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)

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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.

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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 (α-, β-, γ-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 (α)	High speed helium nuclei	Radioactive nuclei	A few Mev[a]	Very easily absorbed
Beta (β)	High speed electrons	Radioactive nuclei	A few Kev[a] to several Mev	Easily absorbed
Gamma (γ)	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 1.6×10^{-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	β		5,600 years
K^{40}	Potassium-40	β	γ	1.3×10^9 years
Ra^{226} [b]	Radium-226	α	(γ)	1,600 years
Decaying to:				
Rn^{222}	Radon (gas)	α		3.8 days
Po^{218}	Radium A	α		3 minutes
Pb^{214}	Radium B	β	γ	27 minutes
Bi^{214}	Radium C	β	γ	20 minutes
Po^{214}	Radium C′	α		0.00015 seconds
Pb^{210}	Radium D	β	γ	22 years
Bi^{210}	Radium E	β		5 days
Po^{210}	Radium F (polonium)	α	(γ)	140 days
Sr^{90}	Strontium-90	β		28 years
Decaying to:				
Y^{90}	Yttrium-90	β		64 hours
Cs^{137}	Caesium-137	β	γ	30 years
I^{131}	Iodine-131	β	γ	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 3.7×10^{10} disintegrations per second. The denominations millicurie (mc), microcurie (μc) and micromicrocurie ($\mu\mu$c), correspond to 3.7×10^{7}, 3.7×10^{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.

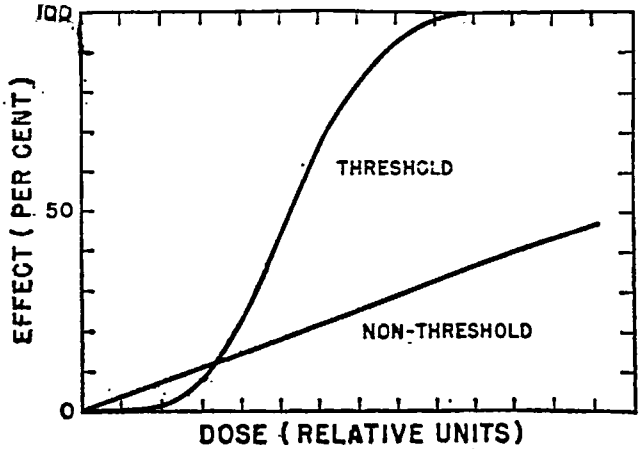

Figure 1. A pictorial representation of the difference between a threshold and a non-threshold situation. Dose increases to the right. Note that the non-threshold line is a straight line; it need not be. (Modified from Langham and Anderson, United Nations document A/AC.82/G/R.130, U.S.A. Congressional 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)	Osteocyte 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/km^2 in Japan, 8mc/km^2 in the United Kingdom, 4-21mc/km^2 in the United States and 3-12 mc/km^2 in the Soviet Union, in the northern hemisphere, and about 4mc/km^2 in Argentina, in the southern hemisphere. At the middle of 1957 a caesium-137 deposit of about 6mc/km^2 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.[D55-67]

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)*[DIII]		*Per capita mean marrow dose: Maximum for any 70-year period (rem)*[DIII]			
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 (α rays, neutrons which give recoil protons) have a higher efficiency in producing most forms of cellular damage than radiation (γ-, 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 γ-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 γ 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, F159–169]

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.[H23] 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 4×10^{-6} and 40×10^{-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 5×10^9 in the interim before current mutation is so expressed, and that the world population below the mean age of breeding is then about 2.5×10^9, 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, birth-weight, 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)* D_{115}		Per capita *mean marrow dose Maximum for any 70-year period (rem)* D_{111}			
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 ⅕ 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 960 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 fission

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.

(*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.

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.

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*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.

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.