and defects | | $< 1 \times 10^{-2}$ |
| | Severe hereditary afflictions | | $< 2\text{-}3 \times 10^{-2}$ |

TABLE XI. LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY I
(A) AUTOSOMAL DOMINANT TRAITS

| *Trait* | *Remarks* | *Phenotype frequency per million* | |
|---|---|---|---|
| | | *Births* | *Living* |
| Achondroplasia | Chondrodystrophy 'Foetalis' | 28 | *28* |
| Arachnodactyly | Marfan's syndrome | 60 | *26* |
| Brachydactyly (major) | Hands and feet affected—mean stature reduced | 6 | *6* |
| Ectrodactyly | Including all types of 'split hand' | 30 | *20* |
| Multiple exostoses | Only a minority are troublesome | 400 | *400* |
| Osteitis deformans | | 30 | *25* |
| Osteogenesis imperfecta | Fragilitas ossium. Several types, all irregular dominant—genetical relationship not known | 60 | *25* |
| Cranio-facial, cranio-cleidal, mandibulo-facial dysostoses | A series of separate disorders individually uncommon | 30 | *20* |
| Hypertelorism | | 20 | *8* |
| Ataxia | Dominant hereditary ataxias—a group of which Friedrich's is the best defined | 200 | *110* |
| Epiloia | Tuberose sclerosis (9 living sporadic cases in N.I.) | 30 | *7* |
| Huntingdon's chorea | (Three families in N. Ireland known) | 10 | *8* |
| Hydrocephaly internal obstructive | Includes stenosis of and forking of aqueduct of Sylvius—probably each due to irregular dominant gene | 1,230 | *25* |
| Peroneal muscular atrophy | Charcot-Marie-Tooth disease | 40 | *24* |
| Spastic diplegia | | 100 | *20* |
| Dystrophia myotonica | | 40 | *24* |
| Muscular dystrophy, limb girdle | Faces affected | 25 | *14* |
| Myositis ossificans | | 20 | *10* |
| Deaf mutism (Deafness total hereditary) | Estimated 3 per cent of all hereditary deaf mutism due to dominant genes | 46 | *46* |
| Deafness perception | Early onset dominant type | 12 | *12* |
| Deafness and cataract | Severe early onset deafness and cataract | 6 | *6* |
| Deafness | Absence of or atresia of external auditory meatus | 12 | *12* |
| Neurofibromatosis | Von Recklinghausen's disease | 300 | *200* |
| Polyposis of colon, multiple | | 100 | *55* |
| Alopecia areata | | 700 | *700* |
| Anhidrotic syndrome | Anhidrotic "ectodermal" Dysplasia | 34 | *5* |
| Cephalo-facial haemangiomatosis | Naevoid Amentia | 30 | *7* |
| Epidermolysis bullosa | | 100 | *40* |
| Pityriasis rubra pilaris | | 20 | *20* |
| Telangiectasis haemorrhagica | | 100 | *12* |
| Tylosis palmaris et plantaris | | 35 | *35* |
| Urticaria pigmentosum | | 90 | *90* |
| Xanthoma tuberosum multiplex | Cutaneous xanthomatosis and essential hypercholesteraemia | 40 | 25 |
| Willebrand's disease | Haemophilia—like syndrome | 25 | *8* |
| Polycythaemia vera | | 45 | *20* |
| Spherocytosis | Acholuric jaundice | 60 | *25* |
| Thrombocytopenia chronic recurrent | | 60 | *45* |
| Porphyria | Dominant type genotype detectable but seldom causes illness | 200 | *130* |
| Diabetes (insipidus) | | 40 | *20* |
| Cystic disease of lungs | (Included here "congenital" bronchiectasis) | *500* | 400 |
| Megacolon | Hirschsprung's disease | 100 | *10* |
| Aniridia | Dominant very irregular degree of manifestation and probably several dominant mutants can cause | 60 | 60 |
| Cataracts "congenital" | Types detected at birth or early—probably several different types | 160 | *150* |
| Cataracts, senile and pre-senile | | 2,000 | *2,000* |
| Choroidal sclerosis | Several types varying in severity and depending largely on location for disability caused | 500 | *500* |
| Colobomata | Common—vary from slight iris defect to big defects of iris choroid and retina involving macula | 250 | *200* |
| Corneal dystrophies | Several types of very variable severity | 140 | *140* |
| Fundal dystrophies | | 150 | *150* |
| Glaucomas, infantile and juvenile | | 100 | *100* |
| Hypermetropia | Can only be arbitrarily accepted as a segregating trait at about 10 | 100 | *100* |
| Keratoconus | | 20 | *20* |
| Macular dystrophies | At least two dominant types occur | 100 | *100* |
| Nystagmus | Familial idiopathic non-albinotic usually lateral | 700 | *700* |
| Retinitis pigmentosa | Relatively mild regular dominant type | 150 | *150* |
| Retinoblastoma | | *58* | 14 |
| Subluxation of the lens | Primary and not part of Marfan's syndrome | 6 | *6* |
| Optic atrophy | | 7 | *7* |
| TOTAL | | 9,555 | 7,100 |

TABLE XI. LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY I (continued)

(B) AUTOSOMAL RECESSIVE TRAITS

| *Trait* | *Remarks* | *Phenotype frequency per million* | |
|---|---|---|---|
| | | *Births* | *Living* |
| Albinism | Usual type with ocular signs. More than one mutant (?allele), can cause | 130 | *130* |
| Alkaptonuria | | 5 | *3* |
| Methaemoglobinaemia | | 5 | *5* |
| Phenylpyruvic acid amentia | Phenylketonuria | 100 | *30* |
| Porphyria congenital | Recessive light sensitive type | 50 | *5* |
| Galactosuria | | 50 | *2* |
| Gargoylism | | 20 | *4* |
| Amaurotic idiocy | Warran-Tay-Sachs disease. Various types with different ages of onset. Different loci mutants? Alleles? | 50 | *5* |
| Hepato-lenticular degeneration | Wilson's disease | 10 | *3* |
| Lawrence-Moon-Biedl syndrome | | 40 | *6* |
| Microcephaly, true | Microcephalic imbecility | 40 | *21* |
| Ataxia | | 40 | *20* |
| Choreo-athetosis | | 70 | *15* |
| Myoclonic epilepsy | | 50 | *6* |
| Spastic diplegia | Spastic diplegia familial often with oligophrenia | 50 | *18* |
| Muscular dystrophy limb girdle type | Face not affected | 30 | *16* |
| Poikilodermia | | 10 | *3* |
| Epidermolysis bullosa dystrophica | | 20 | *6* |
| Ichthyosis congenita | May be more than one type | *10* | — |
| Anophthalmos | | 100 | *50* |
| Corneal dystrophies | Severe recessive type | 5 | *5* |
| Glaucomas | More than one recessive type with buphthalmos | 15 | *15* |
| Macular dystrophies | Juvenile and adult types | 10 | *10* |
| Microphthalmos | Pure type as distinct from those associated with other eye defects. Mental deficiency often associated. | 100 | *100* |
| Myopia, high | Segregating traits overlapping with ordinary refraction variations 3–6 types with other associated defects included here, e.g. with microphakia and spherophakia | 150 | *150* |
| Optic atrophy | Very early onset type | 50 | *50* |
| Retinitis pigmentosa | Probably several independent mutants contribute | 60 | 60 |
| TOTAL | | 1,260 | 738 |

(C) SEX-LINKED RECESSIVE TRAITS

| *Trait* | *Remarks* | *Phenotype frequency per million* | |
|---|---|---|---|
| | | *Births* | *Living* |
| Diabetes insipidus | | 50 | *5* |
| Haemophilia | | 100 | *66* |
| Christmas disease | | 10 | *4* |
| Ichthyosis vulgaris | | 6 | *6* |
| Muscular dystrophy | Duchenne's type | *176* | *24* |
| Megalocornea | ? Only sex limited | 20 | *20* |
| Optic atrophy | Leber's type— ? really sex linked | 15 | *10* |
| Retinitis pigmentosa | | 20 | *20* |
| TOTAL | | 397 | 155 |

(D) SUMMARY OF TRAITS OF CATEGORY I

| *Inheritance mechanism* | *Frequency per million* | |
|---|---|---|
| | *Births* | *Living* |
| Autosomal dominant | 9,555 | 7,100 |
| Autosomal recessive | 1,260 | 738 |
| Sex-linked recessive | 397 | 155 |
| TOTAL | 11,212 | 7,993 |

## TABLE XII. LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY II

| Trait | Remarks | Phenotype frequency per million: Births | Phenotype frequency per million: Living |
|---|---|---|---|
| Abse ɔe of limbs or parts of limbs | Congenital endogenous amputations | 200 | 80 |
| Cleft ɔalate and hare lip, together or separately | Not including these anomalies occurring as parts of syndromes or associated with other gross defects | 970 | 700 |
| Con nital dislocation of hip | Mostly limited in effects to females | 900 | 900 |
| Oste ıecrosis | Includes osteochondritis dissecans and local, e.g. diseases of Kienbock, Kohler, Perthe and Schlatter | 200 | 200 |
| Rad -ulnar defects | Varying degrees of absence and deformity, radius usually primary and determining also hand defects | 205 | 205 |
| Tali ːs-equino-varus | Excluding, where recognized, those with neurological determining causes and when part of severe syndromes e.g. anencephalus | 800 | 700 |
| Vert ɔrae, defects and fusions | A large group including Klippel—Fiel syndrome, Sprengel's anomaly etc. | 400 | 200 |
| Pso ısis | Not known if all of one origin-varying age of onset, duration of attacks and severity | 3,000 | 3,000 |
| Ichı yosis vulgaris | | 1,100 | 1,100 |
| Dea ıess, otosclerotic | | 200 | 200 |
| Ane ɔephalus | i.e. The live born with these defects usually dying shortly after birth, with and without spina bifida or rachischisis | 360 | — |
| Occ ıital meningocoele | | 80 | — |
| Hy ocephalus (Arnold-Chiari) | | 300 | — |
| Lur ɔo-sacral spina bifida | | 800 | 100 |
| Oth r central nervous system malformations | | 320 | — |
| Ca iac malformations | | 1,200 | 400 |
| Di stive tract malformations | | 630 | 100 |
| Ur enital tract malformations | | 200 | 40 |
| TOTAL TRAIT FREQUENCY | | 9,825 | 8,725 |

## TABLE XIII. (A) LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY III

| Trait | Remarks | Phenotype frequency per million: Births | Phenotype frequency per million: Living |
|---|---|---|---|
| D fness total from birth | 97 per cent of all genetic deafness at birth. A number of independent mutants involved. Relative fertility of homozygote about 1/3 | 264 | 264 |
| F rocystic disease of pancreas | A generalized disorder of external secretory glands. For practical purposes, relative fertility of homozygote is zero | 600 | 15 |
| TOTAL TRAIT FREQUENCY | | 864 | 279 |

## TABLE XIII. (B) LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY III (*continued*)

| Trait | Remarks | Phenotype frequency per million: Births | Phenotype frequency per million: Living |
|---|---|---|---|
| aemia, pernicious | Addison's anaemia | 1,300 | 1,000 |
| abetes mellitus | | 4,000 | 3,000 |
| ophthalmic goitre | Graves's or Basedow's disease | 1,700 | 1,500 |
| anic depressive reactions | Based on severity requiring hospital admissions | 4,000 | 2,500 |
| hizophrenia | Based on severity requiring hospital admissions | 1,300 | 1,100 |
| ilepsy | Secondary to disease or injury | 2,500 | 1,200 |
| TOTAL PHENOTYPE FREQUENCY | | 14,800 | 10,300 |

TABLE XIV. DOMINANT CONDITIONS IDENTIFIED IN THE NORTHERN IRELAND POPULATION BUT NOT INCLUDED IN CATEGORIES I AND II FOR THE REASONS STATED

A. BECAUSE THEIR EFFECTS ARE SLIGHT (*most are common*)

*Hand defects:* Brachydactyly thumbs, brachydactyly 1st finger, brachydactyly 1st, 3rd, and 4th fingers; camptodactyly; clinodactyly; polydactyly (not part of syndrome) of radial side and of ulnar side (more common) of hands; syndactyly and symphalangism mostly 3rd and 4th finger (hundreds of cases of the above types are known but have not been sought out for special investigation); Dupuytren's contracture familial.

*Foot defects:* Garber's toe deformity; hallux valgus (familial cases may be associated with metatarsal anomalies); hammer toes (many are familial); syndactyly and symphalangism.

*Other skeletal:* Diaphyseal achalasia, epiphysitis punctata.

*Teeth anomalies* (Other than parts of syndromes): Defective or absent enamel (various types); opalescent dentine; additional teeth (many types); absence of permanent incisors and pre-molars; some such anomalies are present in about 1.3 per cent of the population.

*Skin and hair anomalies:* Adenoma, cystic multiple benign; cysts, epidermoid; dermatomyomat multiple; anonychia and hypoplasia of nails; leukonychia totalis; pachyonychia congenita; hair, white patches; hair kinky; hair woolly; hydroa aestivale; porokeratosis

*Eye anomalies:* Eyelids—spasm, absence of tarsal plates, uncomplicated ptosis; absence fistula of lacrymal ducts; retina, opaque fibres; strabismus convergent and divergent (primary).

*Miscellaneous:* Pelger's anomaly, elliptocytosis.

*Ear anomalies:* Cat's ears, microtia; pre-helicine pits; lobule pits; accessory auricles.

B. BECAUSE EVEN IF THE EFFECTS ARE SEVERE, THE ANOMALIES ARE PROBABLY PRESENT IN LESS THAN FIVE PERSONS PER MILLION

*Skeletal:* Osteo-petrosis (Albers-Schönberg); phocomelia; ankylosing spondylosis; polyostotic fibrous dysplasia (Albright's disease); multiple enchondroma; fibula absence or defect; oxycephaly; acrocephaly; syndactyly.

*Skin:* Ichthyosiform congenital erythrodermia; keratosis follicularis spinulosa (Darier's disease); monilethrix; urticaria pigmentosa; tylosis palmaris et plantaris; pili torti; mal de Meleda; lipodystrophy progressiva without gargoylism.

*Miscellaneous:* Milroy's disease; periodic paralysis; dominant microcytic anaemia; Waardenberg's syndrome; anotia.

TABLE XV. CLASSES OF BIOMETRICAL CHARACTER

| *Character* | *Presumed position of social optimum* | *Position of selective optimum* | *Position of population mean* |
|---|---|---|---|
| Birthweight | At selective optimum | Intermediate finite value | Below selective optimum[151] |
| Intelligence (measured as intelligence quotient) | $+\infty$[a] | Intermediate finite value | Near and possibly even above present selective optimum;[188] far below social optimum |
| Life-span | $+\infty$[a] | Unknown: perhaps $+\infty$[a] | Below social optimum: probably below selective optimum |

[a] "$+\infty$" implies positive and indefinitely large, always greater than the population mean.

REFERENCES


1. Green, M. M., Proc. Nat. Acad. Sci. U.S.A. *40*, p. 92 (1954).
2. Lewis, E. B., Amer. Natur. *89*, p. 73 (1955).
3. Benzer, S., Proc. Nat. Acad. Sci. U.S.A. *41*, p. 344 (1955).
4. Cold Spring Harbor Symposia on Quantitative Biology, *20*, especially pp. 303-334.
5. Demerec, M. *et al.*, Public. No. 612, Carnegie Institution of Washington (1956).
6. Dubinin, N. P., and B. N. Sidorov, Amer. Natur. *68*, p. 377 (1934) and other papers by Dubinin *et al.* in this series.
7. Lewis, E. B., Adv. Genet. *3*, p. 73 (1950).
8. Lederberg, J., *The Chemical Basis of Heredity*, p. 754, ed. W. D. McElroy and H. B. Glass, Johns Hopkins Press, Baltimore (1957).
9. Muller, H. J., *Brookhaven Symposia in Biology No. 8, Mutation*, p. 126, U.S. Dept. of Commerce (1956).
10. Taylor, J. H., P. S. Woods and W. L. Hughes, Proc. Nat. Acad. Sci. U.S.A., *43*, p. 122 (1957).
11. *Effect of Radiation on Human Heredity*, W.H.O. (1957) and UN document A/AC.82/G/R/58.
12. Kaufman, B. P., in *Radiation Biology*, Vol. 1, p. 627, ed. A. Hollaender, McGraw Hill (1954).
13. Giles, N. H., in *Radiation Biology*, Vol. 1, p. 713, ed. A. Hollaender, McGraw Hill (1954).
14. Wolff, S. and H. E. Luippold, *Progress in Radiobiology*, p. 217, ed. J. S. Mitchell, B. E. Holmes and C. L. Smith, Oliver and Boyd (1956).
15. For a review see H. J. Muller in *Radiation Biology*, Vol. 1, p. 475, ed. A. Hollaender, McGraw Hill (1954).
16. Mortimer, R. K., Radn. Res. *2*, p. 361 (1955) and references cited therein.
17. von Borstel, R. C., and M. L. Pardue, Genetics, *41*, p. 665 (1956).
18. Puck, T. T., and P. I. Marcus, J. Exp. Med. 105, p. 653 (1956).
19. Bender, M. A., Science 126, p. 974 (1957).

20. Vendrel , R., in *The Nucleic Acids*, Vol. 2, p. 155, ed. E. ( hargaff and J. N. Davidson, Academic Press, N :w York (1955).
21. Alfrey, ". G., A. E. Mirsky and H. Stern, Adv. Enz. *16*, ). 411 (1955).
22. Avery, ). T., C. M. McLeod and M. McCarty, J. Exp. Med., *79*, p. 131 (1944).
23. Hotchk s, R. D., p. 435 in *The Nucleic Acids*, Vol. 2, ed. E Chargaff and J. N. Davidson, Academic Press, I ew York (1955).
24. Alexan er, H. E., and G. Leidy, J. Exp. Med. *93*, p. 345 .951).
25. Hershe , A. D., and M. Chase, J. Gen. Physiol. *36*, p. 39 ( )52).
26. Putnan F. W., and L. M. Kosloff, J. Biol. Chem. *182*, p. 43 (1950).
27. Cohen, S. S., *The Chemical Basis of Heredity*, p. 651, ec W. D. McElroy and H. B. Glass, Johns Hopkii Press, Baltimore (1957).
28. Wilkin , M. H. F., A. R. Stokes and H. R. Wilson, Nature *171*, p. 738 (1953).
29. E. Cha gaff, *The Nucleic Acids*, Vol. 1, p. 307, ed. E. Cha gaff and J. N. Davidson, Academic Press, New ) ork (1955).
30. Crick, ". H. C., and J. D. Watson, Proc. Roy. Soc. (A), *3*, p. 80 (1954).
31. Uphof D. E., and C. Stern, Science, *109*, p. 609 (1949
32. Spenc ', W. P., and C. Stern, Genetics *33*, p. 43 (1948
33. Caspa and C. Stern, Genetics *33*, p. 75 (1948).
34. Olive C. P., Z.I.A.V., *61*, p. 447 (1932).
35. Raych udhuri, S. P., Proc. 7th Int. Conf. Genet., p. 246 (1941).
36. Raych udhuri, S. P., Proc. Roy. Soc. Edin., *62*, p. 66 1944).
37. Mulle , H. J., *op cit.* ref. 9, p. 25.
38. Oakb g, E. F., UN document A/AC.82/G/R/65.
39. Verba ly communicated by the Delegation of the Unite Kingdom.
40. New mbe, H. B., *Brookhaven Symposia in Biology, o. 8, Mutation*, p. 88, U.S. Dept. of Commerc (1956).
41. New mbe, H. B., Rad. Res., *5*, p. 382 (1956).
42. Holl nder, A., D. Billen and C. O. Doudney, Rad. Res. , p. 235 (1955).
43. Holl nder, A., and G. E. Stapleton, *Proc. Int. Conf on Peaceful Uses of Atom. Energy, 11*, p. 311, nited Nations (1956).
44. Stap ton, G. E., A. J. Sbarra and A. Hollaender, J. Ba t. *70*, p. 7 (1955).
45. Lüni g, K. G., and J. Söderström, Hereditas *43*, p. 5( , 1958 and UN document A/AC.82/G/R/174.
46. Hsia D. Y. Y., K. Driscoll, W. Troll and W. E. Kno , Nature, *178*, p. 1239 (1956).
47. Nee J. V., Amer. J. Hum. Genet. *1*, p. 19 (1949).
48. Tjio J. H., and A. Levan, Hereditas, *42*, p. 1 (19! ).
49. For C. E., and J. L. Hamerton, Nature *178*, p. 102( (1956).
50. Zinc r, N, and J. Lederberg, J. Bacteriol., *64*, also *op. t.* ref. 19 and 20.
51. Morse, M. L., E. M. Lederberg and J. Lederberg, Genetics, *41*, p. 142 (1956).
52. Stadler, L. J., Science, *120*, p. 811 (1954) and previous papers.
53. Glover, S. W., *op. cit.* ref. 4, p. 121.
54. Newcombe, H. B., J. Cell. and Comp. Physio. *39* (Suppl. 1), p. 13 (1952).
55. Reviewed in ref. 15, p. 492 *seq.*
56. Herskowitz, I. H., Genetics, *36*, p. 356 (1951).
57. For an extreme example, see Demerec, M., Proc. Nat. Acad. Sci. U.S.A., *20*, p. 28 (1934).
58. See for example work of Dubovsky, C. R. (Dokl.) Acad. Sci. U.S.S.R., *4*, p. 95 (1935).
59. Muller, H. J., Genetics, *31*, p. 225 (1946).
60. For example, work on Tradescantia, reviewed by Giles, N. H., *Radiation Biology*, Vol. I, p. 713, ed. A. Hollaender, McGraw Hill (1954).
61. Giles, N. H., *Brookhaven Symposia in Biology, No. 8, Mutation*, p. 103, U.S. Dept. of Commerce (1956).
62. Pontecorvo, G., and J. A. Roper, Nature, *178*, p. 83 (1956).
63. Demerec, M., and Z. E. Demerec, *op. cit.* ref. 4, p. 75.
64. Benzer, S., *Brookhaven Symposia in Biology, No. 8, Mutation*, p. 3, U.S. Dept. of Commerce (1956).
65. Benzer, S., Proc. Nat. Acad. Sci. U.S.A., *41*, p. 344 (1955).
66. Benzer, S., *The Chemical Basis of Heredity*, p. 70 ed. W. D. McElroy and H. B. Glass, Johns Hopkins Press, Baltimore, U.S.A. (1957).
67. Penrose, L. S., The Lancet, *2*, p. 312 (1955).
68. Lefevre, G. J., Jr., Genetics, *40*, p. 374 (1955).
69. Russell, W. L., *Radiation Biology*, Vol. 1, p. 825, ed. A. Hollaender, McGraw Hill, New York (1954).
70. Alexander, M. L., Genetics *39*, p. 409 (1954).
71. Ryan, F. J., Amer. Natur. *89*, p. 159 (1955) and earlier references therein.
72. Grigg, G. W., Nature, *169*, p. 98 (1952).
73. Reviewed by D. G. Catcheside, *The Genetics of Microorganisms*, Pitman Press (1951).
74. Reviewed by W. Braun, *Bacterial Genetics*, W. B. Saunders, Philadelphia (1953).
75. Carter, T. C., M. F. Lyon and R. J. S. Phillips, Brit. J. Radiol. *29*, p. 106 (1956).
76. Russell, W. L., Cold Spring Harbor Symposia on Quantitative Biology, *16*, p. 327 (1951).
77. Kaufman, B. P., *Radiation Biology*, Vol. 1, p. 627, ed. A. Hollaender, McGraw Hill (1954).
78. Novick, A. and Leo Szilard, Cold Spring Harbor Symposia on Quantitative Biology, *16*, p. 337 (1951).
79. Fox, M. S., J. Gen. Physiol. *39*, p. 267 (1955).
80. Muller, H. J., Year Book of Amer. Philos. Soc., p. 150 (1945).
81. Amer. J. Hum. Genet. *6*, p. 45 (1954).
82. *Proc. 1st Int. Cong. Human Genet.*, ed. Tage Kemp (1957).
83. For an example, see L. S. Penrose, The Listener, p. 748 (1957).

84. Haldane, J. B. S., *The Causes of Evolution,* Longmans Green and Co. (1932).
85. Sutter, J., and L. Tabah, Population, *8,* p. 511 (1953).
86. Sutter, J. and L. Tabah, Population, *7,* p. 249 (1952).
87. Böök, J. A., Am. Hum. Genet. *21,* p. 191 (1957).
88. Morton, N. E., J. F. Crow and H. J. Muller, Proc. Nat. Acad. Sci. U.S.A., *42,* p. 855 (1956).
89. UN document A/AC.82/G/R.10.
90. See H. B. Newcombe, *op cit.* ref. 11, p. 157.
91. Lejeune, J., and R. Turpin, C.R. Acad. Sci., *244,* p. 1833 (1957).
92. Goldstein, A., and Jane S. Smoot, J. Bacteriol., *70,* p. 588-595 (1955).
93. Penrose, L. S., *op. cit.* ref. 11, gives some examples on p. 101.
94. Glass, H. B., Adv. Genet. *6,* p. 95 (1954).
95. Muller, H. J., Science *66,* p. 84 (1927).
96. Russell, W. L., *Proc. Int. Conf. on Peaceful Uses of Atom. Energy,* Vol. 11, p. 382, U.N. (1956).
97. Reviewed by H. B. Glass, in ref. 100.
98. See K. G. Lüning, *Studies on X-ray Induced Mutations in Various Stages of Spermatogenesis in Drosophila Melanogaster,* Alb. Bonnier, Boktrycheri, Stockholm (1942).
99. Correspondence by A. J. Bateman, C. Auerbach, J. L. Sirlin and R. G. Edwards, Nature *179,* pp. 725-733 (1957).
100. Glass, H. B., *Brookhaven Symposia in Biology, No. 8, Mutation,* p. 148, U.S. Dept. of Commerce (1956).
101. The subject is reviewed by J. V. Neel, *op cit,* ref. 11, p. 137.
102. See H. J. Muller, Amer. J. Hum. Genet. *2,* p. 111 (1950).
103. Muller, H. J., *op cit.* ref. 11, p. 25.
104. Russell, L. B., and M. H. Major, Genetics, 42, p. 161 (1957).
105. Haldane, J. B. S., J. Genetics, *54,* p. 327 (1956).
106. Verbally communicated by the Delegation of the United Kingdom.
107. Carter, T. C., Proc. Roy. Soc. (B), *147,* p. 402 (1957).
108. Muller, H. J., *Proc. Int. Conf. on Peaceful Uses of Atom. Energy, 11,* p. 387, U.N., 1956.
109. Dunn, L. C., Proc. Nat. Acad. Sci. U.S.A., *43,* p. 158 (1957) and earlier papers, also adjacent paper by D. Bruck.
110. Stevenson, A. C., *op cit.* ref. 11, p. 125.
111. See especially Neel, J. V., and W. J. Schull, *The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki,* U.S. Nat. Acad. Sci. (1956) and UN document A/AC.82/G/R.24.
112. Gopal-Ayengar, A. R., *op cit.* ref. 11, p. 115.
113. Document A of UN document A/AC.82/G/R.58.
114. *Exposure of Man to Ionising Radiation Arising from Medical Procedures,* UN document A/AC. 82/G/R.117.
115. Stewart, A., J. Webb, D. Giles and D. Hewitt, Lancet, 2, p. 447 (1956).
116. The subject is reviewed by B. Colombo, Cold Spring Harbor Symposia on Quantitative Biology, *22* (in press).
117. UN document A/AC.82/G/R.16.
118. Lejeune, J., *op cit.* ref. 11, p. 87 and refs. therein.
119. Kaplan, I. I., J. Canad. Med. Assn. *76,* p. 43 (1957).
120. Lejune, J., and R. Turpin, C.R. Acad. Sci., *244,* p. 2425 (1957).
121. Puck, T. T. and H. W. Fisher, J. Exp. Med. *104,* p. 427 (1956).
122. Marcus, P. I., S. J. Ciecura and T. T. Puck, J. Exp. Med. *104,* p. 615 (1956).
123. Neel, J. V., and W. J. Schull, Science, *118,* p. 537 (1953).
124. Turpin, R., J. Lejeune and M. O. Rethore, Acta Genet. et Stat. Med. *6,* p. 204 (1956).
125. Communicated by T. C. Carter.
126. Macht, S. H., and P. S. Lawrence, Amer. J. Roentgenol. *73,* p. 442 (1955).
127. Court-Brown, W. M., and R. Doll *Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis,* H.M. Stationery Office, London (1957) and UN document A/AC.82/G/R.105.
128. Magni, G. E., C. R. Carlsberg, Lab. Physiol. Serv. *26,* p. 273 (1956).
129. Ephrussi, B., *et al,* Ann. Inst. Pasteur, 76, p. 351, 419, 510, 77, p. 47, 64 (1949).
130. Dobzhansky, Th., Cold Spring Harbor Symposia on Quantitative Biology, *20,* p. 1 (1955).
131. Dobzhansky, Th., O. Pavlovsky, B. Spassky and N. Spassky, Genetics, *40,* p. 792 (1955).
132. Dobzhansky, Th., and H. Levene, Genetics, *40,* p. 797 (1955) and references therein.
133. Lerner, I. M., *Genetic Homeostasis,* John Wiley, New York (1954).
134. Wallace, B., Proc. Nat. Acad. Sci. U.S.A., *43,* p. 404 (1957).
135. For indication of cross-over in *Drosophila* males by X-rays or chemical agents, see UN document A/AC.82/G/R.90.
136. Sobels, F. H., and H. von Steenis, Nature, *179,* p. 29 (1957).
137. Whittinghill, M., J. Cell Comp. Physiol. *45,* Suppl. 2, p. 189 (1955).
138. Sturtevant, A. H., and G. W. Beadle, Genetics, *21,* p. 554 (1936).
139. Kemp, Tage, *Genetics and Disease,* Munksgaard, Copenhagen (1951).
140. Penrose, L. S., Adv. Sci., *11,* p. 387 (1955).
141. Allison, A. C., Ann. Hum. Genet. *19,* p. 39 (1954).
142. Crow, J. F., Human Biology, *30,* p. 1 (1958).
143. Neel, J. V., Human Biology, *30,* p. 43 (1958).
144. Stevenson, A. C., UN document A/AC.82/G/R.104.
145. *The Biological Effects of Atomic Radiation,* Summary Reports: Nat. Acad. Sci.—Nat. Res. Council, U.S.A. (1956), UN document A/AC.82/G/R.1.
146. Reed, T. E., Jap. J. Hum. Genet. *2* (Supp.), p. 48, (1957).
147. Panse, F., *Die Erbchorea,* Thieme, Leipzig (1942).
148. See Haldane, J. B. S., Caryologia, Supp. to Vol. XI, Proc. 9th Int. Cong. Genet., p. 485 (1953).

14 Penrose, L. S., Caryologia, Supp. to Vol. XI, Proc. 9th Int. Cong. Genet., p. 521 (1953).
15 . *The Hazards to Man of Nuclear and Allied Radiations*, H.M. Stationery Office, London (1956), UN document A/AC.82/G/R.2.
15 . Karn, M. N., and L. S. Penrose, Ann. Eug. *16*, p. 147 (1952).
15 . Mather, K., Appendix G of ref. 124.
15 . Clayton, G. and A. Robertson, Amer. Natur. *89*, p. 151 (1955).
15 . Haldane, J. B. S., Caryologia, Supp. to Vol. XI, Proc. 9th Int. Cong. Genet., p. 480 (1953).
15 . Robertson, A., J. Genet., *54*, p. 236 (1956).
15 . Fisher, R. A., *Genetical Theory of Natural Selection*, Clarendon Press, Oxford, 1930.
15 . Quoted by Mather in Appendix F of ref. 150.
15 . Penrose, L. S., Proc. Roy. Soc. (B) *144*, p. 144 (1955).
15 . Muller, H. J., *Genetics, Eugenics and the family, 1*, p. 106, Proc. 2nd. Int. Cong. Eug., p. 7 (1921).
16 . Muller, H. J., Vol. I *Radiation Biology*, p. 351, ed. A. Hollaender, McGraw Hill (1954).
16 . *Op cit.* ref. 158, Fig. 14 and data in references.
16 . Russell, W. L., Proc. Nat. Acad. Sci. U.S.A., *43*, p. 324 (1957).
16 . Beeton, M., and K. Pearson, Biometrika, *1*, p. 50 (1901).
16 . Bateman, A. J., Nature, *178*, p. 1278 (1956).
16 . Turpin, R., J. Lejeune and M. O. Rethore, Acta Genet. et Stat. Med. *6*, p. 204 (1956).
16 . Crow, J. F., Amer. J. Roentgen., *73*, p. 467 (1955).
17 . Murphy, D. P., and L. Goldstein, Amer. J. Roentgen., *22*, p. 207 (1929).
17 . Maurer, Zbl. Gynk., p. 819 (1933).
17 . Penrose, L. S., Appendix C of ref. 150.
17 . Penrose, L. S., *op cit.* ref. 111, p. 210 and references contained therein.
17 . Muller, H. J., J. I. Valencia and R. M. Valencia, Genetics *35*, pp. 125, 126 (1950).
17 . Glass, H. B., and R. K. Ritterhof, Science *124*, p. 314 (1956).
17 . Bonnier, G., and K. G. Lüning, Hereditas, *35*, p. 163 (1949).
17 . Demerec, M., Genetics, *22*, p. 469 (1937).
17 . Patterson, J. T., quoted by Alexander in ref. 70.
17 . Demerec, M., Cold Spring Harbor Symposia on Quantitative Biology, *2*, p. 110 (1934).
17 . Girvin, A., Univ. of Texas Publ. 4920, p. 42 (1949).
17 . Based on a table compiled by H. C. Waddington and T. C. Carter, Appendix H of ref. 150.
17 . Konzak, C. F., and W. R. Singleton, Proc. Nat. Acad. Sci. U.S.A. *42*, p. 78 (1956).
18 . Lewis, D., Heredity, *2*, p. 219 (1948).
18 . Lewis, D., Heredity, *3*, p. 339 (1949).
18 . Stern, C. *et al*, Genetics *37*, p. 413 (1952).
18 . Muller, H. J., J. Cell. Comp. Physiol. *35*, Supp. 1, p. 205 (1950) and unpublished (with Campbell).
18 . Fraccaro, M., Ann. Hum. Genet. *20*, p. 282 (1955).
18 . Robson, E. B., Ann. Hum. Genet. *19*, p. 262 (1955).
18 . Novitski, E., and L. Sandler, Ann. Hum. Genet. *21*, p. 123 (1956).
18 . Lejeune, J., and R. Turpin, Comptes Rendus Acad. Sci. *244*, p. 1833 (1957).
18 . Caspar, A., and W. R. Singleton, Rec. Genet. Soc. Amer. Genetics (1957).
18 . Neel, J. V., p. 144 of ref. 11.
19 . Schull, W. J. (in press).
19 . Kemp. T., Cold Spring Harbor Symposia on Quantitative Biology, *15*, p. 129 (1950).
19 . da Cunha, A. B., Adv. Genet. *7*, p. 93 (1955).
19 . Clark Fraser, F., UN document A/AC.82/G/R.218.
19 . Puck, T. T., D. Morkovin, P. I. Marcus and S. J. Ciecura, J. Exp. Med., *106*, p. 485 (1957).
19 . Bharatwal, D. S., and G. H. Vase, UN document A/AC.82/G/R.166.
19 . Mather, K., Proc. Roy. Soc. B., *145*, p. 293 (1956).
19 . Mather, K., Symp. Soc. Exp. Biol., *7*, p. 66 (1953).
19 . Penrose, L. S., Amer. J. Hum. Genet., *9*, p. 167 (1957).

## Appendix

*Calculations concerning survival at or near birth and the distribution of birth-weights*

110. Both Karn and Penrose[151] and Fraccaro[184] have found in samples of several thousand births that the distributions both of survivors S and non-survivors N through birth and the subsequent 30 days are Gaussian. Under these conditions the influence of the mean and variance of the over-all birth-weight distribution upon survival at or near birth can, at least approximately, be treated algebraically. Suppose birth-weight w to be measured from the birth-weight at which S is maximal.

Let $S = S_o \exp - w^2/2\sigma_3^2$

$$N = N_o \exp - 1/2\left(\frac{w - m'}{4_o}\right)^2$$

Then the curve determining survival is

$$\frac{S}{N} =$$

$$\frac{S_o}{N_o} \exp - \frac{1}{2\sigma_1^2}\left(w + \frac{m'\sigma_3^2}{\sigma_4^2 - \sigma_3^2}\right)^2 \quad \exp \frac{1}{2}\left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2}\right)$$

where $\frac{1}{\sigma_1^2} = \frac{1}{\sigma_3^2} - \frac{1}{\sigma_4^2}$

and the over-all survival is $1 - \bar{k}$ where

$$\bar{k} = \frac{\sigma_4 N_o}{\sigma_3 S_o + \sigma_4 N_o}$$

Moreover, optimal survival is at $\omega_{opt} = \frac{-m'\sigma_3^2}{\sigma_4^2 - \sigma_3^2}$

and at this point

$$\left(\frac{S}{N}\right)_{opt} = \frac{S_o}{N_o} \exp - 1/2\left(\frac{m^2}{\sigma_4^2 - \sigma_3^2}\right)$$

Then the survival at $\omega = \omega_{opt}$ is $1 - k_{min}$

where $k_{min} = \dfrac{N_o/S_o \exp - 1/2\left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2}\right)}{1\frac{1}{1} + \frac{1}{1}N_o/S_o \exp - 1/2\left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2}\right)}$

It is desirable to express the relation between $k_{min}$ and $\bar{k}$ in terms of (1) the variance $\sigma_2^2$ of the over-all distribution of birth-weights

$$T(W) = S(W)+N(W)$$

(2) the difference m between the mean of the over-all distribution of birth-weights and the birth-weight for optimal survival, and

(3) the variance $\sigma_1^2$ which determines the shape of the birth-weight-survival relation.

In terms of the parameters describing S(W) and N(W)

$$m = m' (\sigma_3^2/(\sigma_4^2 - \sigma_3^2) + \bar{k})$$

$$\sigma_2^2 = \sigma_3^2 (1 - \bar{k}) + \sigma_4^2\bar{k} + m'^2 \bar{k} (1 - \bar{k})$$

If it is assumed that k is small by comparison with unity, it is possible to write

$$r = \frac{k}{k_{min}} = \frac{\sigma_4}{\sigma_3} \exp 1/2 \left(\frac{m^2}{\sigma_4^2 - \sigma_3^2}\right) + 0 (\bar{k})$$

and so since $\sigma_2^2 = \sigma_3^2 + 0(\bar{k})$ and $\sigma_4^2$ can be eliminated in terms of $\sigma_1^2$ and $\sigma_3^2$

$$r \doteqdot \frac{\sigma_1}{(\sigma_1^2 - \sigma_2^2)\ 1/2} \exp 1/2 \left(\frac{m^2}{\sigma_1^2 - \sigma_2^2}\right) \ldots\ldots (1)$$

Comparison of [1] as observed by Karn and Penrose with values calculated from the above formula and the parameters of their experiments gives

| | $r_{obs}$ | $r_{calc}$ |
|---|---|---|
| Males | 2.07 | 2.23 |
| Females | 2.21 | 2.36 |

111. On the basis of equ. (1) it is possible to estimate the consequences of small shifts in the mean or variance of the distribution of birth-weights, assuming that the survival curve ($k_{min}$, $\sigma_1$) remains constant, by the relations

$$\frac{dr}{r} \Big/ \frac{d\ \sigma_2^2}{\sigma_2^2} = 1/2 \left(\frac{\sigma_2^2}{\sigma_1^2 - \sigma_2^2}\right) + 1/2 \left(\frac{m^2\ \sigma_2^2}{(\sigma_1^2 - \sigma_2^2)\ 2}\right)$$

and

$$\frac{dr}{r} \Big/ \frac{dm}{m} = \left(\frac{m^2}{\sigma_1^2 - \sigma_2^2}\right)$$

Calculated numerical changes in r and in $\bar{k}$ for 1 per cent changes in variance and in departure of mean from optimal birth-weight are given in table XVI calculated from the data of Karn and Penrose and Fraccaro.

112. It has been estimated by Robson[185] and by Penrose[149] that some 40 per cent of the variance of birth-weight in a United Kingdom sample was due to genetic factors, either of the mother or of the foetus. Possibly only a small fraction of this is maintained by recurrent mutation. The other extreme possibility is that recurrent mutation maintains the whole of the genetic component of the variance $\sigma_2^2$. In that event a 10 per cent change in mutation rate might lead to a 4 per cent change in $\sigma_2^2$ and so to changes in survival at and near birth amounting to 0.2–0.7 per cent. If the representative doubling dose for the polygenes concerned were to be 30 rad, this would then correspond approximately to the genetical influence of natural sources of irradiation upon survival at or near birth.

113. The part played by genetic factors in maintaining the difference between the mean birth-weight and that for optimal survival is not known, but the most extreme possibility is again that recurrent mutation may be responsible for the whole of m. In that event a similar change in mutation rate might lead to changes in survival at or near birth amounting to 0.2–0.8 per cent. These calculated upper limits apply to regions in which the total loss of infants at or near birth is in the range 4–7 per cent. They are illustrative of the need to resolve the underlying and more fundamental problem of the part played by mutation in maintaining the current distribution of birth-weights against the pressure of selection acting through this phenotype.

TABLE XVI. CALCULATED CONSEQUENCES OF CHANGES IN THE PARAMETERS GOVERNING BIRTH-WEIGHT DISTRIBUTION

| *Survey Sample* | *Changes due to 1 per cent change in $\sigma_2^2$* | | *Changes due to 1 per cent change in m* | |
|---|---|---|---|---|
| | *Fractional change in r (per cent)* | *Absolute change in $\bar{k}$ (per cent)* | *Fractional change in r (per cent)* | *Absolute change in $\bar{k}$ (per cent)* |
| Karn and Penrose[161] | Males 1.5 | 0.072 | 0.50 | 0.024 |
| | Females 1.3 | 0.053 | 0.84 | 0.034 |
| Fraccaro[184] | Males 1.6 | 0.11 | 0.72 | 0.048 |
| | Females 2.9 | 0.18 | 1.2 | 0.076 |

# Annex I

# 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. Abstracts have been inserted where appropriate.

2. All those reports are included of which a sufficient number of copies for distribution in the A/AC.82/G/R. document series were received before 1 March 1958.

3. The list also includes reports received after 1 March 1958, preliminary copies of which were submitted to the Committee prior to that date.

| *Document Number* | *Country and Title* | *Approximate No. of pages* |
|---|---|---|
| A/AC.82/G/R. | | |
| 1. | UNITED STATES OF AMERICA. *The biological effects of atomic radiation*<br>Summarizes general survey in which committees of experts covered the following subjects: genetics; pathology; meteorology; oceanography and fisheries; agriculture and food supplies; disposal and disposers of radioactive wastes. | 108 |
| 2. | UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND. *The hazards to man of nuclear and allied radiations*<br>General report covers both somatic and genetic hazards associated with radiation, present and foreseeable levels of exposure, and an assessment of the hazards in terms of associated actual and permissible levels. | 128 |
| 3. | BELGIUM. *Preliminary report on modern methods for the evaluation of the biological effects of small doses of external radiation or absorbed radioactive materials*<br>Concludes that the most hopeful measurements are those of:<br>1. DNases and cathepsins in plasma and urine.<br>2. DNA synthesis in vitro by bone marrow or biopsy specimens.<br>3. Platelet counts.<br>4. Antibody synthesis.<br>and that the Committee should re-emphasize the need of appropriate fundamental research in radiobiology. | 25 |
| 4. | JAPAN. (Report consisting of eight parts, as follows:) | |
| | (*Part 1.*) *Researches on the effects of the H-bomb explosion at Bikini Atoll 1954 on animal industry and sericulture in Japan*<br>Gives negative results of analysis by absorption method of radioactivity in milk, eggs and agricultural products following the Bikini explosions of May 1954. Related experimental feedings of animals with radioactive ashes were analysed chemically. | 10 |
| | (*Part 2.*) *The radioactive contamination of agricultural crops in Japan*<br>Gives results of soil and crop analyses for total radioactivity before and after May 1954 Bikini explosions, after subtraction of $K^{40}$ content, and with some radiochemical analysis. Radioactivity after the explosion was detected in soil, crops and other vegetation which are distributed all over Japan. The possible route of contamination is discussed. | 13 |
| | (*Part 3.*) *A preliminary report of recommendations on the modern methods of estimating the biological activity of small radiation dose*<br>Several current hematological findings in Japan are summarized and discussed. | 3 |
| | (*Part 4.*) *The airborne radioactivity in Japan*<br>Analyses of airborne radioactivity by filter and by electrical precipitator are described and compared. Results of analyses 1954–1956 show poor correlation between peaks of contamination and trajectories of high-level air masses. | 28 |
| | (*Part 5.*) *Report on the systematic observations of the atmospheric radioactivity in Japan*<br>Describes methods of collection and analysis of fall-out in dust, rain and snow, and of airborne radioactivity, as used in a wide survey at meteorological stations. Results from April 1954-March 1956 are summarized and discussed and the cumulative depositions of $Sr^{90}$ is calculated. | 56 |
| | (*Part 6.*) *On the distribution of naturally radioactive nuclides in Japanese islands*<br>Surveys of the distribution of naturally radioactive nuclides in Japanese waters and minerals are reviewed and summarized. | 27 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| | JAPAN *(continued)* | |
| | *(Part 7.) Radiochemical analysis of radioactive fall-out observed in Japan*<br>Present methods and results of radiochemical analyses of ash from the fishing boat No. 5 fukuryu Maru and of rainwater and soil samples in Japan. | 24 |
| | *(Part 8.) Fission products in water area and aquatic organisms*<br>Describes fall-out distribution and uptake generally, with special reference to water and aquatic organisms and to the problem of $Sr^{90}$. | 24 |
| 5. | MEXICO. *First report on the studies of radioactive fall-out*<br>Gives full description and comparisons of sticky paper and pot methods, preliminary results May-July 1956 for total beta activity and intended expansion of programme. | 15 |
| 6. | UNION OF SOUTH AFRICA. *Preliminary report on radioactive fall-out*<br>The preliminary result of the measurement of total beta activity of fall-out by porcelain dish method is described and results are given for January-June 1956. $Sr^{90}$ deposition was estimated by chemical analysis. | 2 |
| 7. | UNITED STATES. *Radioactive fall-out through September 1955*<br>Summarizes analysis of daily samples obtained up to end of September 1955 from twenty-six stations in United States and sixty-two elsewhere by gummed film method calibrated against collection in high walled pots (see document A/AC.82/INF.1). Cumulative deposition of mixed fission products, integral gamma doses and $Sr^{90}$ deposits are calculated and compared with other findings, including $Sr^{90}$ content of soils and milk. | 13 |
| 8. | CHINA. *Reports by the Atomic Energy Council of the Executive Yuan of the Republic of China*<br>Briefly notes the radium content of certain Chinese and other waters and the occurrence of radioactive sailfish and dolphin in seas off Taiwan, June 1954. | 8 |
| 9. | CANADA. *Report on waste disposal system at the Chalk River Plant of Atomic Energy of Canada Limited*<br>Describes procedures and results of ground dispersal of radioactive wastes from a natural uranium heavy water-moderated reactor. | 15 |
| 10. | *The Canadian programme for the investigation of the genetic effects of ionizing radiation*<br>Describes a proposal to modify the system of recording of the national vital statistics so as to render useful for genetic analysis the information contained in certificates of births, marriages and deaths (see also document A/AC.82/G/R. 58/Add. 1, annex 12). | 15 |
| 11. | UNITED STATES. *Pathologic effects of atomic radiation*<br>Present knowledge of the pathological (non-hereditary) effects of radiation is surveyed extensively by a committee. Includes separate sections by sub-committees or individual members on: acute and long-term hematological effects; toxicity of internal emitters; acute and chronic effects of radioactive particles on the respiratory tract; delayed effects of ionizing radiations from external sources; effects of radiation on the embryo and foetus; radiation in a disturbed environment; effects of irradiation of the nervous system; radiation effects on endocrine organs. | 100 |
| 12. | CANADA. *Levels of strontium-90 in Canada*<br>Gives figures for $Sr^{90}$ and $Sr^{89}$ in milk powder at seven stations, November 1955-May 1956. The $Sr^{90}$ level averages 4.8 $\mu\mu c$/gm Ca. Cumulative total beta activity and calculated $Sr^{90}$ content of fall-out analysed by United States AEC from gummed papers, are summarized annually for 1953 to 1955. Independent Canadian measurements by methods which are not described differ from these by factors 2-5. | 7 |
| 13. | NEW ZEALAND. *Note by New Zealand*<br>Gives brief notes in reply to the questions contained in individual paragraphs of annexes to letter PO 131/224 of 9 April 1956 (annexes derived from A/AC.82/R.10). Other sections describe: measurements of radioactivity (only radon found) collected from air at Wellington by filter and by electrostatic precipitator February 1953-May 1956, also by an impactor method in 1953 and in rainwater on certain dates November 1955-May 1956; results of measurements of total beta activities of fall-out by sticky paper method May-July 1956. | 12 |
| 14. | NORWAY. *Report of three parts*<br>Suggests taurine biochemistry and lens opacities as biological indicators for low doses. Gives notes on disposal of small amounts of radioactive wastes. Describes and gives results of analyses by pot method in 1956 of total beta activity due to fall-out on ground, in air, in drinking water and accumulated in snow falls. Includes some analyses for $Sr^{90}$. | 9 |
| 14/Add.1 | *Addendum to Part 1* | 7 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| 15. | SWEDEN. *Report of fifteen parts*<br>The fifteen sections cover: consumption of the doses to the gonads of the population from various sources; thorough survey of natural radioactivity including estimates of weekly dose-rates; measurements of gamma radiation from the human body; measurements of fall-out (1953-1956) including total beta activity, gamma ray spectrum and migration of $Sr^{90}$ into soils, plants and grazing animals, content of certain isotopes as well as research upon certain related physical quantities; considerations of occupational (medical) exposures. Methods used are extensively described throughout. | 330 |
| 15/Corr.1 | *Corrigendum to parts 1 and 9* | 2 |
| 15/Corr.2 | *Corrigendum to part 9* | 1 |
| 16. | FRANCE. *Report of three parts*<br>The report includes three main parts:<br>1. Methods of measuring: the radioactivity produced by nuclear explosions and nuclear industry; natural or artificial radioactivity in living beings; the atmospheric radon.<br>2. Reports on measurements relative to: natural radioactivity of rocks; radioactivity of soil and water; natural and artificial radioactivity of air, water and soil; occupational radiation exposure.<br>3. Studies on genetic effects of radiations and on the descendants of patients treated with pelvic radiotherapy. | 106 |
| 16/Add.1 | *Addendum to above report* | 20 |
| 17. | CZECHOSLOVAKIA. *Natural radioactivity of water, air and soil in the Czechoslovak Republic*<br>Briefly draws attention to deviations from reciprocity and to the partial reversibility of many radiation induced phenomena, to the possible use of organisms in a state of abiosis as integral dose-indicators, to certain specially radiosensitive organisms and responses, and to questions of threshold. An extensive survey reviews many studies of natural radioactivity. | 37 |
| 18. | KOREA, REPUBLIC OF. *Report concerning the request for information on natural radiation background*<br>Describes counters used for monitoring radiation background and gives results (cpm) from January 1955 to June 1956. | 10 |
| 19. | AUSTRIA. *Information prepared by the Austrian Government relating to the effects of atomic radiation*<br>Describes radioactive warm springs at Bad Gastein, giving activity levels in water and air. Outlines wide scope of biological and instrumental research at Gastein Institute. | 2 |
| 20. | UNITED KINGDOM. *The radiological dose to persons in the United Kingdom due to debris from nuclear test explosions prior to January 1956*<br>Summarizes measurements of total beta activity and $Sr^{90}$ content of fall-out at ground stations, in rainwater and in the air over the United Kingdom during 1952-1955. Includes calculations of time-integrated gamma ray doses. | 28 |
| 20/Corr.1 | *Corrigendum to above report* | 2 |
| 21. | UNITED STATES. *Project Sunshine Bulletin No. 12*<br>Presents and discusses results of $Sr^{90}$ analyses since 1 December 1955. Includes $Sr^{90}$ concentration in human and animal bones, animal products, vegetation, soil, precipitation, other water, and air. | 59 |
| 22. | *Summary of analytical results from the Hasl Strontium Program to June 1956*<br>Summarizes the data of research on $Sr^{90}$ conducted by Hasl since 1951. Includes the $Sr^{90}$ content in fall-out, soil, vegetation, human and animal bones, human urine, milk, cheese, drinking water, and fish. Fall-out measurements and samples cover not only United States of America but also several other countries. | 9 |
| 23. | ARGENTINA. *Preliminary report on possible methods of estimating the biological effects of small doses of radiation*<br>Among biological effects of small doses of radiation, emphasizes especially: measurement of DNA synthesis using $P^{32}$ and $C^{14}$ radio-autography, histochemical and electron microscopic examination of changes in lymphocytes and other components of peripheral blood. | 13 |
| 24. | UNITED STATES. *The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki*<br>Gives full account of survey of pregnancies in Nagasaki and Hiroshima from 1948 to 1954: sex ratio, congenital malformations, still births, birthweights, neo-natal deaths, certain anthropometric measurements at nine months, and autopsies were compared with parental irradiation histories. No significant correlations were found. | 380 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| 25. | HUNGARY. *Unusual radioactivity observed in the atmospheric precipitation in Debrecen (Hungary) between 22 April-31 December 1952*<br>Describes methods and discusses results of measurements of total beta activity of fall-out at Debrecen, April-December 1952. | 13 |
| 26. | BELGIUM. *Report consisting of five parts*<br>1. Gives results of clinical observations of patients treated with X-rays, Ra or $I^{131}$ and of persons occupationally exposed.<br>2. Gives results of studies relating to: the medical and physical control of persons occupationally exposed; the absorbing materials; and the radioactive contamination of the atmosphere.<br>3. Considers preventive or curative methods of syndromes of acute irradiation. States results of doses received by the occupationally exposed personnel of the *Institut du cancer* of Louvain, Belgium, and of hematological examinations of them.<br>4. Describes methods for measuring the radioactivity in rain and surface waters. Gives results of measurements of radioactivity in rainwaters.<br>5. Describes method for measuring the radioactivity of atmospheric dust by continuous filtering of air. | 50 |
| 27. | SWITZERLAND. *Letter from the "Service fédéral de l'hygiène publique", Bern*<br>Gives brief description of studies on atomic radiations conducted in Switzerland. | 6 |
| 28. | ARGENTINA. *Information summary on the preliminary work carried out in Argentina for the measurement and study of radioactive fall-out*<br>Gives summary description of methods tried in Argentina for measurement of total fall-out radioactivity and airborne radioactivity. | 2 |
| 29. | AUSTRALIA. (*Report consisting of six parts, as follows:*)<br>(*Part I.*) *Human genetics*<br>Report gives recommendation as to the kind of human mutations which could be scored: several dominant autosomal genes should be investigated (gives list of such genetical abnormalities).<br>(*Part II.*) *Plant genetics*<br>Gives plan of research to be organized.<br>(*Part III.*) *Radio-biological unit in the University of Adelaide*<br>To be established.<br>(*Part IV.*) *Natural radiation background and environmental contamination*<br>Describes future organization of investigations on natural radiation background and contamination; radioactivity of food will be determined.<br>(*Part V.*) *Occupational exposure in Australia*<br>Describes monitoring system in application since 1940 and summarizes observations done by the use of film badges (gives statement of per cent of personnel having received a specified per cent of the permissible dosage).<br>(*Part VI.*) *Health and safety precautions in uranium mining and milling in Australia*<br>Describes health and safety precautions in uranium mining and milling. | 17 |
| 30. | UNITED KINGDOM. *Radio-strontium fall-out in biological materials in Britain*<br>Describes methods for determination of $Sr^{90}$ in soils and material of the biological cycle; gives results of measurement effected in England up to spring 1956. | 46 |
| 31. | FEDERAL REPUBLIC OF GERMANY. *Replies to the questions put by the United Nations Scientific Committee on the Effects of Atomic Radiation*<br>1. Levels of natural radiation background.<br>2. Summarizes long-term research in biology and medicine under the direction of *Langendorff* (genetic effects, restorations, physicochemical effects); *Rajewski* (effects of natural radioactivity, accumulation of nuclides in tissues); *Marquardt* (research on natural mutation rates and their modification by irradiations); *Other institutes* (pathological and physicochemical effect). No details given—refers to scientific publications. | 6 |
| 32. | INDIA. *Procedure used in India for collection of fall-out samples and some data on fall-out recorded in 1956*<br>Describes methods for measurements of airborne activity by filtration, and of deposited fall-out with daily and monthly collection. The information includes tables giving results. | 12 |
| 33. | *External radiation dose received by the inhabitants of monozite areas of Travancore-Cochin, India*<br>Contains results of a survey to measure the radiation level of the Indian State of Travancore. The radiation level due to gamma-rays at about three feet above the ground level ranges from 6,000 to 100 mrad/year, approximately. The main contributors are thorium and its decay products. | 9 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|

A/AC.82/G/R.

34 and Add.1 BRAZIL. *On the intensity levels of natural radioactivity in certain selected areas of Brazil* 46

States that Brazil has areas of intensive natural background where thorium sands are present. Gives description of a survey on four sample areas which were selected with regard to:

(*a*) The geological structure and genesis of their active deposits;
(*b*) The extension, configuration and intensity of their radiometric levels;
(*c*) The extent and variety of possible biological observations and experiments.

34/Corr.1 *Corrigendum to above report.* 6

35. WORLD METEOROLOGICAL ORGANIZATION. *Summary of comments of WMO on procedures for collection and analysis of atmospheric radioactivity data* 5

Comments on measurements of fall-out and airborne activity; stresses the importance of co-operation between meteorologists in selecting sites wherefrom to obtain samples.

36. BRAZIL. *Measurements of long-range fall-out in Rio de Janeiro* 13

Gives information on measurements of airborne activity done in Rio de Janeiro, including tables showing decay curves of activity of samples and concentration of fission products in air during the period May-July 1956.

37. UNION OF SOVIET SOCIALIST REPUBLICS. *On the methods of indicating the changes produced in the organism by small doses of ionizing radiation* 13

Gives an enumeration of many methods which might be used as tests for small dosages; but these are based on certain symptoms which have not yet been worked out to give a quantitative response, i.e. vegetative-visceral symptoms, nervous symptoms (like the increase in threshold of gustatory and olfactory sensitivity, etc.), skin vascular reactions, electroencephalogram.

Blood symptoms are also described (alterations of thrombocytes and lack of a leucocytosis response to the injection of Vit. B-12).

Certain "immunological" symptoms are quoted, like the bactericidal properties of saliva and of skin.

38. BRAZIL. *Absorption curve of fall-out products* 5

Is connected with document A/AC.82/G/R.36; gives absorption curve for fission product of an airborne activity sample obtained by filtration.

39. USSR. *Content of natural radioactive substances in the atmosphere and in water in the territory of the Union of Soviet Socialist Republics* 23

Studies content of natural radioactive substances in the atmosphere and in waters; geochemical considerations on mechanism of contamination of waters and description of radio-hydrogeological methods. Gives methods of measurement of airborne activity and results, and includes tables giving content of natural radioactive products in air and waters.

40. *Study of the atmospheric content of strontium-90 and other long-lived fissions products* 8

Gives measurements of airborne fission products ($Sr^{90}$, $Cs^{137}$, $Ce^{144}$ and $Ru^{106}$); methods for collection of samples and their radiochemical analysis; results and comments.

41. *On the behaviour of radioactive fission products in soils, their absorption by plants and their accumulation in crops* 176

Report of two parts:

*Part I.*—Experiments of absorption and desorption by soil of fission products and especially of isotopes such as $Sr^{90} + Y^{90}$, $Cs^{137}$, $Zr^{95} + Nb^{95}$ and $Ru^{106} + Rh^{106}$ are described. Theoretical analysis is also described.

It was observed that $Sr^{90} + Y^{90}$ is absorbed through ion exchange reaction, and is completely or almost completely displaced from the absorbed state under the action of a neutral salt such as $CaCl_2$. Radioactive equilibrium between $Sr^{90}$ and $Y^{90}$ is destroyed during the interaction with soil.

Displacement of absorbed radiocesium is greatly affected by the potassium ions, but not highly affected by $NaNO_3$ or $CaCl_2$ compared with $Sr^{90} + Y^{90}$. Zirconium and ruthenium absorbed by soil exhibit a much lower susceptibility to desorption into neutral salt solution, though their absorption is less complete. The disturbance of the equilibrium occurs also by absorption or desorption.

*Part II.*—The results of experiments on uptake of fission products by several agricultural plants are described. In water culture, the bulk of radioactive isotopes of cesium and strontium is held in the above-ground organ of plant, while Zr, Rh and Ce are mainly retained in the root system. Sr and Cs are likely to accumulate in reproductive organs of plants in larger quantities than Zr, Ru and Ce. The plant uptake is affected by the concentration of hydrogen ions in the solution. Plants' uptake of fission products from soils is considerably smaller than from aqueous solution, and

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|

A/AC.82/G/R.

USSR *(continued)*

cesium was found to be less absorbable from soil, compared with other isotopes, while cesium is among the fission products most strongly absorbed by plants in water culture. These facts can be explained by the absorptive and desorptive capacity of the isotopes of the soil. The properties of soil as well as the application of lime, potassium or mineral fertilizers greatly affect the plant uptake. When a solution of fission products was applied to leaves of a plant, radio-isotopes were observed to pass to other organs. Radiocesium was the most transmovable among the isotopes tested.

42. MEXICO. *First studies on radioactive fall-out* — 15
Revised form of UN document A/AC.82/G/R.5.

43. JAPAN. *The effect of momentary X-ray exposure in a small dose upon the peripheral blood picture* — 8
Decrease in lymphocyte number after single 60 mr exposure in humans. Decrease in lymphocyte count varies from 10 to 50 per cent—the maximum drop occurs thirty minutes after irradiation, and may be followed by an increase in lymphocyte count.

44. *Hematological effects of single exposure to small doses of X-ray* — 17
Hematological effects during routine chest examinations. Dosages up to 3r. Most constantly observed are: increase in neutral red bodies and Demel's granules in lymphocytes and late decrease in mitochondrial index of lymphocytes during the four-hour period following the irradiation. The cytochemical identification of these various granules and their biological significance should be established unequivocally.

45. *Morphological changes of platelets in chronic radiation injuries* — 19
Platelet morphology in chronic irradiation injury in rabbits (chronic 0.115 r/day or 0.231r/day), X-ray workers (dosage not evaluated) and persons exposed to atomic bomb within 4 km from epicentre (nine years after the exposure).
Even if platelet count is normal, area index (proportional to average area) is increased markedly, and may remain so nine years after irradiation and is not necessarily related to low platelet count. Other morphological changes are also shown.
This observation should be repeated by other groups.

46. EGYPT. *Preliminary report on environmental iodine-131 measurement in sheep and cattle thyroids in Cairo, Egypt* — 11
Contains measurement of radioactivity of $I^{131}$ deposited in thyroids of sheep and cattle which were brought from all over Egypt, Sudan and north coast of Libya. Sampling was made during the period from May to October 1956.

47. USSR. *Preliminary data on the effects of atomic bomb explosions on the concentration of artificial radioactivity in the lower levels of the atmosphere and in the soil* — 21
Contains description of methods of measurement of radioactive products in the air at ground level and high altitude and gives results of observations.
Also contains the following conclusions:
(1) The existing technique for detecting the presence of artificial radioactivity in the lower atmosphere and the technique for determining the integral activity of aerosols deposited on the earth's surface makes it possible to estimate the level of contamination of the soil by radiostrontium (strontium-90).
(2) The accumulation of radiostrontium in the soil in various areas of USSR territory is attributable partly to the explosion of atomic bombs in USA and partly to explosions set off in USSR. The lower limit of activity of the strontium-90 which has accumulated in the past two years (1954–1955) is as high as about 30 millicuries per $km^2$ in certain towns (cf., for example, Adler).
(3) Since radiostrontium is readily caught up in the biological cycle, suitable projects must be put in hand to determine the permissible levels of contamination of the soil with radiostrontium (strontium-90) and other biologically dangerous isotopes.

48. *Programme of scientific research on the effects of ionizing radiations on the health of present and future generations* — 6
Describes a programme of research intending to study the effects of radiation at dosages 1 or 2 orders of magnitude above background intensity, of contamination of the air and soil and life in areas of high natural radioactivity.

49. *Summaries of papers presented at the Conference on the remote consequences of injuries caused by the action of ionizing radiation* — 74
Mostly concerned with effects of various radionuclides and external radiation on different mammalian populations (Hematology, carcinogenesis, fertility mostly studied). Twenty-two papers are summarized.

50. *Contributions to the study of the metabolism of caesium, strontium and a mixture of beta-emitters in cows* — 20

A/AC.82/G/R.

USSR *(continued)*

The metabolism of $Cs^{137}$, $Sr^{89,90}$ and a number of mixed beta-emitters has been studied in cows (milk, urine, faeces, tissues).

*Strontium*: about 10 per cent given is absorbed in intestine and 1.45 per cent is retained in bones, and twenty times less in the soft tissues. The rest is excreted by milk or urine.

*Caesium:* about 25 per cent given is absorbed in intestine—one fifth of this is retained in muscle and less than one tenth of this amount in other organs or skeleton; the rest is eliminated in the milk or urine.

51. UNITED KINGDOM. *The genetically significant radiation dose from the diagnosis use of X-rays in England and Wales—A preliminary survey* — 11

Contains an analysis of number of X-ray diagnostic examinations performed per annum in England and Wales, and a subdivision obtained from five selected hospitals into types of examinations, and into age and sex of the patients examined. In addition, an assessment is made of the minimum dose received by the gonads in each type of examination, and the probability of reproduction as a function of age. The results show that it is unlikely that the genetically significant radiation dose received by the population of England and Wales from X-ray diagnosis amounts to less than 22 per cent of that received from natural sources and it may well be several times greater than this figure. Most of this radiation is received in a few types of examinations, undergone by relatively few patients, and by foetal gonads in examinations during pregnancy.

52. ROMANIA. *Organization and results in radiobiological research work in the Romanian People's Republic* — 5

Describes the following:

(1) and (2) Protective effects of narcosis during irradiation only.

(3) After 325 r, up to eleven days narcosis increases biological effects (does not state what criteria of biological effect).

(4) Hibernation (25° C) protects. Hibernation between 18°-25° C enhances effect. Does not state if this is during or after irradiation.

(5) Hematological tests after 350 r.

(6) Caffeine or aktedron during irradiation enhance effect; caffeine or aktedron after irradiation diminish effect.

Suggests roentgenotherapy under conditions of protection (narcosis). Gives programme for radiobiology research in 1956-1957.

53. USSR. Report consisting of two articles: — 10

Part 1. *The effects of ionizing radiations on the electrical activity of the brain*

(*a*) Grigorev's research work states: gamma-rays depress electrical action of human brain. Does not confirm Eldrid-Trowbridge, who do not find effect on monkey.

(*b*) Describes effects of beta-rays of $P^{32}$ (0.05 mc/kg up to 1 mc/kg) on electroencephalogram of dogs. This was followed by radiation sickness (if dose > 0.5 mc/kg) and by hematological effects. A special implantation method of the electrodes is used. Injection of 0.09 mc/kg gives change in amplitude five minutes after the injection (reduction in amplitude). After 0.5 mc/kg lowering of electrical activity lasts for several days. For dosages above 0.1 mc, part of the repression of brain activity is probably a result of the radiation sickness induced by such high dosages.

Part 9. *On the beta-radiation activity of human blood*

Report on radioactivity of human blood: 100 cc of normal blood have a radioactivity of 1.7 to $3.64.10^{-10}$ curies (due to $K^{40}$). Permits the determination of K content of whole blood. Same values are found in different pathological conditions. No data on people working with radioactive material.

54. UNITED STATES. *Some effects of ionizing radiation on human beings* — 106

A report on the Marshallese and Americans accidentally exposed to radiation from fall-out and a discussion of radiation injury in the human being. Gives general and clinical symptomatology in relation to the estimated dosage and to internally deposited radionuclides.

55. *Background radiation—A literature search* — 43

The results of literature search about background radiations dosage to human beings are described and classified into three categories:

(1) Cosmic radiation; (2) terrestrial radiation sources; and (3) radiation from internal emitter. The cosmic radiation is important for the evaluation of natural background, since it is estimated very roughly to contribute about a quarter of total background dosage to the human population at sea level and high latitude. However, its intensity varies with various factors, such as altitude, geomagnetic latitude, barometric pressure,

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| | UNITED STATES *(continued)* | |
| | temperature etc. Facts directly related to biological effects of cosmic rays are also reviewed. | |
| | Radiations from naturally-occurring radioactive isotopes form another important part of the natural background. The contribution which comes from land is mainly due to $K^{40}$, $Ra^{226}$, $Th^{232}$ and $U^{238}$ and the decay products of the last three nuclides. The radium concentrations in surface water and public water supplies in various districts are tabulated. The atmospheric concentration of Rn and Tn is greatly dependent on the locality, atmospheric condition and degree of ventilation, if indoor. | |
| | The population dose due to the natural background radiation is difficult to evaluate in general, because of the statistical nature and varying conditions involved in nations. | |
| 56. | *Operation Troll* | 37 |
| | Operation Troll was conducted to survey the radioactivity in sea water and marine life in the Pacific area during the period from February to May 1955. The general conclusions obtained are as follows: | |
| | 1. Sea water and plankton samples show the existence of widespread low-level activity in the Pacific Ocean. Water activity ranged from 0-570 d/min/litre and plankton from 3-140 d/min/g wet weight. | |
| | 2. There is some concentration of the activity in the main current streams, such as the North Equatorial Current. The highest activity was off the coast of Luzon, averaging 190 d/min/litre down to 600 m (1 April 1955). | |
| | 3. Analyses of fish indicate no activity approaching the maximum permissible level for foods. The highest activity in tuna fish was 3.5 d/min/g ash, less than 1 per cent of the permissible level. | |
| | 4. Measurements of plankton activity offer a sensitive indication of activity in the ocean. | |
| | 5. Similar operations would be valuable in assessing the activity from future tests and in gathering valuable data for oceanographic studies. | |
| 57. | *Gonadal dose in roentgen examinations—A literature search* | 6 |
| | Contains results of literature research which show the estimated contribution of gonadal dose by standard medical roentgenographic procedures. Contribution to the gonadal dose of certain examinations, such as examinations of teeth, skull, chest and extremities, is relatively insignificant, when compared to the case of pelvic and abdominal examinations. It should be noticed that the dose to the foetal gonad is important genetically. | |
| 58. | WORLD HEALTH ORGANIZATION. *Effect of radiation on human heredity*— | |
| | Report of a Study Group (Copenhagen, 7-11 August 1956). | 148 |
| | 1. Document A: Reply to a question raised by the United Nations Scientific Committee on the Effects of Atomic Radiation. | |
| | 2. Report of the study group concerning general questions and recommendations for future progress and research. | |
| | 3. Annexes 2-9 and 11-12 of the above report, being papers presented by various members of the group. | |
| | These annexes were: | |
| | Types of mutation at known gene loci and possibility of hitherto unrecognized mutations being induced. Irradiation of animal populations: results and work needed—T. C. Carter. | |
| | Some of the problems accompanying an increase of mutation rates in Mendelian populations—Bruce Wallace. | |
| | Exposure of man to ionizing radiations, with special reference to possible genetic hazards—R. M. Sievert. | |
| | Detection of induced mutations in offspring of irradiated parents—J. Lejeune. | |
| | Gonad doses from diagnostic and therapeutic radiology—W. M. Court Brown. | |
| | Mutation in man—L. S. Penrose. | |
| | Possible areas with sufficiently different background-radiation levels to permit detection of differences in mutation rates of "marker" genes—A. R. Gopal-Ayengar. | |
| | Comparisons of mutation rates at single loci in man—A. C. Stevenson. | |
| | Effect of inbreeding levels of populations on incidence of hereditary traits due to induced recessive mutations—N. Freire-Maia. | |
| | Detection of genetic trends in public health—Harold B. Newcombe. | |
| 58/Add.1 | Annexes 1 and 10 of the above report of the WHO Study Group on the effect of radiation on human heredity. | 47 |
| | These annexes were: | |
| | Damage from point mutations in relation to radiation dose and biological conditions—H. J. Muller. | |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| | WORLD HEALTH ORGANIZATION *(continued)* | |
| | Some problems in the estimation of spontaneous mutation rates in animals and man—James V. Neel. | |
| 59. | NETHERLANDS. *Radioactive fall-out measurements in the Netherlands* | 6 |
| | Describes methods used for collecting samples of airborne radioactivity and of deposited fall-out, and methods of measurement. | |
| | Includes tables of results for 1955 and 1956; calculation of gamma doses and quantity of strontium-90 computed from total activity. | |
| 60. | UNITED KINGDOM. *Genetic research in the United Kingdom* | 6 |
| | Relevant programmes of genetic research in the United Kingdom and their investigators concerned are listed under the headings: | |
| | (i) Fundamental research upon mechanisms; | |
| | (ii) Population structure; | |
| | (iii) Quantitative data on human mutation. | |
| 60/Add.1 | *Suggestions for research in radiation genetics* | 3 |
| | General considerations are reviewed and a list of suggested programmes of research in the fields (i) to (iii) is appended. | |
| 61. | JAPAN. *Current and proposed programmes of research and investigation related to radiation genetics in Japan* | 16 |
| | A brief survey of current and planned research in Japan relevant to radiation genetics, covering both human surveys and experimental work. | |
| 61/Add.1 | *Table 1 (2) to above report:* | |
| | *Experimental data with beta radiation* | 2 |
| 62. | *Radiochemical analysis of $Sr^{90}$ and $Cs^{137}$* | 6 |
| | Discusses methods of radiochemical analysis of $Sr^{90}$ and $Cs^{137}$, including separation of strontium by precipitation and by ion exchange. Experiments for determining the best conditions for ion exchange separations are reported. | |
| 63. | *Review of the recent researches on the biological effects of ionizing radiation in Japan* | 14 |
| | Contains brief abstracts of fifty-five papers from the Japanese literature dealing with (1) research on biological indicators of the effects of ionizing radiation in small and large doses, and (2) research on counter measures to alleviate radiation injury. Classical and more modern morphological, histochemical and biochemical methods of observation were used for the assessment of radiation damage. Most studies were performed on mammals. It is emphasized that it is very difficult to obtain reliable biological indicators of damage by small doses and that haematological methods are still the most suitable in man. | |
| 64. | UNITED STATES. *Shortening of life in the offspring of male mice exposed to neutron radiation from an atomic bomb* | 12 |
| | Length of life in the offspring of male mice exposed to moderate doses of acute neutron radiation from a nuclear detonation is shortened by 0.61 days for each rep received by the father over the dose range tested. This figure excludes death before weaning age. The 95 per cent confidence limits are 0.14 and 1.07 days per rep. Extrapolating to a proportional shortening of life in man gives twenty days per rep received by the father as the point estimate and five and thirty-five days as the 95 per cent confidence limits. The offspring were obtained from matings made from nineteen to twenty-three days after irradiation and, therefore, represent the effect of irradiation on germ cells in a post-spermatogonial and sensitive stage of gametogenesis. It is probable that irradiation of spermatogonia (the stage that is important from the point of view of human hazards) would give a somewhat smaller effect. However, since the present data show an effect on the offspring which is as large as the shortening of life in the exposed individuals themselves, it seems likely that, even when allowance is made for the conditions of human radiation exposure, shortening of life in the immediate descendants will turn out to be of a magnitude that will warrant serious consideration as a genetic hazard in man. | |
| 65. | *Gamma-ray sensitivity of spermatogonia of the mouse* | 3 |
| | Relates the depletion of spermatogenic cells to killing of spermatogonia, the repopulation being related to the maturation of surviving cells. | |
| 66. | *Some delayed effects of low doses of ionizing radiations in small laboratory animals* | 7 |
| | A quantitative study of the life span, the incidence of leukemia, tumours (lung, liver, overy), and lens opacities as a response to low dosages (less than 100 rads). | |
| 67. | *Effects of low-level radiation (1 to 3 r) on mitotic rate of grasshopper neuroblasts* | 4 |
| | A study of the inhibitions of mitotic rate and of its possible relationship with the alteration of chromosome structure. | |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | UNITED STATES *(continued)* | |
| 68. | *Effects of low doses of X-rays on embryonic development in the mouse*<br>Effects of 25 r applied during different stages of embryonic development on skeletal malformations appearing in the young. | 6 |
| 69. | SWEDEN. *Does there exist mutational adaptation to chronic irradiation?*<br>An account of an experiment in which a population of Drosophila heavily irradiated for many generations was compared with a control unirradiated population in respect of radiation-induced mutability. No significant differences were found. | 7 |
| 70. | JAPAN. *Radiological data in Japan*<br>The report is a compilation of data on radiation exposures in Japan. Data are arranged as suggested by the Scientific Committee at its October 1956 meeting. | 58 |
| 70/Corr.1 | *Corrigendum to above document* | 5 |
| 71. | UNITED STATES. *Occupational radiation exposures in Atomic Energy projects*<br>A series of five tables concerning yearly exposures from 1947 to 1955 from external and internal radiation sources. | 9 |
| 72. | *Worldwide effects of atomic weapons*<br>(A comprehensive preliminary report on the $Sr^{90}$ problem up to 1953).<br>A preliminary report discussing the various aspects of long-range contamination due to the detonation of large numbers of nuclear devices. An improved methodology for assessing the human hazard is developed, and an extensive experimental programme is proposed. | 96 |
| 73. | *Maximum permissible radiation exposures to man*<br>A preliminary statement of the U.S. National Committee on Radiation Protection and Measurement. The recommendations given by the Committee in National Bureau of Standards Handbook 59 have been revised and the maximum permissible dose-levels have been lowered. The concept of "accumulated" dose for occupational conditions differs from the ICRP recommendations of 1956. For the whole population an annual additional exposure of 2.5 times the exposure from natural radiation sources is allowed. | 6 |
| 74. | *Gonadal dose produced by the medical use of X-rays*<br>A survey of diagnostic X-ray exposure with an attempt to estimate the genetically significant dose in the United States. The estimate has been made under the assumption that patients undergoing X-ray examinations have a normal child expectancy. The authors have assumed that the genetically significant dose can then be evaluated as approximately equal to the average gonad dose for patients below the age of 30. Using exposure data which are considered fairly representative of American practice they arrive at 130-140 mrem/year and 50 mrem/year as being the most probable and the minimum figure respectively. | 105 |
| 75. | *Summary of current and proposed programmes of research in the U.S.A. related to radiation genetics*<br>A survey by investigator and title of current and proposed programmes of research in the United States related to radiation genetics. | 10 |
| 76. | FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS. *Principal calcium contributors in national diets in relation to effects of atomic radiation from $Sr^{90}$*<br>Gives a general idea of foods contributing to the calcium uptake of human beings in various parts of the world in relation to the different food habits of these people. Data still quite preliminary. | 4 |
| 76/Rev.1 | FAO. *Principal calcium contributors in national diets in relation to effects of atomic radiation from strontium-90*<br>This paper replaces the preliminary note circulated as UN document A/AC.82/-G/R.76. | 8 |
| 77. | NORWAY AND SWEDEN. *Radioactive fall-out over the Scandinavian peninsula between July and December 1956*<br>In this report, fall-out and rain precipitation figures over the Scandinavian peninsula are discussed. Accumulated monthly fall-out is reported for the period July-December 1956. | 6 |
| 78. | BELGIUM. *Information in eight parts on human genetics submitted by Belgium*<br>Contains the Belgian memorandum on human genetics prepared for the Geneva meeting in April 1957 and a preliminary report on radioactive regions of Katanga (Belgian Congo). Besides this several reprints of Belgian contributions to radiobiology are presented. The topics included are:<br>(1) Steroid metabolism in irradiated rat.<br>(2) Endocrine response of irradiated animals studied by intraocular grafting. | |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| | BELGIUM *(continued)* | |
| | (3) Doses and hazards due to medical radiology.<br>(4) Metabolism and toxicity of cystamine in the rat.<br>Part 1. Current uncertainties in the field of human genetics.<br>Part 2. A preliminary survey of vegetation and its radioactive content in the Katanga area. | 1 |
| | Part 3. Influence of irradiation on the blood level of 17-hydroxy-corticosteroids during the 24 hours following irradiation. | 5 |
| | Part 4. Skin and depth doses during diagnostic X-ray procedures. | 14 |
| | Part 5. General discussion of the need for methods of effective dose reduction in diagnostic X-ray procedures. | 11 |
| | Part 6. Chemical protection (*a*) metabolism of cystamine<br>Part 7. (*b*) the effectiveness and toxicity of cystamine. | 11 |
| | Part 8. Experiments on the ascorbic acid and cholestrol content of the supra-renals of the rat following irradiation of normal and hypophysectomised animals. | 11 |
| 79. | SWEDEN. *A suggested procedure for the collection of radioactive fall-out*<br>Proposes new method for evaluation of the external thirty-year dose due to the deposition of gamma-emitting isotopes, based upon a single beta measurement for each sample and one caesium ratio chemical determination in a pooled sample.<br>A second part of the report describes a collecting procedure using ion exchange resins. | 19 |
| 80. | ARGENTINA. *A geological, radiometric and botanic survey of the region "Los Chañores" in the province of Mendoza of Argentine Republic*<br>Radiometric data on the above-mentioned region are shown on the attachment to the document. | 4 |
| 81. | *Measurements of the cosmic ray intensity in three latitudes of Argentine Republic*<br>Data on the intensity of the cosmic rays in three points of observation at different latitudes in Argentina. | 5 |
| 81/Corr.1 | *Corrigendum to above report* | 2 |
| 82. | *On the absorption of the nucleonic component of the cosmic radiation at −15° geomagnetic latitude* | 1 |
| 83. | *Mutations in barley seeds induced by acute treatments by gamma rays of cobalt-60*<br>A report of experiments on the induction of mutations at a number of loci in barley by irradiation of seeds with gamma-rays of $Co^{60}$ at 10 r/min. | 2 |
| 83/Add.1 | *Addendum to above report* | 1 |
| 84. | *Mutations in barley induced by formaldehyde*<br>A report of experiments on the induction of mutations at a number of loci in barley by formaldehyde. | 1 |
| 85. | *Spontaneous mutations in barley*<br>A report of experiments on spontaneous mutations at a number of loci in barley. | 2 |
| 86. | *A study of radioactive fall-out in Argentine Republic*<br>Describes the methods used in Argentina for fall-out collection and measurement. Value for strontium-90 and total beta activity are given for the first two months of 1957. | 5 |
| 87. | *A research programme in Argentina on the genetic influence in the plants of the ionizing and ultra-violet radiation*<br>A brief summary of projected research in Argentina on the genetic effects of ionizing and ultra-violet irradiations of plants, comprising both surveys of areas of high natural background and a broad range of laboratory experiments. | 2 |
| 88. | *Programme of physical oceanography for the International Geophysical Year* | 33 |
| 89. | *Information on the general programme to be developed in Argentina on items of interest to the Scientific Committee on the Effects of Atomic Radiation*<br>A brief general survey of Argentina research activities related to the effects and levels of ionizing radiations. | 2 |
| 90. | NETHERLANDS. *Chemical steps involved in the production of mutations and chromosome aberration by X-radiation and certain chemicals in Drosophila*<br>A survey of comparative studies of X-ray and chemical mutagenesis in Drosophila, made in an attempt to throw light on possible intermediate chemical steps in the induction of chromosome breaks or mutations by ionizing radiation. | 6 |
| 91. | UNITED STATES. *Strontium-90 in man*<br>Radiochemical analyses of strontium-90 in human bone have been reported. The | 7 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| | UNITED STATES *(continued)* | |
| | values are in accord with the predicted levels based on fall-out measurements and fractionation through the food-chains. | |
| 92. | NORWAY. *Radioactive fall-out in Norway*<br>Contains information on methods and results of measurements of fall-out in Norway. | 19 |
| 93. | *Summary of analytical results from the HASL Strontium Program July through December 1956*<br>Summarizes data on samples collected by the U.S.A. fall-out network since September 1955 up to September 1956. In addition, it summarizes the data of the samples collected for the strontium programme during the period July-December 1956. | 43 |
| 94. | *Environmental radon concentrations—An interim report*<br>Preliminary data showing ambient concentrations of radon in the metropolitan New York area are presented. An attempt has been made to define the variability of concentration of radon in the general atmosphere with location, time, and weather conditions. Samples have been analysed from the outdoor air, inside of buildings, and above and below the surface of the ground. Comparisons with the data obtained by other investigators are also shown. | 8 |
| 95. | *The radium content of soil, water, food and humans—Reported values* | 6 |
| 96. | *Marine biology—Effects of radiation—A selected bibliography*<br>Twenty-four references concerning investigation on the distribution and metabolism of fission products in marine organisms. | 2 |
| 97. | *Sea disposal operation*<br>Some atomic energy activities in the United States have been disposing of radioactive wastes at selected ocean disposal sites since as early as 1946. It is the purpose of this report to describe the extent of these disposal operations including a summary of types of packaging used and of places where the wastes are dumped. The status of related oceanographic research (1956) is briefly touched upon. | 14 |
| 97/Corr.1 | *Corrigendum to the above report* | 1 |
| 98. | CANADA. *Radiochemical procedures for strontium and yttrium*<br>A detailed ion exchange procedure is given for the determination of radiostrontium in different samples. Methods are described for the treatment of various organic materials. | 25 |
| 99. | *Levels of strontium-90 in Canada up to December 1956*<br>Reports the results of radiochemical analysis for strontium-90 activity in milk and milk products and human bone. Natural strontium content determinations in milk and bone are also reported. | 15 |
| 100. | UNITED KINGDOM. *The determination of long-lived fall-out in rainwater*<br>Describes radiochemical procedures for the determination of $Sr^{89}$, $Sr^{90}$, $Cs^{137}$ and $Ce^{144}$ activities in the rainwater. | 4 |
| 101. | DENMARK. *Measurement of activity of airborne dust. Measurements of fall-out deposited on the ground*<br>Results of daily measured radioactivity in air (electrostatic filter method) and in precipitations (collection of rainwater) in Copenhagen for the period 1956. | 3 |
| 102. | AUSTRIA. *Radiological data. Demographic data.*<br>Contains data on RBE dose rate in the gonad due to both natural and artificial sources. Demographic data on the whole population and of special groups are given. | 6 |
| 103. | UNITED KINGDOM. *Modification of immunological phenomena and pathogenic action of infectious agents after irradiation of the host*<br>Evidence is given that whole body irradiation before the repeated injection of antigen both diminishes the peak-concentration of antibody and delays in time the appearance of the peak. The lowest efficient dose was 25r. The tolerance of heterogenous skin grafts or bone marrow cells has been also shown after irradiation; the duration of inhibition of immune response is proportional to dose received. | 2 |
| 104. | *Some data, estimates and reflections on congenital and hereditary anomalies in the population of Northern Ireland*<br>Presents an extremely detailed and thorough medico-genetic survey of the population of Northern Ireland using data accumulated over a number of years, together with very pertinent analyses of the data, the problem of genetic disability and its relation to radiation effects. | 42 |
| 105. | *Leukemia and aplastic anaemia in patients irradiated for ankylosing spondylitis*<br>The incidence of leukemia and of aplastic anaemia was investigated in patients | 135 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| | UNITED KINGDOM *(continued)* | |
| | treated in Britain for ankylosing spondylitis by means of ionizing radiations during the years 1935-1954.<br>Relationship between radiation dose and incidence of leukemia was evaluated. The answers suggest the adoption of working hypothesis that for low doses the incidence of leukemia bears a simple proportional relationship to the dose of radiation, and that there is no threshold dose for the induction of the disease. The dose to the whole bone marrow which would have doubled the expected incidence of leukemia may lie within 30 to 50 r for irradiation with X-rays. | |
| 106. | NORWAY. *Information on radiological data*<br>Summary tables on radiological data in Norway with an extensive set of data on X-ray and natural radiation exposures. | 44 |
| 106/Add.1 | *Addendum to above report* | 2 |
| 107. | NEW ZEALAND. *New Zealand report to U.N. Scientific Committee on Atomic Radiation: Effects of atomic radiation measured in New Zealand to 31 July 1957*<br>A set of notes on the current status of various programmes in New Zealand within the field of interest on the Scientific Committee on the Effects of Atomic Radiation, including preliminary measurement of radioactive fall-out, $C^{14}$ airborne activity, natural and artificial radioactivity, and occupational gonad exposures. | 6 |
| 108. | UNITED STATES. *Current research findings on radioactive fall-out*<br>General survey of the fall-out problem, especially $Sr^{90}$ distribution and uptake in the human body. | 18 |
| 109. | *Dosages from natural radioactivity and cosmic rays* | 2 |
| 110. | NETHERLANDS. *Four reports on quantitative determination of radioactivity*<br>A group of tables containing figures for the radiation doses from natural and man-made sources in the Netherlands. | 48 |
| 111. | NORWAY. *On the deposition of nuclear bomb debris in relation to air concentration*<br>Studies the relation between the deposition of fall-out and the airborne activity. It appears that in 1956-1957 the fall-out in the Oslo area was roughly proportional to the product of precipitation and airborne activity at ground level. | 16 |
| 112. | *Radioactive fall-out in Norway up to August 1957*<br>Gives the results of measurement of fall-out materials in air, precipitation, water and other samples. Measurement of airborne activity at high altitudes are included. $Sr^{90}$ values are computed from total beta activity, a small number of samples having been checked by chemical analysis. Samples of water, milk and urine have been analysed for iodine-131. | 22 |
| 113. | *Radiochemical analysis of fall-out in Norway*<br>Describes the methods used in Norway for determination of $Sr^{90}$, $Cs^{137}$ and $I^{131}$ and contains data of $Sr^{90}$ and $Cs^{137}$ activities in water and milk and of $I^{131}$ in milk, in the period February-June 1957. | 10 |
| 114. | UNITED KINGDOM. *The relative hazards of $Sr^{90}$ and $Ra^{226}$*<br>Methods for calculations of the doses received by soft tissue cavities in bone containing $Sr^{90}$ and $Ra^{226}$ are presented. Non-uniformity factors are given for the dose from $Sr^{90}$. Calculation of the maximum permissible body burden for radium on the basis of a given maximum permissible dose-rate to bone gives a wide range of values, depending on the assumptions made. In the case of radio-strontium, the range of possible values is less. It is suggested that radium be no longer taken as the basis for the calculation of maximum permissible body burden of $Sr^{90}$. | 26 |
| 115. | *Shortening of life by chronic irradiation: the experimental facts*<br>A survey of all published experimental results relating to shortening of life-span of mice due to chronic irradiation.<br>The comparison of effects between gamma-rays of cobalt-60 and fast neutrons is made; the R.B.E. factor used for fast neutrons was 13.<br>A good agreement of experimental results has been found indicating that chronic irradiation both with gamma-rays and neutrons shortens the life of mice in a reproducible manner. No statistically significant data were found below the weekly dose of 10r.<br>The possibility of extrapolation and the possible dose-effect relationship is discussed. | 7 |
| 116. | BELGIUM. *Report on health protection in uranium mining operations in Katanga* | 7 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R. | | |
| 117. | INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION AND INTERNATIONAL COMMISSION ON RADIOLOGICAL UNITS AND MEASUREMENTS. *Exposure of man to ionizing radiation arising from medical procedures*<br>Gives a survey of the present exposure of the gonads due to X-ray diagnostic procedures. Some 85 per cent of the diagnostic dose arises from six to seven types of examinations, which are discussed separately. Estimates of the genetically significant dose are given for some countries. It is recommended that the basic studies be extended and that more detailed analysis be obtained through sampling procedures rather than through the systematic recording of the radiation received by every member of the population. Methods for dose reduction are discussed. | 60 |
| 118. | POLAND. *Report on measurements of fall-out in Poland*<br>Continuous measurements of global beta activity of fall-out are reported for four stations in Poland. | 4 |
| 119. | BELGIUM. *Effect of a lethal dose of radiation on the amount of reducing steroids in the blood of the rat*<br>Indicates that lethal irradiation shows, in the blood, an increase of reducing steroids. This reaction presents a maximum which is not necessarily linked to the variations of the ascorbic acid and of the cholesterol in the suprarenals. | 4 |
| 120. | *Action of hydrogen peroxide on the growth of young barley plants*<br>The growth of coleoptiles of young barley plants treated with hydrogen peroxide is affected in the same way as when the plants are irradiated with X-rays. | 3 |
| 121. | *Action of cystamine and glutathione on X-ray irradiated barley seed*<br>The cystamine and glutathione diminish the effects of X-rays on barley grains; mitosis are still possible after doses which would inhibit them in the absence of these agents. | 3 |
| 122. | *Action of X-rays on the growth of internodal cells of the alga Chara Vulgaris L.*<br>Irradiation of internodal cells of *alga Chara Vulgaris L.* increases the elongation of these cells for doses up to 150 kr; above this dosage elongation is inhibited (c.f. document A/AC.82/G/R.156). | 4 |
| 123. | UNITED STATES. *Radioactivity of people and foods*<br>Potassium and caesium activities measured with whole body counters are reported. The amount of caesium-137 now present in the population of the United States shows no marked dependence on geographical location. | 32 |
| 124. | *Atmospheric radioactivity along the 80th meridian, 1956*<br>Radioactivity levels at the various sites during 1956 are reported for three different collecting systems: air filters, cloth screens and gummed films. Extremely wide variations in the gross radioactivity of fission products in the air have been noted, with the highest levels occurring in the Northern hemisphere. Preliminary results of radiochemical analyses of a few filter collections are included. | 13 |
| 125. | *Radioactive contamination of certain areas in the Pacific Ocean from nuclear tests*<br>Contains a summary of the data on contamination levels in some areas of the Pacific Ocean and results from medical surveys of Marshall Islands inhabitants.<br>Data on gross beta activity, individual isotope contamination and external gamma-exposure are included. | 51 |
| 126. | UNITED KINGDOM. *Radiostrontium in soil, grass, milk and bone in the United Kingdom: 1956 results*<br>Results of strontium-90 analysis of soil, grass and animal bone for twelve stations in the United Kingdom are given. Human bone specimens obtained in 1956 have also been measured. | 28 |
| 127. | ARGENTINA. *Calcium and potassium content of foodstuffs in the Argentine Republic*<br>Describes the methods and results of K and Ca analysis of food in Argentina.<br>It shows that 80 per cent of the dietary Ca is provided by milk. | 17 |
| 128. | UNITED KINGDOM. *Ionizing radiation and the socially handicapped*<br>Collects available data and calculations concerning the numbers in various classes of handicapped individuals in the United Kingdom and the relationships of these numbers to genetic factors, mutation rates and radiation levels. | 9 |
| 129. | CANADA. *Dose from unsealed radio-nuclides*<br>Calculations based upon information on shipments of radioisotopes show that the gonad dose to age 30 from unsealed radio-nuclides during 1956 in Canada is about 0.5 per cent of the dose from the natural radiation sources. The main dose arises from iodine-131. | 11 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R | | |
| 130. | UNITED STATES. *The nature of radioactive fall-out and its effects on man*<br>An extremely diverse and extensive collection of information and expert opinion given as public testimony before a governmental committee, and presented without further evaluation. | 2,000 |
| 130/Add.1 | *Index to above report.* | 51 |
| 131. | *Radioactive strontium fall-out*<br>General survey of the fall-out problem, especially strontium-90 distribution and uptake in the human body. | 26 |
| 132. | UNITED KINGDOM. *The determination of long-lived fall-out in rainwater*<br>A method is described for the determination of long-lived isotopes in samples of rain water. Some attention is paid to the development of the method, including details of the checks to ensure radiochemical purity of the final sources used for counting. | 21 |
| 133. | WORLD METEOROLOGICAL ORGANIZATION. *Excerpt from a letter dated 6 November 1957 received from the Secretary-General of the WMO—Interim international reference precipitation gauge*<br>Brief report of the discussion held by the Executive Committee Panel on Atomic Energy and by the Commission for Instruments and Methods of Observations of the WMO on subjects related to the effects of atomic radiation. | 7 |
| 134. | ITALY. *Report on genetics 1950-57—A brief report on the research work done in the field of genetics in Italy*<br>Extensive notes reporting relevant research work in the field of genetics carried out in Italy during the period 1950-1957. | 47 |
| 135. | JAPAN. *Analysis of $Sr^{90}$, $Cs^{137}$ and $Pu^{239}$ in fall-out and contaminated materials*<br>The report gives radiochemical procedures for $Sr^{90}$, $Cs^{137}$ and $Pu^{239}$ from air filter ash. The counting equipment is described briefly. | 7 |
| 136. | *Primary estimate of the dose given to the lungs by the airborne radioactivity originated by the nuclear bomb tests*<br>The report gives method and results of measurement of airborne radioactivity for Tokyo from 1955 to 1957. Values are obtained for gross alpha and beta activity and radiochemically determined concentrations of strontium-90 and plutonium-239. A method for computation of the dose to the lungs is described. The mean dose during 1955-1957 was of the order of magnitude of $10^{-2}$ rem/year. | 7 |
| 136/Corr.1 | *Corrigendum to above report* | 1 |
| 137. | *A measure of future strontium-90 level from earth surface to human bone*<br>Calculation of the future strontium-90 level is made on the basis of present data on cumulative ground deposit and food contamination.<br>The cumulative ground deposit (mc/km²) is calculated assuming that:<br>1. The total amount of fission products from future tests is known.<br>2. 20 per cent of airborne strontium-90 falls to the earth's surface every year.<br>3. The distribution of fall-out is homogeneous.<br>The metabolism of strontium-90 through the food channel and food habit factor related to calcium and strontium source are taken into consideration.<br>The future human skeletonal dose and maximum permissible level of ground deposit are then calculated. | 14 |
| 138. | *Supplemental review of the recent researches on the alleviation of radiation hazards*<br>This is an addition to G/R 63 and gives abstracts of new developments of radiobiology in Japan. Work on protection by amino acids, cysteamine and some new derivatives of this last compound is reported. Work on the therapeutic effect of a protein diet and of adrenochrome preparation is also reported. | 3 |
| 138/Corr.1 | *Corrigendum to above report* | 1 |
| 139. | *Experimental studies on the development of leukemia in mice with frequent administrations of small doses of some radioactive isotopes ($P^{32}$, $Sr^{89}$, $Ce^{144}$)*<br>The development of leukemia is described in three strains of mice in which the disease has not been observed under control conditions. Nine cases of leukemia have been observed among forty-six animals surviving twenty-one weeks and longer following the first of repeated administrations of $P^{32}$ at three dose levels (0.1, 0.3, and 0.5 μc/gm). Latent periods varied with total dose administered. Larger doses were more effective than small doses. The leukemia was primarily of the myeloid type.<br>Radiostrontium ($Sr^{90}$) and radio-cerium ($Ce^{144}$) were much less and practically ineffective in producing this disease in these animals. Sarcoma of bone was found in strontium-treated animals. It is concluded that leukemia is the result of severe damage | 9 |

A/AC.82/G/R

JAPAN *(continued)*

to the haematopoietic tissues in the bone marrow and lymph nodes. There are many tables and figures, including results of radiochemical analyses of various bones at various intervals following injection.

139/Corr.1 — *Corrigendum to above report* — 1

140. — *Experimental studies on radiation injury by colloidal radioisotope-liver injury by colloidal radioactive chromic phosphate* $CrP^{32}0_4$ — 6

Describes morphological observations on the liver of rats which were injected intravenously with various concentrations of colloidal suspensions (particle size 0.1-1.0 micron) of radioactive chromium phosphate ($CrP^{32}0_4$). Even with high doses (7.5 μc/gm) liver injury did not become manifest until twenty days after injection and correspondingly later with lower doses. Changes in the liver are described but not illustrated. They are greater in the liver than in other organs containing reticuloendothelial cells. The lesions are said to resemble those of virus hepatitis. Large doses of chromium phosphate also produce lesions in the bone marrow with concomitant changes in the peripheral blood.

140/Corr.1 — *Corrigendum to above report* — 1

141. — *Radiological data in Japan II—Concentrations of* $Sr^{90}$, $Cs^{137}$, $Pu^{239}$ *and others in various materials on earth's surface* — 17

Contains data on concentration of $Sr^{90}$ in rainwater, soil, foodstuffs and human bone in Japan obtained by radiochemical analysis in some cases and by computation from the total beta activity in other cases. Besides $Sr^{90}$, data on $Cs^{137}$, $Pu^{239}$, $Zn^{65}$, $Fe^{55}$ and $Cd^{113}$ are also included.

141/Corr.1 — *Corrigendum to above report* — 2

141/Add.1 — *Addendum to above report* — 3

142. — UNITED STATES. *Radioactive fall-out* — 18

General survey of the fall-out problem, especially $Sr^{90}$ distribution and uptake in the human body.

143. — UNITED KINGDOM. *The world-wide deposition of long-lived fission products from nuclear test explosions* — 28

A network of six stations in the United Kingdom and thirteen in other parts of the world has been set up for rainwater collection. Samples are analysed for $Sr^{89}$, $Sr^{90}$, $Ce^{137}$ and $Ce^{144}$. This report contains an account of the results obtained so far, and some discussion of the present and future levels of $Sr^{90}$ in United Kingdom soil.

144. — NORWAY. *Radioactive fall-out up to November 1957* — 24

A review is given of the monitoring in Norway of airborne activity and fall-out of radioactive dust; also radioactive contamination in drinking water is reported.

145. — SWEDEN. *Uptake of strontium and caesium by plants grown in soils of different texture and different calcium and potassium content* — 5

146. — *The radioactive fall-out in Sweden up to 1.7.1957* — 12

Additional data to the report G/R.15 for the period up to June 1957 are given. The total beta activity, accumulated $Sr^{90}$ and $Cs^{137}$ amount and $Sr^{90}$ content in soil are measured.

147. — *Gamma radiation from some Swedish foodstuffs* — 9

Significant increase of gamma radiation from milk, beef, cattle-bone and vegetables was found during the period 1952-1956. No increase of gamma radiation from children in the corresponding period could be observed.

148. — *Progress report on the metabolism of fission products in ruminants* — 3

The excretion of radioactive fission products ($Sr^{90}$ and $I^{131}$) in milk after per oral administration is measured.

149. — *A method for monthly collection of radioactive fall-out* — 7

Describes a collecting procedure using anion and cation exchange resins.

150. — *The computation of infinite plane 30-year doses from radioactive fall-out* — 12

Proposes new method for evaluation of the external 30-year dose due to the deposition of gamma emitting isotopes, based upon a single beta measurement for each sample and one $Cs^{137}$ ratio chemical determination in a pooled sample.

151. — *The control of irradiation of populations from natural and artificial sources* — 3

Describes an automatic system for continuous indication and recording of very low radiation level. Suggests the use of such instrument for public control purposes.

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R | | |
| 152. | UNITED KINGDOM. *The analysis of low level gamma-ray activity by scintillation spectrometry*<br>The application of gamma-ray spectrometry enables measurement of the gamma-activity of $10^{-11}$ curies or less. | 9 |
| 153. | UNITED STATES. *The Chicago Sunshine method: Absolute assay of strontium-90 in biological materials, soils, waters and air filters*<br>Contains a survey of Chicago sunshine research programme on the distribution of strontium-90 in the biosphere. Methods of sample treatment, counting and evaluation of data are reported. Detailed description of analytical chemical procedures is added. | 59 |
| 154. | ARGENTINA. *Normal calcium content of San Juan wines* | 8 |
| 155. | BELGIUM. *Recent research on the chemical protectors and particularly on cysteamine-cystamine. (Document in English)*<br>Discusses the possible mechanisms of action of chemical radioprotectors particularly of those above-mentioned. | 9 |
| 156. | *Effect of X-rays on the growth of internodal cells of the alga Chara vulgaris L*<br>A complicated dose-effect relationship is shown when non-dividing internodal cells are irradiated and their growth tested (cf. document A/AC.82/G/R.122). | 4 |
| 157. | ARGENTINA. *Radioactive fall-out from the atmosphere in the Argentine Republic during 1957*<br>Includes tables of results for first three-quarters of 1957. Total activity and strontium-90 content is measured. | 18 |
| 158. | BELGIUM. *The action of various drugs on the suprarenal response of the rat to total body X-irradiation. (Document in English)*<br>Describes strict difference in action of radioprotectors (cysteamine) or narcotic drugs (morphine and barbiturate) in preventing adrenal changes of irradiated animals. | 8 |
| 159. | *Nervous control of the reaction of anterior hypophysis to X-irradiation as studied in grafted and newborn rats. (Document in English.)*<br>Indicates that the changes of suprarenals after irradiation are consequence of a neuro-humoral chain reaction. The reaction of adrenals seems to have negligible importance in the pathogenesis of radiation disease. | 13 |
| 160. | USSR. *Draft of Chapter F prepared by the delegation of the USSR to the Scientific Committee on the Effects of Atomic Radiation* | 18 |
| 161. | JAPAN. *A sensitive method for detecting the effect of radiation upon the human body*<br>Discovers a new extremely sensitive biological indicator of the effect of ionizing radiation. The acute dose of 50 mr and even less results in significant changes of the phosphene threshold of the eye. Approximately linear relationship between the effect and the logarithm of the dose from 1 mr to 50 mr is derived. Summation of the effect of repeated exposure is found. | 16 |
| 162. | UNESCO/FAO/WHO. *UNESCO/FAO/WHO report on sea and ocean disposal of radioactive wastes, including appendices A, B and C*<br>Summarizes contributions made by different authorities.<br>*Appendix A*: R. Revelle and M. B. Schaefer. General considerations concerning the ocean as a receptacle for artificially radioactive materials.<br>Contains general account of the processes in the oceans and indicates the necessity of research on certain basic problems which would enable the prediction of the consequences of the disposal of large quantity of radioactive material to the sea.<br>Recommends measures of an international character in order to assure safe liquidation of atomic wastes.<br>*Appendix B*: Report prepared by FAO and WHO. Discusses the following questions:<br>1. The geochemical cycle of various elements between the water and the sediments.<br>2. The affinities of the various species of organisms in the oceans for different elements which have radioactive isotopes.<br>3. The possible rate and distance of vertical and horizontal transport of radioactive isotopes by marine organisms.<br>4. The distribution, abundance and rate of growth of the populations in the oceans.<br>*Appendix C*: Abstracts of eight other contributions to the report on sea and ocean disposal of radioactive wastes. | 118 |
| 163. | USSR. *Data on the radioactive strontium fall-out on the territory of the USSR as to the end of 1955* | 1 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R | | |
| 164. | MEXICO. *Third report on the studies on radioactive fall-out*<br>Presents fall-out data for thirteen stations in Mexico covering the period from March to October 1957.<br>Computes approximate figures for infinite gamma dose and $Sr^{90}$ precipitation.<br>Gives preliminary results of $Sr^{90}$ and $Cs^{137}$ content in milk. | 25 |
| 165. | FAO. *General considerations regarding calcium availability in the broad soil groups of the world in relation to the uptake of radiostrontium*<br>Classifies soil groups with low calcium level. Recommends the investigations of the factors influencing $Sr^{90}$ uptake by plants growing on such soils. | 6 |
| 166. | INDIA. *Measurements on the radiation fields in the Monazite areas of Kerala in India*<br>Presents results of measurements in the monazite area with high thorium content. As this area is one of the most densely populated areas in the world, the study of the relation between high level radiation background and eventual biological effect would be of great value.<br>The average dose is 1500 mrad per year, exceeding three times the maximum permissible dose recommended by NCRP (USA). | 6 |
| 167. | UNITED KINGDOM. *Measurements of $Cs^{137}$ in human beings in the United Kingdom 1956/1957*<br>Describes the method of determining the $Cs^{137}$ content in the human body using gamma-ray spectrometry.<br>The average present value is 34.0 $\pm$ 7.6$\mu\mu$c per g potassium. | 5 |
| 168. | JAPAN. *An enumeration of future $Sr^{90}$ concentration in foods and bone*<br>Gives amendments and corrections to the report A/AC.82/G/R.137 based upon new available data. | 6 |
| 169. | BRAZIL. *On the nature of long-range fall-out.* (*Document in English.*)<br>Describes one surprisingly high value of daily collected fall-out activity due to a single big and highly active particle. | 4 |
| 169/Corr.1 | *Corrigendum to above report* | 1 |
| 170. | UNITED KINGDOM. *The disposal of radioactive waste to the sea during 1956 by the United Kingdom Atomic Energy Authority*<br>Summarizes the discharges of liquid radioactive wastes to the coastal sea from Windscale Works during 1956.<br>The results of monitoring indicate that the average activity of the samples remains well below the permissible level. | 3 |
| 171. | *A summary of the biological investigations of the discharges of aqueous radioactive waste to the sea from Windscale Works, Sellafield, Cumberland*<br>Summarizes the results of preliminary hydrographic and biological studies and of regular monitoring of the marine environment in the period 1952-1956. About 2,500 curies of radioactive wastes monthly has been discharged during this period. Due to the favourable local conditions, the upper limit for safe liquidation is determined to be more than 45,000 curies per month. | 12 |
| 172. | JAPAN. *The estimation of the amount of $Sr^{90}$ deposition and the external infinite gamma dose in Japan due to man-made radioactivity* | 10 |
| 173. | SWEDEN. *Transfer of strontium-90 from mother to foetus at various stages of gestation in mice*<br>Shows that no significant fixation of $Sr^{90}$ by the foetus can be detected before the fifteenth day of gestation. The increase of radioactivity corresponds to the intensity of ossification processes. | 2 |
| 174. | *The recovery phenomenon after irradiation in Drosophila melanogaster*<br>*1. Recovery or differential sensitivity to X-rays*<br>Experimental results—lower rate of chromosome aberrations induced by X-ray if irradiated in anoxia in comparison with irradiation in air-support the hypothesis of recovery. | 29 |
| 174/Add.1 | *The recovery phenomenon after irradiation in Drosophila melanogaster*<br>Indicates that both the spontaneous recovery and the differential sensitivity in spermatogenesis in Drosophila are responsible for the changes in the rate of chromosome breaks under different conditions of irradiation. | 8 |
| 174/Add.2 | *The recovery phenomenon after irradiation in Drosophila melanogaster*<br>Chromosomes breakage *per se* or their rejoining by recovery seems to have no genetic consequences. | 5 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R | | |
| | SWEDEN *(continued)* | |
| 175. | *Reports on scientific observations and experiments relevant to the effects of ionizing radiation upon man and his environment already under way in Sweden* | 4 |
| 175/Add.1 | *Report on experiments on the influence of selection pressure on irradiated populations of Drosophila melanogaster*<br>Attempts to determine the influence of high selection pressure in a population on the spread of radiation-induced genetic changes. No results are as yet available. | 3<br>3 |
| 175/Add.2 | *Studies on the mutagenic effect of X-rays*<br>Summarizes the results of the work on radiation-induced chromosome breakage under various conditions (K. G. Lüning). | |
| 175/Add.3 | *Does there exist mutational adaptation to chronic irradiation?*<br>The results do not confirm the assumption that under the increased radiation-background mutational adaptation occurs due to incorporation in the population of mutational isoalleles with lower mutability. | 8 |
| 175/Add.4 | *Some results and previews of research in Sweden relevant to human radiation genetics*<br>Summarizes the present state of knowledge and recommends:<br>1. Large-scale international investigation of genetic consequences in females who have been controlled by means of X-rays due to congenital dislocation of the hip.<br>2. The study of genetic effects of radiation on human cell cultures. | 10 |
| 175/Add.5 | *Summary of papers of Lars Ehrenberg and co-workers with regards to the questions of the U.N. Radiation Committee*<br>Summary of papers of L. Ehrenberg and co-workers on genetic effects of radiation. | 7 |
| 175/Add.6 | *Studies on the effects of irradiation on plant material carried out during recent years at the Institute for Physiologic Botany of Uppsala University* | 2 |
| 175/Add.7 | *Swedish mutation research in plants* | |
| 175/Add.8 | *Dr. Gunnar Östergren and co-workers*<br>Study on experimentally induced chromosome fragmentation (G. Östergren). | 1 |
| 175/Add.9 | *Investigations carried out by Dr. C. A. Larson (human genetics)* | 1 |
| 176. | *Some notes on skin doses and bone marrow doses in mass miniature radiography* | 2 |
| 177. | *Investigations into the health and blood picture of Swedish women living in houses representing different levels of ionizing radiation*<br>No difference was found either in general health-state or in blood picture among the various groups of individuals (over 2,000 women) living in different types of dwelling. | 37 |
| 178. | *Other haemopoetic functions: Read-off methods in radio-haematological control*<br>Proposes a statistical method of evaluating total white-cells count as a control test of radiation damage. | 11 |
| 179. | FRANCE. *Atomic Energy Commission. Centre of Nuclear Studies at Saclay, Gif-sur-Yvette (Seine et Oise), France. Measurement of environmental activity: Methods and results*<br>Gives results of measurements of both natural and artificial radioactivity in the environment. | 7 |
| 179/Corr.1 | *Corrigendum to above report* | 1 |
| 180. | *Biological methods available for use in the quantitative detection of ionizing radiations*<br>Surveys and evaluates the biological methods usable for the quantitative estimation of absorbed dose. | 43 |
| 181. | SWEDEN. *Bone and radiostrontium*<br>The local radiation dose to the bone tissue and to the bone marrow after administration of bone-seeking isotopes is discussed. The figures are compared with the maximum permissible body burden. | 4 |
| 182. | *Radiation doses to the gonads of patients in Swedish roentgen diagnostics. Summary of studies on magnitude and variation of the gonad doses together with dose reducing measures.* | 3 |
| 183. | THE NETHERLANDS. *Report of the Committee of the Royal Netherlands Academy of Sciences concerning the dangers which may arise from the dissemination of radioactive products through nuclear test explosions*<br>Report on the amount of radioactivity, its world-wide spreading and its biological risk as a consequence of test explosions. | 48 |
| 184. | *Radioactive fall-out measurements in the Netherlands until December 31, 1957* | 8 |
| 184/Corr.1 | *Corrigendum to above report* | 1 |

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R | | |
| 185. | NEW ZEALAND. *Report on some aspects of radiation protection work in New Zealand*<br>Contains:<br>1. Description of radiation protection measures in New Zealand.<br>2. Results of routine monitoring of radiation workers.<br>3. Preliminary results of statistical study on genetically significant gonad dose from X-ray diagnosis. | 21 |
| 186. | FRANCE. *Doses received by the genital organs of children during X-ray examinations*<br>Suggests the improvement of the radiological techniques and certain protective measures for decreasing the gonad dose from radiography. | 15 |
| 187. | MEXICO. *Summary of radioactive fall-out data recorded in Mexico* | 1 |
| 188. | BRAZIL. *Summary—strontium-90 analysis in dry milk and human urine* | 2 |
| 189. | *On the composition of long-range fall-out particles*<br>A single fall-out particle of large dimensions and relatively high activity was found by daily monitoring of fall-out. A detailed investigation of the nature and activity of this particle is presented. | 7 |
| 190. | *On the uptake of MsThI in naturally contaminated areas*<br>Gives preliminary results of an investigation on the uptake of natural radioisotopes by plants and animals in thorium-bearing area. | 3 |
| 191. | UNITED ARAB REPUBLIC. *Radioactive fall-out in Egypt: December 1956-February 1957* | 5 |
| 192. | *Radioactive fall-out in Egypt: March-December 1957* | 7 |
| 193. | *Some somatic changes observed in Culex Molestus Forskal 1775*<br>Shows differences in the uptake of $P^{32}$ in dependence upon the development stage and sex. The explanation of sex-difference is discussed. | 6 |
| 194. | FRANCE. *Gonad doses in radiodiagnosis*<br>Summarizes the systematic study on the gonad dose due to diagnostic examination by means of X-rays. | 64 |
| 195. | ITALY. *Data on radioactive fall-out collected in Italy (1956, 1957, 1958)* | 6 |
| 196. | USSR. *Draft chapter on "Genetic Effects of Radiation" for the report to be transmitted by the Scientific Committee on the Effects of Atomic Radiation to the General Assembly in 1958* | 14 |
| 197. | *Draft chapter on "Conclusions and Recommendations" for the report to be transmitted by the Scientific Committee on the Effects of Atomic Radiation to the General Assembly in 1958* | 17 |
| 198. | *Contamination of the biosphere in the vicinity of Leningrad by the products of nuclear explosions*<br>Contains the description of methods used for monitoring the fall-out deposition. Results for the period 1953-1957 are given. Data on specific activity of water from the river Neva, the sea and the water supply system are also included. Accumulated radioactivity on the ground and external dose from radioactive deposit are then computed. Special attention is given to the contamination of the biosphere by $Sr^{90}$. Data are based on Hunter and Ballou's calculation. | 28 |
| 199. | *Study of the strontium-90 content of the atmosphere, soil, foodstuffs and human bones in the USSR*<br>The strontium-90 content of the air, soil, milk and cereals in various districts of the USSR was determined by radiochemical analysis. Preliminary results on the $Sr^{90}$ content in bones from children in the Moscow district give the average value of 2.3 S.U. in the second half of 1957. A few data on $Cs^{137}$ concentration in the air are attached. | 24 |
| 200. | *Uptake of radioactive strontium by plants and its accumulation in various agricultural crops*<br>Detailed analysis of $Sr^{90}$ uptake by plants in relation to their biological characteristic (plant species, vegetative period) and the properties of the soil.<br>Both factors can influence to a large extent the incorporation of $Sr^{90}$ during the biological cycle. | 27 |
| 201. | *Some results of a study of the bone system after injury by radioactive strontium*<br>Reviews the experimental results obtained in the studies on the effect of bone-seeking radioisotopes. The progressive pathological changes leading to the development of bone tumours are described. The disturbances in the osteogenetic processes during | 14 |

A/AC.82/G/R

USSR *(continued)*

the initial stages after contamination are marked pretumorous changes; their histological characteristic and their pathogenetic significance are discussed.

202. *Blastomogenic effects of strontium-90* — 10
Summarizes and evaluates the results so far published on the cancerogenic effect of strontium-90 in bone. In particular, the minimum and optimum tumour-producing doses, the latent period and the distribution of strontium-90 are discussed. The connexion between the blastomogenic effect and the development of leukemia is briefly mentioned.

203. *The radiation hazards of explosions of pure hydrogen and ordinary atomic bombs* — 27
Compares the hazards of the long-lived radioactive substances dispersed throughout the world after the explosion of a fission and a pure fusion bomb. Radiation doses to the gonads and bones are calculated and the number of persons affected (hereditary diseases and leukemia) then computed. The conclusion is drawn that a pure fusion bomb cannot be regarded as less dangerous to mankind than a fission bomb.

204. *Towards an assessment of the hazard from radioactive fall-out* — 32
An attempt to assess the various forms of hazard involved in the contamination of the earth's surface with long-lived radioactive fission products. The particular importance of strontium-90 is stressed. Effects of small doses of radiation and the concept of maximum permissible dose are discussed.

205. *Nature of the initial effect of radiation on the hereditary structures* — 40
A survey of the present knowledge of the nature of the primary mechanisms through which ionizing radiation damages the hereditary structures.

206. *Radiation and human heredity* — 22
Emphasizes the importance of the basic scientific principles of radiation genetics for the assessment of radiation-induced changes in human heredity. The natural mutation rate for various hereditary abnormalities is compared with the observations so far available on irradiated human population. The comparison of natural and induced mutagenesis both in experimental organisms and in men is the basis on which the doubling dose for man was estimated as approximately 10 r. The lack of exact knowledge and the urgent need for it is stressed.

207. *The effect of radiation on the histological structure of monkey testes* — 25
Presents the results of histological analysis of monkey testes two years after exposure to a dose of 150-450r. While the recovery process proceeds rapidly and is apparently complete in animals irradiated after the attainment of sexual maturity, harmful disturbances have been found in young animals even two years after exposure.

208. *The cytogenetic effects of radiation exposure on spermatogenesis in monkeys* — 18
Presents the results of cytological analysis of monkey testes two years after exposure to a dose of 150-450r. Extensive damage to the spermatogenesis was found. The frequency of chromosome re-arrangements in mammals considerably exceeds that in Drosophila after exposure to the same dose, being 65 per cent and 1.6 per cent after 500 r respectively.

209. BELGIUM. *Radioactive fall-out measured at the CEN during 1955-1956 and 1957* — 9
Describes methods and results of fall-out measurements in the period 1955-1957.

210. *Average dose received by the personnel of CEN, MOL, from 1954 to 1957* — 3
Summarizes the results of monitoring the professional exposure in nuclear energy education centre in Belgium. Film strip enables the differentiation of the proportion of the exposure between beta, gamma and neutron radiation. Only average doses of the personnel are given.

211. FRANCE. *Study of the gonad dose during systematic X-ray examinations (Preliminary note dealing only with the irradiation of male gonads)* — 6
Measurement of the gonad dose resulting in males from systematic standardized X-ray examination of the chest indicate that the exposure is very low. An average of 9 mrem for a period of 30 years is computed. The dose to the lungs is discussed with relation to the increase in frequency of lung cancer.

212. *Determination of the absorbed dose/exposure dose ratio in bone and muscle by the equivalent-gases method. Principle of the method and preliminary results* — 22
Describes the method for determination of the dose absorbed in various tissues using ionization chambers filled with gas mixtures of equivalent density.

| Document Number | Country and Title | Approximate No. of pages |
|---|---|---|
| A/AC.82/G/R | | |
| | FRANCE *(continued)* | |
| 213. | *Recovery following the action of ionizing radiation*<br>The authors first discuss the problem of recovery which they consider hypothetically. They attempt to show that it is a phenomenon which, although appearing very complex at first glance, can be simplified by relating the recovery to a definite effect.<br>They contribute a series of experiments showing that recovery is a very general phenomenon, common to all living things, and related to the metabolic activity of living matter.<br>They report a new method of experimental analysis which greatly facilitates interpretation of the results. They believe that the study of recovery should be developed on a much larger scale. | 26 |

## Appendix

# LIST OF SCIENTIFIC EXPERTS

The scientific experts who have taken part in the preparation of the report while attending Committee sessions as members of national delegations are listed below. The Committee must also express its appreciation to the many individual scientists not directly connected with national delegations whose voluntary co-operation and good will contributed in no small measure to the preparation of the report.

ARGENTINA:
- Dr. C. Nuñez *(Representative)*
- Dr. D. J. Beninson
- Professor E. Favret
- Dr. N. Nussis
- Dr. J. A. Olarte

AUSTRALIA:
- Dr. C. F. Eddy *(Representative—first session)*
- Mr. D. J. Stevens *(Representative)*
- Dr. A. R. W. Wilson

BELGIUM:
- Professor Z. Bacq *(Representative)*
- Mr. R. Boulenger
- Dr. M. Errera
- Professor F. Twisselman

BRAZIL:
- Professor C. Chagas *(Representative)*
- Dr. B. Gross
- Professor N. Libanio
- Professor C. Pavan
- Father F. X. Roser, S.J.

CANADA:
- Dr. E. A. Watkinson *(Representative)*
- Dr. R. K. Appleyard
- Dr. P. M. Bird
- Dr. W. E. Grummitt
- Dr. Colin Hunter
- Dr. G. H. Josie
- Dr. C. A. Mawson
- Dr. H. B. Newcombe
- Dr. F. D. Sowby

CZECHOSLOVAKIA:
- Professor F. Herčík *(Representative)*
- Professor F. Běhounek
- Dr. M. Hašek
- Dr. L. Novák
- Professor V. Sobek
- Dr. I. Ulehla
- Dr. V. Zelený

EGYPT*
- Dr. A. Halawani *(Representative)*
- Dr. H. T. Daw

FRANCE:
- Professor L. Bugnard *(Representative)*
- Dr. A. Allisy
- Dr. J. Coursaget
- Dr. H. Jammet
- Dr. J. Labeyrie
- Dr. J. Lejeune

INDIA:
- Dr. V. R. Khanolkar *(Representative)*
- Dr. A. R. Gopal-Ayengar
- Dr. A. S. Rao

JAPAN:
- Dr. M. Tsuzuki *(Representative)*
- Dr. Y. Hiyama
- Dr. D. Moriwaki
- Dr. K. Murati
- Dr. M. Nakaidzumi
- Mr. S. Ohta
- Dr. N. Saito
- Dr. E. Tajima

MEXICO:
- Dr. M. Martínez Báez *(Representative)*
- Dr. F. A. Andrade
- Dr. H. Zalce

SWEDEN:
- Professor R. M. Sievert *(Representative)*
- Dr. B. A. A. Aler
- Dr. R. G. Björnerstedt
- Professor G. Bonnier
- Professor T. O. Caspersson
- Professor C. A. T. Gustafsson
- Dr. A. G. A. Nelson

* Now in the United Arab Republic.

UNION OF SOVIET SOCIALIST REPUBLICS:

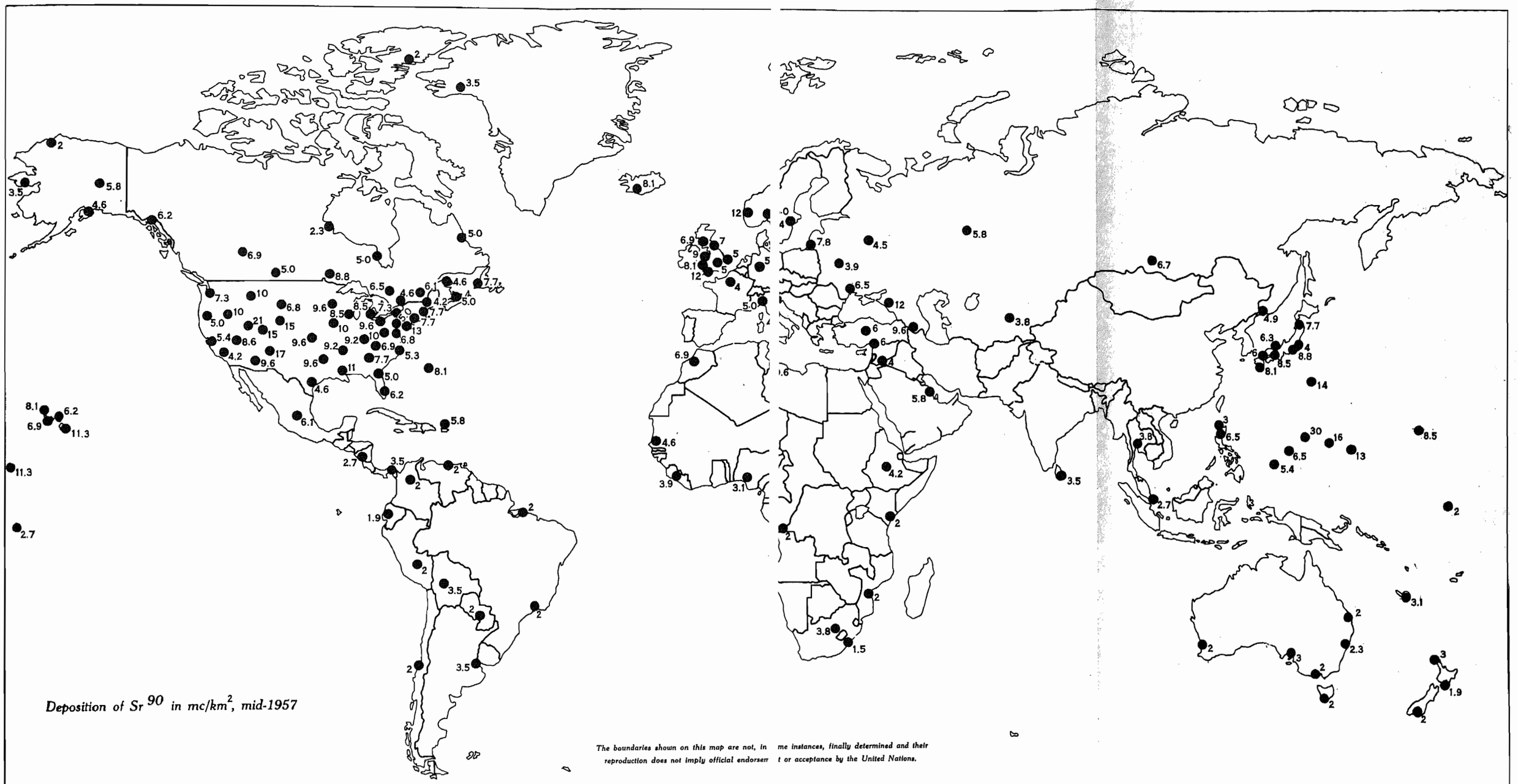
Professor A. V. Lebedinsky *(Representative)*
Professor K. K. Aglintsev
Professor B. M. Isaev
Professor P. M. Kireev
Professor A. N. Kraevsky
Professor A. M. Kuzin

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Professor W. V. Mayneord *(Representative—first session)*
Dr. E. E. Pochin *(Representative)*
Dr. T. C. Carter
Mr. A. C. Chamberlain
Dr. W. G. Marley
Mr. N. G. Stewart

UNITED STATES OF AMERICA:

Dr. Shields Warren *(Representative)*
Professor G. W. Beadle
Dr. A. M. Brues
Professor J. Crow
Professor Th. Dobzhansky
Dr. C. L. Dunham
Mr. Merril Eisenbud
Professor Sterling Emerson
Professor G. Failla
Dr. J. H. Harley
Dr. J. S. Laughlin
Professor J. V. Neel
Dr. M. Zelle




*The boundaries shown on this map are not, in me instances, finally determined and their reproduction does not imply official endorsem t or acceptance by the United Nations.*

MAP NO. 1062 UNITED NATIONS
MAY 1958

# SALES AGENTS FOR UNITED NATIONS PUBLICATIONS

**ARGENTINA**
Editorial Sudamericana S.A., Alsina 500, Buenos Aires.

**AUSTRALIA**
H. A. Goddard, A.M.P. Bldg., 50 Miller St., North Sydney; and 90 Queens St., Melbourne.
Melbourne University Press, 369/71 Lonsdale Street, Melbourne C.1.

**AUSTRIA**
Gerold & Co., Graben 31, Wien, 1.
B. Wüllerstorff, Markus Sittikusstrasse 10, Salzburg.

**BELGIUM**
Agence et Messageries de la Presse S.A., 14-22 rue du Persil, Bruxelles.
W. H. Smith & Son, 71-75, boulevard Adolphe-Max, Bruxelles.

**BOLIVIA**
Librería Selecciones, Casilla 972, La Paz.

**BRAZIL**
Livraria Agir, Rua Mexico 98-B, Caixa Postal 3291, Rio de Janeiro.

**BURMA**
Curator, Govt. Book Depot, Rangoon.

**CAMBODIA**
Papeterie-Librairie Xuân Thu, 14, Avenue Boulloche, Pnom-Penh.

**CANADA**
Ryerson Press, 299 Queen St. West, Toronto.

**CEYLON**
Lake House Bookshop, Assoc. Newspapers of Ceylon, P.O. Box 244, Colombo.

**CHILE**
Editorial del Pacífico, Ahumada 57, Santiago.
Librería Ivens, Casilla 205, Santiago.

**CHINA**
The World Book Co., Ltd., 99 Chung King Road, 1st Section, Taipeh, Taiwan.
The Commercial Press Ltd., 211 Honon Rd., Shanghai.

**COLOMBIA**
Librería América, Medellín.
Librería Buchholz Galería, Bogotá.
Librería Nacional Ltda., Barranquilla.

**COSTA RICA**
Trejos Hermanos, Apartado 1313, San José.

**CUBA**
La Casa Belga, O'Reilly 455, La Habana.

**CZECHOSLOVAKIA**
Ceskoslovensky Spisovatel, Národní Trída 9, Praha 1.

**DENMARK**
Einar Munksgaard, Ltd., Norregade 6, Kobenhavn, K.

**DOMINICAN REPUBLIC**
Librería Dominicana, Mercedes 49, Ciudad Trujillo.

**ECUADOR**
Librería Científica, Guayaquil and Quito.

**EL SALVADOR**
Manuel Navas y Cía., 1a. Avenida sur 37, San Salvador.

**ETHIOPIA**
International Press Agency, P.O. Box 120, Addis Ababa.

**FINLAND**
Akateeminen Kirjakauppa, 2 Keskuskatu, Helsinki.

**FRANCE**
Editions A. Pédone, 13, rue Soufflot, Paris V.

**GERMANY**
R. Eisenschmidt, Kaiserstrasse 49, Frankfurt/Main.
Elwert & Meurer, Hauptstrasse 101, Berlin-Schöneberg.
Alexander Horn, Spiegelgasse 9, Wiesbaden.
W. E. Saarbach, Gereonstrasse 25-29, Köln (22c).

**GREECE**
Kauffmann Bookshop, 28 Stadion Street, Athènes.

**GUATEMALA**
Sociedad Económica Financiera, 6a Av. 14-33, Guatemala City.

**HAITI**
Librairie "A la Caravelle", Port-au-Prince.

**HONDURAS**
Librería Panamericana, Tegucigalpa.

**HONG KONG**
The Swindon Book Co., 25 Nathan Road, Kowloon.

**ICELAND**
Bokaverzlun Sigfusar Eymundssonar H. F., Austurstraeti 18, Reykjavik.

**INDIA**
Orient Longmans, Calcutta, Bombay, Madras and New Delhi.
Oxford Book & Stationery Co., New Delhi and Calcutta.
P. Varadachary & Co., Madras.

**INDONESIA**
Pembangunan, Ltd., Gunung Sahari 84, Djakarta.

**IRAN**
"Guity", 482 Ferdowsi Avenue, Teheran.

**IRAQ**
Mackenzie's Bookshop, Baghdad.

**IRELAND**
Stationery Office, Dublin.

**ISRAEL**
Blumstein's Bookstores Ltd., 35 Allenby Road, Tel-Aviv.

**ITALY**
Librería Commissionaria Sansoni, Via Gino Capponi 26, Firenze and Roma.

**JAPAN**
Maruzen Company, Ltd., 6 Tori-Nichome, Nihonbashi, Tokyo.

**JORDAN**
Joseph I. Bahous & Co., Dar-Ul-Kutub, Box 66, Amman.

**KOREA**
Eul-Yoo Publishing Co. Ltd., 5, 2-KA, Chongno, Seoul.

**LEBANON**
Librairie Universelle, Beyrouth

**LIBERIA**
J. Momolu Kamara, Monrovia.

**LUXEMBOURG**
Librairie J. Schummer, Luxembourg.

**MEXICO**
Editorial Hermes S.A., Ignacio Mariscal 41, México, D.F.

**NETHERLANDS**
N.V. Martinus Nijhoff, Lange Voorhout 9, 's-Gravenhage.

**NEW ZEALAND**
United Nations Association of New Zealand, C.P.O. 1011, Wellington.

**NORWAY**
Johan Grundt Tanum Forlag, Kr. Augustsgt. 7A, Oslo.

**PAKISTAN**
The Pakistan Co-operative Book Society, Dacca, East Pakistan.
Publishers United Ltd., Lahore.
Thomas & Thomas, Karachi, 3.

**PANAMA**
José Menéndez, Plaza de Arango, Panamá.

**PARAGUAY**
Agencia de Librerías de Salvador Nizza, Calle Pte. Franco No. 39-43, Asunción.

**PERU**
Librería Internacional del Perú, S.A., Lima and Arequipa.

**PHILIPPINES**
Alemar's Book Store, 749 Rizal Avenue, Manila.

**PORTUGAL**
Livraria Rodrigues, 186 Rua Aurea, Lisboa.

**SINGAPORE**
The City Book Store, Ltd., Collyer Quay.

**SPAIN**
Librería Bosch, 11 Ronda Universidad, Barcelona.
Librería Mundi-Prensa, Lagasca 38, Madrid.

**SWEDEN**
C. E. Fritze's Kungl. Hovbokhandel A-B, Fredsgatan 2, Stockholm.

**SWITZERLAND**
Librairie Payot S.A., Lausanne, Genève.
Hans Raunhardt, Kirchgasse 17, Zurich 1.

**THAILAND**
Pramuan Mit Ltd., 55 Chakrawat Road, Wat Tuk, Bangkok.

**TURKEY**
Librairie Hachette, 469 Istiklal Caddesi, Beyoglu, Istanbul.

**UNION OF SOUTH AFRICA**
Van Schaik's Bookstore (Pty.), Ltd., Box 724, Pretoria.

**UNITED ARAB REPUBLIC**
Librairie "La Renaissance d'Egypte", 9 Sh. Adly Pasha, Cairo.
Librairie Universelle, Damas.

**UNITED KINGDOM**
H. M. Stationery Office, P.O. Box 569, London, S.E.1.

**UNITED STATES OF AMERICA**
International Documents Service, Columbia University Press, 2960 Broadway, New York 27, N. Y.

**URUGUAY**
Representación de Editoriales, Prof. H. D'Elía, Plaza Cagancha 1342-1° Piso, Montevideo.

**VENEZUELA**
Librería del Este, Av. Miranda, No. 52, Edf. Galipán, Caracas.

**VIET-NAM**
Papeterie-Librairie Xuân Thu, Boîte Postale 283, Saigon.

**YUGOSLAVIA**
Cankarjeva Zalozba, Ljubljana, Slovenia.
Drzavno Preduzece, Jugoslovenska Knjiga, Terazije 27/11, Beograd.
Prosvjeta, 5, Trg. Bratstva I Jedinstva, Zagreb.

[58E2]

*Orders and inquiries from countries where sales agents have not yet been appointed may be sent to: Sales and Circulation Section, United Nations, New York, U.S.A.; or Sales Section, United Nations, Palais des Nations, Geneva, Switzerland.*

Printed in U.S.A.

Price: $U.S. 2.50; 18/- stg.; Sw. fr. 10.50
(or equivalent in other currencies)

14957—July 1958—6,050