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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.

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ANNEX F

FUNDAMENTAL RADIOBIOLOGY

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I. DISSIPATION OF PHYSICAL ENERGY
(Space and time factors)

Introduction—Direct and indirect effects

1. The effect of radiation is induced by the processes of absorption, when the energy of radiation is dissipated in the irradiated matter. Apart from excitation, the ionization of molecules is believed to be largely responsible for the initiation of primary chemical reactions. There are at present two major theories of the mechanism of action of radiations on living organisms: the theories of direct and indirect action. The first one claims that effective ionizations take place *in* key cellular structure or in their immediate vicinity: the probability that their alteration causes cellular damage is dependent on their biological specificity. This has often been called the "target theory", and, since Dessauer, Crowther, Holweck and Lacassagne, Timofeeff-Ressovsky and Lea, the concept has had the support of many physicists; it is being constantly revised to take into account many new fundamental acquisitions.[1,2,3,4,5,6,7]

2. The "theory of indirect action," on the contrary, claims that the biologically specific cellular structures are altered as a result of their chemical reaction with free radicals formed in irradiated water or other molecules not belonging to these structures.[8] As with most conflicting theories which have had ardent supporters on both sides (another good example is the corpuscular and electromagnetic theories of light), it is very probable that the two are complementary. Indeed, it is almost certain that the same cellular component can be affected in a way which is liable to produce identical biological effects by both mechanisms.[9,10,11] Methods have been

developed in recent years which enable the existence of unpaired electrons resulting from the ionization process to be demonstrated not only in crystalline amino acids and other small molecules, but also in proteins, plant embryos and other kinds of cells.

3. An attempt will be made to draw a brief picture of some fundamental aspects of the problem.

Linear energy transfer (LET) and relative biological effectiveness (RBE) of different kinds of radiation

4. The efficiency of radiation *per ionization* to induce a particular effect is often found to vary for different types of radiation. Let us at first consider an event which is caused by one ionization such as the inactivation of an enzyme or virus: in the case of small structures *in vitro*, the radiation producing a low ion density will be more effective than that giving a high ion density, because some of the ionizations of the latter will be wasted. On the contrary, a radiation with a high density of ionization will be more effective when several ionizations are simultaneously or in a relatively short time needed in the sensitive structure. Thus, the *relative biological effectiveness* (RBE) of radiations varies with their *linear energy transfer* (LET). This term describes the spatial distribution of the transfer of physical energy in matter—and accounts for the loss of energy of the radiation, not only through ionizing processes, but also through other processes such as dissipation of heat or excitation of atoms. It is a theoretical implication of these facts that some of the primary effects of radiations take place within a shorter time than that needed for the processes initiated by ionization or excitation to lose their initial spatial distribution (perhaps as short as 1 millionth of a second); and also that the primary biological receptors of radiation are not themselves homogeneously distributed throughout the cell.[12]

5. In mice, the relative biological efficiency (RBE) increases greatly with ion density, for killing with low intensity radiation, for shortening of the life-span, for inhibition of tumour growth, and for cataract induction; the increase, however, is smaller when one considers effects on the gonads (sterilization), on the skin (epilation), on the blood white-cell count, or on the induction of many chromosome abnormalities in Drosophila.[12,14,15] Some chromosome abnormalities in Tradescantia have a very high incidence with high density irradiation.[13] Mutations in micro-organisms and some in Drosophila are only slightly influenced by the LET.[12]

6. Reviews on the subject by Lea[1] and Zirkle[12] have shown that much could theoretically be achieved by comparing the effects of ion density. Lea had attempted to use the data available to him at the time, on the decrease in incidence of chromosome breakage with decreasing ion density, as an argument for the target theory. However, it appears from Zirkle's paper that changes in RBE for comparable effects are often very difficult to include in a general theory, because in many instances the direction of change in RBE is not the same for similar effects in different materials and the RBE may be strongly dependent on conditions of irradiation such as the oxygen tension. It is at present very difficult to make definite generalizations.

7. The mode of dissipation of radiation energy inside living cells is not yet understood, although our knowledge of the physical aspects of energy loss is adequate and hypotheses on the distribution of free radicals along the radiation tracks have been suggested. However, it is not clearly understood how this physical energy becomes apparent in chemical changes such as ionization and excitation. It might be of interest to use inert structural models or do such experiments as comparing the LET for a virus inside and outside the host cells to get a better picture of the sequence of events. When completely understood, the use of radiations of different LET may lead to precise estimates concerning the size of the biological structures affected.

Dose-effect relations

8. When a homogeneous substrate is irradiated, the energy is distributed in an unpredictable way and the probability of a molecule being hit depends on its concentration and on its volume. The concentration of the intact substrate decreases as radiolysis proceeds, and it can be predicted on theoretical grounds for low density radiations that, if one ionization suffices to cause the effect, the expression relating the remaining intact structures ("survivors") to dosage will be *exponential*. When a relatively small number of ionizing events is needed, the number of responses observed will, however, be approximately proportional to the dosage.[16,17,18] This sort of effect has no *threshold*—which means that any dosage, however small, is effective in producing some alteration.

9. On the contrary, if several ionizing events or "hits" are needed, the response only becomes manifest after a certain dosage has been accumulated in the sensitive structure: the dose effect curve is then *sigmoid*.[16,17,18,19] In this case there is a *threshold* which, however, may only be statistical, as when two identical cellular structures need to be *irreversibly* altered for the effect to become manifest, which is so for recessive lethal mutations in yeasts.[16] Other threshold effects appear when recovery of the altered structure or replacement of killed cells takes place, as is often the case in multicellular organisms where many interferences may take place between the primary physical event and its biological expression.

10. The meaning of the dose-effect relationship is often difficult to understand because the curve may change quite dramatically when the conditions of irradiation are altered (aerobic or anaerobic irradiation; change of culture medium); this difficulty is most likely to occur when one studies a complex phenomenon like cell death, whose cause may be multiple and not identical in different circumstances.[20]

11. However, several radiobiological processes are known to give exponential dose-effect curves under specific environmental conditions, as in the case of many lethal effects on viruses and on micro-organisms.[21,22] Diploid yeast cells[19,23] or mammalian cells[24] in tissue culture have a sigmoid dose-effect curve when x-irradiated. In the case of diploid cells, the sigmoid type of curve is consistent with a 2 hit process, the exponential response being explained on the assumption of a single hit. One of the best present arguments for the "target" concept comes from the fact that in the case of small viruses the "target" size can be estimated with a good approximation[21] and that survival curves of protected bacteriophage are very similar *in vitro* and during the very first minutes of infection.[22] These results can be

explained on the basis that the primary ionization takes place inside the sensitive structure. In the case of a mutation this is the gene. It is, however, difficult to accept the concept without modification at the present time, on account of the possible contribution of diffusable radicals from water or other molecules in the immediate vicinity of the target. However, it is believed that radicals only diffuse for distances of about 30Å. As most effects have not been fully expressed when the radiation has ceased to be delivered, there is a time interval during which restoration may occur, and whether this takes place or not may alter the dose-response curve. Very little is known about what happens during this time: the chain of events may be relatively "simple" in the expression of a point mutation in micro-organisms or perhaps even in a mammalian germinal cell, but it is certainly very complex when the induction of malignant growths is considered. The number of *mutations* in bacteria,[21] Drosophila,[25] and perhaps mouse populations,[26] *increases* linearly with radiation up to moderate dosages, as do certain of the chromosome aberrations[27] and perhaps the induction of leukemia.[28,29] However, the determinations do not extend as low as the background radiation, and much uncertainty remains at these low levels, although it is highly probable that the background radiation causes some of the mutations which occur naturally, thus contributing to some extent to the evolution of living organisms and to their load of mutational hazards. *This means that as far as we know at present, biological effects will follow irradiation, however small its amount.* It has thus become very important to establish with great accuracy the shape of the dose-effect curve in the lower dose range, in order to estimate the contribution of the natural radiation for different effects. The number of experimental animals needed to obtain a good accuracy increases enormously as the dose decreases and the response becomes smaller or less frequent. For human populations, as each individual is important, the only reasonable "experimental sample", when small doses are concerned, is the total population of living human beings. In this case, the only sound procedure is to get a better understanding of the fundamental processes which are occurring. *This may actually be the only way of answering some of the basic problems underlying low dosage irradiation.*

Time intensity factor

12. The time taken to deliver a given dosage of radiation can be varied in order to give very high or very low *intensities* per unit time. A change in intensity will not affect the end result when separate ionizing events contribute *independently* to the observed effect; this should hold true for some of the exponentially responding events although it is not true for all. On the contrary, in the case of events responding by sigmoid curves, several ionizations may be needed almost *simultaneously* (this is the case when recovery processes exist); here, a given dose becomes less effective if delivered in a long interval of time.[31,32,39] However, this is not always the case, and for inactivation of both homologous chromosome regions of a diploid cell, it is known that protraction of irradiation does not alter the effect.

13. The physiological conditions of *Drosophila* sperm are very constant for a considerable length of time, and it has been found that the induction of mutation by irradiating the males does not vary with the intensity of irradiation.[30] The same is true for the induction of most malformations in the mouse embryo. However, in some cases the severity of malformations is *greater* if a given dose is fractionated.[33] A change of intensity by a factor of one million does not alter the number of phage induced in E. Coli.K_{12}.[37,38] In contrast, the number of certain chromosome aberrations in Tradescantia microspores or Vicia seeds[34,36] — like chromosome exchanges, which require the simultaneous occurrence of two breaks —are often highly dependent on the time taken to deliver the dosage: more exchanges are obtained for higher intensities. When the duration of irradiation is increased, one reaches a time for which the effectiveness does not decrease any more; this time is related to the lapse during which the breaks remain open. However, this picture is complicated by the fact that the rate of rejoining depends on respiratory activity.[35] The killing of complex organisms like mammals, being the result of extremely complex cellular damage, is very efficient for high intensities but much less so for low ones.[40,41,42]

14. The time during which radiation is delivered becomes very important if the system being studied undergoes some *change* during this time: the radiosensitivity of many cellular processes varies during the *mitotic cycle* and one can expect a greater radiation effect if the intensity is high during the most sensitive period of this cycle. Secondary biological reactions may interfere with the expression of damage and, if recovery or selection occur, one can expect a greater effect if the intensity is high for the same given dosage. For these reasons, *it does not appear justifiable, unless the fundamental pathways of radiation damage are known, to consider that an effect observed after high intensity irradiation will necessarily follow the application of the same dosage at low intensity.*

Inactivation by transmutation of radioactive elements

15. Certain radioactive substances taken up by the organisms in specific structures may affect them not only by the radiation they emit, but also by the fact that the emission of these radiations is often accompanied by recoil effects or transmutation into an atom having new chemical properties. Thus P-32 can be incorporated into important biological structures like viruses or chomosomes, and in the first case it has been shown that the inactivation due to transmutation of P-32 into S-32 is more efficient than the one due to the β particles being emitted.[44,45] It is conceivable that strontium could replace calcium or magnesium, which are probably structural constituents of chromosomes.[46] It has been claimed that a low calcium environment increases the number of spontaneous and induced chromosome breaks in Tradescantia.[47,48] If these facts were of general application, the disintegration of strontium-90 or strontium-89 might affect cells not only by emitting β radiation, but also by transmuting to yttrium, which has new chemical properties. Such possibilities will have to be discussed, and *the role of trace amounts of metals and of alkaline earths in important cellular structures should be known before one dismisses its possible importance in biological effects of radionuclides which, apart from emitting radiation, have a specific function.*

16. Although Ca-45 has not been found by radioautography in the bone marrow cells of rats previously injected with 200 μc,[49] nuclear aberrations have been observed in allium which had been grown in the presence of Sr-90,[50] and further work on the subject should be done to settle this problem, which is of great importance in understanding the possible cellular damage induced by radionuclides. Their specific radioactivity inside cellular structures as well as their rate of turnover and their

chemical function may be important in inducing cellular damage.

II. Radiation chemistry

17. It is only by understanding the mechanisms of action of radiations on the different cellular constituents that one can hope to understand what is happening in irradiated cells and also to use these basic findings in the search for protecting agents. Much useful information on the chemical effects of radiation has been gathered by submitting various chemicals to irradiation *in vitro* (radiation chemistry); however, on account of our very incomplete knowledge of cellular structure and chemistry, biological constituents should be studied after irradiation of the living organisms (radiation biochemistry) if one is looking for full understanding of radiobiological processes. Furthermore, as will be pointed out, specific constituents and not bulk chemical properties should be studied whenever possible. Molecules may be altered by *indirect* and *direct* effects of radiation.

Indirect effects

18. It is known that the most abundant of all biological constituents is water: it constitutes 70 per cent of most living cells except for certain plant seeds and may sometimes constitute more than 95 per cent, but an unknown proportion of it is bound water and constitutes part of the cellular structures. This has prompted much research into the radiochemistry of water.

Effects of radiation on water and substrates in aqueous solution[51,52]

19. It is usually accepted, although by no means demonstrated, that water when chemically pure undergoes ionization and, as a result of this—and of secondary reactions, the sequence of which is hypothetical—splits into OH^0 (hydroxyl radicals) and H^0 (hydrogen atoms), which recombine; in the absence of any impurity, nothing apparently will have happened because the radicals cannot enter any other reaction. Traces of H_2 and H_2O_2 are thought to be formed during this process. The formation of radicals takes place in the short time of 10^{-11} -10^{-12} sec.[53]

20. The existence of OH^0 radicals has been demonstrated: certain radiation reactions leading to the polymerization of acrylonitrile can best be explained on the basis of an OH^0 radical mechanism, as also the oxidation of benzene to phenol.[51,52]

21. On the other hand, the existence of free H atoms is still questioned on account of the high oxidizing power of radiation on substrates in aqueous solutions; several mechanisms of radiolysis have been suggested, which do not make necessary the postulation of the existence of H^0 atoms.[51] It may be easier to interpret many biochemical reactions of radiation when a better understanding of the radiolysis of water has been achieved. This should certainly be of great importance for the logical approach to protection mechanisms. Although the existence of a free hydrogen atom is doubted by some, many authors have assumed that it does exist, and much present thinking is based on this assumption. It will make the discussion easier if we tentatively adopt this view, whenever a mechanism involving this radical is suggested. If oxygen is present as it is when a solution is in equilibrium in air, O_2H^0 (perhydroxy radical) and H_2O_2 (hydrogen peroxide) are also formed in addition to H^0 and OH^0.[51]

22. When the water contains various solutes, these are the site of chemical reactions due to H^0, OH^0 and O_2H^0 radicals formed in the solution through the radiolysis of water. These radicals have reducing or oxidizing properties and can react with the substrate, oxidizing or reducing it or transforming it in turn to a new free radical. Thus, if many solutes are present, they may be altered by radicals coming either from water or from the other solutes; this last mechanism although not too well studied could very well be of some importance in very complex systems. When macromolecules are irradiated, the yield of altered molecules per ion is usually smaller than expected from what happens to smaller molecules of similar chemical properties; this is thought to be due to the fact that bonds, broken in these structures, are not able to come apart (they are held together by the other intact bonds in the structure or cannot come apart by normal diffusion processes) and the radicals formed presumably recombine. Such a "cage effect" would be chiefly expected in concentrated solution and in complex cellular structures.[54] There are probably also some biologically inert chemical groups whose alteration would not impair the biological activity of some macromolecules.[55]

23. Although some reduction reactions occur when substrates are irradiated, most reactions appear to be oxidative.[52,56] From experimental data it is apparent that a substance is reduced only when it possesses a very high normal redox potential (greater than 0.9 - 1.0 for effects of X-rays in the absence of oxygen).[57]

Nature of the chemical effects

24. Ionizing radiations may alter inorganic as well as organic substrates. The following reactions can be taken as examples:[51]

Oxidizing reactions may be effected by OH^0 radicals

(*a*) By simply removing an electron from an ion $Fe^{2+} \rightarrow Fe^{3+}$—a reaction used for chemical dosimetry;

(*b*) By removing an H atom, leaving a radical which can combine with another one[51]
$2CH_2\,COOH \rightarrow 2C^0H_2\,COOH \rightarrow COOH\text{-}CH_2\text{-}CH_2\text{-}COOH$;

(*c*) By substitution of a hydrogen by an OH^0 as in the oxidation of benzene to phenol.[51,58]

25. In a similar manner, small organic molecules like alcohols, aldehydes or acids undergo oxidation, and the last-named compounds are often decarboxylated.[51,59,60] They are also sometimes capable of undergoing polymerization by the formation of a chemical bond possibly between two radicals as in the second reaction above: acetic acid is capable of giving succinic and even still more complex organic acids. Amino-acids may be oxidatively deaminated,[51] and if they have sulfhydryl groups these are oxidized to disulfur (S-S)[64] and sometimes to sulfoxide, as in the case of cysteine.[60,61]

26. *Reducing reactions* may be obtained as follows:

(*a*) OH^0 radicals may act on strongly oxidizing agents (this is the case for iodate and ceric salts).[51]

(*b*) In certain cases, organic redox indicators have been reversibly bleached in the absence of oxygen.[62] The mechanisms are at present difficult to understand on account of the questionable existence of the free H atom.

(*c*) Coenzyme I (Diphosphopyridine nucleotide) can be reduced by radiation to an abnormal derivative (probably a dimer of the natural molecule) but only in the presence of a hydrogen donor like ethanol.[63]

27. *Complex molecules*, such as enzymes and other proteins,[65] nucleic acids, lipids and polysacharides, are also altered *in vitro* as a result of the action of ionizing radiations; enzymes and desoxyribonucleic acid (in the case of the transforming principle of bacteria) may lose their biological properties.[68,69] In most cases the nature of the reaction has not been analyzed and cannot be until we know more about the structure of these macromolecules.

(*a*) One of the most sensitive chemical groups of proteins is the sulfhydryl group (-SH): two adjacent groups are oxidized by OH^0 to -S-S resulting in the loss of biological activity when, as in some enzymes, this activity is associated with the reduced form. S-S bridges also cause cross-linking reactions between two adjacent molecules.[65,81]

(*b*) Other specific oxidation reactions of some macromolecules have been found, including the deamination or decarboxylation of proteins,[66] and the oxidation of structures containing double bonds, as in the case of unsaturated fatty acids;[66] but large dosages have usually been necessary in order to make measurements possible.

(*c*) Cross linking may occur through the formation of a carbon to carbon linkage as the result of the combination of two macromolecular free radicals, possibly formed by direct or indirect action.[71,72] This process has, however, mostly been studied in artificial high polymers like polyvinylalcohol, but it is also very likely to take place in cells where the local concentration or the orientation of macromolecules relative to each other may be advantageous for such a process, as in chromosomes or during the formation of other oriented cellular structures. There is in fact good evidence for its occurrence in protein[73] and in DNA.[74]

(*d*) Some effects of ionizing radiations on complex molecules of biological interest have been definitely shown to be due to OH^0 radicals: this is so for the inactivation of ribonuclease, carboxypeptidase or the SH enzymes. These effects can be duplicated by chemically produced OH^0.[75] In the case of bacteriophage S_{13}[76] or catalase,[78] however, it has been suggested that they become inactivated as a result of a reducing mechanism but, on account of the problematic existence of independent H atoms in usual conditions of irradiation, one can probably not be certain of the exact mechanism, since new experiments[77] may yet lead to other interpretations. In many cases the mechanism of inactivation has not been worked out.

(*e*) The physical chemical properties of these molecules may be altered: the asymmetry of nucleic acids,[66,67,70] of fibrous proteins[80] or of hyaluronic acid[79] may be decreased, possibly but not necessarily as a result of a depolymerization; the absorption spectrum of these various compounds is often altered, indicating a chemical alteration of the chromophore group;[75] the stability of proteins and nucleic acids towards heat or other denaturing agent is usually decreased.[70]

Direct effects

28. In the case of a *direct* effect,[1,52] the ionization caused by the radiation concerns the molecule or structure under study. It is probable that the energy released in one part of such a molecule will be transferred over the whole structure and ionization or excitation phenomena will not necessarily occur at the point of first interaction. If the molecule becomes ionized, reactive free radicals may be formed and the existence of unpaired electrons has been proved in experiments using paramagnetic resonance; in the absence of water, these radicals are found to exist for periods as long as weeks or months.[83,84] In the case of water solutions, the life of the radicals is much shorter (a few minutes). Such studies have also been made in irradiated cells, indicating the existence of free radicals.[84,85]

29. Cross-linking between macromolecules may occur, as in polyethylene, probably by the reaction of an ionized molecule on a normal one.[86] The absence of an electron from a chemical bond may make this bond unstable and cause it to be hydrolyzed or broken, and some ions may also react with normal molecules causing them to cross link, as in some synthetic polymers.[73] The absorption of energy from the ionizing radiation does not always result in the expulsion of an electron: when ionization does not occur, the group of atoms may become *excited* for a period perhaps as short as 10^{-8} sec. thus being rendered more reactive with other molecules and susceptible to chemical alteration.[87] Excitation is the only process responsible for the alteration of substances by ultraviolet or visible radiations, and the use of these types of radiations is thus extremely useful in this respect.

30. *The physical state of a protein molecule* can be made to vary, and it has been shown that when an originally globular protein like pepsin is unfolded at an air-water interface and is irradiated as a monomolecular layer it is much more sensitive than when the "stretched" molecules have been compressed into fibres.[88]

Distinction between direct and indirect effects

Dilution effect

31. It is possible to distinguish between direct and indirect effects in a simple system by increasing the concentration of the molecules under study. In the case of indirect effects, the yield of altered solute molecules decreases with increasing concentration of the solute.[89,90] It has thus been calculated that in a 1 per cent solution of the enzyme carboxypeptidase, more than 90 per cent of the inactivation is indirect; in a 20 per cent solution, only 60 per cent of the effect is indirect.[90]

Desiccation and protection

32. One can also obtain information on the relative importance of direct and indirect mechanisms by comparing the yield of a radiation reaction on the same substrate after desiccation, in a completely protected solution and in the absence of any protector, although it is probable that one will not be able to secure absolute protection against indirect effects.[91]

Temperature coefficients

33. One can expect, if diffusible free radicals play a part in the *indirect* effect, that the contribution of this type of effect could be reduced considerably by freezing the solution.[92] This has been experimentally proved. However, irradiation of dry substances at different

temperatures shows that the *direct* effect of ionizing radiation also varies with the temperature, which makes the use of temperature coefficients more hazardous, but nevertheless useful.[82]

Oxygen effect

34. The existence of an oxygen effect (paragraph 38) was considered until recently as a criterion for indirect effects; however, as the radiosensitivity of dried proteins and polymers varies with oxygen tension,[93,94] this is no longer a good test until more is known about the mechanism of oxygen effects.

35. A major problem in radiobiology is to determine the relative contribution of direct and indirect effects[3] and its solution will also be of great help in developing methods of chemical protection. A first attempt has been made with yeasts; it can be shown that when they are irradiated in the dry and hydrated state the order of magnitude of both types of effects is very similar.[95] However, the molecular organization of most structures (chromosomes, cytoplasmic particles, nucleoli, cell membrane) is hardly understood, nor is the contribution to these structures of free or bound water and the possibility of diffusion of the free radicals formed during irradiation into or around them. A better understanding of all these fundamental problems would undoubtedly be of great value.

Effect of LET

36. According to the type of radiation used, yields per ion pair formed may vary as a result of different LET. It has been calculatted for water solutions that radiation giving high specific ionizations (α particles, slow neutrons, soft electrons) produce high concentrations of H^0 and OH^0 radicals along the ionization track;[96] their efficiency per ion pair in water solution will thus be smaller, when they are compared to γ or x-rays or high energy electrons. In the first case, the radicals, being more densely distributed in space, will have a higher probability of recombining or neutralizing each other, and this explains the lower yield of reactions such as the oxidation of tyrosine, the inactivation of the enzyme carboxypeptidase or of several viruses when the high specific ionizations are used.[12]

37. These densely ionizing particles form H_2, O_2, H_2O_2 and presumably HO_2^0 as a result of the radiolysis of H_2O_2 in water, *even in the absence of oxygen* and there are instances where H_2O_2 has been shown to be responsible for part at least, of the effect of these particles; it has been estimated that local concentration of H_2O_2 may reach molarity along the track of α particles.[96]

Oxygen effect

38. In *aerated* water solutions, irradiated with X or γ rays, H_2O_2 is formed, and it is thought that the radical O_2H^0 (perhydroxyl) is also produced as a result of the reduction of molecular oxygen by an H^0 atom;[51,97,100] in these, the radio-oxidation yield of many substrates is strikingly increased, sometimes by a factor of 3 to 6. In the case of the more densely ionizing particles, as these radicals are formed even in the absence of oxygen, one finds hardly any oxygen effect.[51,98,99] In some instances, new oxidation products appear, as when irradiated alanine becomes oxidized to pyruvic acid[101] (the latter also occurs as a natural oxidation product of alanine through the action of aminoacid oxidase).[51] In some degradation reactions of polymetacrylate, oxygen is necessary;[97,102] organic hydroperoxides or peracids also arise by the oxidizing action of O_2H^0 on organic acids.[51,103,104] The rate of inactivation of certain non-SH enzymes does not appear to depend on the presence of oxygen, but SH enzymes are far more radiosensitive when oxygen is present.[105] Other biological materials such as the desoxyribonucleic acid[67,68,102] or bacteriophage[76] (a desoxyribonucleoprotein) appear to be inactivated by ionizing radiations, by mechanisms chiefly independent of the presence of oxygen. This is also true for the induction of bacteriophage in E. Coli K12.[37,106] But it has been shown that DNA irradiated in the presence of oxygen is capable of forming hydroperoxides which arise almost certainly from the indirect effect of the perhydroxyl radicals on pyrimidine bases.[107] However, the excited DNA molecule itself can form similar compounds by reacting with molecular oxygen and this will result in the direct formation of hydroperoxides.[108] It has recently been shown that *dehydrated proteins* (trypsin) *also show an oxygen effect* when irradiated with sparsely ionizing radiation (X or γ rays); this may be due to O_2^- ions.[93]

After-effects

39. It has often been observed that the molecules under study continue to undergo alteration *after* the exposure to irradiation has ceased. This is the case for the oxidation of tyrosine,[109] or for the inactivation of some proteins,[110] nucleic acids,[67] bacteriophage,[111] other nucleoproteins[113] hyaluronic acid.[79] Pneumococcal DNA when tested for transforming activity does not appear to show any after-effect after irradiation in 1 per cent yeast extract.[68]

40. The after-effect seems to be the result of a primary process taking place chiefly in the presence of dissolved oxygen but it may not be sufficient in itself to inactivate the molecule. It could be due to the H_2O_2[111] or to the organic hydroperoxides[112] formed in the solution, but other hypotheses have been presented.

41. The case of desoxyribonucleic acid has been the most studied: many mechanisms—such as the oxidative formation of labile phosphate links with the sugar rings of the macromolecular chain or the slow unwinding of the double helical structure of desoxyribonucleic acid—have been postulated.[114,115,116] Although H_2O_2 formed in the solution does not appear to be necessary in the case of desoxyribonucleic acid,[116] it may have a very pronounced effect on bacteriophage S_{13} which becomes more sensitive to this agent after irradiations; S_{13} also becomes more sensitive to some reducing agent like ascorbic acid.[76] As the after-effect does not appear to occur after irradiation in the dry state (in the case of DNA)[55] it does appear to be the consequence of an indirect effect of irradiation. One will not be able to estimate its contribution in irradiated organisms until one knows more about direct and indirect action *in vivo*.

Radioprotection

In water solution

42. In a radiation-induced reaction taking place in water, the fact that the major part of the effect is of indirect origin has fundamental as well as important practical consequences.

43. Any other solute, reacting with the free radicals formed at the expense of the water molecules, will render them less available to the substance under study and protect it possibly by a competitive mechanism.[8,117] Many organic or inorganic compounds are efficient *in*

vitro, amongst these thiourea, aniline, phenol, cysteamine and its oxydation derivative cystamine,[97] and S-2-Aminoethylisothiuronium° Br°HBr (AET).[118]

44. Substances capable of reacting with essential groups of enzymes may, when present during irradiation, protect the group; removal of the agent after irradiation uncovers an unaltered group and this has been shown to be the mechanism in the case of SH enzymes protected *in vitro* by some SH reagents.[65,119] Many enzymes are also protected by their substrate,[120] their coenzyme or by competitive inhibitors,[121,122,123] probably also because the biologically active sites of the enzyme molecules are masked by the protector. It has been suggested, furthermore, that the SH group of cysteamine can protect SH groups of enzymes by becoming linked to them reversibly through S-S bridges. Similar dissociable complexes can be postulated in other instances.[124,125]

45. If organic radicals originating from irradiated molecules are prevented to diffuse from one another, one favours their rejoining. This is also a possible mechanism of radioprotection and it can probably be achieved by freezing at *low temperature*.[126]

46. Reducing the oxygen tension will inhibit those effects of radiation which are known to be increased in oxygen. There are many ways of producing anoxic conditions, including the use of chemicals, such as hydrosulfite, cysteine or cysteamine,[127,129] and of more usual respiratory inhibitors. *In vivo*, many reducing organic substrates which consume the cellular oxygen by way of the normal respiratory processes probably also produce anoxic conditions.[20,128] It is difficult at present to know the exact contribution of these mechanisms in the case of certain protecting agents like cysteine or cysteamine; it is probable that it varies according to the type of substrate, the presence of other solutes and the concentration of the different substances.

In the dry state

47. However, it is possible to protect molecules in the dry state. It has been shown that the four first substances listed above, (paragraph 43) when incorporated into a synthetic polymetacrylate, protect it during irradiation even when in the dry state.[55] In the solid state, no water radicals being present, the protective action is probably due to a transfer of energy through the polymer molecules to the radioprotector. This would be the mechanism of protection in the case of a *direct* action of radiation on the molecule. The ribonucleic acid of tobacco mosaic virus also appears to be protected against direct effects by cysteine.[130]

Restoration

48. Restoration is a process starting in the irradiated material, by which the original product can be obtained with its normal characteristics.

49. Reducing agents when added after irradiation have been shown to be capable of restoring the full enzymatic activity of a number of SH enzymes. The restoration is complete only at very low dosages; as dosage is increased, reversibility is less and less complete, which shows that different sites of one molecular species are altered with different efficiencies.[65]

50. Although some compounds are normally oxidized or reduced during normal cellular processes, the radiobiological oxidations or reductions may lead to a product which is not the natural one and which cannot be restored to an active biological compound by natural processes.[63] Coenzyme I *is reduced* by X or γ irradiation to an unnatural product only in the presence of alcohol which is oxidised to acetaldehyde; the reaction cannot be reversed by enzymatic oxidation. The great majority of radiochemical reactions are apparently irreversible *in vitro*. If a radiation reaction similar to the last one described were to take place *in vivo*, natural enzymatic processes could restore the *substrate* to its natural state, and the acetaldehyde formed could be reduced again to ethanol.

Present status of the "target" theory

51. According to its original meaning given by Crowther in 1924, a "target" in radiobiology is a sensitive cellular structure whose inactivation by one or several ionizations (hits) would result in the observed biological effects.[131] When ionization takes place exclusively in the sensitive structure (direct effects) the dosage to effect relationship has enabled one to calculate a target volume. In the case of dry or highly protected small viruses which are inactivated by a single efficient ionization, it has been possible on this basis to measure their volume and molecular weight and obtain values in agreement with those obtained by other methods. As water is a major cell constituent, it can be expected that part of the biological effect of radiations is of an indirect nature: this raises new problems as to the applicability of the target hypothesis to living cells. If all indirect effects could be suppressed, as it is thought they are in dried seeds, there would be no problem. At present there is no certain way of doing this: loading the organism with chemical protectors, freezing the cells or reducing the oxygen tension may not do it efficiently because it cannot be foreseen to what extent a chemical protector will reach the cellular structure under consideration, and because free radicals may remain frozen at or near their site of origin until the cells are thawed for biological assay. Therefore, more knowledge is needed about the relative importance of indirect effects and about the distances over which free radicals may diffuse before being neutralized or before reaching the cellular targets. In order to have a clear-cut criterion which can be observed, the biochemical or biological reactions controlled by the targets should be well defined. Probably, when these conditions are satisfied, it will be possible to use the target concept as a useful analytical tool. Work in this direction is in progress.

III. Biochemical Effects

52. The *sequence of chemical events* from the moment when the cell constituents are subjected to radiation up to the time the biological effects become apparent can conceivably be discovered with biochemical techniques. The search for an immediate or initial biochemical event will thus be the first step in this attempt. Two approaches have been used by studying the effects on cellular constituents and on biochemical mechanisms.

Cellular constituents

53. The search for structural damage to important cellular constituents can be done by assaying, as soon as possible after irradiation, the biological or the physicochemical properties of various cell components of which the integrity appears to be important for the economy of the cell. Enzymes or nucleic acids can be examined in this way, but although high doses have been used no definite clues have so far been reached, despite the very great number of observations. The general conclusion seems to point to the apparent radioresistance of the majority of

cellular proteins; and even sulfhydryl groups, which are very radiosensitive in dilute solution,[132,134] do not appear to be considerably damaged *in vivo*.[126,133] Similarly, essential coenzymes and vitamins do not seem significantly altered immediately after irradiation.[126] This is due to the fact that only a very small percentage of the constituents are affected unless very high dosages are applied.[126]

54. It must be realized that in such attempts to identify radiosensitive molecular species by looking for the oxidation of SH groups or changes in molecular asymmetry these molecules are usually considered in bulk, and even when specific analysis is undertaken, it is often found, as is the case of coenzyme A, that no alteration can be detected.[135] These negative findings do not exclude the possibility that a small number of molecules of a type controlling key mechanisms (cell division for example) or having a particular location may still be altered —but at present, general knowledge about the existence of such specific molecules is lacking.

55. In the case of genetic constituents (desoxyribonucleoproteins), which presumably constitute a class of relatively few molecules each having a very high degree of biological specificity, the alteration of a single unit would result in some cellular damage which would become expressed at the end of the chain of reactions it initiated.

56. The question of the radiosensitivity of nucleic acids *in vivo* seems still to be controversial, although evidence indicates that *nucleoprotein* complexes are probably dissociated in many tissues as a result of moderate irradiation.[67,126] It has been calculated, on the basis of *in vitro* measurements, that a dosage of 100 r could damage 100 to 200 molecules of DNA in a mammalian cell,[137] and this figure does not disagree with the data indicating the stability of pneumococcus DNA when irradiated *in vivo*[136], the dosages used in these experiments not being sufficient to cause any significant inactivation.[69] Thus, a very much lower dosage than 1 r would be theoretically sufficient to alter permanently some genetic constituent in a single cell. In this case, not all cells would have one of their DNA molecules affected. However, nothing is known on the possible interactions that intact cells could have on the affected ones, either by influencing their recovery processes or by competing effectively with them (selection). Knowledge on the behaviour of an affected cell in a normal population would be of great interest to understand low dosage effects.

57. There is no reason to believe that ribonucleoproteins are not as radiosensitive as the desoxyribonucleoproteins, but very little is known about the number of units of each type which a cell is likely to possess and even less of the specific reactions they control. Chromosomal ribonucleoproteins could very well be concerned with the duplication of genetic material in dividing cells, as suggested by recent work on bacteriophage synthesis.[138,139,140]

58. Still less information is available concerning the possibility of other cellular constituents playing key roles; many remain to be discovered and further fundamental research is required.

Biochemical mechanisms

Energy-forming systems

59. More information is available from the study of integrated biochemical reaction chains, like those of *glycolysis* and *respiration*, when studied at various times after irradiation. These systems result in the building up of compounds rich in chemical energy which can be used for biosynthetic reactions and cellular work. In radiosensitive organs like bone marrow, spleen and thymus, such reactions as aerobic phosphorylations seem already to be impaired thirty minutes after irradiation by 50 r (effects on mitochondria), but it cannot yet be stated whether these radiobiological processes are the cause or the result of other biochemical damage.[141,142]

Synthetic mechanisms

60. In dividing tissues, the most constant finding is an inhibition of the synthesis of desoxyribonucleic acid.[131,143,144,145] In micro-organisms like yeasts, the homogenity of the population makes experiments more easily interpretable; and it has been found that this inhibition is only temporary and that synthesis resumes after various lengths of time.[144] In other instances, there may be a short time-lag before this inhibition occurs. However, the mechanism of DNA synthesis, although beginning to be experimentally approached, is not understood. As has already been pointed out, it may be dependent even in normal cells on protein or ribonucleic acid metabolism; and in bacteriophage it is probably dependent on such metabolism by the host cell. The nature of the initial step of radiation damage remains to be determined. On the basis of bacteriophage inactivation, it has been suggested that the DNA model, or template, on which the new molecules are thought to be formed, has been altered in such a way as to make its reduplication impossible. The temporary inhibition of DNA synthesis may lead to abnormal DNA formation and this is perhaps related to the killing of cells and to mutation, but in what exact manner is not known.

61. So far, the syntheses of ribonucleic acid and proteins and lipids in bulk do not appear to be consistently impaired by radiation and may even be enhanced, but these compounds are very complex and their study in bulk form, the manner in which it has mostly been carried out so far, cannot be regarded as adequate. Proteins and RNA, bound to the chromosomes and other nuclear and cytoplasmic structures, are probably very complex and each fraction should be studied independently.[144] This will only become possible, however, when more is known about the chemical composition of cellular structures and when refined analytical procedures are available.

62. The inhibition of *induced protein synthesis* in micro-organisms has usually been found to be resistant to radiations, except in the case of hydrogenlyase in E. Coli.[146] In mammals, a few cases of induced synthesis of enzymes are known: the tryptophane peroxidase activity of rat liver can be increased if the animal is injected with large amounts of tryptophane. This process is inhibited by radiations, but this inhibition only becomes apparent after two or three days.[150] However, if tryptophane is *not* given to the animal, an *increased* activity of the peroxidase during the first few hours after irradiation can be observed, but this increase does not occur in adrenalectomised rats and is therefore due to a secondary adrenal stimulation.[151,152] There are therefore two conflicting mechanisms which have opposed effects. It has furthermore been shown that the occurrence of infection in irradiated mammals can be related to an impaired synthesis of *antibodies* if irradiation takes place before the injection of the antigen;[146,147,148,149] this is not necessarily due to the depletion of antibody-forming cells, but

might be related to the inhibition of the *induced synthesis* of a specific protein, a complex process generally considered to be related to the metabolism of ribonucleic acid, but which is not understood. The complete process of immunological response (the sequence of events between the invasion of the organism by an antigen and the synthesis of a new specified antibody) is also not properly understood and the cells which are concerned are just beginning to be identified. The process of induced synthesis is believed to be related to ribonucleic acid metabolism, and in micro-organisms it is quite sensitive to U.V. light absorbed by their constituents which affects the synthesis not only of the new proteins but also of ribonucleic acid.[153]

Effects on transport mechanisms in the cell membrane

63. Enzymatic systems at the surface of the cell membrane take a prominent part in the active transport of metabolites through the cell membrane,[154] but, although cell permeability has often been said to be affected after irradiation,[155,156] few critical experiments have been performed. It has been shown, for instance, that lethal irradiations and still higher dosages have often led to a leak of potassium ions into the medium; this has been proved in erythrocytes, in muscle but not in liver.[157] Similar phenomena, if existing in nerve cells, could be a basis for explaining some of the nervous symptoms of irradiation. Surface mechanisms can be affected in yeasts by U.V. light 365 mμ. without apparently producing other effects than delaying mitosis; these surface lesions cause considerable loss in potassium.[158]

64. The loss of small organic molecules like adenosine triphosphate has been shown to occur from irradiated micro-organisms,[159] and techniques of tissue culture will make it possible to establish whether such behaviour applies also to mammalian cells. In mammals, it is known that amino acids and other small molecules (taurine for instance) are released in the blood stream and urine,[160,161] and this might be the result of impaired permeability.

65. The exact significance of these various biochemical effects is difficult to discuss because our present knowledge of the sequence of biochemical mechanisms taking place in a normal cell and their interrelationship is still very fragmentary.

IV. Cytological effects

66. In order to explain the biological effects of radiation, cytologists have tried for the last half century to identify abnormal cell structures.

Nucleus

67. *In the cell nucleus*, the most conspicuous damage is in the *chromosomes*, which are very sensitive and frequently grossly altered; irradiation as low as 25 r or even less is sufficient to induce chromosome aberrations in embryonic nerve cells[162] or in many plant tissues.[163,164]

68. Irradiation causes the breakage of chromosomes, which probably occurs during exposure; this is followed by normal or abnormal recombination of the broken ends; but these may remain separate. As not only the molecular integrity but also the order of the genes on the chromosomes is important, this damage may lead to genetical effects simulating mutations. Point mutations are molecular alterations of genes usually not accompanied by visible aberrations, and they may perhaps concern only a very few sub-units (nucleotides) of genetical material;[165,166] however, a point mutation could occur at the point of breakage and reunion of the chromosome and in this case the damage would be visible. Two types of mechanisms for chromosomes breakage appear to be possible;[35] the first would be the result of the breaking of weak ionic bonds, the second the rupture of stronger covalent bonds. In the first case, restitution is possible in the absence of external energy sources; in the second, energy of respiratory origin is necessary. This interpretation is by no way definitive; it is the one which best fits the present experimental data, but its simplicity is obviously a reflection of our ignorance of the over-all molecular structure of chromosomes and of the dynamic mechanisms of chromosome function. It is presumed that ionization must take place in the gene itself or in its immediate vicinity to cause a mutation.

69. Less defined damage, making the chromosomes stick to each other, is also observed; the result of this stickiness is, as is often also the case for well-defined abberations, an uneven distribution of chromosomes between the daughter cells, which affects the process of mitosis or the survival of the cells.[162,167] Staining abnormalities of the nucleus have frequently been observed.[70,168]

70. New techniques have only recently been developed for mammals, making possible in them the identification of all the chromosomes in a sufficient number of cells for the quantitative study of aberrations, which would lead to the establishment of dose effect relationships in men. Observations of this kind will be extremely laborious and one cannot expect much information before many competent observers have been trained.

71. The morphology as well as the number of *nucleoli* (small nuclear spherules characterized by their high content of ribonucleic acid) may be altered in mammalian cells.[169] The total cellular volume may increase as a result of irradiation, as the volume of the nucleus often does; the nucleoli may become swollen, fragmented or vacuolated.[167,170] The precise function of the nucleoli in normal cells is far from completely known, but it may be related to such diverse processes as cell differentiation, protein synthesis and coenzyme synthesis, and their obvious relationship with the chromosomes in many instances make these organelles of prominent interest for the proper functioning of the cell.[171]

Cytoplasm

72. Nuclear swelling is often accompanied by cytoplasmic swelling, and giant cells are often observed after irradiation of micro-organisms as well as of mammalian cells.[172] The fact that the dry weight or total nitrogen increases at the same time indicates that many synthetic reactions have not been interrupted. Swelling of cells (or elongation of bacteria) appears to be the result of an impaired cytoplasmic cleavage.[173,174,175,176,179] This cellular swelling has often been the basis of a misinterpretation: many references to the *stimulation of growth* of irradiated organisms can be cited. Actually, as in the case of seedlings, this is merely the result of the elongation of non-dividing cells:[176,177,178] the inhibition of one process (cell division) may result in the increase of available energy or building blocks for other reactions, thus merely shifting one steady state to another. The energy of radiation and its random distribution is such that the chances of obtaining deleterious reactions appear greater than those for specifically removing inhibitory processes, another logical mechanism by which stimulation could be explained. Effects of radiation should always be thoroughly analysed before they can be assumed to be useful to the irradiated subject.

73. The cell cytoplasm is known to contain a variety of particular structures, the exact identity of which has not yet thoroughly been worked out.[180]

74. *Mitochondria* are the largest of cellular particles; they contain most of the enzymes and coenzymes responsible for cellular respiration which release the major part of energy used in biochemical reactions; they also have important functions in lipid metabolism.[192] They have been observed to swell or show abnormal staining in irradiated spleen cells,[181,182,183] a finding which has been supported by biochemical evidence (inhibition of oxidative phosphorylation).[184,185] If, after irradiation, the behaviour of the various biochemical functions which are attributed to mitochondria were compared, it should be possible to draw a consistent picture of their alterations;[185] unfortunately the experiments have seldom been carried out in comparable conditions.

75. The following have been described:

(*a*) An inhibition of respiration and phosphorylations chiefly in thymus and spleen; the phosphorylation processes appear to be more sensitive than respiration.[184,186,187]

(*b*) An increase of spleen adenosine-triphosphatase which seems to be independent, at least initially, of the inhibition of phosphorylation.[186]

(*c*) An altered lipid metabolism characterized chiefly by an increased synthesis of the phospholipids of the liver;[188] however in spleen and thymus it is slightly lower or remains normal. It must be emphasized, however, that lipid synthesis may not necessarily be linked to mitochondrial integrity, as suggested by a number of experiments.[189,190,191]

76. Thus, the different reactions to radiation of three different mitochondrial functions do not appear to respond identically. This raises the problem of the identity of the mitochondria performing all these three functions. Much better controlled work, where several properties of the same particles are investigated in identical conditions, could help to solve this important problem, and radiations could perhaps in this instance be useful as an analytical tool: the site of lipid metabolism could be a radioresistant type of mitochondrion.

77. It must finally be kept in mind that respiratory processes appear, as in yeast, to be controlled by nuclear or cytoplasmic factors;[193] the latter may or may not be identical with the cytoplasmic particles carrying the respiratory enzymes themselves. An alteration of these controlling mechanisms could very well be the origin of late radiation effects on these functions.

78. *Microsomes* form another class of smaller, cytoplasmic structures organized in a reticulum, as seen by the electron microscope.[194,195] They have a strong affinity for basic dyes, a condition which is strikingly augmented in tissues undergoing differentiation and actively synthesizing protein; in the course of these processes, ribonucleic acid, chemically related to the desoxyribonucleic acids constituting the nuclear genes, undoubtedly plays an important part. There does appear to be a functional relationship between microsomes and nucleoli, but its nature is not understood. These particles are at present considered to be the major site of protein synthesis.[171]

79. Surprisingly, electron microscopy has not been much used for the study of the structure of the irradiated cytoplasmic reticulum and the scanty observations so far performed in the thyroid and in the testes have not revealed any damage to this reticulum.[196]

80. If the microsomes are considered from a dynamic point of view and the cellular functions to which they are related are studied, several conclusions can be tentatively reached.

81. In general, *protein synthesis* does not appear to be impaired immediately after irradiation,[198] and it is, on the contrary, often enhanced: however, this increased activity is often followed by a depression, as in the case of the synthesis of the protein moiety of hemoglobin.[197,199] This bimodal response to radiation, often found for protein synthesis, makes it difficult to interpret the variations of the serum proteins[200] in irradiated animals where a very complex picture is often obtained and when the many results available are difficult to compare on account of different methods and timing of the experiments.

82. The inhibition of the *induced synthesis* of tryptophane oxidase and antibodies are perhaps also related to microsome activity.[150]

83. *Cholesterol synthesis* is also related to the integrity of microsomes[201] and is often enhanced after irradiation; when it is inhibited as in spleen, this only becomes apparent after twenty-four hours.[97]

84. In most cases, the effects of radiation on microsome function probably do not become expressed immediately after irradiation. It will not be possible to understand these late effects until the fundamental facts about protein synthesis and their relation to nuclear activity are known. Experiments on enucleated unicellular organisms have shown that the nucleus has a definite but remote control over the cytoplasmic ribonucleoproteins;[171] the irradiation of non-nucleated cytoplasm in the amoeba has shown that at least ultra-violet light affects cytoplasmic ribonucleoproteins quite rapidly.[202]

85. *Lysosomes* form a type of cellular particle chiefly studied in liver; they are intermediate in size between microsomes and mitochondria;[180] they are characterized by a high content of iron and by their association with several enzymes like desoxyribonuclease II, ribonuclease, cathespin, glucuronidase, and acid phosphatase. As the activity of the first three of these enzymes has been found to increase in tissue homogenates or in the blood stream after irradiation,[203,204,205,206,207] it could be suggested that this is a result of damage to the lysosomes; critical experiments in which enzymes are assayed simultaneously in an irradiated animal might prove this hypothesis. In the case of cathepsin, the increased activity can be related to the disappearance after irradiation of an enzyme inhibitor normally present in the blood.[207,208]

86. *Chloroplasts*,[209,212] the chlorophyl-containing cytoplasmic particles of plant cells, and *kinetosomes*,[210] the particles related to flagella in protozoa, are both endowed with genetic continuity: this gives to these structures great theoretical importance. If the speed of multiplication of these structures can be reduced to a greater extent than that of cell division, one can expect to find that some of the daughter cells have completely lost them. The reverse could also be true, and recent work on moderately irradiated grasshopper testes[196] has shown in the electron microscope the appearance of supernumerary tail filaments and centrosomes, probably related to the kinetosomes of protozoa. These observations have led their authors to an interesting theory of radiation damage based on the synergistic action of non-specific molecular displacements leading to the formation of abnormal

structures.[196] Extensive work on irradiated plant cells has led to the demonstration that the activity of several enzymes bound to the chloroplasts were altered.[211]

V. Biological effects

87. The effects on homogeneous populations of cells will be considered first, and then those on complex organisms.

Homogeneous cell populations

88. Cell populations such as micro-organisms, protozoa, unicellular algae, cultures and surviving suspensions of cells from multicellular organisms like fibroblasts, bone marrow cells, gametes and certain cancerous cells have been extensively studied.[1,213,214,215,217,218] Recent techniques make possible the culture in liquid media of almost any type of mammalian cell;[177,178] these cells are capable, *in vitro*, of forming organized structures recalling the original tissue they come from,[216] which should be of great value in studying problems of cellular organizations and in understanding multicellular organisms. These cell populations have been irradiated in rather comparable conditions, and they have been shown to react in very similar ways.

89. When *fundamental properties* of the cells such as survival, *cell multiplication* or mitosis, *increase in dry weight, differentiation* of non-mature cell types, cell *movements*, or *permeability* of the cell membranes are studied, one can usually describe a *common pattern of reaction to radiation.*

90. On the other hand, cells performing *specialized functions* may react to radiation in a specific manner related to this function. In *multicellular* organisms, important *interactions between the different tissues* have also to be considered.

Mitosis (i.e., cell division)

91. Cells are rarely killed immediately, but usually die after having attempted division or after having undergone one or several divisions. Mitosis itself is interfered with and is usually *delayed*, if irradiation happens early enough in the mitotic cycle. This has been examined most elegantly by direct observation on hanging drop preparations of neuroblasts from grasshopper embryos.[167] These experiments have shown the existence of a very critical stage of cell division during the period when the chromosomes condense as visible threads and when both the nuclear membrane and nucleolus disappear. Irradiation *before* this critical stage usually makes the whole process stop for a duration depending on dosage; *after* it has passed this stage, the mitotic events do not appear to be interfered with if dosages are small. It is remarkable that, if applied at the right moment before the critical period, dosages as small as 8 or 16 rad will delay the progression of mitosis in this type of cell. These observations are essentially similar to the previous analyses on fibroblast cultures;[220,221] they also fit rather well with the experiments on irradiated gametes of the sea-urchins, where cleavage of the fertilized embryos obtained by the conjugation of irradiated gametes (either or both of which have been irradiated) is also delayed, if irradiation occurs before early prophase in this case.[222] If irradiation occurs afterwards, it is the subsequent cleavage which is slowed down. This general picture of mitotic delay may be subject to some alteration when different types of cells are considered; less direct methods of observation may have led to a different timing of the critical period in other cells.[219,221] Also, in each cell type, although the general course of mitosis is quite similar, the duration of each phase and sometimes the exact denomination of the stage considered may vary to a considerable extent, which makes exact comparisons very difficult.

92. The exact cause of the inhibition of mitotic division is not known. It has been suggested that it is related to the inhibition of DNA synthesis[214,223] which occurs frequently — but some instances where cell division is inihibited with apparently normal DNA metabolism will force us to reconsider this view.[224] DNA synthesis, as stated previously, is a complex process; it is perhaps associated with chromosomal protein[225] or RNA synthesis,[138] of which next to nothing is known. It has been suggested on the other hand that an interference of radiation with the oxido-reduction of sulfhydryl compounds known to occur during cell divisions[228,229,230] might also be one cause of its inhibition; inhibition of mechanisms of cytoplasmic cleavage[226] or of spindle formation[227] are other plausible hypotheses.

Mutations

93. It has been stated earlier that cells which do not die after several divisions are said to recover. This statement is very imprecise, because all that is known is that these cells *look* as if they had recovered. However, in certain instances although they continue to have a quite normal appearance, they have undergone *mutation.* These changes have been observed most clearly in bacteria, moulds, and other unicellular autotrophic or heterotrophic organisms; and very recently, the studies of cultures of isolated mammalian cells have suggested that such mutant forms also exist amongst the survivors.[231] These mutations are characterized by the fact that the surviving cell as well as *most of its descendants* have been affected in a way which makes them *permanently* incapable of performing some biochemical reaction. If this biochemical reaction (for instance, the formation of an essential building block) is necessary for the cell to grow and multiply, the mutation will lead to the arrest of growth and multiplication, and finally the cells will die, if this essential building block is not provided in the culture medium. It is believed that *there is a period of time following irradiation during which the process of mutation is not fully established.*[232,233,234,235] What takes place during this time is not known—but it is possible, at least in the case of ultra-violet irradiation of micro-organisms, that the expression of damage depends on the synthesis of some protein. Although this time-lag gives the possibility of interfering with mutagenesis[234,236]—a subject which will be discussed more thoroughly in another section—it is generally accepted that this damage *once fully established cannot be reversed by non-genetical processes.* In addition to induced mutants there are always a certain number of *spontaneous* ones, which arise in the absence of any added external agents.

94. *Back mutation* (reverse mutation), the apparent reversal of the previous mutation and the evolution from dependency to independence of some specific metabolite, may occur spontaneously or by irradiation of the mutant; apparently there is what could be called a true recovery of the cell or at least of that part of the cell which had first been altered.[237] However, the spontaneous phenomenon has a small probability of occurring and the process of back mutation, *unless it could be directed*, is not a practical recovery process.

95. Other mutagenic agents (lower energy radiation like ultra-violet light,[238] many toxic compounds and chemical analogues to normal building blocks)[239,240] are all useful in helping to clarify the mechanism of mutations. Chemical analogues, for instance, compete with normal building blocks and may often replace them in important macromolecules like nucleic acids, sometimes preventing their reduplication or their normal functioning. Comparison of ultra-violet lights of different wavelengths will indicate which of them is most effective and enables the nature of the chemical groups absorbing the energy to be determined. The use of these agents is of very great importance in elucidating the mechanism, not only of mutation, but also of chromosome breakage and of mitosis, which they are capable of disturbing.[239]

96. Genes presumably control the biochemical mechanisms (many of which are located in the cytoplasm) responsible for producing enzymes or other specific cellular constituents.[241] It is possible to imagine that, as a result of irradiation, the block in the reaction chain between gene and enzyme-forming system could occur in some intermediate *cytoplasmic* structure. If this structure is one which, like the chromosomes and the genes they carry, has to reproduce itself at each mitosis in order that each daughter cell be identical to its parents, and if damage has rendered the reduplication of the original structure impossible, one will obtain a *cytoplasmic mutation*. Nothing much is known about these, but the induction in yeasts of respiratory deficient strains by poisons or radiation and the demonstration that this deficiency is not necessarily of nuclear origin, indicates the existence of heritable cytoplasmic characters.[193,242]

Movement

97. *Cell mobility* can be stopped by irradiation, but usually very high dosages are needed for such an effect. Irradiation of spermatozoa[244] may result in the loss of motion, probably as a consequence of the inhibition of phosphorylation;[243] this causes them to become infertile, but the dosages are much larger than the ones required to delay cleavage of the fertilized egg. Nothing specific is known of the effects of radiation on the cellular migrations which occur in the developing embryo. On the other hand, radiation is known to inhibit phagocytosis in mammalian polymorphonuclear white blood cells,[245] but phagocytosis is a complex phenomenon and this effect is not necessarily due to the inhibition of movements. Alterations of cytoplasmic or nuclear movements inside living cells might also give useful indications, but so far their quantitative measurement is difficult.

Membrane phenomena and ionic equilibria

98. The statement frequently made that radiation alters the cell permeability needs to be specified. The exchange of inorganic or organic molecules and ions between cells and their natural environment is a very complex process, because many substances have to be concentrated inside the cell against a concentration gradient, a process which requires energy,[154] and inhibition of permeability could result from the inhibition of energy-forming systems. This is the case for K^+ or carbohydrates; in the case of the latter, complex enzymatic systems, located on the cellular membrane, have been described, and it would furthermore not be surprising that this organized structure be upset by radiation as are other patterns of cellular organization.

99. It has been shown in many cases that potassium leaks out of many irradiated cells like erythrocytes,[246,247,248] and cardiac muscle,[250] but not out of liver or kidney,[251] or striated muscle.[249]

100. The entry of glucose or amino acids into cells is also dependent on surface enzymes, and it should be clarified whether an inhibition of these systems might affect secondarily synthetic or energy-forming mechanisms. In micro-organisms (*E.Coli*, yeasts), it is known that the induced synthesis of many enzymes is not inhibited by X-rays[252] for doses which completely arrest cell multiplication, which indicates that the inductor substrates are still capable of penetrating into the cells. However, quantitative studies have not been performed. On the other hand, it has been proved that in similar organisms (*E.Coli*) irradiation leads to the diffusion of many nucleotides[159] into the outside medium, as well as of potassium, which has already been discussed (paragraph 63).

101. In mammals, it has been found that when glucose is injected under the skin immediately after irradiation, its entrance into the blood stream is slowed down.[253] The passage of metabolites from the hypodermal region into the blood capillaries could be a more complex phenomenon, because it involves the passing of the molecule through an organized tissue. The same applies to the inhibition of the intestinal absorption of glucose, which is diminished three to six days after total body irradiation in rats. However, in this case the inhibition is accompanied by important cytological damage.[254] The case of the barrier separating the eye from the blood stream[255] as well as many others[156] have also been studied with similar results.

Cell death

102. Irradiated cells die either immediately (i.e., during irradiation) or after a certain delay: in the former case, much higher dosages are needed, and death can be attributed to a general denaturation of cellular constituents. Many conflicting results on cell death have appeared in the literature; this can be accounted for by the difficulty in defining cell death: in micro-organisms, for instance, death has been defined as the inability to form visible colonies on agar plates. Furthermore, the primary cause of cellular death may differ from one system to another, and it is not necessarily unique; any of the cytochemical, biochemical, physiological or genetical effects of radiation so far discussed could each take part in killing the cell. A mutation in a micro-organism leading to the inability to form an essential building block will be "lethal" *only* in the case where the culture medium does not contain this substance.

103. Delayed death of dividing cells occurs after one or several cellular divisions have taken place,[220,256,257] and it may often be linked to chromosome damage,[258] but it could also be due to nutritional or other deficiencies, such as occur in a non-dividing population. Delayed death is caused by much more specific damage than immediate death, and its study is thus of far greater interest. The doses required for obtaining delayed death may be different not only for cells of different species,[1] but also for closely related cells such as different strains of the same bacterial species.[259]

104. Recent experiments on *cultures* originating from different single mammalian cells have shown a very similar sensitivity;[231] this probably results from the fact that in these abnormal conditions cells undergo relatively

rapid division, whereas in the whole organism this process may be extremely slow and may differ from one tissue to another. When penetrating radiations are used, it can be assumed that each cell of an irradiated population receives the same amount of radiation. In an average-sized mammalian cell, submitted to an irradiation of 1 r, several hundreds of ionizations occur, and the probability of a structure being damaged will depend on several factors, including its size and the radiosensitivity of its constituent molecules *in vivo*. It has been calculated that 100 r to a mammalian cell nucleus produce 100-200 hits into the DNA; 1,000 r to a bacterium will produce of the order of 5 to 20 direct hits in the DNA alone, and every radical which might reach the DNA could damage another molecule.[69] Alterations of DNA could be one cause of late cellular death, but other cellular constituents are also damaged. It can be shown that some cells die while others recover and apparently behave again like normal ones. This probably results from differences in the distribution of the energy to "critical" and to less "critical" molecules and it has to be remembered that it is the remaining physiological activity of each cell constituent which will determine the final biological effect.

Effects on viruses and K particles in Paramecia

105. Radiation effects on such specialized biological systems may at first appear to be out of place in a general survey as this one, aiming at understanding radiation hazards to man. However, these systems are very closely related to chromosomes (and presumably the genes they carry) and to many cytoplasmic particles; they consist of nucleoprotein, and the mechanism by which viruses reproduce autocatalytically offers the best model at present available for the study of the reduplication of cellular nucleoproteins. Viruses are very important in radiobiology, because they can be studied both as chemical entities *in vitro* and they can be irradiated independently of the cells they multiply in. Bacterial viruses (bacteriophage),[260,261] some of the animal viruses and the cytoplasmic K particle of *Paramecia*[262] are desoxyribonucleoproteins, like the bulk of the chromosomes; plant viruses and some animal viruses are ribonucleoproteins, others are desoxyribonucleoproteins.

106. Bacterial viruses are the ones most attention has been paid to, and the following fundamental facts have been discovered and have in some cases been confirmed using other viruses.

107. Ionizing or ultraviolet radiation applied *in vivo* or *in vitro inactivates them, i.e. interferes with the possibility of their being self-duplicated inside the cell.*[260,261,262]

108. For certain strains, non-irradiated bacteriophages are capable of growing in bacteria heavily irradiated by X-rays or ultraviolet radiation, indicating very clearly that *the self-duplicating structure itself* has to be affected and that the bacteria remain capable of supporting phage multiplication.[263,264]

109. If the conditions of infection are such that there are *several* ultraviolet inactivated bacteriophage per cell, for certain strains of bacteriophage, the intact parts of each virus can *recombine* into a complete new unit, which is again capable of duplication (this is called *multiplicity reactivation*).[265] This is a crude and probably quite inaccurate way of explaining a complex mechanism of which little is known. This type of reactivation has also been described for X-rays.[266]

110. Experiments like these may have very general implications for the understanding of damage and of recovery processes taking place in cells of more complex organisms and therefore should be vigorously encouraged.

Effects on lysogenic cells

111. Certain types of bacteriophages invade their host but do not multiply in the usual way; on the contrary, they appear to become integrated into the bacterial desoxyribonucleoprotein and thus reduplicate simultaneously with the bacterial nuclear material without causing any apparent trouble to the cell. However, extremely low dosages of irradiation as well as a variety of other agents induce the transformation of this "prophage" to a virulent bacteriophage, which will multiply and finally lyse the infected cell.[267] In certain strains of lysogenic bacteria, a dosage of 0.1 r may give a measurable induction, and the linearity of the dose-response curve for this "genetic" effect has been demonstrated down to such low dosages.[37,106] What characterizes induction is that it takes place in almost 100 per cent of lysogenic cells, whereas mutation only takes place in a small number.

112. Experiments on infected micro-organisms have also shown that a virus is capable of becoming integrated into the genetic material of the host and of *transducing* some genetic characters from one genetic type of host to another.[166,268] It is not unlikely that processes similar to bacterial transformation by DNA or to transduction involving the transfer of genetic material from one type of cell to another, also exist in mammals. If such phenomena were discovered, *directed reversed mutations might become possible in mammals.*

Differentiating cell populations

Embryonic development

113. Gametes arise from the differentiation of stem cells, the oogonia or spermatogonia, which takes place in the gonads. This differentiation (oogenesis or spermatogenesis) is a process during which the double genetic equipment (*diploid*) existing in the stem cells as well as in the somatic cells is halved evenly through the complex process of *meiosis* to give daughter cells, which will produce gametes containing only one gene of each kind (*haploid*). Fertilization will result in the fusion of the parent nuclei, and the usual diploid number of the somatic cells is thus obtained.

Irradiation of gametes

114. We have seen that when either of the gametes is irradiated, the first cleavage of the fertilized egg is delayed; if the embryo is then left to develop, the cleavage divisions usually proceed apparently quite normally up to the blastula stage. However, embryonic development usually comes to a permanent stop before the completion of blastulation or during early gastrulation; this is one of the numerous examples of delayed death.[269] The fundamental biological situation is that gastrulation is the first stage of development during which *cellular differentiation* occurs: this process is preceded by a striking increase in the metabolism of ribonucleic acid (both in the cytoplasm and nucleolus), as is the case in most biological processes where intense protein synthesis and differentiation is taking place.[270] Furthermore, during gastrulation important cellular movements lead to the formation of three different cellular layers which ultimately become organized in tissues

and organs. Some of the cells in certain layers are capable of *inducing* specific differentiation processes in others. There is not just a change in the "geographical" relationship of the cells as a result of these movements, but their apparent uniformity up to the stage of the blastula is lost; this is demonstrated by the fact that the *nuclei* lose the general potentialities they had until then.[271]

115. The cause of the death of embryos obtained from oocytes fertilized with irradiated sperm appears certainly to be related to *nuclear damage:* the sperm cell contains only very little cytoplasm, and the damage can remain hidden, as it may do in mutations, over many cellular generations. Cell divisions appear to be blocked as a result of incomplete fusion of the maternal chromosomes with the abnormal ones of male origin, a situation leading eventually to abnormality and uneven distribution of chromosomes between daughter cells.[269,272,273,274,275] It is important to notice that the process of cell division becomes inhibited at a stage of development where the genetic material is presumed to initiate differentiation. If, however, the fusion of the abnormal paternal chromosomes with the normal maternal ones is completely prevented (which can be done by using *higher* dosages of radiation), a situation arises where the abnormal nucleus is eliminated, and in this case an *apparently normal* embryo will develop if the species studied are capable of parthenogenetic development.[269,272,275] This is one example, amongst others, where dosage-effect relationships appear to be non-linear and even paradoxical; *higher* dosage producing *less* final damage than lower ones. The explanation is that complex mechanisms of development, secondary to the initial damage to the chromatin are observed: this damage, however, is probably related in a simple way to the amount of irradiation received. A similar paradoxical situation may be found in the experimental inductions in the embryo of certain abnormalities such as microphthalmia[273] and this can be logically explained by the existence of some competition with other lesions at higher dosage.

116. In the wasp *Habrobracon*[276] and in silk worm[277] the reverse situation is possible, and the fusion of a normal sperm cell with a highly irradiated egg cell may lead to an androgenic embryo (containing only its *father's* chromatin). Experiments such as this point again to the very important role of radiation damage to the cell nucleus. Nuclear damage (genetic) is probably also responsible for the various forms of abortion or of malformations of offspring born of parents, one or both of which have been irradiated. In this case, the development of the embryo ceases at some stage of organogenesis, sometimes even after birth. However, as different *stages of gametogenesis* have different radiosensitivities, one expects to have a different probability of abnormal offspring when mating occurs at different times after irradiation.[273] The longer the time lapse before conception, the smaller the probability of abnormal development, because it has been found that the earlier stages are the least sensitive ones, at least in mice.[25,278] With slight irradiation, development may in many cases proceed and this will result in more or less dramatic expressions of genetic damage visible in the offspring.

Irradiation after fertilization

117. If irradiation is given at different *stages of embryonic development*, the inhibition of cell division and differentiation and cell death may cause the development to be either completely or partially stopped. In the mouse, the pattern of response to irradiation (200 r) of the embryo is the following: irradiation of the mother after fertilization but during the pre-implantation period leads to a high incidence of prenatal death; however, the survivors have very few major abnormalities; this means that only the slightly affected embryos survive. In contrast, if irradiation occurs after the embryo is implanted in utero, during the period of organogenesis, death usually occurs only after birth—but it is much less frequent; on the other hand, there is a very marked increase of malformations of the embryo. During early embryonic development (if irradiation takes place during the formation of the neural folds), malformations may occur in the eyes, brain and medulla but also in the kidney and liver. Irradiation at a slightly later stage of organogenesis gives rise chiefly to abnormalities of the skeleton of various types. There appear to be short critical periods of development during which certain types of abnormalities arise with very great frequency.[279]

118. The exact mechanism of all these effects, which are all possible in humans, is far from being well understood on account of our ignorance of many important facts concerning embryonic development, such as the nature of *induction* (interaction between neighbouring tissues), the cause of *morphogenetic movements* or the nature of *genetic expression*, that is, the mechanism by which one single cell is capable of becoming differentiated into a multitude of daughter cells performing a variety of functions.

Dosage-effect relationships

119. These have been studied in certain cases, and for most bone abnormalities they have been found to be of the *sigmoid type.*[280] In the case of the decreased weight of the foetus at birth, the dosage relationship is *linear,*[280] and litter size appears to fall off logarithmically with dosage to the gametes.[281] A constant finding is that a higher dose not only increases the incidence but also the degree of malformation and the length of the sensitive period during which a specific response can be induced.[280] It has been shown that a dose as small as 25 r to the mouse embryo has led to the induction of minor but nevertheless well defined abnormalities. It is difficult at present to know how such small doses could affect human embryos, but it can be expected that very minute malformations of the brain, which could perhaps not be detected in experimental animals, will result in some kind of psychological disorders. Responses to lower dosages still could probably be detected if a greater number of animals and more refined tests were used. The case of leukemia, also believed to be inducible by irradiation of the human embryo,[282] is discussed in detail in chapter V and annex G.

Adult organisms

Differentiation

120. Some undifferentiated cells are carried on into the adult organisms and these stem cells go on differentiating throughout life: the white blood cells are formed in the bone marrow and in the lymphatic tissues (lymph nodes and spleen and other organs). The lymphatic tissues are considered to be of major importance in antibody formation. The red blood cells originate from bone marrow and during embryonic life from spleen and liver. In rodents, myelopoesis and erythropoiesis continue in spleen during adult life, but not in man. This is one of many physiological differences it is essential not to overlook when one transposes the results from experimental animals to man.

121. Adult organisms contain other tissues *continuously regenerating* from stem cells, such as epithelia (skin, gut, etc.) or bone; finally there are tissues in which *few cell divisions* take place (liver, kidneys, pancreas, brain, or conjunctive tissue).

122. As in the case of isolated cells, experimental evidence points to the *particular radiosensitivity not only of rapidly dividing cells, but also of the embryonic or stem cells which are still due to undergo cellular differentiation.*[41] This can be shown when one observes the survival or the cytological alterations of these cells. The mature lymphocyte, however, which does not belong to either of these classes is an exception to this rule; its great sensitivity to radiations[283,284] is not well understood but may be related in some way to the fact that the nucleus is surrounded by unusually little cytoplasm which may diminish spontaneous recovery mechanisms or to the fact that it is a cell with a very short life-expectancy. It is also sensitive to many other stimuli. The situation is different from that in the spermatozoon, whose haploid nucleus plays an important role both in cell division and in differentiation processes which do not occur in the case of the lymphocyte, whose diploid nucleus may be more resistant than the sperm nucleus.

Mutations in multicellular organisms

123. Genetic mutations are found when gametes or the cells they originate from have survived irradiation and undergo fertilization.[285,286]

124. Many mutations are not lethal, and genetic abnormality of one of the gametes is believed to be the cause of many forms of congenital malformations: in this case, embryonic development is only very locally inhibited, and this leads to abnormalities such as harelip, cleft palate, spina bifida or the many deficiencies of the nervous system like congenital blindness, deafness or mental deficiencies. Hereditary diseases due to well defined biochemical deficiencies are also known to occur in mammals, and in a few instances they have been quite thoroughly analysed: in man the missing enzyme has sometimes been identified, as in galactosemia[288] and in phenylpyruvic oligophrenia[287], a form of mental deficiency related to abnormal phenylalanine metabolism.

Mutations in somatic cells

125. Mutations in somatic cells will affect the lineage of these cells but will not be carried to the offspring. These mutations have been shown to take place at a frequency of the same order as that found in the germ cells before meiosis (gonia)[25,289,290,291] and they have been found to occur in irradiated tissue culture; such mutations might play an important part in the determination of malignant growths.

126. It is very probable that the mechanism of mutation in higher organisms is very similar to that in micro-organisms; and the importance of fundamental studies in bacteriophage, microbial or fruit-fly genetics is that they enable us to get answers much more rapidly and in much better defined environmental conditions than can be hoped for in the case of the higher animals. Tissue culture, which is complex in the case of these organisms, may become of primary importance for the study of genetical mechanisms in mammalian cells, since such studies have become possible by culturing isolated mammalian cells in the same way as micro-organisms: mutations have been induced in such cultured cells.[292,231] Many somatic effects may have their origin in such mutations or in chromosome damage of non-germinal cells either as a result of death or loss of specific cell functions.

Carcinogenesis and other somatic effects

127. These effects, as well as their possible genetic origin, are discussed in chapter V and in annex G.

VI. Variables in radiation effects

Physiological conditions

128. Physiological conditions may vary in many ways and this can influence radiation responses.[41]

129. *During cell division (mitosis and meiosis)* there are different phases of radiosensitivity which one has attempted, not too successfully so far, to link to the different phases of new chromosome formation and nucleic acid synthesis which occur during these events. The survival of cells, the incidence of mutation and the alterations of chromosomes all undergo striking changes in radiation response, depending on the stage of the division cycle during which the organisms are irradiated, but it is difficult to generalize as to which is the critical stage since it can vary from one effect, or from one organism, to another.[227,293,294]

130. The induction of abnormalities or the lethal effect in developing embryos after irradiation of immature gametes of either sex, is strongly dependent on the stage of gametogenesis during which irradiation takes place. The first *meiotic* division is the period when it is possible to induce the greatest number of dominant lethals in the mouse oocyte.[278] In the case of the male, spermatogonia are the most sensitive and it seems that the degeneration occurs during the interphase or the first prophase following irradiation. The period of greatest sensitivity for various effects induced during embryonic development need not be identical.

131. *The age of cells and organisms* may affect their radiosensitivity: in an aged *bacterial suspension*, when the cells have reached their stationary phase, they become less sensitive to radiation;[295] but what is usually called an old culture is simply an "undernourished" one which has ceased to divide because the stationary phase only begins when some nutrient begins to be deficient; modern continuous cultures in media constantly renewed. By means of the chemostat might help to demonstrate whether aging occurs in micro-organisms or cellular suspensions of dividing cells of more complex organisms. The possibility of aging would exist if the daughter cells were not identical; and such a condition would arise if cytoplasmic material endowed with genetic continuity were not distributed evenly between daughter cells. It is probable that in aged cultures the radioresistance is greater because the bacteria have stopped dividing.

132. In the case of *higher organisms*, there is usually a great sensitivity during foetal life and the LD_{50} is less than half that of the adult, and, as has been already shown, the type of lesion depends on the time of embryonic development during which the radiation is delivered. In certain strains of mice, 200 r on the ninth day of gestation is 100 per cent lethal; on the tenth day, twice this dosage is required and after birth greater dosages still are needed. The sensitivity continues to decrease until adult life is reached: the LD_{50} is 500 r at forty days and reaches 670 r at 140 days for CAF_1

mice.[296,297,298] The sensitivity then remains very constant up to the last months of life—when it again increases sharply. A similar pattern of response exists in rats;[299] *Drosophila*[300] and birds,[301] on the other hand, have a much more constant radiosensitivity throughout their adult life.

133. These variations of resistance with age may be due to changes in mitotic rate (there are no divisions of somatic cells in *Drosophila*) or to changes in metabolic activity of different tissues, or to the fact that foetal tissues are undergoing active differentiation, or because the recovery processes of the aged cells have become inefficient.

134. *Nutritional and other physiological conditions.* Starvation of micro-organisms may render them more resistant, as seen in paragraph 131, but in other instances, or in reference to other types of effects, they can become more sensitive: fermentation by yeasts cultivated in a medium poor in ammonium salts is inhibited by doses which do not affect the same process when these nutrients are normal.[302]

135. There are few data on the effects of nutritional conditions on the radiosensitivity of the mammal, although a certain number of radiation effects concerning adrenal metabolism (weight, ascorbic acid, cholesterol) have the same sensitivity after one or seven days fasting.[303]

136. *Other conditions:* Anaemia apparently renders mice more sensitive to radiation, as is shown by the lower LD_{50} of certain anaemic strains. Exercise, on the other hand, does not seem to have much effect in mice.[304] It is possible, however, that in human populations, undernourishment and strain may affect the recovery processes.

137. *Oxygen tension.* The irradiation of water solutions in the presence of oxygen results in the formation of D_2H^0 radicals, in addition to H^0 and OH^0. This radical could also be formed *in vivo*. This would explain that when the *oxygen tension is diminished*, a lower response to irradiation occurs;[305] this is true for the survival of mammals,[306,307] and of birds,[308] for certain mutations[309,311] but not all,[310] for chromosome damage,[312] for various effects on embryonic development[313,280] and for certain biochemical reactions dependent on oxygen. Chemical metabolites or poisons whose presence in tissues reduces the oxygen tension may have similar effect. Lowering the oxygen tension may reduce the response to irradiation by a factor of 3 to 5 in the case of high energy radiation having a low ionizing density (X and γ rays, fast neutrons); when the oxygen tension is increased, these effects are not enhanced, which indicates that in air the oxygen tension is sufficient for the maximum effect. In the case of the densely ionizing α particles or slow neutrons, there is no oxygen effect.[305]

Comparative radiosensitivity of living organisms

138. When the survival rates after irradiation of different types of living organisms are compared, the sensitivities are found to vary very widely.[314] Mammals appear to be the most sensitive of all classes of organisms and doses able to kill 50 per cent of animals in thirty days ($LD_{50/30}$) range from about 200 rad for the guinea pig to 900 rad for the rat, the best estimate for man being 400 ± 100 rad. Cold blooded animals have an $LD_{50/30}$ which can rise to 3,000 r for the triton and perhaps 20,000 r for the snail. Bacteria and other micro-organisms cannot be compared on exactly the same basis, but it often takes as much as 100,000 r or sometimes much more to prevent 50 per cent of the organisms of many species from developing colonies, and certain protozoa may need more than 300,000 r to kill them.

139. Various factors may explain these differences. In cold blooded animals, either low *metabolic rates* or low cell division rates imply that radiation damage will take longer to develop; but this will not hold true for micro-organisms, which divide much faster than mammalian cells and resist much higher doses.

140. There may also be varying *oxygen tensions* in different organisms which could account for different radiosensitivities.

141. In the same species, organisms of different *genetic strains* may vary in radiosensitivity to lethal effects. This has frequently been observed in micro-organisms but it holds true also for mammals, where different strains of mice have different $LD_{50/30}$.[318,319] It has also been shown that similar genes in different species of *Drosophila* may mutate at rates which can differ by a factor as high as 2.[236,315,316] It has furthermore been shown that the frequency of production of developmental abnormalities may depend very much on the genetic strain: in Balb.C mice, certain malformations of the spine occur in 100 per cent of animals irradiated with 200 r during the 8th ½ day of gestation, whereas in the hybrid (C57×NB) F_1 no such malformations occur.[317] *For practical purposes, this means that observations obtained from one human population do not necessarily apply to a genetically different population.*

142. In some organisms such as adult insects where no cell divisions take place, one expects, and finds, a higher radioresistance; but in this case the gonads, where cell divisions do take place, appear also to be rather radioresistant; on the other hand, we have seen that embryonic cells may be very sensitive,[320] as in grasshoppers.

143. The presence of natural radioprotectors may be yet another factor: some organisms like insects are known to have a higher concentration of aminoacids (which are fair radioprotectors) in their body fluids. The degree of oxygenation of the tissues should also be taken into consideration.[320]

144. Finally, the number of sets of genes (*ploïdy*) has certainly something to do with radiosensitivity, as has been demonstrated for yeast and certain other micro-organisms, in which diploïd strains (containing two sets of genes) are more resistant than haploid ones (containing only one set).[320,321] Not only the number of sets of genes, but the number of chromosomes and their length appear to be important; the greater their number or the shorter their length, the more resistant the organisms seem to be. This holds true at least in the case of the plants which have been studied in this respect.[322]

145. Many of these suggestions are mere working hypotheses and nothing systematic has ever been done to find out about these different factors. Work in this direction may lead to the discovery of better ways of protection.

Adaptation to radiation

146. Little is known about the possibilities of organisms becoming adapted to radiation; the following suggestions may however be made.

147. Increase in catalase (an enzyme destroying hydrogen peroxide and possibly neutralizing other peroxides) in algae from the Bikini area has led to the hypothesis that this might be the result of some adaptive enzymatic processes induced by the unusual amount of peroxide detectable in the sea water.[323]

148. *Selection* might be expected to lead, in certain populations of mixed species, to the predominance of the most resistant strain. Furthermore, it is quite conceivable that irradiation itself induces a mutation which increases or decreases the radiosensitivity of an originally homogeneous population of cells. However, work done on *Drosophila*[236] and yeasts[324] does not indicate that breeding in a high radiation background leads to the appearance of more resistant genes. The UV irradiation of E Coli B, on the other hand, has selected a small number of radioresistant mutants (B/r)[259] occurring in normal cultures as a result of spontaneous mutations with the rate of about 1×10^{-5} mutations per bacterium per generation; one would expect that under chronic irradiation one could select this strain to some extent.

149. Tumours have often been claimed to become radioresistant when treated with X-rays; it is however difficult at present to give any sound explanation for such a behaviour; adaptation of the cells has been given as one reason[325,326,327,329] but it is difficult to dismiss the fact that the oxygen tension may decrease as a result of pathologic changes in the blood vessels and that the polyploidy of the tumour cells may enhance their radioresistance.

150. Another possible interpretation is that tumour cells may become incapable of further cell division *in vivo*, although when cultured they can resume division. Recent experiments tend to indicate that small dosages of X-rays (25 r) to embryonic mice makes them somewhat more resistant to exposure to X-rays during their adult life; this is however true only for females, the males appearing on the contrary to be adversely affected.[328] This apparent beneficial effect of low doses of X-rays on females is compensated by the fact that the number of litters they were able to bear fell from 5 for the control to 0.5 for the 80 r group; furthermore the number of young per litter was also greatly reduced —it may therefore be the fact of not bearing offspring which is responsible for the increase in life-expectancy.[330]

151. The study of the biology of species living in regions of high natural radioactivity may lead to some information concerning this problem. However, such work, although it may lead quite rapidly to definite ideas concerning the behaviour of short lived organisms or to the identification of pathological symptoms in man, will need to be carried on over many years or decades for the reactions of humans to such conditions to be understood. The mechanism of possible changes in these populations will need to be worked out in the laboratory where genetic strains as well as experimental conditions can be accurately controlled.

152. In certain experiments, the conclusion has been drawn of the favourable effect of small doses of radiation ("biopositive influence", "stimulating effect") both from external and internal sources.[331,332,333] However, further analysis usually explains this as a consequence of pathologically shifted functional equilibrium, where one biological function, taken in isolation, may appear to be stimulated. Also, the possibility of stimulating the initial stages of plant development and growth, followed by higher crop yield, is reported with various contradictory results.[334,335,336]

Secondary effects

153. One important problem is to know whether irradiation applied to one site of a cell or organism can induce an effect in another part.

Nuclear cytoplasmic relationships at the cellular level

154. Such secondary effects can be expected on account of the close physiological relationship between the different cellular organelles. It is known that if the normal isolated nucleus of an amoeba is put into the irradiated cytoplasm of another amoeba that had previously been enucleated, mitosis is inhibited in the reconstituted amoeba at cytoplasmic dosages only three times those producing the same effect in a normal organism.[337] It has also been shown that unspecific chromosome damage can be induced in an intact frog oocyte nucleus introduced in the irradiated cytoplasm of another oocyte[338] and ultra violet irradiation of the cytoplasm of the giant unicellular *Acetabularia Mediterranea* induces very rapidly some cytochemical alterations in the nucleolus which had been shielded during irradiation (this last effect is hardly apparent in the case of X-rays).[339] However, nuclear damage to *Acetabularia* is also demonstrated if only the nucleus is irradiated. In the course of experiment on eggs of *Drosophila*, the much greater sensitivity of the nucleus when directly irradiated is evident: it takes much more energy to kill the offspring by irradiating the cytoplasm of the egg alone than by irradiating the nucleus;[340] the same holds true for attempts to induce chromosome damage by micro-irradiating other parts of the cell.[341] Primary nuclear damage appears to play a prominent role in processes where nuclear activity is important as in cell division, mutations or many lethal effects. However, this does not mean that the cytoplasm does not participate in radiation damage. In some cells where no division occurs, cytoplasmic processes may become efficiently inhibited; this is the case of non-nucleated cytoplasms of *Amoeba* and *Acetabularia* which survive for shorter periods than if they contain a nucleus;[202,342,343] In this case, the role of the nucleus could be associated with some repair processes which cannot take place as efficiently in its absence, perhaps on account of the fact that the synthesis of cytoplasmic ribonucleic acid becomes seriously impaired in cytoplasm which has been deprived of its nucleus for some time.[171]

Peroxide formation in irradiated cells

155. One of the possible agents for these secondary effects could be organic or other peroxides arising during irradiation. It has been found that bone marrow cells incubated *in vitro* produce peroxides when the cells originate from an irradiated rabbit.[344] The significance of this finding is difficult to understand on account of the fact that many tissues (although not bone marrow) from non-irradiated rabbits also produce peroxides *in vitro*. Not much is known of the effects these peroxides might have on other cellular populations. It has, however, been demonstrated that many lysogenic bacteria show a diminished response when put in the presence of catalase (catalase reactivation after U.V. and X irradiation).[345] Another argument for the formation of peroxides in irradiated organisms is that even with small dosages (17,000 r) to yeasts grown in anaerobiosis, these organisms synthesize catalase or peroxidase when kept in

anaerobiosis, a condition during which they normally only have traces of the enzymes.[346] The synthesis of new enzymes is believed to be induced by peroxides formed during irradiation.

156. Radiation is also capable of inducing the formation of peroxides outside the cells, and irradiation by X or U.V. rays of organic culture media is mutagenic for the bacteria which are cultured afterwards; the effect can be prevented by catalase.[347]

Multicellular organisms

157. It has been found repeatedly that the *nucleic acid metabolism* of a carcinoma is temporarily decreased as a result of irradiation of the animal bearing it, although it had been completely shielded during the irradiation.[348,349] It has also been demonstrated that tumours originating from non-irradiated thymus cells can develop if these cells are grafted on a totally irradiated host whose thymus had previously been removed;[350] damage (by radiation or other means) or removal of the thyroid may lead to pituitary cancer.[351] No final explanation of effects of this type can be given; the first mentioned could be due to diffusible organic peroxides produced during irradiation and very small quantities of peroxides have been found in irradiated mice.[352]

158. On the other hand, normal regulatory processes located in the irradiated part of the animal can certainly be affected: hormonal effects, which are dealt with in chapter V, must be considered.[353] Stimulation of the pituitary as a result of thyroid disfunction is probably the cause of the pituitary tumour mentioned above (paragraph 157). *The exact relationships between hormones and biochemical processes in normal organisms should be known to understand many effects of radiation in the mammal.*

VII. Alterations of radiation effects by foreign agents

Protection

159. *Protecting agents* are those whose *presence during irradiation* decreases the response of an organism to radiation. Many experiments reported earlier (paragraphs 38, 42 to 47) constitute a basis for finding chemicals capable of protecting living organisms against radiations. However, our ideas on the mechanisms of protection *in vivo* are often conflicting, for the simple reason that the fundamental processes of radiobiology are not understood.

160. The idea of protecting organisms against radiations arose about a decade ago, as a result of the discovery of the indirect nature of radiation effects on dilute solutions. However, as stated earlier, it is very much doubted at present whether effects of radiation on organisms necessarily occur through indirect mechanisms. It can furthermore be expected that the relative contribution of direct and indirect mechanisms will vary for different biological effects and in each case the possibility of protection may thus be different.[355,356,358]

161. There are many possible ways by which radiation damage might be diminished: (*a*) loading the organism with chemicals capable of reacting with H^0, OH^0, and O_2H^0 radicals may divert these from reacting with important cellular constituents; (*b*) protecting agents could also act by covering the sensitive site of cell constituents, and this type of mechanism could be operative both for direct and indirect effects;[357] (ch) all agents capable of decreasing the intracellular oxygen tension can be expected to afford protection against direct or indirect effects which are oxygen dependent;[354] (*d*) finally, a protector might conceivably give more chemical stability to a macromolecule and favour the rejoining of broken bonds or divert energy from it. It is, however, at present very difficult to choose between any of these possibilities.

162. Very many experiments have been performed, very many chemicals have been tested and many effects have been found susceptible of a certain amount of protection.

163. The *survival* of unicellular and multicellular organisms have been quite considerably increased by the use of various agents. *SH* and *amino reagents* (cysteine, cysteamine or cystamine, glutathione) or the methyl derivative, methionine, as well as thiourea have been used successfully on micro-organisms and mammals.[355,356,358] Very similar possibilities have been found with S-2-aminoethylisothiuronium . Br . HBr (AET)[118] which is less toxic and may thus be used in many mammals, including monkeys and dogs.[359] As far as is known, there have been no attempts to use this compound in man. Further analysis has shown that at neutral pH a rearrangement of the AET to guanidine form occurred, so that the effective compound was 2-mercaptoethylguanidine hydrobromide (MEG).[360]

164. These protecting agents appear to have greater efficiency in promoting recovery processes rather than in preventing the initial damage observed: this is most striking in the case of the white blood cells and of the metabolism of spleen nucleic acid which seem to follow a similar pattern of response.[361]

165. The *number of chromosome aberrations*[161,362,367,368,369] and in some instances the *number of mutations*[118] have also been reduced when similar protective agents were used during irradiation. Successful experiments on plant cells have been reported, but cysteine does not reduce chromosome aberrations in mouse thymus,[363] although nucleic acid integrity does appear to be protected by thiourea or cysteamine[366] in the same organ. In *Drosophila*, however, and in micro-organisms, mutations have not so far responded to the protective action of cysteine or cysteamine.[364] In micro-organisms a protective action probably exists, but it is often difficult to interpret the experiments because increased survival as a result of protection could lead to an enhanced opportunity for a mutation to become expressed.[118]

166. These agents have in common the properties of having an amino-group and a sulfur atom (which often is in the form of a sulfhydryl group) and both these are believed to be important.[370] However, they can act independently because many amines are also found to be satisfactory protectors in the absence of a sulfhydryl, and a sulfhydryl group alone may be efficient in some instances.[370,371,372] It has often been suggested that the sulfhydryl group decreases the intra-cellular oxygen tension and this has been found to be the case in few living systems protected with cysteine or cysteamine.[129]

167. Many other agents have been used with a varying degree of success and the mechanism of action of some of these does seem to be dependent on the decrease of cellular oxygen, as in the case of the protection of micro-organisms with hydrosulfite.[20] A certain number of natural metabolites (succinate, glucose, alcohol) have protecting properties in a few instances, probably by consuming the cellular oxygen in the course of their

normal enzymatic oxidation.[118] Anoxia can also be obtained with a certain number of drugs like morphine which depress the respiratory centres: in that case a protecting effect is also found.[373] Cyanide, a strong inhibitor of respiratory enzymes, has been found to be an efficient protector of mice, although it would tend to increase the intracellular tension of oxygen.[374] On the other hand, seeds irradiated in its presence show a greater mutation rate when it is used in low concentrations, but a smaller one when the concentration is increased.[375] However, in these conditions an increased number of chromosome breakages is observed.[376]

168. It is not clear at present to what extent the protection is complete, because although damage is not lethal it may well be present and only become apparent at a later stage. It has been shown that rats, protected during irradiation, develop a large number of tumours;[377,378,379,380] these might have developed in the non-protected animals had they lived, as in the case of mutations in micro-organisms; and it is difficult to know if the primary events of induction of cancer have or have not been diminished. Nothing much is known on the protection against other late damage or against the early aging of irradiated organisms.

169. Protecting agents are much less efficient in the case of alpha rays or neutrons.[381,382] As was seen (paragraph 37) in these cases reduction of the oxygen tension is not expected to have any effect.

Sensitization

170. Radiosensitizing agents have been used in cancer therapy, but the fundamental aspects of sensitization are certainly much less known than in those in the case of protection. There are a few instances of enhanced reactions to irradiation in the course of *in vitro* experiments,[383] but these are not at present susceptible to application *in vivo*. It has, for instance, been shown that the oxidation of ferrous sulfate by X-rays is enhanced in the presence of various alcohols or of benzene.

171. As a result of the systematic study of many chemicals, it has been found that *synkavit*,[384] a derivative of vitamin K, increases the radiation induced mitotic inhibition in chick fibroblasts cultured *in vitro;* this effect was carried on in the absence of synkavit for several generations; and if rats are treated with the compound before irradiation their mortality is increased. Synkavit is also capable of increasing the permanent regression after irradiation of experimental tumours in the rat or of cancer in man. All that is known about the mechanism of action of this agent is that it becomes concentrated in the tumour as compared to the other tissues and that in tissue cultures its effect can be abolished by guanosine; this may indicate some interference with nucleic acid metabolism. If one increases the oxygen tension of tumours where it is usually low, one increases their radiosensitivity, a finding which has proved to be useful in cancer therapy.[385]

172. It is not known to what extent natural radiosensitizers might accumulate during certain steps of normal metabolic processes and thus alter the radiosensitivity.

Recovery

173. When organisms are irradiated, many processes, inhibited at first, recover. The synthesis of desoxyribonucleic acid is often decreased immediately after irradiation, but only temporarily; other biochemical effects which appear later are also temporary and display apparent recovery. In irradiated mammals, bone marrow and gonads can recover at the expense of the surviving cells which multiply and repopulate these organs, but permanent damage, leading for instance to more rapid aging, to an increased radiosensitivity or to the development of cancer, may have been established.

174. The lapse of time existing between irradiation and the biological expression of the primary damage, gives an opportunity of preventing the development of the lesion or of enhancing the spontaneous recovery processes.

175. *Recovery agents* are those which are effective when given *after irradiation*. Various methods for promoting the recovery of irradiated organisms have been described and can roughly be classified into two groups:

176. (*a*) *Those whose object is to destroy some intermediate compound* before the damage is definitively established: as in the *photorestoration* of a great number of effects of ultra-violet light,[386,388] the *catalase restoration* of lysogenic bacteria treated with ultra-violet light[340] or, in one instance, the effects of X-rays.[387] The first of these processes, in the case of ultra-violet irradiated bacteriophage is only possible if illumination takes place in the presence of extracts of normal bacteria; the second appears to lead to the destruction of organic peroxides formed during irradiation.

177. Restoration achieved in some instances by cooling or heating the irradiated cells[388] may inhibit the expression of injury before it is definitively established but none of these mechanisms is properly understood.

178. (*b*) *Those whose object is to replace a damaged compound or cell.* The provision of nutrients to micro-organisms which have lost the capacity of synthesizing them could be considered as one possible mechanism of recovery; recovery is however only apparent, because the fundamental damage has not been removed.

179. True recovery would depend on the possibility of replacing the damaged molecules or cells by non-irradiated ones. Experiments on bacterial transformations or on genetic recombinations in micro-organisms have shown that it is possible to control some alteration of their genetic characters. The mechanisms of the greater radioresistance of diploid compared with haploid cells may well have their origin in closely related mechanisms. On these grounds, the use of intact desoxyribonucleic acid to replace the irradiated compound inside the chromosome becomes a possibility. One successful experiment of saving ultra-violet irradiated Salmonella with intact DNA has been reported.[389]

180. It is possible to replace whole cell populations of irradiated animals and thus promote their survival; this can be done by injecting intact bone marrow from a non-irradiated donor into the circulation of a lethally irradiated one. This type of experiment was at first performed as a consequence of the demonstration that the death incidence of mice was considerably decreased when hematopoietic organs (like bone marrow of the hind limb, spleen or liver) are shielded during irradiation. Bone marrow injections have since proved to be successful in dogs, hamsters, monkeys.[391] Only tissues containing cells capable of forming granulocytes (mostly polymorphonuclear white blood cells), red blood cells or platelets are capable of this activity. These cellular suspensions are effective in preventing acute death from X or γ rays but apparently death caused by neutrons is much more difficult to prevent.[390,391,392,393]

181. As a result of injected bone marrow, the blood cells and platelets tend to reach normal values again, the weight of the body, of the thymus and spleen increases and immunological defence which had disappeared also becomes functional again. However, many of the lesions caused by radiation are not diminished after bone marrow injection: the greying of hair is not influenced and the fertility of gametes is not restored,[395] tumours develop with greater frequency in protected or parabiotic animals[396,397,398] and the normal life-expectancy of the animal remains decreased.[394] All these facts seem to demonstrate that only acute death has been prevented by the graft.

182. Important immunological problems are brought up by such experiments as they were in the case of the first blood transfusions: it is well known that mammals are only able to accept definitively grafts from subjects belonging to the same genetic strains (isologous grafts). For instance, one has known for a long time that grafts from one human being to another (homologous grafts) are usually eliminated rather rapidly, as in the case of skin grafts; this is also the case when grafts are made between different species of animals like rats and mice (heterologous grafts). This incompatibility originates from the fact that mammals possess immunological defence mechanisms which make them synthesize new antibodies to any foreign protein entering their blood circulation. However, it has been found that the immunological response of mammals is strongly inhibited in the days following total body irradiation, and in these circumstances both homologous grafts (from other strains of mice) and heterologous grafts (from rats) of bone marrow are capable of saving lethally irradiated mice. Cells of the donor animal have been characterized in the receptor animal by specific genetical or immunological identification;[390,399] and the repopulation of the myeloid and of the lymphoid tissue has been demonstrated. In the case of heterologous grafting of thymus tissue from rats into irradiated mice, the cells appear at first to be exclusively of rat origin but the later appearance of an agglutination reaction with specific mouse antisera indicates that thymus cells of mouse origin may be recovering.[400]

183. The survival of the animals injected with bone marrow becomes, however, dangerously compromised after a certain time, because, whether homologous or heterologous grafts are used, the incompatibility between these and the cells from the receptor animals reappears. The discussion has arisen as to whether the recovered cells from the irradiated organisms are again able to synthesize antibodies against the injected cells or whether these are making antibodies against the cells of the irradiated host.[401,402]

184. There have been recent attempts to stimulate bone marrow regeneration. It has been shown that alkoxyglycerols obtained from bone marrow, as well as some of their derivates, stimulate the white blood cells counts of patients irradiated for therapeutic purposes; this increase seems to concern the neutrophil polymorphonuclears and has also a beneficial effect on the platelet count.[403] It has also been found that the bactericidal properties of the blood serum were diminished in irradiated rats; this could be due to a loss of properdin, presumably a natural non-specific antibody. Treatment of these animals with a fraction from serum rich in properdin appears to increase the survival.[404,405]

185. Experiments on cell transfer have been made in attempts to replace leukemic cells, which can be destroyed by high dosages of irradiation, by normal marrow tissue with the hope of preventing further development of leukemia. Experiments performed on mice have shown that such a treatment is capable of increasing considerably the survival time of experimental leukemic mice.[406] One such attempt is now being made in a case of human leukemia.

186. The multiplication of donor cells in the irradiated host has unquestionably been established; however, this does not necessarily exclude a possible effect of subcellular fractions. The idea of the possible recovery capacity of bone marrow or spleen nucleoproteins was put forward a few years ago but was later abandoned on the ground that a small number of intact cells were present in the fractions injected.[407] It is, however, not possible at present to exclude the possibility that sub-cellular fractions do play a role in these recovery phenomena and, on account of the tremendous importance of proving or disproving this hypothesis, both for fundamental and applied purposes, work on the biological activity of nucleoproteins in normal or irradiated mammals is of great interest and should certainly be very actively pursued.

187. It will probably become possible to enhance similar recovery processes in human beings, but this *will* certainly require a much better understanding of immunological processes and of interactions between cellular populations before it becomes a reality.

VIII. Conclusions

188. Radiobiology has certainly made great headway within the last fifteen years. It has had, like cancer research, strong governmental support in many countries, and both these aspects of medicine have the common feature that *many* cellular mechanisms appear to be simultaneously concerned. This is why effects of radiation are as diverse as are cellular functions. The visible damage will probably depend on which particular mechanism is most sensitive at the time of irradiation, on its relative importance to the over-all economy of the cell and on the possible interference of other less damaged processes. Mutations, carcinogenesis, and the inhibition of mitotic activities, of cellular differentiation and of immunological processes, to name but a few examples of radiation damage, affect extremely complex cellular mechanisms, which, despite the efforts of many able scientists, remain one of the most provocative challenges. It thus becomes vital, if effects of radiation are to be understood and possibly prevented, that the functioning of normal cells and the organization of cellular populations be known. Radiobiology is not a science in itself; it is but an applied science and it rests entirely on our knowledge of the great principles of biology which cannot be studied independently of one another. The understanding of some aspects may at times progress more rapidly than that of others, but in the long run all these have to be integrated into one harmonious picture. The problem is not merely to push forward the study of genetics or of carcinogenesis, because it is obvious that these problems are dependent on most other aspects of cell physiology. Our ignorance of fundamental biology (taken in its widest possible sense) is undoubtedly the major factor limiting our understanding of radiation effects on man.

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Annex G

MAMMALIAN SOMATIC EFFECTS

TABLE OF CONTENTS

I. Shortening of the life-span in experimental animals

The experimental effect of single doses on short-term survival

1. The short and long-term effects of whole-body exposure to a single dose of radiation have been studied in a variety of mammals. When "survival time" (duration of life after exposure) is studied as a function of radiation dose, the results with all species have shown fundamental similarities that may be illustrated here with the data of a hypothetical experiment.

2. The plan and results of the hypothetical experiment are shown in table I and figure 1. The animals were young adult males, 100 days old on irradiation. They were of a species with a relatively short life span of 2½ years. Slightly different results would be obtained with females. Greater effects per unit of radiation dose would be obtained with immature animals or with sick animals.

3. The mortality-time curve (figure 1) illustrates three major periods:

(*a*) The acute period lasting about one month, for which the LD_{50} is 600 rem;

(*b*) The intermediate period whose duration of 1.5-2 years depends on the radiation dose, and during which practically no deaths occur;

(*c*) The terminal period during which the population dies out rapidly.

4. Long-term somatic effects develop during the intermediate period and some of them become "limiting factors" for survival in the terminal period. The complete quietude of the intermediate period indicated in figure 1 is therefore misleading—the intermediate period is, in fact, a period of increasing morbidity. The rate of increase may be slow or fast, depending on the radiation dose and also on various biological factors, many of which are predetermined genetically.

5. The long-term decrease in life-span, illustrated in figure 1, is dealt with quantitatively in the sixth column ("Days") of table I. The decrease is not proportional to the acute mortality (column 4). The decrease can also be expressed as a percentage of the normal life span (column 7), which in the present experiment was 900 days. It is useful to express life-shortening in per cent of normal life span for purposes of comparing results of experiments involving species that differ in life-span.

Table I. Hypothetical experiment

The animals (males, 100 days old) received a single whole-body exposure on experiment-day 0. The table records the doses given to the various groups, and the resulting changes in their median life-spans.

Group	Radiation dose rem	Number of live animals		Median survival time of animals alive on day 30 days	Long-term decrease in life-span	
		Day 0	Day 30		Days[a]	Per cent of control[b]
1.....	0	100	100	800	—	—
2.....	300	100	100	710	90	10
3.....	500	100	82	650	150	17
4.....	600	100	50	600	200	21
5.....	700	100	11	530	270	30
6.....	800	100	0	—	—	—

[a] The difference between the datum for group 1 (800 days) and the data for other groups in column 5 (median survival time).
[b] The life span of the controls (group 1) was 900 days.

6. The dependence of biological effect on radiation dose is illustrated in figure 2. In the case of acute mortality (deaths within thirty days of exposure calculated from table I, column 4), the dose-effect curve shows a threshold—the first deaths occur somewhere between 300 and 500 rem. In the case of the long-term decrease in life-span (per cent of normal life-span) the course of the curve as drawn does not show a threshold and indicates that even at the smallest radiation doses there is some decrease in life-span (see paragraph 11).

7. Biological effects not only depend on radiation dose but also on dose rate. In the hypothetical experiment, the animals received a single dose at 50 rem/min. The same results would have been obtained with dose rates of 5 or 500 rem/min. Below 5 rem/min., however, the effect per unit dose diminishes. In the case of acute mortality, it does so relatively rapidly. It may do so quite differently in the case of the various kinds of late injuries, including those shortening the life-span.

The acute LD_{50}

8. Recent determinations of the acute LD_{50} (single, whole-body exposure) for mature mammals are given in table II. Values for immature and senescent animals would be lower than those tabulated. It has been pointed

Table II. Acute x- and gamma-ray LD_{50} of mature mammals[a]

Species	LD_{50} (rads)	Number of determinations
Swine.....	190–310	4
Goat.....	240	1
Dog.....	240–320	6
Man.....	300 (?)	0
Guinea pig.....	380–490	3
Monkey.....	520	1
Mouse.....	520–670	7
Hamster.....	590–800	3
Rabbit.....	680–750	3
Rat.....	790–820	2

[a] The original reports are listed in reference 1. All doses are estimates for the middle-longitudinal axis of the animal under conditions of approximately homogeneous soft tissue dose distribution. The dose rates ranged from 5–60 rads/min. The LD_{50} is that dose killing half the animals within 30 days of exposure. Almost all of the deaths occur within three weeks.

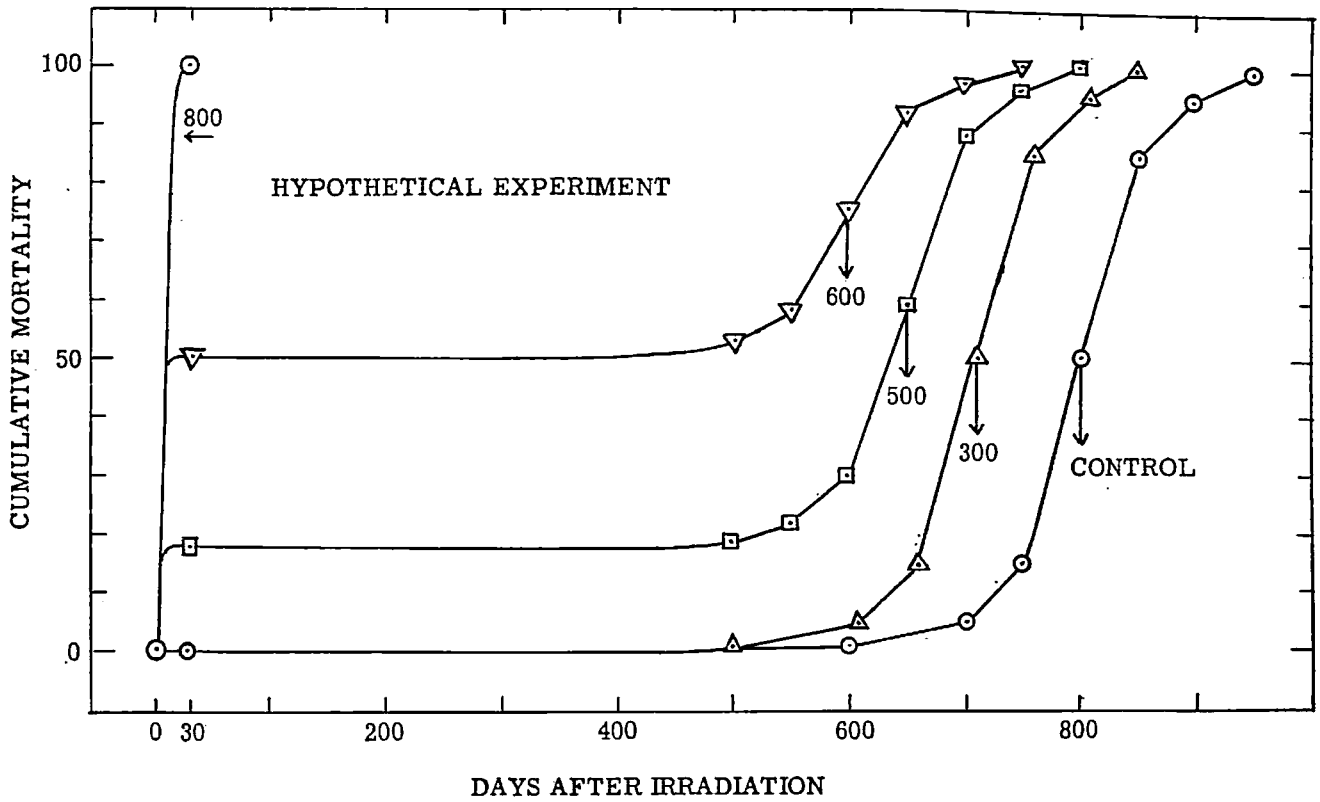

Figure 1. Hypothetical experiment–Cumulative mortality after a single whole-body exposure. The dose in rem is specified for each curve.

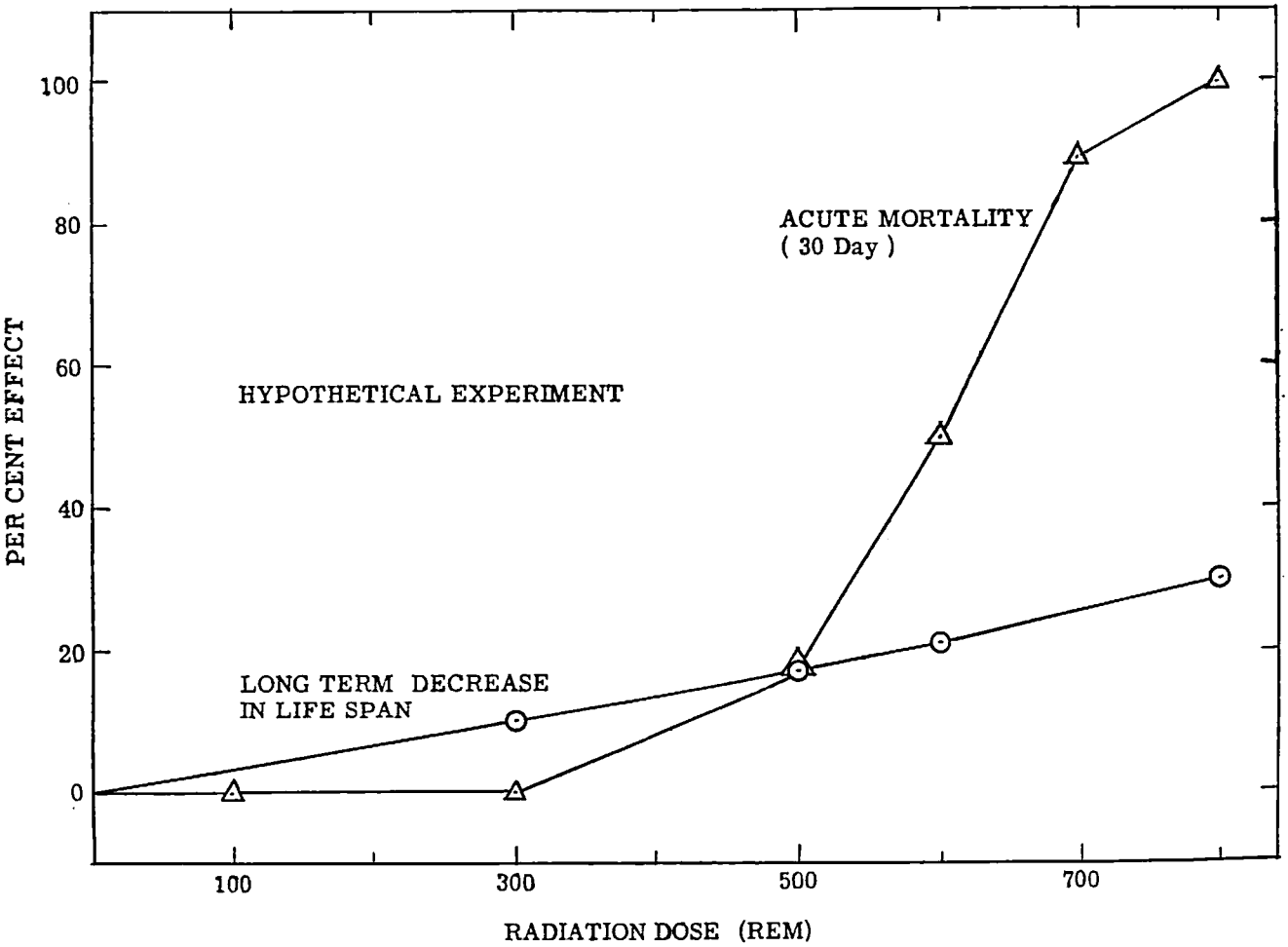

Figure 2. Hypothetical experiment–Effect as a function of dose. Acute mortality shows a threshold whereas long term decrease in life-span does not.

out[1] that the values fall into two groups. Those for the "larger" mammals are in the range 200-300 rem; those for the "smaller" mammals are in the range 400-800 rem. The only monkey listed (M. mulatta) falls into the "small" animal class. The estimate for man is close to the determinations for the guinea pig and dog, suggesting that studies with these species may be of special importance. It is to be noted, however, that the figure for man is speculative.

Acute effects in single organs

9. A very great number of somatic effects have been described that occur within hours, days, or several weeks of irradiation. Doses as low as 5 rem, for example, have a measurable although brief effect on the mitotic index of the skin of mice.[2] In the range from approximately 25 to 200 rem, simple *quantitative* relations between somatic effect and radiation dose have been demonstrated in such organs as the lymph node, spleen, thymus, testis, and intestine,[3] using both microscopic and gross methods of examination (e.g., weighing). In these examples, restitution occurs relatively quickly, during the course of some days or weeks, and often seems complete.

Recovery from whole-body exposure

10. When two or more exposures instead of one are employed, some restitution occurs during the interval(s) between them. One method to study the rate of restitution is to give a non-lethal dose on day 0 and to determine the LD_{50} on various days thereafter. Suppose that the LD_{50} of unirradiated animals is 600 rem. Furthermore, suppose that after 300 rem on day 0 the LD_{50} is:

(*a*) 300 rem on day 1;
(*b*) 450 rem on day 2;
(*c*) 600 rem on day 8;
(*d*) 600 rem on day 20.

It may be concluded therefore that acute recovery from 300 rem was complete by day 8, since by then the LD_{50} had returned to "normal", and half-complete by day 2. Experiments of this type (table III) have shown that the rate of recovery depends on genetic factors, and therefore varies with the strain and species of animal.[4] The rate also depends on the magnitude of the dose—large doses may, so to speak, inhibit the recovery process *per se*.

TABLE III. TIME FOR 50 PER CENT RECOVERY FROM A SINGLE WHOLE-BODY EXPOSURE TO X-RAYS[a]

Animal	*Number of strains*	*X-ray dose (rem)*	*50 per cent recovery time (days)*
Mouse			
Young	1	260	7.4
Adult	6	200–400	1.6–3.0
Adult	1	600	12.0
Rat	2	310	4.9 and 8.5
Hamster	1	320	6.1
Monkey (M. mulatta)	1	260	4.8

[a] Recovery measured under the particular conditions described in paragraph 10. The original reports are listed in reference 4.

The experimental effect of single doses on long-term survival

11. Data on life-shortening in mice and rats after a single whole-body exposure to X- or gamma-rays at the time of puberty or young adulthood are summarized in figure 3.[5] The radiation dose is expressed as a percentage of the acute LD_{50}, e.g., a dose of 300 rem is called 50 per cent if the acute LD_{50} is 600 rem. In the various experiments, the LD_{50} (in r) varied from 500 to 800 r. The curve fitted to the points in figure 3 is on the assumption that life-shortening is directly proportional to dose. For mice and rats it appears that life is shortened by about 10 per cent following a "25 per cent dose". The curve drawn through the points in figure 3 runs straight to the origin, indicating that radiation decreases the life-span no matter how small the dose may be. It is to be noted that the figure only suggests this conclusion, but does not prove it.

12. The data in figure 3 are based on exposure in youth or early adulthood. Comparable data for exposure during middle age or old age are not available.

13. It is known from clinical as well as laboratory evidence that partial-body exposure decreases the life-span much less than whole-body exposure (when the effects of roughly similar doses in rads are compared). There is a paucity of information, however, concerning the quantitative dependence of the life-span on (*a*) the region or organ irradiated and (*b*) the absorbed dose. The data from an experiment of this type are given in table IV.[6] More information of this kind is needed.

TABLE IV. DECREASE IN LIFE-SPAN—PARTIAL AND WHOLE-BODY X-RAY EXPOSURE COMPARED IN THE MOUSE[a]

Region exposed	*Dose (rem)*	*Median survival time after exposure (days)*	*Significantly different from control ($P \leq .05$)*
Control	0	676	—
Entire animal	530	582	Yes
Entire chest	720	646	No
One-half chest	570	654	No
and caudal	1140	591	Yes
2cm. of trunk	1700	525	Yes

[a] Female mice, 170 days old when irradiated. With the doses employed there were no acute deaths. Data from reference 6.

The experimental effect of chronic exposure on long-term survival

14. The experimental literature on the shortening of life by chronic exposure to radiation, and its bearing on the maximum permissible dose for man, are discussed in the article by R. H. Mole,[7] presented in its entirety following paragraph 15. Among other details, the report considers whether a threshold dose exists below which the life-span is unaffected. The report finds the evidence equivocal. A significant conclusion might be established for animals if very great numbers of them were used in such experiments. The report points out, however, that even if such a conclusion were established, its application to the human case would require a theoretical basis to justify such an extrapolation. Such justification is lacking at present.

15. Of the experimental groups referred to in paragraph 14, two (mouse, guinea pig) that received less than 1 rem per week lived a greater total number of days than their respective controls. In a more recent experiment[8] with Sprague-Dawley male rats exposed throughout

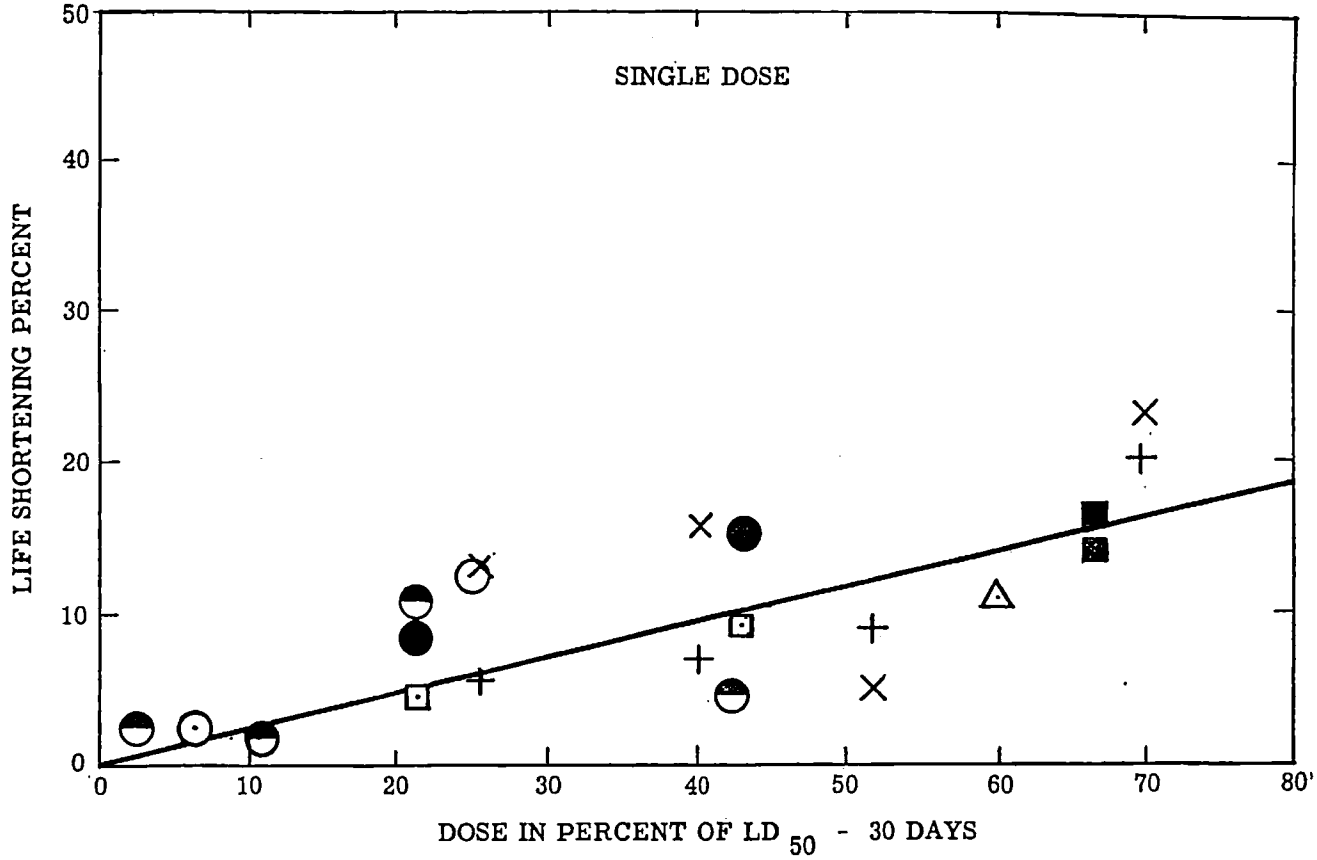

Figure 3. Life shortening (percentage) in mice and rats after a single, whole-body exposure to X- or gamma-rays. The dose is expressed as a percentage of the acute LD_{50}. The figure is taken from reference 5 where the original reports are listed.

adult life to 0.8 r/day of Co^{60} gamma-rays, the median survival times were as follows:

Temperature of environment	*Survival time (days)*	
	Control	*Irradiated*
5° C.....	240	305
25° C.....	460	600

Although there were only twenty-two animals per group, the differences between the irradiated and control groups were consistent throughout the course of the experiment.

Shortening of life by chronic irradiation: the experimental facts* by R. H. Mole

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It is probably true to say that more is known of the biological effects of radiation than of any other environmental hazard except bacteria. Certainly the chronic toxicity of no chemical substance has been investigated as thoroughly as the chronic toxicity of whole-body irradiation by penetrating gamma-rays or fast neutrons. The incentive has been obvious: the very large industrial hazard during the war-time development of the atom bomb, and afterwards the increasingly widespread risk associated with the remarkable development of atomic energy as a source of industrial power and of a unique series of military weapons. Chronic toxicity experiments in the strict sense must cover the whole life-span of the experimental animal and thus take years to carry out, even with the relatively short-lived laboratory mouse. The results of war-time work in the United States have become generally accessible in the past few years[1-5] and work carried out in this laboratory is just beginning to be published.[6] A brief survey of the experimental results relating to shortening of the life-span may provide a few facts in a field of current general interest and perhaps raise the academic question of how the results of chronic toxicity experiments, as such, may be generalized—a question which needs an answer before they may be used to help solve the practical problem of setting safe limits to the environmental exposure of man to irradiation.

Experimental methods

Daily irradiation has been given to animals in a variety of ways, for details of which the original reports should be consulted.[1-7] The more important experimental features are summarized in table I. There are two important differences between the experimental arrangements of Henshaw *et al.*[3] and Evans[2] on one hand, and those of Lorenz *et al.*[4] and of this laboratory on the other. In the first two sets of experiments, the animals had to be transferred individually each day from their living cages to the irradiation boxes and back again, and each daily dose of radiation was given in a few minutes. In the second two sets of experiments, the animals were irradiated in their living cages, undisturbed by additional handling with its accompanying traumatic effects, and the daily dose of radiation was spread over 8-24 hours. In general, the experimental animals were examined

* UN document A/AC.82/G/R.115; also published in Nature *180*, 456-460, 1957. For table 1, figures 1 and 2, and bibliography referred to in this article, see immediately following the article.

daily and the time of death noted. Post-mortem examinations to determine tumour incidence and the cause of death were usually made, but the experimental reports differ very greatly in the detail with which these findings are given. For this reason, and since shortening of life-span is often considered the most sensitive experimental index of the toxicity of chronic irradiation, survival-time is the only experimental end-point considered here.

Results and their interpretation

By chronic irradiation is meant daily irradiation five, six or seven days a week at dose-levels which allow survival for at least six months. All the experiments on chronic irradiation for the duration of life which have ever been carried out, so far as is known, are referred to in table I and, where possible, shown in figure 1. The duration of life of an irradiated group of animals has been expressed as a proportion of its corresponding control and plotted against the weekly dose of radiation on a logarithmic scale. The results from this laboratory are shown in black symbols. They provide the first direct experimental comparison between gamma-rays and fast neutrons for chronic irradiation, where the dose of fast neutrons was measured in terms of energy absorbed in tissue. The relative biological efficiency factor for the fast neutrons used as compared with cobalt gamma-rays was 13.

This factor has been applied to the other two fast-neutron experiments, where the fast-neutron dose was measured in arbitrary units and where a somewhat uncertain conversion factor (table I) has to be used for estimating the tissue dose. In this way the results of all the experiments with fast neutrons as well as those with gamma-rays from other laboratories have been plotted, using open symbols, together with our own results in figure 1. The agreement, when mice were used as experimental animals, is remarkable, and suggests, in spite of the various uncertainties in the comparisons, that chronic irradiation shortens the life of mice in a reproducible manner.

It should be noted that there are eight experimental points at weekly doses of less than 10 r. or its equivalent in neutrons, and that the duration of life in none of these experimental groups was significantly different ($P \geq 0.05$) from its control.

The experimental results have been put down as they were obtained. More sophisticated analyses of some of these results have been made elsewhere.[1,5,6,9,10] The purpose of such analyses has usually been to find some regularity in the results which would allow extrapolations to daily doses smaller than, and to species other than, those used experimentally.

Curve fitting

Three curves have been fitted to the mouse data and are shown in figure 1.

(1) The straight line which provided the relative biological efficiency factor of 13 from our second experiment (Neary *et al.*, II, table I) is clearly a good fit to its results, and is also reasonably close to the only experimental group in our first experiment with a markedly decreased survival-time. The simplest interpretation of such a linear relation is that there is a threshold of between 1 and 2 r. daily below which no shortening of a mouse's life will be produced by daily irradiation. This may be considered confirmed by the repeated experimental failure to find a demonstrable shortening at weekly doses of less than 10 r. (see above). Considering the nature of the data, it would be difficult to have a clearer experimental demonstration of the existence of a threshold.

(2) The biologist, almost as a reflex, attempts to fit a Gaussian curve to quantitative data. Such a curve is shown as a dashed line in figure 1, and clearly fits all the experimental data very well. The meaning of the fit at weekly doses of less than 10 r., where none of the points differs significantly from the base line, is less clear.

(3) Boche (1946, 1954)[1] suggested that shortening of life-span was proportional to the total accumulated dose,

$$t - t_0 = kdt$$

where t and t_0 were the mean life-spans of irradiated and control animals, d was the daily dose of radiation and k was a constant. This curve ($k = -0.04$ for gamma-rays) is shown in figure 1 as a dotted line, which also fits all the experimental points very well.

Curves 1 and 2 are empirical; curve 3 has some claim to a theoretical basis, the idea that the bigger the total dose of radiation the bigger the effect, that is, the shorter the mean life-span. For daily exposures which kill in less than six months, however, the converse is found to be true.[4,9,11] This is not as paradoxical as it may seem, once the importance of recovery processes is appreciated; but it makes data on the effects of high daily doses (on shortening of life by much more than 50 per cent) of little value in helping to decide which is the best of several curves, each purporting to describe the effects of low daily doses.

Curves 2 and 3 are clearly so close together that over the experimentally determined range they cannot be distinguished. (The possibility that this algebraic similarity has a much wider biological significance is being investigated.) Each curve appears to fit all the points better than the straight line of curve 1, but this may be a spurious consequence of experimental uncertainties. In two experiments the exact conversion factor from arbitrary units of fast neutrons to rads is unkown (see above) and factors numerically different from those used (table I) but just as plausible (see literature) would make the fit look less good. There seems to be no intrinsic reason why different mouse strains *should* behave identically, and the curvilinear arrangement of the experimental points may merely reflect differences of strain and of dose.

Each of the second two formulations indicates that there is no absolute threshold for shortening of life by chronic irradiation. The apparent threshold suggested by curve 1 may be thought of either as an absolute or as an effective threshold, depending on whether shortening of life is considered in proportional or absolute terms. If time is necessary for the effects of daily irradiation to show themselves, and if this time is longer the lower the daily dose, then an effective threshold *must* be reached at a dose-level which takes longer than the life-span to produce its effect. If so, each species would be expected to have its own threshold, and the longer the natural life-span the lower this would be. The only relevant experimental data are those of Lorenz *et al.*[4] on chronic irradiation of guinea pigs and these are included in figure 1. The effect of 1.1 r daily was possibly greater than in mice (though still not significantly different from its control) and the apparent threshold possibly a little less. The difference in life-span between mice and guinea pigs is probably not large enough to decide the point, and in an event there are no confirmatory data for guinea pigs as there are for mice.

The data for guinea pigs do show that species differences occur. Boche[1] suggested on, admittedly tenuous evidence, that the constant k (curve 3) is αt_0, where α is the same for all mammals. If this were true, the mouse data should not agree so well, since t_0 for the different mouse strains differed. If the mean mouse t_0 is 600 days, $\alpha = 7 \times 10^{-5}$ (rather different from Boche's own estimate), and this has been used to construct the theoretical curve for guinea pigs ($\alpha t_0 = -0.09$ curve 3, figure 1); the fit to the experimental points is poor.

Nature of the experimental material

In any event, too much should not be read into the results because of the nature of the experimental material. First, the results have all been expressed in terms of mean survival-times. This is really a rather unsatisfactory parameter to use, as may be seen from figure 2, which illustrates the shape of the mortality curve of normal control female CBA mice. The shape of the human mortality curve in the more materially advanced human civilizations is similar, but that of mice with a high spontaneous incidence of leukemia may be very different.[4,12] The mean survival-time and its statistics are markedly affected by the occasional early deaths and no great precision in mean survival-time can be expected. A small decrease in mean survival-time could occur either because of a small increase in the frequency of earlier deaths or because of a small reduction in life-span of the upper two quartiles. In fact, an analysis of cause of death in relation to duration of life is imperative in order to see whether irradiation decreases life-span by increasing the frequency of particular causes of death which kill earlier than the average, or merely by making all causes of death kill at an earlier age.[6]

Second, the nature of a chronic toxicity experiment usually, if not invariably, makes it impossible to randomize treatments and to ensure that the only difference between experimental groups is the treatment being investigated. For example, if animals are arranged at different distances from a source of radiation, the animals will occupy different parts of a room for their whole lives and it will be impossible to be sure that environmental temperature, humidity, degree of air movement and other relevant factors possibly not even thought of are exactly the same for each different dose-group. Thus the differences in, say, mean survival-time between different groups, will be due to the differences in radiation-level plus any other relevant environmental differences. This is not just a theoretical point. Differences of the order of 5 per cent in the mean survival-time of female CBA mice have been found during the past few years not only between different "lots" of controls but also between two sets of randomly chosen controls kept, so far as could be, in the same environment but some 20 feet away from each other.[6] The apparent increase in survival-time at the lowest daily dose used by Lorenz *et al.*[4] (figure 1) may well be due to the fact that the animals at this dose-level were kept without air conditioning in a different room from all the other groups, including the controls. Such variability is to be expected by the biologist, but it should also enjoy caution in extrapolation of the results of analysis of intrinsically inexact data.

Replication on a sufficiently large scale, though often completely impractical, could overcome this particular difficulty. In fact, however, replication is almost completely lacking from the experiments listed in table I. The logic of experimentation is that experiments are repeated and give the same result. Yet with the exception of a still unfinished investigation,[10] no one concerned with duration-of-life irradiation experiments has ever repeated his experiment even once—for which there are perhaps understandable reasons. The nearest to repetition so far has been the two experiments carried out in this laboratory,[6,13] where although the same mouse strain was used the radiation doses were different. From this point of view the value of figure 1 is to demonstrate that an experiment has been done, that is, that the same result has been obtained several times over.

Lastly, it should be pointed out that in all the experiments considered here irradiation has been for the duration of life. This may not be the most appropriate experiment to carry out. Recent,[6,14,15] as well as older,[4,16] evidence has shown that, in some circumstances at least, not all radiation is of equal value, the first of a series of daily doses having proportionately greater effects in shortening life and inducing leukemia than the later daily doses. This is presumably one aspect of the time factor; time is needed for the effects of irradiation to develop to the point where biological damage can be detected,[11,14,17] and/or the reactivity of the biological object may change with age.[11] But if the phenomenon is true of weekly doses of less than 50 r., which has not yet been demonstrated, formulae which give equal weight to each of a series of doses as Boche's, cannot be properly extrapolated. Further, if at relatively high daily doses much of the radiation is wasted, so far as producing an effect is concerned,[11] then an observed linearity of response against total dose (curve 3, figure 1) may imply a decreasing ability of radiation to harm as the daily dose decreased.

There has also been very little work yet on the problem of whether the effect of chronic irradiation is altered by changing the distribution in time of, say, a constant weekly dose. The data of table I and figure 1 suggest that it matters little whether a daily dose is given in a few minutes or spread out over many hours; but other as yet uncompleted observations[14,17] suggest that the delayed effects of irradiation may depend as much on the way the irradiation is given as on the total dose. In these experiments there was no wasted radiation: on the contrary, as much time as possible was allowed for the full development of any damage that radiation may have caused. Such experiments may give a relation between shortening of life and dose of radiation very different from those shown in figure 1, and indeed this might well be anticipated by anyone aware of the normal complexity of biological phenomena. Dose-response curves should not be extrapolated without fully realizing the nature of the experimental material on which they are founded.

Possibilities of extrapolation

It should first be emphasized how unusual it is to pay any attention to the ends of a biological dose-response curve. Normally, the aim of the biologist is to work in the middle ranges and, if irregularities appear at the ends, this is regarded as just to be expected, not necessarily deserving investigation.

The current maximum permissible level of radiation for occupational exposure of man, 0.3 r. weekly (Recommendations of the International Commission on Radiological Protection), is indicated in figure 1. Extrapolation suggests that this dose-level would shorten the lives of mice by nil, 0.02 or 0.2 per cent, depending on which of the three curves described earlier is taken to be

correct. As already shown, the experimental data on chronic irradiation at low doses are not sufficiently exact to distinguish between the curves, and the adequacy of fit at high levels of irradiation seems quite irrelevant. Thus the value of any attempt at extrapolation must depend on whether there is some theoretical reason for preferring one mathematical form to another. When this question is settled, there is the additional problem of extrapolating from one species to another.

One principle of selection often used nowadays in general discussion on radiation as it affects mankind, and at first sight self-evidently sound, is to take the most pessimistic assumption suggested by experiment or theory for the relation between dose and effect. Lorenz[8] used a very similar criterion when discussing the effects of daily irradiation on the difficult tissues and organs of different species. He concluded that man should be considered to be as sensitive as that species of animal found experimentally to be the most sensitive. Clearly this is no absolute criterion; as the range of species examined is widened, the apparent sensitivity of man must decrease. A consistent use of this criterion would involve denying the possibility of chemotherapy, or of selective killing by pesticides. It does not seem realistic to maximize pessimism as a means of choosing the best dose-response curve.

The most plausible reason for thinking that species differences among mammals in their reactions to irradiation are likely to be smaller than in their reactions to chemical agents is that the penetration of radiation into cells is not affected by the series of permeability barriers which every chemical agent has to pass before reaching the site of its action.[18] The uniformity of the acutely killing dose for all mammals gives supporting evidence. However, the chronic toxicity of radiation would be expected to depend on a balance between the continuing damage produced by the radiation and the ability of the irradiated animal to keep pace with the damage by repair. The ability to repair and its rate must depend on many of the structural and metabolic features which distinguish strains and species, and, for this reason, strain and species differences in the dose-response curves for chronic irradiation might be expected. Some of the experimental facts can best be understood in this way.[6]

An alternative view is to assume that the chronic toxicity of radiation is due to processes where repair of damage does not occur, like genetic mutation. It may then be plausibly argued that the genetic material of all mammals is very similar, both physically and chemically, and that therefore dose-response curves will in general be the same for all species. Such a view would suggest that damage should be proportional to total dose, as in Boche's formula (curve 3, figure 1), and would be consistent with the somatic mutation theory of carcinogenesis and the fact of carcinogenesis by ionizing radiation. But there are difficulties in the way of equating damage and total dose, as already suggested, and really very little evidence in support of the mutation theory of carcinogenesis. The theory is an easy one to accept; but even with the most recent advances in technique its testing seems almost impossible to envisage. However, in the experimental animal there is no simple relation between carcinogenesis and dose of radiation, and for mouse leukemia there is good evidence of the great importance of an indirect mechanism.[19] Moreover, the experimental evidence suggests that radiation shortens life apart from inducing cancer, and this is not easy to understand in terms of mutation.

If the results of animal experiments are to be carried over to man, there must either be very good evidence that all mammals behave alike, or sufficient human evidence of similarity with experimental animals to inspire confidence in the process of filling the human gaps from animal experience. It will at least be generally agreed that experimental dose-response relations which cannot satisfactorily account for all experimental results are scarcely worth applying to the human case. In the absence of a satisfactory theory, it seems pointless to expend the enormous experimental effort required to define the relation between daily dose and life-span for mean survival-times of 95 per cent and more of the control: it is only in this region that extrapolation to man is of any particular interest.

I would like to thank my colleagues for allowing me to make use of unpublished material.

TABLE I.

Of preceding paper by R. H. Mole

Reference	Source and type of irradiation G=Gamma rays N=fast neutrons	Unit of dose (conversion factor to rads)	Details of irradiation exposure: Days/week	Details of irradiation exposure: Duration of daily dose	Symbol used in Fig. 1	Experimental animal: Mouse strain	Experimental animal: Age at start of irradiation (days)	Experimental animal: Control life-span from start of irradiation (days)	No. of animals used	Method of reporting survival-time
Henshaw *et al* (ref. 3).....	^{182}Ta G	r.	6	minutes	▽	*CF*[1] (females only)	?	440	820	Median[a]
	Graphite reactor N	r. (2.0)	6	minutes	△					
Evans (ref. 2).....	Cyclotron N	N (2.5)	5	minutes	□	*CF*[1] Swiss	28–42	420 475	500	Median[b]
Lorenz *et al.* (ref. 4).....	Radium G	r.	7	8 hr.	○	*LAF*[1]	52–85	703	240	Mean
Neary *et al.* I (ref. 6).....	Graphite reactor N	rad	6–7	16–24 hr.	■	*CBA*	75–95	780	500	Mean[c]
Neary *et al.* II (ref. 13)...	Graphite reactor N	rad	7	16–24 hr.	▲	*CBA*	45–75	818	320	Mean[c]
	^{60}Co G	r.	7	24 hr.	●	*CBA*				
Thompson *et al.* (ref. 16)..	^{60}Co G	r.	7	24 hr.	+	Rats (Sprague-Dawley, females only)	90–120	585	42+	Mean
Lorenz *et al* (ref. 4).....	Radium G	r.	7	8 hr.	×	Guinea pigs (hybrid)	137–196	1,372	112	Mean

[a] Mean survival times calculated from data provided by Hollaender and Stapleton (1948, personal communication) have been used in fig. 1.

[b] Mean survival-time of the two strains combined were also reported and have been used in fig. 1 because standard errors were also given. However, irradiation stopped when 8–30 per cent of an experimental group was still alive, so that the mean survival times include variable proportions of radiation-free time.

[c] There were real sex differences in control life-span and possibly also in the effects of irradiation. The data have been pooled to make them comparable with those of the other authors.

The data of Henshaw (ref. 7) have not been included because the mean life-span of his controls was less than a year. The data of Boche (ref. 1) have not been included for a variety of reasons: his monkeys had tuberculosis, his mice salmonellosis; the dogs and rabbits were irradiated in small numbers and irradiation stopped after two years, long before the end of the natural life-span; irradiation of the rats also ceased after two years when 16–36 per cent of the lower level and control groups were still alive and were killed, which prevents estimation of mean survival-times.

Evans's X-ray data (ref. 2) have not been included because mean survival-times were not given. The control life-span was not given by Hagen and Simmons (ref. 5). In each of Sacher's (ref. 5) and Mole's (ref. 11) experiments with daily X-irradiation of mice, one experimental group survived about seven months; they are omitted because no groups surviving longer are available and because the relative biological efficiency for X- to gamma-rays for chronic irradiation is not known.

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II. LIFE SHORTENING EFFECTS IN MAN

16. Data were examined relating to the mortality of medical specialists in order to learn if those exposed to X-rays had a shortened life-span. In one extensive analysis,[9] utilizing the mortality data for specialists 35-74 years of age who died during 1938-1942, the *mortality ratio* was calculated for each specialty. The mortality ratio is the ratio of the number of deaths observed to the number that specialty would experience if subject to the specific death rate calculated for all physicians. These mortality ratios are given in parentheses in the last column of table V. It is seen, first, that specialists have a lower mortality than physicians in general; the specialist mortality ratio is only 0.78. Secondly, the various specialties appear to have different mortality ratios, from 0.99 to 0.62.

17. The mortality ratios of the various specialties were recalculated,[10] using the death rate for all special-

ists instead of all physicians (table V). The ranking of the mortality ratios by this method agreed with that of paragraph 16. Eight specialties had mortality ratios greater than unity, but in no case was the difference statistically significant.

18. The extent to which repeated small exposures to X-rays shorten the life of man is a matter of speculation. In the past, radiologists were so exposed, but from the mortality statistics it cannot be demonstrated that the life-span of this group of medical specialists has been shortened relative to that of other medical specialists[11] although this has been suggested.[12] It is known, however, that the incidence of leukemia is increased in these men.

III. Cancer in man

19. It is generally agreed that the incidence of cancer* in man can be increased by exposure to ionizing radiation. Quantitative data will be considered relating the incidence rate of cancer to radiation dose and to time after exposure. For introduction, the method of calculating the incidence rate and the influence of certain variables on it will be discussed briefly.

20. The prevalence of cancer may be defined as the number of cases per unit of population at a specified time, e.g. 15 cases per 10,000 on January 15.

21. The cancer incidence rate R may be defined as the number of new cases per unit of time and population occurring during a specified interval of time, e.g., 5 per 10,000 per annum. Alternatively, it may be said that an estimate of the probability that an individual in the population will acquire a cancer equals 5/10,000 or 5×10^{-4} per annum. R is an important statistic in the calculations to be made below.

22. The total effect of exposing a population to radiation is estimated in terms of the total number of cases, N_x, induced per unit of population. If the rate after exposure is constant at R, and if prior to exposure it was constantly R_o, then $(R-R_o)$ is the number of extra

* Cancer is a generic term and, as used here, includes leukemia and all forms of so-called neoplastic or malignant disease.

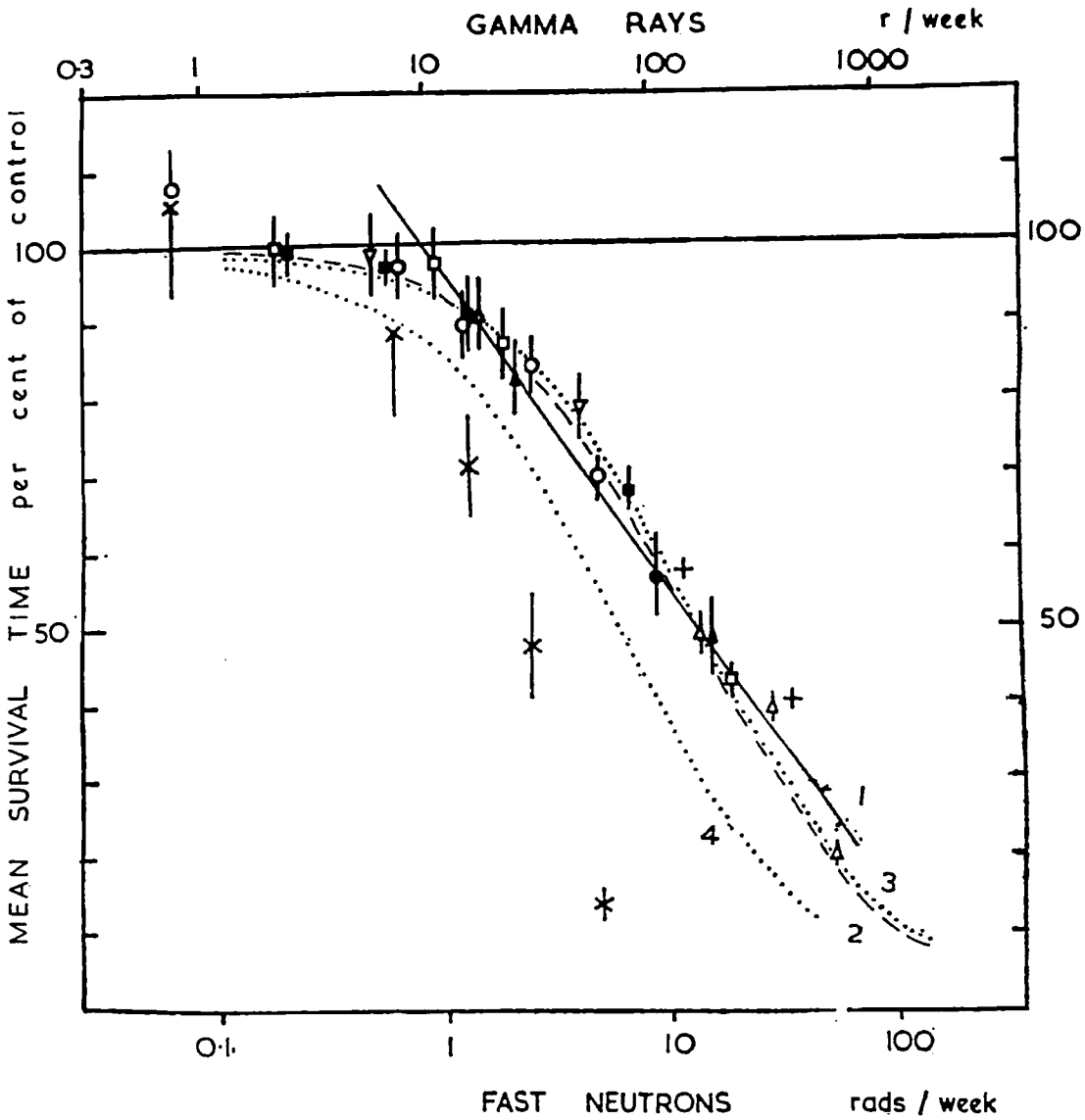

Figure 1 (of preceding paper by R. H. Mole). Mean survival-time (per cent of control) and weekly dose of radiation (logarithmic scale).
The symbols are given in table 1. The curves are numbered as in the text, where they are discussed. The gamma and neutron scales are in the ratio 13:1 (see text).

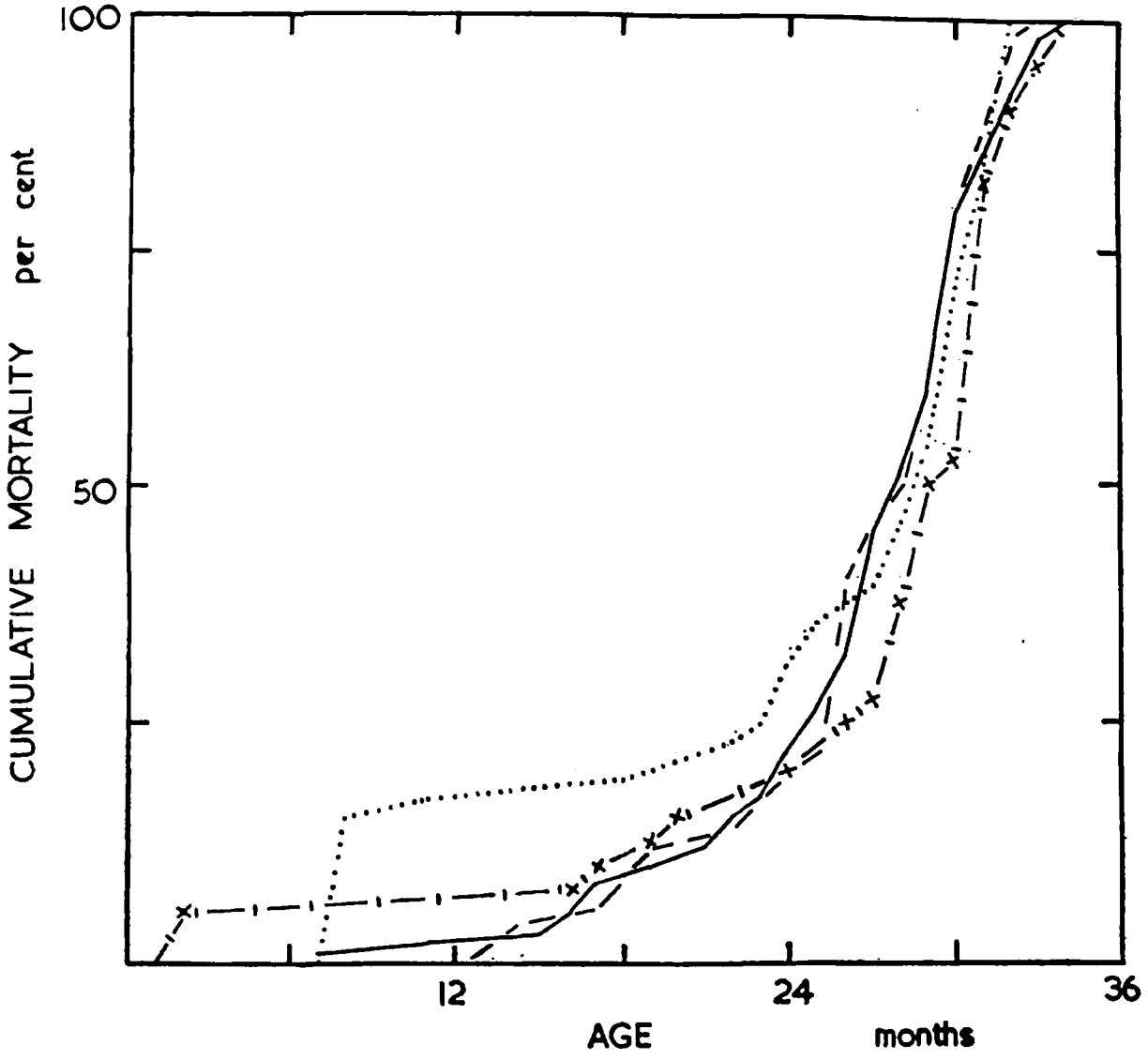

Figure 2 (of preceding paper by R. H. Mole). Cumulative mortality of female CBA mice (four different control groups 1951-54). All times plotted from same starting age of 70 days.

TABLE V. MORTALITY RATIO (ALL CAUSES OF DEATH) FOR MEDICAL SPECIALISTS

Rank	*Specialty*	*Observed deaths*	*Expected deaths*	*Mortality ratio*[a]
1.	Tuberculosis	43	34.2	1.26 (0.99)
2.	Dermatology	60 (58)[b]	47.8	1.25 (0.98)
3.	Roentgenology and radiology	96 (91)[b]	82.4	1.16 (0.90)
4.	Anesthesiology	17	–	– (0.88)
5.	Orthopedic surgery, proctology, urology and industrial surgery	199	179.1	1.11 (0.86)
6.	Neurology and psychiatry	142	133.0	1.07 (0.83)
7.	Public health	99	94.3	1.05 (0.83)
8.	Surgery	360	346.7	1.04 (0.81)
9.	Obstetrics and gynecology	112	116.3	0.96 (0.75)
10.	Eye, ear, nose and throat	502	523.4	0.96 (0.75)
11.	Internal medicine and pediatrics	378	423.6	0.89 (0.69)
12.	Pathology and bacteriology	38	48.1	0.79 (0.62)[c]
	ALL	2,046		1.00 (0.78)

[a] The ratio of (*observed deaths in a specialty at ages 25 to 74 years*) to (*expected deaths on the basis of age specific death rates for all specialists, 1938–1942*). The ratios were calculated from data made available by Dr. M. Spiegelman. The figures in parentheses are the published[9] mortality ratios for specialists based on the age specific death rates for all physicians (instead of all specialists) at ages 35 to 74 (2,046 deaths). Note that the ranking of the mortality ratios is the same for both methods of calculation.

[b] Omitting deaths from leukemia.

[c] Pathology only.

cases per unit of population per annum. In a period of T years,

$$N_x = (R - R_0)T \qquad (1)$$

Although simple in principle, the use of equation (1) is somewhat difficult in practice. First, R is not a constant, but varies with times. In general, exposure is followed by an initial period during which few if any radiation-induced cases occur. The duration of the initial period may be shorter after large doses than after smaller ones. Thereafter, depending on the particular cancer studied and the nature of the population, there will be a second period during which the vast majority of radiation-induced cases occur. This period might last for five years or for twenty-five. We are now only in the process of learning what the duration of such periods may be. Secondly, precise values of R_0 may not be available. In the case of some kinds of cancer there is some evidence that R_0 is changing relatively rapidly (e.g. leukemia). For these, it would be necessary to estimate the changes in R_0 as a function of time independently of the changes in R. Thirdly, the numbers of radiation-induced cases actually dealt with are very small, as will be seen below.

23. Having obtained a method for estimating N_x, it becomes feasible to investigate how N_x depends on the dose of radiation, D. Is N_x, for example, a simple linear function of D, is it a non-linear function or is there a threshold dose below which radiation is without effect? Before attacking such a problem, it is important to note that the same dose may result from a single exposure, multiple exposures, or a long period of continuous exposure. Such differences in dosage may lead to major differences in the end results and therefore must be explicitly dealt with when making comparisons or extrapolations.

24. It is worth special note that the factor of time has entered the problem in more than one way. In equation (1) paragraph 22, there is the term T, often referred to as *period at risk*. In paragraph 23, the role of time in dosage is considered; this may be referred to as *period under exposure*. The period under exposure may last for only a minute and thus be an insignificant fraction of the years at risk. On the other hand, in the case of long-lived isotopes, for example, the period under exposure may be a matter of many years and thus partially or even completely overlap the period at risk.

25. Constitutional factors are known to influence the production of cancer in man. These include race, age, sex, nutrition and other environmental and genetic influences. All of these factors have to be taken into account in discussing the production of cancer in man through exposure to ionizing radiation, especially when comparing the effects in one group with those in another.

26. The total of all human data that can be used for the quantitative analysis of cancer-induction by radiation is meagre. For example, only sixty-eight cases of leukemia are involved in the Hiroshima data of table VII. It is important that full use be made of such data while at the same time recognizing and giving due weight to their limitations. In the case of the calculations, extrapolations and applications that follow, the reader is urged to note the simplifying assumptions that may have entered into the analyses, especially in regard to the following items:

(a) *Absorbed dose.* In what organ is the absorbed dose to be determined? If the dose is not uniform throughout the organ, how shall it be averaged or otherwise expressed? Should the integral absorbed dose be considered?

(b) *Temporal factors.* What allowance, if any, should be made for multiple or continuous exposure? Is each successive year at risk of equal significance?

(c) *Constitutional factors.* What is the nature of the irradiated population with respect to age, general health, genetic constitution, etc.?

(d) *Dose-effect curve.* Is there a threshold? Is the effect a linear or some other function of dose? Can a factor be determined that will relate N_x to D?

Leukemia in man

27. Demographic data relating the incidence of leukemia to radiation exposure come from four population groups whose exposures were either a hazard of war or profession, or were incurred during diagnostic and therapeutic medical procedures.

Atom bomb survivors in Hiroshima

28. The most recent information on the incidence of leukemia in the Japanese survivors of the 1945 atomic bomb is given in a report which is reproduced in paragraph 33 below. From the condensed summary in table VI of the Hiroshima data, it is seen that the incidence of leukemia in the population exposed at 0-1,499 metres from the hypocentre has been twenty times greater than in the population exposed at 1,500 metres and beyond. Thus at the end of 1957, N (0-1,499 m.) = 5570; N ($>$ 1,499 m.) = 280. N is the total number of cases per million persons present at the time of the explosion. Taking the cases at 1,500 metres and beyond as a crude estimate of the natural incidence of leukemia, the number of cases N_x due to radiation may be estimated as 5,570 — 280 = 5,290, or in round numbers 5,300 per million.

TABLE VI. LEUKEMIA IN SURVIVORS AT HIROSHIMA, 1948–1957[a]

	Number of cases[b]		
		Distance (metres) from hypocentre	
Period of onset	*Total*	*0–1,499*	*1,500 and beyond*
1948–49	12	8	4
1950–51	20	18	2
1952–53	23	16	7
1954–55	14	9	5
1956–57	11	5	6
TOTAL: 1948–57	80	56	24
N (cases per 10^6)	835	5,570	280
R (average of cases per year per 10^6)	84	557	28

[a] Data from reference 13. The full report from which these and the data of table VII were taken is given below.

[b] 10,051 persons were exposed at 0–1,499 metres; 85,768 were exposed at 1,500 metres and beyond.

29. The data in table VI indicate that the biennial rate of leukemia in the heavily exposed population reached its maximum in 1950-1951 and has been declining since then. If this tendency continues, practically all cases of radiation-induced leukemia probably will have occurred by 1960, within fifteen years of exposure, so that at lease 80 per cent of them may be said to have occurred already, within ten years of exposure. In these circumstances, the annual rate of leukemia taken by itself is not

TABLE VII. LEUKEMIA INCIDENCE FOR 1950–57 AFTER EXPOSURE AT HIROSHIMA[a]

Zone	Distance from hypocentre (metres)	Dose (rem)	Persons exposed	L (Cases of leukemia)	$\sqrt{L}$	N[b] (total cases per 10^6)	N_x (Radiation-induced cases per 10^6)	N_x/rem	P_L ($N_x/10^6$/year/rem)
A	under 1,000	1,300	1,241	15	3.9	12,087 ± 3,143	11,814	9.1	1.14×10^{-6}
B	1,000–1,499	500	8,810	33	5.7	3,746 ± 647	3,473	6.9	0.86×10^{-6}
C	1,500–1,999	50[c]	20,113	8	2.8	398 ± 139	125	2.5	0.31×10^{-6}
D	2,000–2,999	2	32,692	3	1.7	92 ± 52	−181	−90	-11×10^{-6}
E	over 3,000	0	32,963	9	3.0	273 ± 91	Control	—	—

[a] Based on data in reference 13. Prior to 1950 the number of cases may be understated rather seriously.

[b] The standard error is taken as $N(\sqrt{L}/L)$.

[c] It has been noted [15, 16] that almost all cases of leukemia in this zone occurred in patients who had severe radiation complaints, indicating that their doses were greater than 50 rem.

a good index of the total radiation effect; it is the total number of case N_x that should be employed as such a measure.

30. Considering the exposed population by itself, the segment that was closer to the hypocentre has had the greater incidence of leukemia. However, the quantitative relation between *leukemia incidence in Hiroshima* and *radiation dose* is not yet known. Before such a relation can be formulated it will be necessary to have better estimates of the *absorbed dose in rem* than have been available hitherto. The estimates must be made both for the various dose zones in which the population was distributed, and, also, for every individual case of leukemia, taking into account both its position within the zone and the shielding immediately around it. Such work is under way.

31. None the less, using such data as were available, estimates have been made of the potency of this bomb radiation in causing leukemia.[14] The exposed populations of Hiroshima and Nagasaki were considered to have been exposed in a number of zones for each of which a mean dose was assumed. The extra probability of leukemia occurring in an exposed person per rem and per year elapsed after exposure was then calculated for the population of each zone:

$$P_L = \frac{\text{average extra number of new cases per year (1948–1955)}}{\text{number of persons exposed} \times \text{dose (rem)}}$$

In zones A (1,300 rem), B (500 rem), and C (50 rem), the values of P_L were calculated to be 0.9, 0.7, and 0.7×10^{-6}, respectively. This finding was taken to support the suggestion that the extra leukemia incidence is directly proportional to radiation dose, and conversely, to argue against the existence of a threshold for leukemia induction.

32. P_L might be used in estimating N_x, the total number of extra cases of leukemia that follow a dose of radiation. The average value of P_L in paragraph 31 is 0.8×10^{-6} based on statistics for the years in which the leukemia rate is considered to be maximal. Taking 15 years to be the entire period of leukemia production (period at risk), the total number of cases (per individual exposed per rem) $= 15 \times 0.8 \times 10^{-6} = 12 \times 10^{-6}$. On this basis if each of a million persons receives 1 rem, a total of 12 extra cases of leukemia will eventually develop.

33. It is of interest to apply the above method to the latest data on leukemia incidence in Hiroshima, using the same zoning system and estimates of dose (table VII). Contrary to previous findings, the present findings indicate that P_L decreases markedly as the dose falls, that therefore leukemia incidence is not a linear function of dose, and that a threshold for leukemia induction might occur. In fact, according to table VII a dose of 2 rem is associated with a decreased leukemia rate. It is to be emphasized again, however, that the estimates of dose employed in the present and previous analyses are much too uncertain to permit drawing conclusions relative to the vital points in question. The calculations are made only to illustrate how variable the results may be when inadequate data are utilized.

LEUKEMIA IN HIROSHIMA CITY ATOMIC BOMB SURVIVORS* by

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It has become generally accepted that an increased incidence of leukemia follows the acute or chronic exposure of various experimental animals and of man to ionizing radiation.[1] Recently an attempt has been made to establish a quantitative relation between the probability of radiation-induced leukemia and the unit-dose of radiation received, on the basis of data from studies of various groups of radiation-exposed human beings.[2]

The survivors of the atomic bombings in Hiroshima and Nagasaki, Japan, comprise two such groups. Reports concerning the occurrence of leukemia in these populations over a period through June 1956 have been published at intervals by various staff members[3] of the Atomic Bomb Casualty Commission.[4] In addition, an unpublished compilation of certain specific detailed information requested by the British Medical Research Council was prepared in September 1955.[5] An analysis of these data appeared in a publication of the Medical Research Council[6] and a portion was also published in a report of the National Research Council.[7]

Since that time a review has been made of all the leukemia cases known to the Atomic Bomb Casualty Commission, and a master list has been compiled. Some of the cases on the September 1955 listing have been dropped for various reasons, and many cases have been added. No detailed official report has been published recently in the hope that more adequate dosimetry data might become available. This wish is nearing fulfilment because of the joint initiation of a large programme of

* Science *127*, 699-700, 1958, for table 1 and bibliography referred to in this article, see immediately following the article.

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dosimetry studies in 1955 by the Atomic Bomb Casualty Commission and a group of interested organizations including the Atomic Energy Commission's Division of Biology and Medicine, the National Academy of Sciences — National Research Council, the U.S. Air Force School of Aviation Medicine, Los Alamos Scientific Laboratory, and Oak Ridge National Laboratory. The programme is designed to make possible the assignment of a specific neutron or gamma ray dose or both in rads to the record of each survivor in the Atomic Bomb Casualty Commission's files for whom sufficient pertinent information is available.

A detailed interim report on leukemia in the Hiroshima atomic bomb survivors is presently being prepared by various staff members of the Atomic Bomb Casualty Commission and the National Research Council. It will include the best currently available dosimetry information resulting from the afore-mentioned collaborative effort. However, because of the present interest in data pertinent to radiation leukemogenesis and the desirability of making available current information obtained by the Atomic Bomb Casualty Commission, table I, summarizing results of the leukemia survey in Hiroshima as of December 1957, is presented at this time.

Certain limitations of these data should be pointed out. The programme was initiated in 1947 but the present level of intensity of effort was not achieved until about 1950. Therefore, while it may be assumed that the numbers of cases shown for the years 1950 through 1956 are fairly accurate, the numbers that arose in the preceding years may be understated rather seriously. With respect to 1957, it is probable that additional cases remain to be discovered with onset in that year.

The denominators of the incidence rates are estimates, subject to errors of presently unknown magnitude. The 3 June 1953 Residential Census of Hiroshima was conducted by the Hiroshima Census Bureau and was presumably of a reasonable degree of accuracy. The categorization by distance from the hypocentre was made on the basis of Atomic Bomb Casualty Commission investigations of 50.8 per cent of the males and 44.6 per cent of the females who reported themselves exposed to the bomb. However, it was found that 3.1 per cent of those reportedly exposed were in fact not in the city at the exact time of the bombing.

Apart from the uncertainties regarding the population on 3 June 1953, it may be incorrect to assume that migration in and out of the city during the period from 1950 to the present was the same for persons exposed in different distance categories. However, despite the current lack of pertinent information, the simple expedient of multiplying the June 1953 population values by eight to obtain estimates of person-years at risk has been adopted since the census date is roughly near the midpoint of the interval under study. This procedure seems reasonable at present, although the magnitude of any resultant error is hard to estimate.

In addition to the above-mentioned points, which have to do with the intrinsic accuracy of the data presented, a further caution should be strongly emphasized. The uncertainties involved in inferring radiation dose from distance alone are too large to support conclusions beyond the previously reported qualitative one that those survivors who received large doses of radiation—that is, who were within 1,500 metres of the hypocentre, had a significantly higher incidence of leukemia than those beyond that distance, who received relatively little or none.[3] The relationship of incidence to distance as presented in table I cannot be given a more quantitative interpretation because there are too many variables, as yet unresolved, which cannot be ignored.

TABLE I.
Of preceding paper by Niel Wald
LEUKEMIA IN HIROSHIMA ATOMIC BOMB SURVIVORS WHO WERE RESIDENTS OF HIROSHIMA CITY AT THE TIME OF DIAGNOSIS (DIAGNOSES VERIFIED BY THE ATOMIC BOMB CASUALTY COMMISSION)

Year of Onset	*Total*	*Distance from hypocentre (metres)*				
		Under 1,000	*1,000–1,499*	*1,500–1,999*	*2,000–2,999*	*Over 3,000*
1945						
1946						
1947	3		1		2	
1948	7	2	4		1	
1949	5	1	1	1	1	1
1950	9	3	5			1
1951	11	3	7	1		
1952	11	3	5	1		2
1953	12	2	6	2	1	1
1954	6	2	2	1	1	
1955	8	1	4	2		1
1956	6		1	1	1	3
1957	5	1	3			1
TOTAL	83	18	39	9	7	10
Estimated population*	95,819	1,241	8,810	20,113	32,692	32,963
Number of cases with onset in 1950–1957	68	15	33	8	3	9
Estimated person-years at risk	766,552	9,928	70,480	160,904	261,536	263,704
Annual incidence of leukemia per 100,000	8.9	151.1	46.8	5.0	1.1	3.4

* Based on Hiroshima Census Bureau's Daytime Population Census of Hiroshima City, 3, June 1953.

For example, the presently available estimates of the air dose in Hiroshima have a large uncertainty, the magnitude of which is itself not yet definite. Also, experimental dosimetry studies at Oak Ridge National Laboratory emphasize the need for detailed information, such as is being collected by the Atomic Bomb Casualty Commission, concerning the shielding situation of any particular survivor at any distance. It is conceivable that the radiation received within a light frame house (the most common shielding situation) may vary from an amount almost equalling the outside air dose to one equal to the outside air dose attenuated by perhaps a factor of two, depending on the position of the person in the house.

In determining the relationship of radiation exposure to the incidence of leukemia, such detailed data must be examined not only for each leukemic survivor, but also for enough of the population at risk to permit calculation of statistically significant incidence rates. Until this information becomes available from the dosimetry programme, it is premature to attempt precise quantitation of dose-effect relationships in radiation leukemogenesis on the basis of the Hiroshima and Nagasaki radiation-populations.[8]

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8. Grateful acknowledgement is made for the biostatistical assistance of Mr. Seymour Jablon, National Research Council, and also for the aid of Dr. Lowell Woodbury, head of the Biostatistics Department of the Atomic Bomb Casualty Commission, and his staff. Appreciation is also expressed for the help of Dr. Robert M. Heyssel, who provided the hematological data for 1957, and for the co-operation of the physicians of both the Atomic Bomb Casualty Commission and the city of Hiroshima, who make the long-term Hiroshima leukaemia study possible.

Leukemia in radiologists

34. The most recent estimate of the leukemia death rate for United States radiologists (ages 35 to 74 years) is based on the data of 1938-1952, inclusive.[14] During this period there were 17 deaths, corresponding to an average annual rate of 610 per million. The rate observed in the population at large (corrected for age distribution) was 121 per million.

Leukemia in children

35. Two reports have associated leukemia in children with previous X-ray exposure during infancy or the prenatal period. In the first,[17] a study was made of 1,700 United States children treated during infancy for a condition known as enlargement of the thymus gland. The untreated siblings of the irradiated children served as controls. There were 17 cases of cancer, including 7 of leukemia in the irradiated group; there were 5 cases of cancer, but none of leukemia in the control group (tables VIII and IX).

TABLE VIII. EXPECTED AND OBSERVED RATES FOR CANCER[a]

	Treated children		*Untreated siblings*	
	Expected	*Observed*	*Expected*	*Observed*
All cancers	2.6	17 (?19)	2.7	5
Leukemia	.6	7 (? 8)	.6	0
Thyroid cancer	.08	6	.08	0

[a] Data from reference 17.

TABLE IX. DISTRIBUTION OF NEOPLASIA ACCORDING TO AMOUNT OF RADIATION[a]

	Under 200 r.	*Over 200 r.*	*Unknown*
Number treated	604	804	313
Cases of leukemia	2	5	(?1)
Other cancers	0	4	0
Carcinoma of thyroid	0	6	0
Adenoma of thyroid	0	6	3

[a] Data from reference 17.

36. In a British study[18] of the history of 547 mothers whose children had died before the age of ten from leukemia and other cancers, it was found that 85 of the mothers (15.5 per cent) reported that they had had diagnostic abdominal radiography involving the foetus during the relevant pregnancy. In a comparison series of 547 mothers with healthy and living children only 45 (8.3 per cent) reported radiologic exposure during the relevant pregnancy (table X).

TABLE X. LEUKEMIA AND CANCER INCIDENCE IN OFFSPRING RELATED TO X-RAY EXAMINATIONS IN THEIR MOTHERS DURING THE RELEVANT PREGNANCY[a]

Type of cancer in child	*Number of cases*	*Number of mothers and foetuses exposed to*	
		Abdominal examination	*Examination of other parts of body*
1. Leukemia	269	42	25
Controls (living)	269	24	23
2. Other cancers	278	43	33
Controls (living)	278	21	32
3. Total cancer	547	85	58
Total control	547	45	55

[a] Data from reference 18.

37. The suggestion has been made that a proportion of the leukemias and cancers in the first group, namely

7.2 per cent, may have been caused by the exposure during intrauterine life of the patients in question. However, radiological examination of other parts of the body was not correlated with increased cancer incidence.

38. The data indicate a correlation between leukemia and other cancers in childhood and irradiation of the foetus, although alternative possibilities cannot be excluded. It is possible that some mothers who give birth to leukemic children might be in greater need for diagnostic X-ray service during pregnancy and that in the present cases leukemia or cancer may have resulted independently of exposure sustained during intrauterine life.

39. In any event, the clinical indications for the X-ray examinations of the mothers of these particular children are not known, nor is information available on the types of examinations performed and on the actual doses of X-ray received by the mothers and the foetuses. Additional data and final evaluations of their significance are known to be in course of publication (British Medical Journal).

Leukemia after X-ray therapy for ankylosing spondylitis

40. A dependence of the incidence of leukemia on radiation exposure has been demonstrated in a study of 13,352 cases of ankylosing spondylitis treated during 1935-1954 at 82 radiotherapy centres in Great Britain.[19] In this series, 28 patients were certified to have died of leukemia and 12 of aplastic anemia, as of 31 December 1955. The numbers of expected deaths were 2.9 for leukemia and 0 3 for aplastic anemia. (The over-all death rate per million persons for leukemia in England and Wales has been as follows: 21 in 1935, 34 in 1945, 49 in 1954). A thorough study of the series led to the following tabulation of cases with blood disease:

Group	*Males*	*Females*
Leukemia (A)	35	1
Probable leukemia (B)	5	0
Aplastic anemia	4	0
Undecided	2	2

41. To study the distribution of cytological types, all available cases of leukemia in patients with ankylosing spondylitis, both treated and untreated were tabulated:

	X-ray treated series	*per cent*	*Untreated series*	*per cent*
Lymphatic leukemia	3	(8)	3	(38)
Myeloid leukemia	31	(78)	4	(50)
Monocytic leukemia	6	(15)	1	(13)
Type unspecified	9		0	

There is a relative deficiency of the lymphatic type of leukemia among the X-ray treated cases, and the difference between the two series was found to be just significant ($P = 0.05$).

42. Only male cases of leukemia and "probable leukemia" (groups A and B) were available in adequate numbers for further statistical analysis. After a single course of treatment, the evidence of 10 cases indicated that leukemia occurred within 5 years. When all cases were considered, i.e. those receiving multiple courses over a period of years as well as those receiving a single course in a month or so, it was noted that leukemia was diagnosed within 5 years of the last treatment in 35 of 37 cases.

43. The radiological treatment of ankylosing spondylitis usually consisted of irradiating the spine and the region of the sacroiliac joints. In some cases other regions were also treated. Most (7,215) of the patients in the present series received only one course of treatment, but some (1,119) received as many as four courses over a period of years. Preparatory to examining the relation between leukemia incidence and radiation dose elaborate studies were made so that for each course of treatment in each case there could be determined:

(*a*) *The spinal dose:* the mean dose to the spinal marrow, based on the average of 3 points (upper sacral, mid-dorsal, mid-cervical).

(*b*) *The integral dose:* the integral dose to the whole body.

The distribution of doses in the entire population of 11,287 men was estimated from the doses of a randomly drawn sample of 1,878 men. The dose of each leukemia case was determined individually. For multiple courses of treatment due allowance was made for the years at risk at each dose level. Dose-classes were then established (e.g., 250—499 rem, 500—749 rem), and the crude incidence of leukemia determined in each class. In addition, the standardized incidence of leukemia was determined, i.e., the incidence standardized for age.

44. In studying the dose-effect relationship, the following assumptions were made:

(*a*) The significant parameter of dose is the mean dose to the spinal marrow. (The spinal marrow was always irradiated; the amount of irradiated extra-spinal marrow was variable.)

(*b*) There is an absolute waiting period of one year after exposure during which no cases occur. Thereafter, each year at risk has equal weight. (The authors considered this to be an over-simplification, but used it as a practical method of dealing with the many cases that had received multiple courses of treatment).

(*c*) Fractionation of dose did not diminish its effectiveness.

(*d*) The probability of inducing leukemia is directly proportional to the number of man-years at risk. The number of man-years at risk equals the product of (number of individuals given a particular dose) × (mean years since exposure—1).

(*e*) Constitutional factors may predetermine a greater radiosensitivity in this population, but no allowance can be made for it.

45. Results from these studies are summarized in table XI and figure 4. It is clear that the incidence of

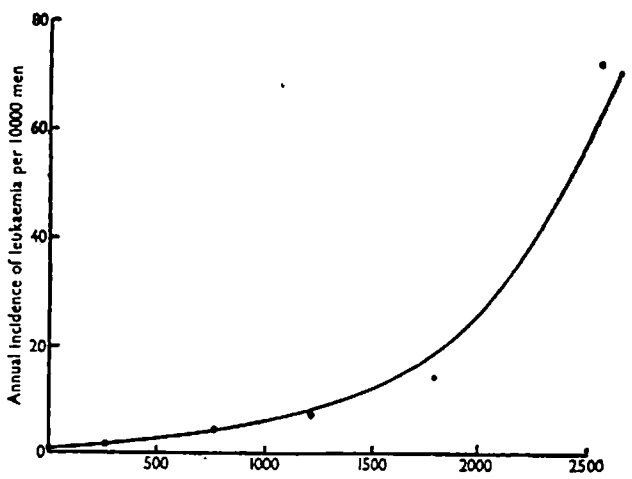

Figure 4. The incidence of leukemia, standardized for age, in relation to the mean dose of radiation to the spinal marrow: all male patients in the study series and 'A' and 'B' cases of leukemia, excluding co-existent cases. (Figure 4 is Figure 1 in the original reference 19.)

leukemia increases with radiation dose and that the relation between them is not linear. The curve through the points in figure 4 is drawn to reach the control rate at zero dose without indicating a threshold for the induction of leukemia. It should be noted, however, that only one case of leukemia received a dose of less than 400 rem and that this case had lymphatic leukemia and had had large doses of extra-spinal irradiation. Therefore the course of the curve between this dose and zero must be regarded as practically undetermined. The slope of the curve between 750 and 1,250 rem appears to be relatively constant and is equal to about 0.6 new cases per year per 10^6 men per rem to spinal marrow.

46. The data for the limited group of patients that received irradiation to the spinal axis only are given in table XII. In this group, 18 patients developed leukemia. Analysis of these data[20] suggested a threshold of 54 rem by one method and of 130 rem by another. These estimates, however, are subject to great uncertainty owing to the small number of cases in the series and the lack of data for the range in question. Statistical analysis indicated that the threshold might lie anywhere between 0 and 460 rem. The slope of the dose-effect curve was about the same as that given in paragraph 45.

Theoretical considerations for estimation of radiation hazards

47. The quantitative statement of a radiation hazard involves the precise relation between the total number of radiation-induced cases N_x and the radiation dose D, throughout an extended range of dosage. At present, such a statement cannot be satisfactorily made for any kind of human cancer. For certain purposes, however, a very crude estimate may be better than none at all and two methods have been proposed with this end in mind.

48. The first method assumes (1) that *all* cancer is caused by ionizing radiation and (2) that the annual cancer rate is directly proportional to the annual radiation dose. The total cancer incidence rate R in the United States, for instance, is now about 2,800 cases per annum per million population. The annual background radiation dose rate is about 0.1 rem, and the dose rate from other sources is perhaps another 0.1 rem. The average annual dose rate per individual is thus about 0.2 rem. The potency factor k is, therefore,

$$k = \frac{2800}{0.2} = 14 \times 10^3, \qquad (2)$$

i.e., 1 rem will produce a total of 14,000 new cancer cases when a population of one million has been exposed. Such a figure appears to be absurdly large. It has been suggested that such a calculation applies only to certain kinds of cancer but not to others. There appears to be no scientific basis for such a selection, however.

TABLE XI.[a] THE NUMBERS OF PATIENTS WHO DEVELOPED LEUKEMIA, AND THE CRUDE AND STANDARDIZED INCIDENCE RATES: AFTER DIFFERENT MEAN DOSES OF THERAPEUTIC RADIATION TO THE SPINAL MARROW: MALE 'A' AND 'B' CASES, EXCLUDING CO-EXISTENT CASES

	Mean dose to spinal marrow (r.)													
	0[b]	*Less than 250*	*250–499*	*500–749*	*750–999*	*1,000–1,249*	*1,250–1,499*	*1,500–1,749*	*1,750–1,999*	*2,000–2,249*	*2,250–2,499*	*2,500–2,749*	*2,750 or more*	*All doses*
No. of men developing leukemia														
'A' cases	—	1	2	6	3	7	2	3	1	2	3	1	1	32
'A' and 'B' cases	—	1	3	6	4	8	3	3	1	2	4	1	1	37
Crude incidence per 10,000 *men per year*														
'A' and 'B' cases	0·49	2·16		4·59		6·99			12·18			63·65		5·98
Standardized incidence per 10,000 *men per year*														
'A' and 'B' cases	0·49	1·98		4·66		7·21			14·44			72·16		5·98

[a] This table was table 19 in the original reference.[19]

[b] The rate given for 'zero' therapeutic dose is the corresponding rate among men of the same age-distribution and observed over the same period, calculated from the mortality from leukemia experienced by the whole male population of Britain.

TABLE XII.[a] THE INCIDENCE OF LEUKEMIA AFTER DIFFERENT MEAN DOSES OF THERAPEUTIC RADIATION TO THE SPINAL MARROW: MALE 'A' AND 'B' CASES GIVEN ONLY SPINAL IRRADIATION, EXCLUDING CO-EXISTENT CASES

	Mean dose to spinal marrow (r.)										
	0	*Less than 250*	*250–499*	*500–749*	*750–999*	*1,000–1,249*	*1,250–1,499*	*1,500–1,749*	*1,750–1,999*	*2,000 or more*[b]	*All doses*
No. of man-years at risk following exposure to dose	—	5,404	7,673	6,573	8,262	7,411	2,782	897	566	679	40,247
No. of men developing leukemia											
'A' cases	—	0	2	4	3	4	0	2	1	1	17
'A' and 'B' cases	—	0	2	4	3	5	0	2	1	1	18
Crude incidence per 10,000 men per year											
'A' and 'B' cases	0·49	1·53		4·72		6·75[c]			8·12[d]		4·47
Standardized incidence per 10,000 men per year											
'A' and 'B' cases	0·49	1·44		4·83		6·82[c]			8·70[d]		4·47

[a] This table was table 20 in the original reference.[19]

[b] Average dose, 2,290 r.

[c] For the group receiving 1,000–1,499 r. the crude incidence is 4·91; standardized incidence 5·06.
For the group receiving 1,000–1,749 r. the crude incidence is 6·31; standardized incidence 6·82.

[d] For the group receiving 1,500 r. or more the crude incidence is 18·68; standardized incidence 19·86.
For the group receiving 1,750 r. or more the crude incidence is 16·07; standardized incidence 16·82.

49. The second method uses the results of the British study of leukemia incidence in a radiation-treated population, discussed above. (The data for Hiroshima have not been used owing to the uncertain dosimetry.) To compensate for the paucity of data, a number of assumptions are made in the following analysis:

(*a*) The significant parameter of dose is the mean dose to the entire red marrow. In uniform whole-body exposure, the doses to the entire red marrow and the spinal marrow are the same. When only the spinal marrow is irradiated, the mean dose to the entire red marrow is probably about 40 per cent of the spinal dose.

(*b*) The total number of years at risk is 15, and each year has equal weight. This assumption was arrived at from the following considerations. The mean period of observation in the British study was 5 years; this would set a lower limit for all types of cases. Those 10 cases of leukemia that received only one course of treatment all occurred within 5 years of that treatment. For the population exposed at Hiroshima the cancer rate began falling after 8 years, and a complete period at risk of 15 years has been suggested. The maximum duration of the period at risk cannot be greater than the duration of life after exposure. In the case of a population of children, this could be 65 years, in the case of the usual mixed population, the average would be about 35 years.

(*c*) Fractionation or protraction of dose does not diminish its effectiveness.

(*d*) Constitutional factors may be neglected.

(*e*) Cancer production is a linear function of radiation dose. Linearity has been assumed primarily for purposes of simplicity. In the case of the British data for doses below 1,300 rem, a linear relation provides a fairly accurate fit.

(*f*) There may or may not be a threshold dose. The two possibilities of threshold and no-threshold have been retained because of the very great differences they engender.

50. The potency factor k, equal to N_x/D, can now be calculated. For a single exposure of the entire red marrow to 1 rem, the average annual leukemia rate is estimated to be 1.5 cases per million persons exposed. If the total number of years at risk is assumed to be 15, k is equal to 1.5×15, or approximately 20 cases per million exposed per rem. These calculations are based on observations following single large exposures. However, under conditions of prolonged exposure at lower dose rates, the period of risk may be longer. In the calculations of chapters V and VII where a *maximum* estimate is wanted, the period at risk is assumed to equal the average remaining life-time of the exposed population (35 years). The value of k has therefore been taken as 52 cases per million per rem in the calculations in paragraph 128 of annex D and in paragraph 61 of chapter V of this report.

51. The use of k to predict the number of cases of leukemia depends on the magnitude of the threshold. If there is no threshold, N_x is equal to the product of k, D, and the number of persons exposed. If a threshold is assumed, there will be no cases in persons who have received less than that dose.

52. Besides the alternative possibilities of a linear relation with or without a threshold, it is possible that a non-linear relationship may exist, as has been found, for example, in the case of many chromosome abnormalities.[21] As noted in paragraph 45 and illustrated in figure 4, the incidence of leukemia in the British study was a curvilinear function of dose, not a linear one. A curve providing a good fit to these data is obtained when leukemia incidence is considered to be proportional to the square of the radiation dose. In general, curves of this type predict a finite incidence of leukemia at small doses. However, this incidence may be very much lower than that predicted by a linear function based on all of the same data.

53. The methods used above to estimate the risk of leukemia after radiation exposure are of general use. They may be applied both to other cancers and also to non-cancerous lesions such as occur in the eye (cataract), the skin and in the bones. Their use is contingent upon the availability of adequate statistical estimates of the incidence of the disease in question related to the radiation doses received by the population at risk. It may be noted that such methods do not depend on detailed knowledge of how the radiation induces the lesion within the cell, e.g. by somatic mutation or some other alleged or hypothetical mechanism. At present, adequate statistical data are not available for bone tumours or for tumours of other organs to make such estimates of risk. However, it is known that pertinent studies are under way for bone tumours in man that are caused by radioactive substances.

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Annex H

THE GENETIC EFFECTS OF RADIATION

TABLE OF CONTENTS

I. MUTATION

1. The mechanics of mutation

The gene

1. The conventional concept of the gene has been that of a functional hereditary unit. In recent years this concept has required a more precise definition, since sensitive tests of allelism have indicated that a single functional gene may be separable into component elements by recombination and so shown to be capable of many pseudoallelic differences.[1,2] Single mutational events which modify or prevent the action of the functional unit may affect different large or small parts of this unit.[3] During the same period, it is notable that features of the genetics of natural populations have indicated the extent to which individual functional genes can be involved in larger complexes and lack complete autonomy.[4] Possibly the most striking manifestation of this is at present in *Salmonella typhimurium*, in which it appears possible that there are integrated linear sequences of adjacent gene-structures responsible for whole sequences of biochemical operations, assembly-line fashion.[5]

Gene mutations

2. Take in its widest sense, mutation means any change of the genetical constitution not due to recombination, ranging from whole genomes to alleles. Often mutation is used in a more restricted sense, viz. as change of the action of some specific gene. This is commonly referred to as point mutation, which, however, may be a misleading term, as it is known, especially from the work on *Drosophila* by Dubinin and others,[6,7] that a change of the position of a gene may change its habit of action. Moreover, the idea of a point mutation, as distinct from a deletion or rearrangement, was formerly based upon the smallest unit of structure microscopically visible. Because recent structural analysis of the gene has seemed to penetrate almost as far as the much smaller ultimate units of its physico-chemical structure, believed to be the single nucleotides, it has already been suggested that the term "point mutation" be reserved for mutational events involving only one such unit.[8] Such ideas do not by themselves affect the distinction between intragenic and intergenic mutations[9] and may, indeed, clarify these; for example, it remains possible that further investigations of genes and chromosomes[10] will lead to a distinction between a structural backbone and separate attached genes. There is no doubt that advances in this field will eventually add greatly to the refinement of current ideas concerning all aspects of mutation.

3. In man, the primary genetic concern is with all transmissible hereditary changes which simulate the change to a new allele. These are perhaps best grouped together under the term "apparent gene mutations", whatever their structural nature. However, other forms of genetic damage require consideration in connexion both with somatic effects and with the requirement that mutations must survive transmission through the germ cells if they are to be observed. These latter forms include both gene mutations and chromosome structural changes in somatic cells, which may well have a sensitivity to the radiation-induced process quite similar to that of germ line cells.[10a] Mutations and chromosome changes in these cells could bring about consequences, recognizable for the organism as serious somatic effects, ranging from death or incapacity of cells fulfiling vital specialized functions to unrestricted proliferation.

Chromosome breaks

4. It remains a major question to what extent chromosomal or other genetic effects may be responsible for cell death or damage in somatic or germinal tissues of man.[11] Visible chromosomal alterations resulting from irradiation have been studied in cytologically favourable material, principally of plants and of insects. They commonly arise through one or more chromosome breaks in the cell rejoining in some new configuration. A frequent result is dominant lethality through loss of substantial chromosome parts or interference with cell division. In spite of the difficulties of objective numerical scoring of cytological phenomena, many quantitative investigations have been made upon them:[12] it has been shown that the more densely ionizing radiations are relatively more effective in producing them[12,13] and that the numbers observed or recovered can be considerably affected by various post-irradiation treatments if these are applied sufficiently early.[12,14] In this way, recent work has suggested that there are some breaks at ionic bindings, which reheal very rapidly, and others at co-valent bonds, which heal more slowly,[14] as well as two separate effects of radiation, one in causing the breaks and the other in affecting the rejoining mechanism.[14] The effects of oxygen, both at the time of irradiation and during the subsequent rejoining process, have played an important and controversial part in this advance.[15] It would be of interest to learn to what extent investigation of post-irradiation modifiers of the rejoining process showed biochemical relationships parallel to those observed with modifiers of the cell lethality induced by irradiation.

5. Many investigations have connected ploidy with radiation resistance in unicellular organisms, especially the extensive work of Mortimer and his colleagues on yeast;[16] and this, together with the increased RBE of the more densely ionizing radiations, has led to the idea that much radiation-induced cell lethality has its origin in dominant genetic changes. Certain cases are, however, known in which this is not true; instead, lethality results from an imbalance or block in metabolism (as in very heavily irradiated Habrobacon eggs,[17]) or a generalized failure of the mitotic process hardly to be ascribed to individual processes of the break-rejoin type. On the basis of a two-hit killing curve for mammalian tissue culture cells of various ploidies, Puck has recently argued that radiation-induced death in these is chromosomal in origin;[18,19a] cytological evidence will perhaps be required before such a conclusion can be considered as finally established. However, the reduction in growth rate observed by Puck *et al.* in colonies derived from diploid mammalian tissue culture cells which had survived X-irradiation already provides *prima facie* evidence that even at doses of the order of 100 r, most surviving cells have suffered dominant deleterious changes.[18,19a] Moreover, Bender has recently demonstrated a rather high sensitivity of tissue culture cells derived from human kidney to chromatid breaks induced by X-rays.[19]

The hereditary material

6. Recent years have remarkably advanced the knowledge of genetic material and of the role played in it by desoxyribonucleic acid (DNA). Indirect evidence from

different sources has long led cellular physiologists to believe that DNA, in close association with protein, forms part of genes and chromosomes; this has included the relative DNA content of haploid and diploid cells of various tissues of an organism,[20] cytochemical evidence, including the almost complete restriction of the presence of DNA to the cell nucleus and the association of DNA synthesis with cell division.[21] More recently, a very close association has been demonstrated between the assimilation of radioactive tracers incorporated in DNA, and chromosome division.[10] In addition, other evidence has inclined many geneticists to believe that DNA may be the actual material whose configuration constitutes genetic information; this evidence includes:

(*a*) The transformation of hereditary characters of cells of *Pneumococcus*[22] and *Haemophilus*[24] bacteria by application of solutions of pure DNA.

(*b*) The role played by DNA in the growth and heredity of the coliphages of the T series.[25,26]

(*c*) Indications from current work that increased mutation in microbial systems occurs under conditions of deficiency for an essential constituent of DNA such as thymine, or in presence of a competitive analogue of a constituent, such as bromouracil.[27]

All such phenomena carry the promise of new lines of investigation of the mechanisms of gene mutation.

7. Concurrent investigations have remarkably advanced understanding of the chemistry and structure of DNA, particularly the X-ray diffraction studies of Wilkins *et al.*[28] and the complementary biochemical relationships uncovered by Chargaff and others,[29] leading to the remarkable double helical structure proposed by Crick and Watson,[30] so suggestive of the exact replicative process required for the transmission of hereditary characters, and already so productive of fresh ideas concerning the mechanics of mutation.

8. While none of these arguments is alone conclusive, and while it is recognized that the genetic material of cells of higher organisms is organized into very substantial stainable structures, which must be more complex physically and chemically than the fine DNA fibrils visible only under the electron microscope,[21] nonetheless very many geneticists believe that the ultimate carrier of genetic information is likely to be the arrangement of nucleotides in DNA.

9. In that event, total radiation-induced mutation rates, in the widest sense of change of the hereditary information, might be expected to be quantitatively correlated with the DNA content of the cells of the germ plasm together with the biochemical operations which construct and maintain DNA. It at least seems reasonable that when comparisons of mutation rates between different species or physiological conditions are made, parallel DNA comparisons should be kept in mind. The DNA contents of some relevant types of cell are listed in table VII. Most kinds of cell nuclei contain enough DNA to form a structural molecule of great length which could only be packed inside the nucleus by much folding. This has given rise to the recent suggestion, now appearing on purely structural grounds, that the chromosome may consist of a multi-stranded structure.[10] If the structure turned out to be, say, a proteinaceous backbone with attached DNA molecules as side arms forming the genes (a possibility which is not excluded), the distinction between inter- and intragenic mutations could eventually come to have a very real physical basis, and the two kinds of mutation could differ in mechanisms.

Linearity of dose-mutation curve

10. The experimental justification for speaking of radiation-induced mutation rates at low doses rests upon *Drosophila* data, in which the linearity of the dose-mutation curve, when it is investigated under sufficiently rigorous conditions, has been confirmed down to X-ray doses of 25 rad for irradiation of spermatozoa by the painstaking work of Stern and his collaborators,[31-33] following earlier experimenters.[34-36] Muller[37] has recently argued cogently that there is no point in pressing the test of linearity below 5 rad, and has indicated that this limit could be reached in *Drosophila* by techniques at present available. Many geneticists would agree with the implication of the cited passage, that linearity can already be safely accepted, without the enormous labour involved in its extension to still lower doses—at least in the absence of a definite proposed basis for expecting a non-linearity. However, it must be borne in mind that linearity has not been tested in this range of doses for spermatogonial irradiation. In the case of irradiation of these cells it is still difficult to conceive *a priori* of a non-linearity at low dose, followed by a linear portion of the curve at medium or high exposures. However, Oakberg[38] has shown that some classes of spermatogonial cells of the mouse are very sensitive to the lethal effects of low doses (5 rad — 100 rad) of gamma-radiation. If these same classes were to turn out also to be unusually sensitive to the induction of mutations by radiation, the curve of recovered mutations as a function of dose might turn out to be linear in the range of moderate doses, but to have considerably higher slope in the very low dose range where an appreciable proportion of the cells surviving irradiation belonged to the sensitive group.

11. The Committee has been informed of current experiments upon mice which will enable the linearity of the dose-mutation curve for irradiation of spermatogonia, oögonia and oöcytes to be checked down to 37.5 rad.[39] Attention must, however, again be drawn to the dependence of the whole quantitative assessment of genetic effects of low doses upon an assumed linearity and for irradiation of a particular type of cell in a dose-range not experimentally investigated.

Mechanism of mutation

12. Many attempts have been made to affect the process of induced mutation after its initiation by exposure to ionizing radiation. Some of these have been successful to a greater or lesser degree,[40-44] and this fact is of cardinal importance as demonstrating at least the possibility of interference between the irradiation and its principal genetic consequence. Unfortunately, in many of these cases the precise genetic nature of the mutational event is not known; association with chromosome breakage or rejoining may therefore be suspected. Moreover, many of the experiments refer to microbial material, in which it is possible that the gene structures are far more exposed and more easily able to be reached and affected by external agents than are the mammalian chromosomes. Nevertheless, it is a hopeful sign that recent experiments reported to the Committee have extended the demonstration of post-irradiation interference to a well-known class of apparent gene mutations, the sex-linked recessive lethals of *Drosophila*.[45] These experiments seem to show that a finite interval of at least some tens

of minutes exists in *Drosophila* before "fixation" of radiation-induced mutations.

13. In connexion with any possibility of ultimate practical use of chemical or other modifiers of induced mutations, it is well to remember that, in many populations, the largest man-made exposures of the gonads occur through comparatively large doses delivered relatively infrequently in the course of medical work at controlled times. The possibilities of modifying the mutational effects of radiation should be considered in the light of the more general discussion of modifiers of radiation effects in chapter IV and annex F of this report.

Other possibilities of interference between irradiation and its effects at the cellular level

14. Interference with and control of genetic consequences of irradiation does not end with the completion of the mutational process. However, to look further requires that the completed mutations be detectable. The number of conditions in which carriers of unexpressed deleterious genes can be detected has recently increased greatly;[46,47] this trend is closely associated with advances in general biochemical and immunological genetics, and it is to be hoped that Governments will foster and encourage its progress. A second field closely related to this and other aspects of the present subject is that of human chromosomal cytology. We are indeed a long way removed from the beautiful situation which prevails in *Diptera* where giant salivary gland chromosomes can be studied in minute detail; nevertheless recent technical advances in the field have been considerable[48,49] and can give us great hopes of progress. Such advances may bring about radical changes in human genetics and especially human radiation genetics.

15. Other radical possibilities for dealing with radiation-induced mutation, besides the cumbersome and often painful process of selection, beyond question exist. An example which must be considered, in the light of technological advance, is that of the natural or controlled transfer of genetic characters. This phenomenon is well-established in microbial materials,[50] although usually but not always with very low frequency,[51] and as an eventual aid in the elimination of harmful genes or their consequences it cannot be entirely dismissed as speculation.

Comparison between natural and radiation-induced mutations

16. There has been a widespread belief among geneticists, based largely upon the classical work of Stadler in corn[52] that radiation produces in general a different type of mutant allele from those which occur naturally—more extreme, less likely to be reversible, more frequently a loss of function. However, Stadler's work may not be entirely typical even of plant material.[188] Muller has recently reviewed the evidence against existence of such a distinction.[9] Certainly, both the mechanism of production and the distribution among loci of radiation-induced and natural mutations differ;[53] there is also some indication of small differences in the proportions of mutation to the different alleles at a single locus.[54] Minute one-hit deletions do occur under the action of radiation,[55] and some radiation-induced point mutations in *Drosophila* may be associated with breaks or structural changes near them.[56] Moreover, evidence in *Drosophila* is against any appreciable correlation between natural mutation rate and radiation-induced mutability where either individual genes,[57] strains,[58] or physiological conditions[59] result in altered natural rates. Very little correlation is also found between radiation-induced mutability and the natural rate in the sample of thirty biochemical back-mutations examined by Glover.[53] However, the wide variations in the ratio of radiation-induced to natural mutability found both in the work of Glover on bacteria and in extensive work on plants[60] do not seem to be correlated with the type or severity of the forward or back-mutation involved, and it is generally accepted that the ratio of visibles to lethals is much the same for natural and radiation-induced mutations in *Drosophila*, although no explicit study of this point has been made. Moreover, a very detailed investigation by Giles[61] of purple-adenine and other mutants in *Neurospora* has shown no evidence for a qualitative or quantitative difference between radiation-induced and spontaneous mutations at the same locus. The evidence of Stadler primarily relates to the compound *A* locus; consequently, a possible explanation is that *A* has a very low sensitivity to radiation-induced point mutation. It is therefore reasonable to accept as a tentative assumption that spontaneous and radiation-induced mutations are qualitatively similar; wide differences in the two mutation processes exist but are functions of individual loci, and are not appreciably correlated with the type or severity of effect exerted by the mutant allele.

17. In connection with this problem, attention may be drawn to certain organisms such as *Aspergillus*,[62] bacteria,[63] and coliphage,[64-66] in which very sensitive tests of allelism are possible: tests which may be calculated[51] in some cases to be adequate for resolution of recombination distances corresponding to one nucleotide pair if genes are primarily constituted of DNA. Such investigations might eventually shed much light on the real magnitude of the structures disturbed by various types of mutational event of different origin, and indirectly on the "quality" of mutations caused by different agents. Unfortunately, all the above organisms are microbial and not necessarily representative of the larger chromosomes of higher organisms.

18. In man, little information yet exists concerning the relative sensitivities of genes to specific mutagens. However, a notable beginning has been made upon the problem by Penrose,[67,198] who has analysed the mean parental age at birth of propositi showing various conditions, and correlated these shifts with hypotheses as to the principal kinetically different classes of mutagens, such as natural radiation (expected to raise both mean paternal and maternal ages by an equal small increment), copy-error (expected to raise mean paternal age somewhat), or chemical mutagens (which might under some circumstances raise the mean maternal age in such a way that incidence increased more than linearly with age). Thus the prospect already exists of the analysis of human genes in terms of sensitivities to different kinds of mutagen.

Detection of mutation

19. An apparent gene mutation can be detected if it results in a new allele which differs so much in its action from the original one that it can be scored by appropriate methods. There exist different alleles (isoalleles) whose phenotypic effects cannot at present be distinguished but which may differ in other respects as, for example, mutability.[68] Studies of natural and induced mutations are restricted to those which can be distinguished pheno-

typically, and measurements of their frequency will consequently be minimum figures for the total mutation rates of the genes concerned.

20. In *Drosophila* as well as in mice the rate of visible mutations at specific loci has been studied after matings of the stock to be tested with animals of the opposite sex containing the marker genes whose mutation frequency is to be examined. By this method the visibles scored include both those which are recessive lethals in homozygous condition and those which are homozygous viable, provided only that they are visible and viable as heterozygotes with the allele in the marker stock.[189] As reported by Russell,[69] six out of twenty-one tested mutants induced in spermatogonia of mice were lethal, seven were semi-lethals and eight were viable. The corresponding data from Alexander's[70] test of mutations in spermatogonia in *Drosophila* yielded three lethals, one semi-lethal and four viable. Excluding rare heterozygotes combining a recessive viable visible with a recessive lethal visible, what could be scored in any corresponding study in man might be only those recessive visibles not rendered unscorable by their association with recessive lethals. Supposing the same relationship between viable and lethal visibles as in mice, one might easily underestimate the total mutation rates of genes in man by a factor of two or three.

21. In estimating mutation rates it must also be borne in mind that the same phenotypic effect need not mean a genetically identical condition. In man, as in many other organisms, several different genotypes may exist which give rise to indistinguishable phenotypic expressions. In the case of man one must think of classes of genes each causing a similar effect, rather than of specific single genes. The number of genes in each such class may vary considerably, causing a strong variation between the observed rates of natural mutations in the various classes. Thus in man, because test breeding cannot be used to pin down an alteration to a specific locus, a mutation rate is always in fact measured for the whole class of genes giving rise to one altered condition, recognizable trait, or clinical entity.

22. In recent years many important studies of the mutational process have been made in unicellular organisms. There are, however, several major problems in the measurement of gene mutation rates in single cell material, including a lag between application of radiation or other mutagenic agent and the observable expression of mutations which enables them to be counted: this lag can be due to various factors, segregational or physiological.[71] Furthermore, there is always a possible effect of non-mutant cells upon the survival of mutants during tests.[72] A different problem, peculiar to back-mutations, is the difficulty of distinguishing apparent back-mutation at the same locus from suppressor or modifier effect. For this problem, which is related rather closely to the important question of the reversibility or otherwise of radiation-induced as compared to spontaneous mutations, there are great advantages to microbial material in which both kinds of forward and reverse mutations have been and are being explored. Both radiation-induced and spontaneous mutation rates have been measured with relatively high precision in unicellular organisms, especially bacteria, under a variety of conditions;[73,74] it is to be hoped that the techniques and methods developed will yield equally valuable results when applied to the clones of mammalian tissue-culture cells now available.

2. Mutation rates*

Natural mutation rates

23. The basic difficulty in any quantitative study of natural mutation rates is to obtain large enough numbers, for these rates are low (tables I, II) and cannot of course, be raised artificially for purposes of study. Consequently, investigation has been confined to organisms which can be handled or are present in rather large numbers, such as bacteria, *Drosophila*, and humans. The limit to the information on natural mutation rates which can be derived from the very extensive and careful control observations in mice, in the work both of Carter, Lyon and Philips[75] and of Russell[69,76] illustrates the difficulty. Because chromosome structural changes occur naturally at much lower frequencies even than apparent gene mutations[77,80,164] and the study of rates has been confined almost entirely to the latter events, only these will be considered here. In man, individual cases, once found, can be followed up with relative ease even in large populations, because the family and individual are indentifiable by name, etc. As a result, it is possible that more information about natural mutation rates for single phenotypic entities exists for man than for any other organism. In man, however, as in other organisms, the basic problem of small numbers governs consideration of the field.

The rate and variation of natural mutations in experimental organisms

24. In other organisms than man, it has been possible by experiment and test breeding to examine more closely the variations in natural mutation rates as well as the absolute magnitudes. The general ranges of the latter do not vary very widely (table II).

Physiological variations

25. As noted above in another context, physiological variables affecting natural mutation rates of individual loci have been examined in bacteria by Novick and Szilard[78] who concluded that the number of mutations increased as a function of chronological time rather than cell division. This may, however, not be generally true:[79] moreover, the genetic material of bacteria may not be entirely representative of that of higher organisms. Moreover, the general lack of systematic variation of doubling dose among species of widely different generation times, militates against any assumed dependence of number of natural mutations upon chronological time.

26. Work on physiological variables in *Drosophila* has been carried out in relation to mutation at classes of loci, such as the recessive lethals, rather than at single loci. Differences between natural strains[174] and between sexes[80] and dependence upon age[80] have been established for a number of organisms. These variations in natural mutability are not known to be correlated with variations in the radiation-induced rates.

* Strictly, the term mutation rate refers to the rate of occurrence of mutational events and not to the frequency of mutant gametes among tested gametes, although it is also commonly used to refer to this latter measure. The distinction must, however, be borne in mind in certain situations: for example, if it is desired to compare true natural mutation rates estimated for free living unicellular forms of life with the frequencies of appearance of mutant gametes in higher organisms, since the latter do not directly reflect the rates of occurrence of mutational events in the germ line cells (see table II).

Variations between loci

27. The difficulty, even in *Drosophila*, of obtaining enough data to document significant variations in natural mutation rates between loci other than exceptional unstable genes further underlines the basic problem of numbers in the investigation of natural mutation rates. Variation between loci, and in certain cases between isoalleles at the same locus is, however, well-known in this organism.[68] It has been far more extensively documented in the bacteria, at least for back-mutations; the rates of these vary from 10^{-8} to the lower limit of detection near 10^{-10}: they are correlated with mutability by radiation to only a very small extent.[53]

28. In extreme cases variations between loci may originate in genes which are themselves unstable or confer instability upon others. Where mutator genes affect all or a large part of the genome, they may in addition be partially responsible for variations in spontaneous mutability between strains. Again, such genetic modifications of spontaneous mutation rates is not known to be correlated with change in radiation-induced rates.

Natural mutation rates in man

29. Penrose, Neel and others have tabulated a number of calculated rates for single clinical entities in man (see table I). In examining these values, it is necessary to bear in mind the limitations of the data and of the methods of calculation by which they are obtained.

Direct methods: autosomal dominants and sex-linked recessives (table I)

30. In the case of clear-cut autosomal dominant visible entities, the mutation rate is in principle directly estimated by observation of propositi whose parents and other close relatives are normal. The various technical difficulties such as failures of ascertainment and occurrence of phenocopies, degree of penetrance, and the proportion of cases not due directly to fresh mutation have been discussed in the literature.[81,82] The experimentally ideal dominant visible combining full penetrance, complete ascertainability and responsibility for total sterility would be of reduced value, since it could not be proved directly to be genetic in origin. Moreover, in practice studies are commonly made upon the natural mutation rates in those populations where they are known to be highest, simply in order to obtain enough documented cases to make the results statistically significant. It is therefore questionable whether the observed rates are representative. They cluster around 10^{-5} per gamete in a distribution which is rather skew. If a population of 10^7 is surveyed during five years for an ideal condition, observable during thirty years, it already constitutes a considerable labour, and yet significant results are unlikely to be obtained unless the mutation rate exceeds 10^{-6}. In practice, no such ideal conditions exist. It is very probable that some of the well-documented human mutations[83] have much lower frequencies. Perhaps the possibility should be faced that the sample of spontaneous mutation rates which have been measured in man is not representative, and that the true centre of gravity of the rates for this group of entities lies at or below 10^{-6} rather than near 10^{-5} per gamete. This encourages the suspicion that among the autosomal recessive visibles for which rates have been calculated indirectly, more than hitherto suspected might show heterozygous advantage. There is need for Governments to foster extension of the scope of existing methods, especially to conditions which are rare or of weak or irregular expression.

Indirect methods: autosomal recessives (table I)

31. The mutation rate for autosomal visible recessives is calculated indirectly, by a process originally due to Haldane.[84] The observed number of propositi, together with an estimated selective disadvantage in the homozygote, is used to calculate the rate of disappearance of the mutant alleles concerned from the population, and a balancing rate of forward mutation is inferred from an assumption of genetic equilibrium. The uncertainties concerning possible existence of small selective effects in the heterozygote and of large departures from equilibrium render extremely uncertain the values obtained in this way: indeed, perhaps the most notable use of such figures has been to deduce *a priori* expectation of heterosis from a few "unreasonably high" calculated mutation rates, although most of them lie in the same order of magnitude as those for dominant entities (see table I).

Lower limit to detection of recessives

32. An autosomal recessive with a selective disadvantage of only 1 per cent in the heterozygote, in a population whose coefficient of inbreeding was 0.01 per cent, would, if its mutation rate were 10^{-6}, show up phenotypically in no more than about 1 in 10^8 of the population. Even if the condition were fully penetrant, a mutation rate would be very difficult to estimate. Such genes, if their natural mutation frequencies were in the range of 10^{-7}, could hardly be observed at all. There is therefore reason to believe that the best documented sample of recessives for which indirect estimates of mutation rate are available may be unrepresentative. If this is because they show very slight heterozygous advantage, the mutation rates calculated for them are also too high; but then there is a fallacy in the converse argument, that because many of these turn out upon investigation to be heterotic, most human mutant alleles are so.

Consanguineous marriages

33. The study of consanguineous marriages does not lead to estimates of natural mutation rates but to estimates of the numbers of recessive alleles present in populations. In principle, these marriages constitute a test-breeding for the presence of recessive alleles through the associated degree of homozygosity ($\frac{1}{16}$ for first cousins) which they bring about. It may, however, be questioned whether a truly comparable control group can ever be obtained, although internal controls by comparison of different degrees of consanguinity are usually available. The limited number of studies made show as yet no very consistent picture. Of them, those by Sutter and Tabah[85,86] and by Schull[190] are the most extensive, and that by Böök[87] the most intensive. Morton, Crow and Muller,[88] by an ingenious argument, have shown how to present the over-all reduction in viability, which is observed in three of the surveys, in the form of an equivalent number of alleles which would be lethal if homozygous, or lethal equivalents, carried per head of population. From the surveys analysed by them they conclude that 3-5 lethal equivalents acting before maturity were present per individual in the population, a figure with which the survey reported by Schull is in satisfactory agreement. Unfortunately, the intensive examination carried out by Böök shows an entirely different picture of viability, although in a very small sample; the total deaths, including prenatal and up to age 30, in Böök's sample, were almost identical in the cousin marriages and the controls.

34. The content of deleterious recessive genes of a population, whether expressed in lethal equivalents or otherwise, is an important parameter indicative of its genetic state. It is also a valuable standard of comparison for actual or postulated mutation rates. There is, however, another possible use for it. Comparison can be made of the total recessives in lethal equivalents, derived from vital statistics only, with intensive investigation of all the known recessive lethals present, such as that undertaken by Böök. (Ideally, the total reduction in viability and fertility up to the second generation beyond the cousin marriages should be employed, (see paragraph 113 below) and the intensive examination should cover all known recessive conditions.) In this way it might be possible to obtain some idea of what proportion of recessive damage is covered by the known effects, and what proportion remains unknown: a factor of great importance to our confidence in any estimates or predictions, based as they must be upon current limited knowledge. This possibility is discussed in more detail in paragraph 113.

35. It is clear that improved recording of such consanguineous marriages, in maternity hospitals or centres of vital statistics, would be of great value and should be encouraged by Governments if they wish to be aware of the general state of genetic well-being of their peoples.

36. The Committee has been informed of large-scale current or planned surveys of consanguineous marriages both in Japan, where the frequency of these is high, and, as regards vital statistics, in Canada.[89,90]

37. It has, unfortunately, not been possible so far to establish total natural mutation rates in man for very large classes of genes, such as that formed by the sex-linked recessive lethals of *Drosophila*. Such large classes, if they could be investigated upon a firm genetic basis, might more easily provide adequate numbers for reliable statistical analysis than can be obtained from the laborious search for specific rare conditions. In this connexion, it is of interest that Lejeune and Turpin[91] have recently attempted to interpret the decrease of sex-ratio at birth with age of either parent in terms of a mutational hypothesis. There is, however, no certainty that the secondary sex-ratio does decrease with the age of the mother,[186] and the combined data upon irradiated and aged fathers appears at present to involve contradictions. Since there does appear to be a decrease in sex-ratio with age of the father,[186,187] it seems a reasonable possibility that mutations to sex-limited detrimental autosomal dominants are concerned and that they are due to natural irradiation or other non-cumulative, time-independent causative agents (Penrose's Class I,[67] see paragraph 18 above). It would evidently be of great value if clear-cut interpretations could be established in some other mammal, such as the mouse, since secondary sex-ratio data are widely recorded in large populations, although not always in a form suitable for genetical analysis, and they are relatively free from the ambiguities of fine diagnostic distinctions. The possible interpretation of sex-ratio data is further discussed in paragraph 64 below.

Mutator and unstable genes

38. In any consideration of variations in spontaneous mutation rates, the evidence of mutator genes and unstable genes, well-established in corn, in *Drosophila* and in bacteria,[92] must be borne in mind, together with the fact that these commonly do not affect the rate of induction of mutations by irradiation. Minor effects of this kind might be more common than are supposed and could perhaps give rise to some variations in natural mutation rates between human populations. If that were so, these in turn could be expected not to give rise to any corresponding variation in radiation-induced rates. Although variations in frequencies of appearance of mutant phenotypes between different human populations are well known to occur,[93] they have been inadequately documented, especially for dominant conditions. In the case of recessives they are usually attributed to past selective differences, although it is conceivable that genetic drift also plays a part.[94]

Radiation-induced mutation rates

39. Radiation-induced gene mutations have not yet been observed with certainty in man, and so no quantitative dose-mutation relation exists for the genes responsible for any specific clinical entity. In consequence, quantitative assessments of the mutational affects of the irradiation of human populations must rely at present upon tenuous arguments and upon extrapolations which are often of uncertain validity. In any event they depend upon the well-established results of the investigation of radiation-induced mutation in other organisms.

Magnitude and variation of radiation-induced mutation rates in organisms other than man

40. Since the field of mutational radiation genetics was opened by Muller in 1927,[95] it has been established in all the many organisms tested that ionizing radiations can induce apparent gene mutations: hence the same is believed true of man. X-ray induced mutation rates have been measured for a large number of single loci, especially in *Drosophila*. Both the range and average of such rates are known for a wide variety of individual visible markers through measurements made under very carefully controlled conditions, and so also is the total rate for certain large classes of markers such as the sex-linked recessives of *Drosophila*. A number of rates observed in experimental species are listed in tables III, IV and V.

41. In mammals, the most extensive investigation of the X-ray induction of mutations at single loci so far carried out is that for mice,[69,75,76,96] in which the rates at seven autosomal recessive visible loci have been investigated in spermatogonia; the average of these rates is found to be about fifteen times the average for a comparable group of loci in *Drosophila*.[70]

42. Extensive research has been conducted upon the variation in sensitivity to radiation-induced mutation with physiological condition. In the male it has now been established that the mutability is low in spermatogonia, rises to a peak during the time of formation of spermatids, falls to a second minimum in immature spermatozoa, and then rises up to the time of ejaculation, both in *Drosophila*[97,98] and the mouse.[99] In the female *Drosophila*, the öogonia show a mutability similar to that of spermatogonia while late öocytes are very mutable.[37,100] The subject has recently been reviewed by Glass.[100] *Drosophila* is also the only organism for which extensive determinations exist of the relative rates of mutations in different selective and other classes, either at single loci or summed over large parts of the genome.[101,102]

43. Muller[103] has pointed out that evidence in *Drosophila* indicates that mutation rates in somatic and gonial

cells are about equal. Extension of this principle to other species[104] and eventually to man might make possible very informative conclusions from investigations on somatic mutation rates *in vivo* in man.

44. Calculations have been made by Haldane[105] and others concerning the practicability of observing not single locus rates but total rates over a large part of the genome in a mammal such as the mouse. Such an experiment upon the very large scale necessary might be of considerable value at this juncture in the process of extrapolation to man; it would, however, involve the expenditure of a great many scarce mouse-geneticist-years. The Committee has been informed of the existence of a pilot experiment on these lines.[106]

45. The concept of genes as finite structures of different sizes which carry hereditary information largely in the form of different arrangements of nucleotides in DNA has recently made possible one particularly interesting interspecies comparison concerning induced mutations.[107,108] There is evidence that in mice the total rate of induction of recessive lethal mutations in sperm is higher than the corresponding rate in *Drosophila* by a factor of about 20.[107] The same is true for the rate of mutation per locus averaged over several different loci, and in addition there is a similar difference of about twenty-fold in the same direction in the DNA content per nucleus. This suggests that perhaps mouse genes are not more numerous but are larger than *Drosophila* genes —that the extra DNA has gone into building genes that are bigger and more complex rather than more numerous. The possible application of such an idea to man, an organism in which mutational events cannot in general even be assigned to definite loci by test crosses, but which has a DNA content per nucleus similar to that in the mouse, might lead one to expect rather high mutation rates, both spontaneous and induced, when measured "per clinical entity", as well as all the complexities and peculiarities of large multiple allelic series, of which a notable example has been uncovered by Dunn in the t-alleles of the mouse.[109] Penrose[93] has already drawn attention to the possibility of some unusually complex genes in the X chromosome of man, in connexion with very high observed natural mutation rates.

Radiation-induced mutation rates in man

Surveys of radiation-induced gene mutations in man

46. Whatever approach is adopted to the problem of radiation-induced mutation rates, the gonad doses received both by control and by experimental groups will have to be known.

47. In principle, the simplest method to obtain a quantitative relation between dose and radiation-induced gene mutations in man is to make a comparative survey of the progeny of an irradiated ("experimental") and a comparable un-irradiated ("control") population. Those surveys published so far are concerned only with the first generation born of irradiated parents. However, it is easy to show that, as human matings cannot be controlled, examination of the first generation provides more information in itself than examination of subsequent generations.

48. In the last analysis, all the observed quantities come down to variations in frequency, and therefore:

(*a*) All studies must be accompanied by the examination of a control sample presumably issued from genetic stock identical to that of the irradiated sample. This condition greatly restricts the value of the results published so far.

(*b*) All the results obtained are subject to an inevitable sampling error which necessitates the collection of a very large amount of data.

A number of quantitative characters, such as birth-weight, size and various anthropometric measurements, as well as statistical data, such as neo-natal mortality, have been suggested and examined. Unfortunately, the precise genetic component in these variables is not known; on the contrary, they are known to be dependent upon factors which are economic (standard of living), demographic (age of parents, order of birth, etc.) and sociological (medical care).

49. The characters that can be utilized may be grouped in two categories, according to whether they are connected with dominant (or sex-linked) visible mutations or with dominant (or sex-linked) lethal mutations. The detection of visible dominants is carried out in practice by the observation of malformations at birth. It is in fact reasonable to assume that an increase in the frequency of dominant mutations associated with visible effects would manifest itself to some unknown extent as an increase in frequency of malformations. The same would be true of visible sex-linked recessives in boys born to irradiated women. Lethal mutations may be revealed in four ways:

(*a*) Increase in frequency of miscarriages (virtually impossible to determine with certainty);

(*b*) Increase in frequency of still-births (much more feasible but subject to the demographic considerations mentioned in connexion with neo-natal mortality);

(*c*) Reduction in fertility, or even sterility (virtually impossible to measure in man);

(*d*) Disturbance in the ratio of the sexes at birth (deviation in the sex-ratio, an easily observable criterion).

50. The various studies which may be taken into account at the present time are listed, together with pertinent results, in table VI. Given the very uneven quality of the data presented by the various authors, and the particular way in which they were arranged by each of them, it is impossible to add together the figures from the separate surveys. In general, none of the investigations makes a definitive demonstration of a genetic phenomenon. Only the decrease in the sex-ratio, which is found in the three studies of irradiated mothers, seems to be acceptably established as a reality. Although no one of these studies concerning sex-ratio yields statistically significant results by itself, the fact that all three deviate in the same direction gives some confidence concerning the reality of the effect. Although several of the studies to date raise the possibility of an increase in congenital malformations among the offspring of irradiated persons, the findings in this regard are much less consistent than those concerning the sex-ratio. In this connexion, it must constantly be borne in mind that where many comparisons are being drawn between two groups, on the basis of chance alone one in twenty of these comparisons will yield differences exceeding the 5 per cent level of significance. Further observations regarding the possibility of an increase in congenital defect or early death are highly desirable.

51. In summary, it seems possible, although only with great difficulty, to distinguish a detrimental effect of irradiation on the first generation issuing from irradiated parents. The possibility of firm demonstration and

measurement of this phenomenon suggest that all these studies be extended on the largest scale possible, wherever practicable surveys can be made with a reasonable probability of yielding positive significant results in a comparison with adequate controls.

52. In view of this possibility of future surveys of the progeny of irradiated persons, it seems worthwhile to indicate the criteria which determine the value or "resolving power" of any such study. In brief, five points must be considered:

(*a*) The dose to the parents of the individuals under study;

(*b*) The number of individuals whose parents have been so exposed;

(*c*) The number of characteristics of genetic significance to be recorded;

(*d*) The manner in which information on these characteristics is collected;

(*e*) The availability of a suitable control group.

53. To illustrate the manner in which (*a*) and (*b*) may be taken into consideration, a particularly simple hypoethetical case has been selected, that of the detection of an ideal autosomal dominant visible allele causing complete sterility:

Suppose the gene concerned to mutate at a rate m per gamete in the control population and at an increased rate fm per gamete in the irradiated population. If the doubling dose for the mutational step concerned is D_2 rad and the mean genetically significant exposure *per parent* of the irradiated group is D rad, then

$$f - 1 = D/D_2$$

If P progeny of the irradiated group and Q of the unirradiated are examined with complete ascertainment for the visible allele, the numbers expected to be observed are respectively 2mfP and 2mQ. The observed difference in rate between the two groups is $\Delta = 2m(f - 1)$ and has an approximate variance due to the limited sample size of

$$\sigma_\Delta^2 = 2m(f/P + 1/Q)$$

In consequence, even if no other sources of error are considered,

$$\chi^2 \geq \frac{\Delta^2}{\sigma_\Delta^2} = \frac{2m(f-1)^2}{(f/P + 1/Q)}$$

If we require that $\chi^2 \geqslant 4$ for a significant increase of mutation rate in the irradiated group to be established, and denote $\chi^2/4$ by R, then for a significant increase in mutation rate at a single locus,

$$R = \frac{m}{2}(f-1)^2 \Big/ (f/P + 1/Q) \geqslant 1$$

In terms of D and D_2

$$R = \frac{m}{2}(D/D_2)^2 \Big/ \left(\frac{1 + D/D_2}{P} + 1/Q\right)$$

For example, in the study of Neel and Schull,[111] the progency of irradiated parents numbered 3.3×10^4 and the progency of control parents, 3.2×10^4, while the average excess radiation exposure to the combined parents of the former group is about 17 rad. Because of the known heterogeneity of exposures, R for any single locus must be computed by adding together the calculated R values for the various exposure classes, which add up to 2.3×10^{-2} on the assumption that the representative doubling dose is 30 rad. With respect to the possibility of significant findings based on mutation at *any one locus*, then this study (and any other study to date) is far below the level of significance.

54. Where multiple traits are involved in the inquiry, the power of the study is a function of the precise number of traits under consideration. For example, if one were to make the over-simplified assumption that mutation at any one of 100 loci resulted in completely penetrant, dominant mutations responsible for congenital defect, assuming independence in the expression of mutation at these loci, the calculated resolving power of the previously mentioned study becomes 2.3, and the failure to observe a significant effect of radiation on the frequency of congenital malformations in the aforementioned study might indicate that the assumed doubling dose was too low.

55. The sex-ratio is one of the more conveniently studied indicators of possible genetic damage. Information on this point is relatively easy to collect and has a high degree of objectivity. The calculations corresponding to those of paragraph 53 are relatively simple and proceed as follows:

Suppose a group of mothers receive gonad doses averaging D_m prior to conception of children, and suppose the irradiation causes a shift in the secondary sex-ratio s which is linear with the dose

$$\Delta s_m = k_m D_m$$

Suppose P_m progeny of these mothers are examined, the variance in the determination of the sex-ratio of the progeny of the group, due to limited sample size, will be

$$\sigma^2 = \frac{s(1-s)}{P_m}$$

Since s is always approximately ½, this may be written

$$\sigma_\Delta^2 = \frac{1}{4P_m}$$

If such a group is compared with Q_m progeny of a control group the variance of the observed difference is

$$\sigma_\Delta^2 \frac{1}{4P_m} + \frac{1}{4Q_m}$$

and the significance of the observations is determined by

$$\chi^2 = 4k_m^2 D_m^2 \Big/ \left(\frac{1}{P_m} + \frac{1}{Q_m}\right)$$

If we require $\chi^2 \geqslant 4$ before the shift can be considered significant, then

$$R_m = k_m^2 D_m^2 \Big/ \left(\frac{1}{P_m} + \frac{1}{Q_m}\right) \geqslant 1$$

Similar formulae can be derived for comparison of the progeny of irradiated fathers with controls, where

$$R_t = k_t^2 D_t^2 \Big/ \left(\frac{1}{P_t} + \frac{1}{Q_t}\right)$$

A number of completed surveys, irrespective of the significance of their results, all show decreases in s when the mother is irradiated from which values of k of the order of -1×10^{-4}/rad can be derived. If this figure is adopted for purposes of calculation, then

$$R_m = 10^{-8} D_m^2 / \left(\frac{1}{P_m} + \frac{1}{Q_m}\right)$$

On the basis of the present limited information, values of R_f have been calculated using a similar numerical value of k but of opposite sign

$$R_f = 10^{-8} D_f^2 / \left(\frac{1}{P_f} + \frac{1}{Q_f}\right)$$

Clearly, if k_f and k_m do in fact differ in sign, then significant results may occasionally be obtained by the comparison of progeny of irradiated mothers with those of irradiated fathers, even where neither group differs significantly from the controls. On the basis of the numerical values adopted here, the same condition upon significance would then become

$$R_{f,m} = 10^{-8} \left(D_f + D_m\right)^2 / \left(\frac{1}{P_f} + \frac{1}{P_m}\right)$$

where P_f is the number of progeny of irradiated fathers examined and P_m is the number of progeny of irradiated mothers examined. The resolving power of comparisons with controls of progeny both of whose parents have been exposed will, under these circumstances, involve $D_f - D_m$ and be relatively poor if the doses to the two parents are quite similar. If k_f and k_m were to have the same sign, the situation would be reversed. By way of a numerical example, the data of Turpin and Lejeune[117,118,165] may be considered. In this study, P_m is 136 and Q_m is 236. For the purposes of this calculation, D_m and D_f will both be set at 450 rads. Then R_m may be calculated to be 0.175. The calculated R_f for the same data is 0.52. In passing, it might be noted that because of the many somatic factors thought to influence sex-ratio, one would as a matter of principle have more confidence in the genetic origin of a sex-ratio change among the offspring of irradiated fathers than among offspring of irradiated mothers.

56. That comparisons of the progeny of irradiated and non-irradiated groups must be carried out on rather a large scale, if there is to be any prospect that they will yield significant positive results, is emphasized by the high proportion of non-significant results obtained in the completed surveys of table VI. Moreover, they may require rigorous and complex analyses of controls,[111] and therefore involve considerable effort of a very specialized kind. While negative results on a sufficient scale can be of great value in excluding the most alarming possibilities,[111] only positive ones will suffice for a quantitative relation between dose and mutation frequency. In this connexion, a survey of the high radiation area of Kerala[112,195] appears to have a potentially somewhat greater resolving power than any previously made, if an equally intensive investigation over a ten-year period is assumed.

57. At its first session, this Committee requested advice from the World Health Organization about the possibility of setting up a standard of recognition for one or more clearly recognizable medical conditions thought to be largely or solely genetic in origin. In their discussions of this, the geneticists of the study group which framed the reply of WHO made clear that they strongly questioned the feasibility of using a single condition as an indicator of the mutation level in large populations.[113] Their feeling appeared to be based in part on the manifold uncertainties which exist concerning almost every single likely indicator condition,[110] and in part upon the belief that reliability of results in this field depends upon intensive study of every case. The study group recommended that simultaneous investigations always be carried out on several conditions.[113] Indeed, the sense of the document cited is such as to cast some doubt upon the practicability of such surveys, in view of the associated difficulties of obtaining sufficiently large numbers. It does not, however, rule out large-scale survey plans if the urgency of the situation warrants them. Moreover, if the objective were to survey one population serially in time so as to be able only to establish limits of possible relative increases in the mutation rate, without any interpretation as to cause, some of the difficulties might diminish.[110] One such difficulty seem to lie in combining the intensive examination of cases, which is the classical approach of human genetics, with the extensive survey of very large populations which is required if adequate numbers are to be obtained for studies of mutation rates at or near the spontaneous rate in man. This difficulty is emphasized by the sharp limit of about 3×10^6 set in discussion upon the size of human population which can be covered by an institute conducting epidemiological surveys of the classical type (see also ref. 11).

58. The difficulties of comparative surveys of high resolving power have led Penrose[93] to propose a modified approach, by which a given class of mutant propositi would first be collected from a large population heterogeneous in radiation exposure as well as in other respects, and only then would personal histories, including radiation histories of the parents, be compiled for the propositi and a comparable control group. The method is a powerful one for the wider field of general human genetics, since it can serve as a basis for quantitative investigations of other mutagens than radiation. As applied to the radiation problem, this same possibility of alternative and perhaps unknown causes complicates the choice of a legitimate control group. Moreover, the burden of work is in part thrown into a sphere where rather considerable difficulty also prevails: the quantitative compilation of individual histories of irradiation.[114] In order to obtain a quantitative dose-effect relation from a survey of this type, it is necessary to know not only the incidence of the condition under investigation in the general population, but also the general incidence in that population of individuals having similar radiation exposures to those of various classes of propositi. Many features of the approach are exemplified by the recent work of Steward *et al.*[115] on a somatic radiation problem.

Possible aids in extrapolation of radiation-induced mutation rates from other species to man

59. In view of the difficulties of a formal human radiation genetics, it is necessary to consider possible ways in which radiation-induced mutation rates can be measured in systems closer to the *in vivo* germ cells of man. In this connexion a new field of work has been opened by the ability of Puck and his collaborators to grow colonies of tissue-culture cells, the majority of which are viable and able singly to give rise to fresh colo-

nies[121,122] The well-developed methods of microbial genetics can in principle now be applied to such cultures both for natural and radiation-induced mutations, although certain features are believed by many workers still to limit the applicability of the material to this problem:

(*a*) Tissue-culture cells usually need a more complex medium than the whole organism from which they originate.

(*b*) Well-established lines tend to be poly- or aneuploid. They resemble both each other and the malignant HeLa strain, with which Puck first developed his techniques. In certain types of radiation experiment, this difficulty may be circumvented, as in the work of Bender,[19] who used tissue-culture cells very recently derived from human kidney (within four transfers) in a cytological study of induced chromosome breaks. But the repeated propagation of lines of stable diploids from single cells appears to be a prerequisite for systematic studies of gene mutation in human tissue-culture.

(*c*) Some workers in the field doubt whether any line of normal (i.e. non-malignant) cells has really been successfully propagated as such (but see Puck).[18,121,122,194]

(*d*) It is not yet known what is the exact relevance of studies on the mutational behaviour of somatic cells *in vitro* to that of mammalian germ cells *in vivo*.

Points (*b*) and (*c*) can perhaps be circumvented in part by applying the technique to cultures derived as freshly as possible from normal tissues. However, a difficulty of principle remains: the tissue-culture cell is a free living organism, whereas the ancestral tissue cell is part of an organism so that its growth, division and differentiation are subject to the developmental controls of that organism. In view of the close connexion of all, and especially the genetic, effects of radiation upon the cell with the process of cell division, some initial caution in interpretation is undoubtedly required. Nevertheless, the future role to be played by the tissue-culture methods in the making of comparisons between species so as to provide a basis for extrapolating from the known *in vivo* mutation rates or rates of occurrence of gross structural changes, does not seem open to doubt.

60. There is some evidence[103,104] that the frequencies of radiation-induced mutations in somatic cells is similar to that in gonial cells. If this correlation could be extended to the variation between species, attempts to measure induced and/or natural mutation rates in human somatic cells *in vivo* might provide information of great value as a guide in estimating mutation rates in human genes.

Continued need of research in fundamental genetics

61. It cannot be too strongly emphasized that there is little basis either for planning or for interpreting *ad hoc* radiation genetic surveys in man, or for making calculations concerning radiation-genetic effects in man, except the great volume of fundamental research upon other organisms which has been carried out for its intrinsic interest alone, and directed wholly as a contribution to human understanding. This foundation must be extended and strengthened, and must not be weakened in the interests of the applied superstructure.

3. The representative doubling dose

62. Provided that the dose-mutation rate relation has a linear form

$$m = m_0 + kD$$

the relative increase of mutation rate per unit dose is readily expressed by the ratio k/m_0. Another convenient parameter to use is the reciprocal of this ratio, m_0/k, which is the radiation dose required to produce a number of mutations equal to those occurring naturally, or the "doubling dose" (D_2). For a whole series of mutations m_i whose effects sum up or are collectively observed $\sum_i m_i = \sum_i m_{0i} + D\sum_i k_i$

and one can define a mean D_2 as $\frac{\sum_i m_{0i}}{\sum_i k_i} = \overline{D}_2$.

This procedure can be used to estimate a $\overline{D}_2$ for as representative a group of human genes as possible. It is not necessary to know how many genes are involved or of what kinds, provided that they can reasonably be assumed to be a representative sample and provided that there is assumed to be no correlation between D_{2i}, k_i or m_{0i} and the degree or kind of manifestation. The representative $\overline{D}_2$ should then express the dose-effect relation for any set of radiation-induced mutational events in so far as this itself depends upon a sufficiently representative sample of human genes: usually the sets will be of a kind in which the mutations at a very large number of loci are summed, both in calculating and in making use of $\overline{D}_2$.

Estimates of the representative doubling dose for human genes

General levels in other species

63. It has been pointed out[145,150] that a number of doubling doses calculated for different species cluster around the range 30-60 rad (table VIII). However, the significance of this fact for present purposes is limited by several considerations:

(1) The majority of the experimental radiation exposures concerned were of gametic cells. Where irradiation of gonial cells is concerned, it is true that the best estimate that can at present be made for a group of genes in the mouse (the only mammal so far investigated) is of the order of 30 rad, but this must be compared, for instance, with values for *Drosophila* ranging up to 400 rad (see table VIII).

(2) No satisfactory interpretation of the observed concurrence or range of values exists, and consequently any empirical extrapolation to man would have to rest upon an unsure basis.

(3) The lack of correlation of observed doubling doses with life-span can be interpreted as an indication that mutation at a constant rate in chronological time is not the dominant factor in determining the natural rates in the experimental species. But man is so much longer-lived than the experimental organisms that in his case an appreciable fraction of natural mutations is already quite likely to result from time-independent causes such as irradiation from natural sources. (See Penrose[140] for a preliminary investigation of this point).

Sex ratio

64. Observations have been made of a shift of the sex-ratio in the progeny of irradiated mothers (see paragraphs 50, 55). In a first attempt to make use of the available data, Lejeune and Turpin[120] have proposed a comparison between the effect of irradiation and the

effect of aging. These authors have calculated a significant decrease of the sex-ratio with the aging of the mother alone, the partial regression coefficient being -3.36×10^{-4} for an aging of five years. Taking a value of -6×10^{-5} for one rad as an estimate of the decrease of the sex-ratio following irradiation of the mother (table VI), and assuming that both decreases are related to the same extent to newly arising sex-limited detrimental mutations, they have proposed a doubling dose of

$$\frac{-3.36 \times 10^{-4} \times 6}{-6 \times 10^{-5}} \doteqdot 30 \text{ rad} \Big/ \begin{matrix}\text{From age 0} \\ \text{to age 30 years.}\end{matrix}$$

Unfortunately, as these authors themselves recognize, such a calculation cannot be considered as legitimate before many problems have been solved. The needs include:

(1) A good estimate of the gonad dose effectively received by the mothers;

(2) A better estimate of the decrease of the sex-ratio with irradiation, including a test of linearity of the relationship between these quantities, which is implicit in all current calculations concerning sex-ratio;

(3) An explanation of the apparent contrast between the sex-ratio's decrease with the father's aging[186,187] and the possible *increase* observed after acute irradiation of the father's gonads;[111,124]

(4) The study of other variates such as birth rank[186] which might interact with the real effect of the aging of the mother.

65. Only some preliminary data relevant to the problem of irradiation of the father are available, but these indicate that a sex-ratio decrease after chronic irradiation may perhaps have occurred in man[126] and in the mouse.[125] The latter body of data, although not significant at the 5 per cent level, yields at face value a representative doubling dose in satisfactory agreement with other data for this species.

66. In summary, while the possibility exists in principle of deriving a representative doubling dose by comparing the changes in secondary sex-ratio when parents either age or are irradiated, the relevant phenomena are, at present, not sufficiently well established either quantitatively or qualitatively for this procedure to be reliable. Yet relevant surveys of the secondary sex-ratio are more readily and widely carried out in human populations than are others which must depend upon finer diagnostic distinctions. Consequently, more extensive quantitative data concerning comparable irradiated and non-irradiated human populations should continue to be sought. In particular, it may be worth attempting to search for a decrease of sex-ratio among the progeny of not too heavily irradiated human males; the conclusion of such a test might go far to determine the utility of the parameter in considerations relevant to the human genetic radiation hazard.

67. It is not at present certain, even in *Drosophila*, whether the postulated genetic causes of shifts in the sex-ratio play the quantitative roles expected of them; and data of this kind are needed. It is also possible that further investigations upon experimental animals, especially among the progeny of male mice irradiated at low doses, together with similar observations upon irradiated female mice, may show that in both cases a doubling dose can be derived from sex-ratio shifts which is of the same magnitude as that calculated from purely mutational experiment. Establishment of such facts would greatly strengthen interpretation of corresponding observations upon man.

68. Although today it is not possible to assign any definite confidence to the use of the sex-ratio as an indication of mutation rates, it must be borne in mind that the parameter, even if not totally satisfactory, is the only one easily surveyed in entire populations, and that it represents the "cheapest" genetic trend available to research workers in terms of technical effort expended in surveys.

Induction of leukemia

69. A reasonable probability now exists that, in an intermediate dose range, the radiation-induced incidence of leukemia is a linear function of the exposure of the bone marrow, whatever the manner of delivery of the dose. Upon this hypothesis, it has been calculated that 30-50 rad mean exposure of the red marrow might suffice to double the natural incidence of leukemia among an adult group.[127]

70. Leukemia certainly involves a transmissible hereditary change in the tissue cells concerned, a "mutation" in the widest sense of the word. Whether the process of its induction in somatic cells corresponds qualitatively or quantitatively in any way to the process of apparent gene mutation as it is normally thought of in germ cells is extremely doubtful. Nevertheless, it is not entirely excluded from providing an indication of the relative sensitivity of human cells to natural and radiation-induced genetic changes. The indication must, however, be regarded with great reserve: even if the most helpful possibility eventually proved true, and leukemogenesis were primarily a process of somatic gene mutation, a single very atypical gene in a somatic cell might be responsible, and might be entirely unrepresentative of transmissible germ-line mutations.

Survey of Japanese cities

71. Although the results were negative, the extensive observations of Neel and Schull[111] in Nagasaki and Hiroshima provide some evidence of a lower limit for the representative doubling dose for human genes, at least for the dominant mutations which would have been observed by these authors. A difficulty of the type of survey conducted by Neel and Schull must be mentioned here: in order to obtain significant data, it is necessary to continue collection of it for some considerable time. Among a population who have been subjected to heterogeneous, heavy exposure, there may perhaps be some infertility of a progressive kind selectively induced among the most heavily exposed groups. In that event, incipient positive results may be masked by later data collected in the attempt to make the observations more significant. It is possible that the significance of the observations made in this kind of survey, because of its scale, complexity and uniqueness, can only be evaluated adequately by the authors. It therefore seems reasonable to accept the opinion of Neel and Schull that their negative results make it improbable that the representative doubling dose for human genes irradiated in gonial cells lies below 10 rad.

The natural exposure

72. The representative doubling dose for human genes undergoing chronic irradiation cannot be less than the

genetically significant exposure of natural origin. In most areas this is about 3 rad per generation. In exceptional areas, the natural radiation may contribute so heavily to the natural mutation rate that the observed representative doubling dose would be increased.*

Current best estimates

73. Not one of the arguments in paragraphs 63-71 gives a reliable estimate of the representative doubling dose, yet each depends upon a different, independent set of unproven ideas. This Committee recognizes a need, in our existing state of knowledge, to make use of every available source of information, however tenuous. It considers that the separate arguments and repeated independent observations of small changes, in spite of the statistical limitations upon their significance, provide a reasonable indication when taken together; the representative doubling dose for human genes irradiated in pregametic cells is likely to lie between 10 and 100 rad. There is supplementary evidence that it cannot be less than 3 rad. The Committee notes that the value 30 rad is compatible with the whole of the probable range cited, within a factor of about 3: it therefore has a certain degree of utility for purposes of calculation wherever a "most probable" value of the representative doubling dose is required.

4. Estimates of total rate of radiation-induced mutations in the genome of man

74. Because radiation-induced mutation has not yet been observed with certainty in man, it is not possible to give a satisfactory estimate of total induced mutation rate: indeed, this is hard enough even in *Drosophila*.[108] Nevertheless, it could be hoped that the total rate might bear some relation to total genetic material: such a hope has recently been supported by the only available comparison, that between calculated total induced recessive lethal rates and DNA contents in the mouse[107] and *Drosophila*.† The DNA content of human cells is about 6/5 that of mouse cells, according to Vendrely.[20] Hence, upon the stated hypothesis, it might be expected that roughly one recessive lethal per 250 rad would be induced in human sperm by irradiation. Again by analogy with both the mouse and *Drosophila*, which behave alike, it might be expected that in spermatogonia only about one quarter as many gene mutations would occur. However, in *Drosophila* it has been estimated that the total rate of mutation to appreciably deleterious alleles is about four times the recessive lethal rate.[105] In the assumptions made so far, it has been possible to rely upon common quantitative behaviour of two diverse species. But the induced mutation rates for single loci of mice, as well as the total recessive lethal rate, are greater than those of *Drosophila* by a factor of 20, corresponding approximately to the ratio of DNA contents per cell. This has suggested that perhaps the individual genes of the mouse are not more numerous but are larger and more complex than those of *Drosophila*. In turn, the ratio of total to recessive lethal mutations might be very greatly affected. That this is perhaps not so is suggested by comparison of the induced mutations at sets of visible recessive loci in the two organisms. In both cases, some two-thirds of the experimentally induced mutations have been found upon investigation to be lethal. The similarity could be a property peculiar to visible loci: but it at least suggests that the ratio of total to recessive lethal mutation rates may be the same for these two and possibly other species. If the *Drosophila* ratio is applied to man on these tenuous grounds, a total induced rate of appreciably deleterious mutations of about one for every 250 rad applied to the gonial cells is suggested. It will be clear to the reader that based as it is upon so many tenuous hypotheses, this figure, must be regarded with the very greatest reserve. In particular, it applies only to the sum of oligogenes with individually detectable effects and neglects the polygenes involved in quantitative inheritance, an especially serious omission for organisms which may have considerably larger and more complex genes than *Drosophila*, and may therefore be relatively much more liable to small changes giving rise to many isoalleles even at known loci.

II. THE GENETIC CONSEQUENCES OF IRRADIATION

1. The connexion between mutation and genetic damage: Selection

75. The fate of a mutant allele newly introduced into a population is determined by selection. Hence the connexion between mutation and the genetic damage due to it depends primarily upon the selective properties of the mutant alleles concerned and, in particular, upon the degree of dominance or recessivity of these. Our ignorance of the relevant facts in man is very complete and urgently requires rectification.

76. It is useful to precede inquiry into the action of the selective process upon mutant alleles by an inquiry as to the origin of genetic variation in natural populations and its connexion with fitness. The question is an old one, especially in connexion with plant material, where the great extent of natural genetic variation was early observed, and where breeding experiments early gave rise to the controversial notion of "hybrid vigour". However, much of the agronomic literature is primarily concerned with the externally applied criterion of "yield" rather than with fitness. Moreover, natural populations of plants differ decisively from those of animals in the aspects of genetic structure which are of immediate concern here.

77. What may be called the classical view of the adaptive norm of a natural population supposes the optimal allele to be homozygous at most loci: this situation of maximum fitness is disturbed by mutation, continually restored by selection: rarely, due to chance, to change in external conditions in time or space, or to change in other parts of the genotype, a mutant allele will prove itself advantageous, displace the former predominant allele at the same locus, and become the new wild-type allele (see review in ref. 130). In recent years this view has been increasingly strongly challenged

* The parameter of biological interest is, of course, the ratio of the spontaneous mutation rate to the induced mutation rate per unit dose. In man the spontaneous and induced components of the natural rate cannot be separated, and it is convenient to define the representative doubling dose in terms of the total natural rate. However, in situations such as that described here, the distinction between the spontaneous and natural rate becomes of importance and must be maintained.

† A figure for tht total rate of induced recessive lethals has also been given for yeast by the careful work of Magni.[128] It appears at first sight to disagree with the hypothesis put forward here, because of the exceptionally low DNA content of the yeast cell (table VII). However, yeast is known to possess a relatively extensive non-chromosomal genetic apparatus.[129] It has therefore not been used here for comparison.

by some,[130] especially in connexion with the accumulation of extensive evidence concerning the prevalence and the superiority in many respects of structural heterozygotes in natural populations of *Drosophila*,[131,132] a finding which is itself, however, compatible with the classical view of genic homozygosity as the adaptive norm. It has also been argued on more general grounds[133] that heterozygosity is the adaptive norm at most loci and that heterozygotes are in fact intrinsically better able to adapt themselves and maintain their own stability in the face of changing environmental conditions. A recent experiment by Wallace[134] seems to indicate that even random unselected radiation-induced heterozygosity in general confers an advantage, at least upon individuals otherwise homozygous for certain pairs of arbitrarily chosen chromosomes in laboratory populations of *Drosophila*.

78. These two views lead to different general expectations concerning the consequences of mutation. On the first, most mutants alleles will contribute to the limited degree of heterozygosity, will be harmful, and will require to be eliminated, diminishing the fitness of the population. On the second, mutational events, although the majority of them will still be harmful and will require to be eliminated, will scarcely affect the great degree of heterozygosity already existing, and will diminish the existing reproductive fitness to only a correspondingly small extent. However, this is a consequence of the fact that since the mating of diploid heterozygotes produces some homozygotes, on the second hypothesis the population must pay for its built-in adaptability and plasticity by a permanently reduced fitness due to these.

79. Unfortunately, while evidence now exists for the second view of natural populations of *Drosophila*, this particular organism has certain features (principally chromosomal inversions) which bestow upon it a special capacity for carrying structural heterozygotes, together with all the consequences which may flow from this capacity; these features include the absence of crossing-over in the male,[135–137] coupled with a mechanism for eliminating undesirable products of cross-over between structurally different chromosomes from the egg in the female.[138] There is no reason to suppose man to possess either this particular structural mechanism or an optimal degree of genetic heterozygosity, although the possibility is not excluded that equivalent mechanisms may be found. Hence the Committee is compelled to assume that the general genetic structure of human populations corresponds more closely to the classical model in so far as this relates to known genes having individually detectable effects. There is, however, no basis in our present limited state of knowledge for deciding whether the genes responsible for quantitative inheritance do or do not maintain themselves by overdominance in so far as they affect the over-all fitness. It must be emphasized that upon all the hypotheses discussed here, the great majority of radiation-induced mutations will be to alleles which are in the first instance harmful and unlikely to be retained in the population.

2. Approaches to quantitative assessment of the genetic consequences of irradiation of human populations

80. On the classical basis, the irradiation of human populations is expected to result in mutations to alleles whose expressions are harmful and lead to their elimination: the expressions of these alleles also contribute to the genetic component of human ills.

81. As yet, nothing is known of the rate of induction by radiation of the mutations responsible for any specific condition in man. In consequence, the discussion which follows will be restricted to broad categories of effects. Only by such a grouping together of the consequences of mutation at a large group of loci can a representative rate of induction of mutations per gene, or a representative doubling dose, be applied: these are the only two parameters expressing a dose-effect relation so far available.

82. It is natural, in applying the results of an experimental science, to try to use a synthetic approach, assessing an effect from the accumulated knowledge of various causes. In the present instance, this means attempting to assess the magnitude of the social consequences of increased mutation by using mutation frequencies per rad at particular loci to build up a combined estimate from the effects of induced mutation at all loci. To use this method, let the total mutation rate to the set of alleles responsible for any specific condition denoted by i be k_iD, where D is the genetically significant dose of radiation to the population. By a theorem originally due to Haldane[84] there must on the average be k_iD subsequent eliminations of the mutant alleles through differential failure of reproduction. These are often referred to as genetic deaths, although they may take place through phenomena such as very early abortions, which are of no social significance, as well as through more or less severe disabilities or even premature death. Suppose a fraction p_i are eliminated by socially serious expressions and think of p_i as including some weighting factor whereby such qualitatively diverse end-results as death, physical disability, mental deficiency, etc. may somehow be quantitatively compared. Then the contribution to the social burden is k_ip_iD and the whole contribution of the dose D to the future social burden is $\sum_i k_ip_iD$ over all such specific conditions. The above argument continues to hold whether the mutation involved is to an allele which from the selective point of view is conditionally or unconditionally deleterious, although if the mutant allele is only conditionally deleterious then (*a*) it cannot be eliminated in those situations in which it is selectively favourable, and (*b*) the total elimination rate at any one time may greatly exceed the mutation rate, because the increased fertility of carriers under the selectively favourable conditions increases the gene frequency. If the natural mutation rate m_i is known, then k_i can be re-expressed in terms of the doubling dose D_{2i} by $k_iD_{2i} = m_i$ and for all mutations or a large class of them a mean doubling dose $\overline{D}_2$ can be defined by the equation $k\overline{D}_2 = m$ where $k = \sum_i k_i$ $m = \sum_i m_i$. It is unfortunate that in man we do not know any individual k_i or D_{2i}. Still more unfortunately, the fractions eliminated by socially serious expressions, p_i, are unknown and may depend upon rather small positive or negative fertility differentials in those who carry the mutant allele without expressing it, if they greatly out-number those in whom it is expressed. Nor can a mean p_i be estimated for mutant human alleles. As a result, the synthetic approach leads to an estimate in such terms that it cannot as yet be satisfactorily related to the social consequences.

83. There is an alternative formulation of the problem by an analytic approach, based upon analysis of the

present social burden in terms of naturally occurring hereditary defects. In this, it is asked, (*a*) what is the social burden b_i due to a given condition denoted by i, whose occurrence is related to the presence of adverse genes? (*b*) Of the genetic burden b_i, what fraction f_i is due to recurrent mutation? (*c*) By what fraction g_i will this be increased immediately or in the future by a given fractional change c_i in the natural mutation rate m_i? If the change c_i is caused by a genetically significant dose D to the population,

$$c_i m_i = k_i D \text{ or } c_i = D/D_{2i}$$

For all conditions or a large class of them the total genetic burden may be written $b = \sum_i b_i$, that due to recurrent mutation $fb = \sum_i f_i b_i$ and that due to a given dose D as $\sum_i g_i f_i b_i$. If it is assumed that $g_i = c_i$, this may be written as

$$D \sum_i \frac{f_i b_i}{D_{2i}}$$

It may be assumed that b_i and f_i are independent of D_{2i}. Then the increased burden may be written

$D/\bar{D}_2 \quad \sum_i f_i b_i$ which may be written $(D/\bar{D}_2)\ f\ b$

where $f = \sum_i f_i b_i \,/\, \sum_i b_i$

That is, the genetic burden due to a given dose equals

$$\frac{\text{given dose}}{\text{doubling dose}} \times \begin{pmatrix}\text{part of genetic burden}\\ \text{maintained by recurrent}\\ \text{mutation}\end{pmatrix}$$

The relation between induced mutation rate and exposure enters here only through the representative doubling dose. In the present state of knowledge, the analytic approach is more certain than the synthetic approach, because the relation between induced mutation rate and exposure enters only through the representative doubling dose.

84. Even supposing the necessary quantitative relations between mutation rate and dose or radiation exposure to be known, calculation of the social consequences still requires knowledge of one of the sets of parameters, p_i or f_i, dependent upon selective behaviour of the mutant alleles. The two approaches are compared from this point of view in table IX. It will be seen that, under conditions in which mutation contributes a large part of the social burden, f_i is relatively well known but p_i is not. Moreover, there is some reason to believe that most heterozygous carriers of individually detectable, socially deleterious recessive alleles are slightly less fertile than average.[88,182,183] If this is true, most f_i are known but most p_i are not. It is concluded that, for most purposes, the analytic approach starting from the current social consequences of unfavourable alleles is to be preferred to the alternative method at the present stage of knowledge.

85. Certain assumptions are implicit but not stated in the analytic approach to the problem adopted here:

First, it has been assumed that the genetic component of the social burden is directly related to the expressed effects of unfavourable alleles. However, the actual social burden realized in a population will be modified by environmental factors such as the extent of care devoted to those affected. For this reason, the actual social burden resulting from a given genetic situation may be heaviest in those countries having the best medical care of the afflicted.

Second, the genetic component of today's social burden has been assumed to be related to the present natural rate of occurrence of mutations and to present selective conditions. Certainly this assumption is not true —the number and distribution of recessive alleles is determined by a long history of past mutation rates and past conditions of selection—yet with our present limited knowledge of the distant past and future no alternative assumption seems to present a possible basis of calculation. A number of considerations indicate that the errors involved may not be too serious:

(*a*) Because of recent improvements in medical care the present genetic burden may be below equilibrium with today's rates of elimination of undesirable alleles, so that the effects of a given increase in mutation rates are underestimated. On the other hand, further improvements in medical care are likely in the future to reduce the socially serious effects of mutations. This process cannot by itself affect the influence of mutation upon the Darwinian fitness of the population, but may affect the future social burden due to present mutations if it occurs without a corresponding effect upon the rates of elimination of the socially deleterious alleles. If this elimination takes place largely through rather trivial effects in heterozygous or other carriers of unexpressed alleles, alleviation of the expressions in grossly affected individuals might be accomplished with little influence upon the process of elimination. We would then have overestimated the future social burden from present mutations. Thus the two sources of error due to improving medical care act in opposite senses.

(*b*) In spite of changes in diet and living conditions of all kinds, there is no reason to suppose that natural mutation rates have changed very greatly; for example, chondrodystrophy, which, in man, is largely a dominant disease, has been prevalent at a low frequency since ancient times.[139] Selection has, by contrast, certainly undergone great changes. This fact is relevant to the recommendation, contained in the report of a WHO study group submitted to this Committee,[11] that research be initiated upon selection in primitive communities while the opportunity to do this still exists.[11] But many of the specific detectable conditions with which we shall be concerned here either arise from dominant alleles, and hence do not in general persist for so many generations as recessives, or else they confer a reduction in selective fitness which has not yet been greatly modified by advances in medical practice. The working assumption may therefore be not too greatly in error for the broad categories of effects to be considered. In point of fact, the effect of improved living conditions and improved medical care is far from obvious. Penrose[140] has pointed out that, besides preserving less fit individuals, this change may in recent years have removed the selective advantage of alleles which confer a degree of protection against an infectious disease in the heterozygote while being grossly deleterious in the homozygote: the classical example is sickle cell anaemia.[141] How many such situations exist is debatable. However, the consequences of improved medical care could be called eugenic rather than dysgenic in such cases. It must also be borne in mind that the total potential intensity of selection in populations has, at least in recent years, not been changing anything like as rapidly as the qualitative basis of it.[142,143] It may be observed here that the possible dys-

genic effect of future improvements in social and medical care is limited by the fact that no more deleterious mutant alleles can be saved for later generations than arise by mutation; moreover, a subsequent withdrawal of improved medical care by some social catastrophe will not cause more losses than would have occurred anyway had it never been present. Only the distribution in time will be altered. Thus, in a constant population, the dysgenic effect of a changing selection does not increase the total number of seriously affected individuals but by contrast, the dysgenic effect of increased mutation does increase the total number of seriously affected individuals. Finally, it has been assumed that radiation-induced mutations and spontaneous mutations are qualitatively similar: that there is no correlation between D_{21} and the degree or kind of manifestation (f_1, b_1, p_1) of a given mutation. This assumption has been discussed in another section and is acceptable to the Committee.

86. On the basis of the above arguments, the Committee considers:

(*a*) That the most satisfactory assessment of the genetic consequences of irradiation of human populations which can be attempted at the present time must be based on the present social burden due to hereditary conditions. Because it must employ the representative doubling dose, it must be restricted to rather broad categories of effects;

(*b*) That the sources of error in an assessment of this kind may not be too serious;

(*c*) That two principal sources of error are related to the extent to which selection changes in the transition from a technologically primitive to a technologically advanced environment and to the extent to which alleles responsible for socially serious conditions may confer small favourable differentials of fertility in the heterozygous, impenetrant or other "carrier" states. Both require to be investigated.

3. The current social burden of genetic origin in human populations, its connexion with mutation and radiation exposure

87. In order to make use of the representative doubling dose discussed earlier, there will be considered here only broad categories of damage, each of which may be caused by mutation at any one of many loci, such as the sums of specific clinical conditions or traits within various genetic categories, or biometrical characters such as intelligence, life-span or birthweight, each likely to be dependent upon many genes, or fertility.

Specific traits

88. For the present purpose, the available information concerning the incidence in man of specific diseases or disabilities of genetic origin is severely limited. Only very few sizeable populations have been surveyed, notably in Denmark,[139] Michigan, U.S.A. and Northern Ireland.[144] Moreover, good quantitative data are only available for clear-cut traits or disorders, and, even here, the genetic interpretation of the facts is almost never straightforward.[110] In the past, various estimates have been made of the frequencies of such specific traits, but the basis of the estimates has not always been clear. Sometimes it has been uncertain whether the trait frequencies referred to were those at birth or in the whole population. The latter estimate would always be expected to be lower, particularly if the trait was severe in its effects. Independent over-all estimates, both in the literature and in reports to this Committee, seem to be in reasonable superficial agreement with each other and are summarized in table X; each of these implies consideration of one or another category out of a total of some 500 clear-cut disorders or traits.[139] However, it has seldom been specified which traits are included and which excluded in them.

89. In order to formulate, upon a precise basis, over-all estimates to which a representative doubling dose can reasonably be applied, the Committee has made use in the present report of a single, definite list of traits and their estimated frequencies of appearance in a single population, namely that compiled by Stevenson[144] for the population of Northern Ireland. In so doing, it is recognized that the frequencies of specific traits will be different in other populations, so that some listed here may not occur at all, and others not in the present list will be prevalent. Nevertheless, such comparisons as can be made of the population frequencies of traits in different parts of Europe, North America and Japan suggest that, while the contributions of individual traits to the total may differ considerably in different populations, the totals, and their division into principal categories, will not vary appreciably so long as present methods of detection are employed.

90. The list of traits compiled by Stevenson has been broken down into separate categories in the following manner, which differs somewhat from that used in the original compilation.[144]

Category I (table XI (a)-(b)): Category I includes traits determined by single, harmful mutant alleles. The majority of these are dominant with a high degree of penetrance, but some are autosomal recessive and a few are sex-linked. Most are not recognizable in the affected person at birth. It seems reasonable to assume that in respect of these traits there is no significant selective pressure in either direction against apparently unaffected carriers of the mutant alleles, although this cannot be proved in our present state of knowledge. It would therefore be expected that the ultimate consequence of an increase in mutation rate at each or all of these loci would be a direct effect upon trait frequency. About 110 different mutations are required to explain these traits. No doubt some similar, but separately identifiable, traits are determined by alternative alleles. Of these mutant alleles about 72 are dominant, 30 autosomal recessive and 8 sex-linked recessive. The estimated total of live-born affected is 1.1 per cent.

Category II (table XII): Category II includes a considerable number of traits mostly detectable at birth. A proportion of them sometimes determines intra-uterine death, but this fraction of these conditions is ignored in the present context. Maternal health and intra-uterine environment appear to play a considerable part in determining whether and to what degree they are expressed. Their familial patterns in a community seldom satisfy the criteria of a single mutant expression. In all there is a familial concentration of cases greater than would occur by chance. In some, the family pattern approaches some of the criteria of those included in category I, and it will be clear to the reader that arbitrary decisions have had to be made. The estimated total of live born affected is 1.0 per cent.

Category III (table XIII (a)-(b)): Category III comprises two unequal classes of traits. The first and smaller proportion (category III (*a*); table XIII (*a*)) consists of traits which appear to follow closely the ex-

pected family patterns of a single recessive mutant genes, but show a frequency too high to be explained on a basis of mutation pressure alone, unless it is assumed that mutation occurs many times more frequently at the relevant loci than at those loci giving rise to dominant mutations in man or than in the general range of all types of mutation in experimental animals. In the data for Northern Ireland[144] and elsewhere in the United Kingdom, only fibrocystic disease of the pancreas and deaf mutism clearly fall into this category, although other conditions well-known elsewhere such as sickle cell anaemia and thalassemia also belong to it. It is possible, although neither provable or disprovable at present, that the gene frequencies in these conditions are maintained mainly by relative selective advantage in the heterozygous carriers. In deaf mutism several independent mutants contribute to the trait frequency. The two conditions together determine about 37 per cent of the total frequency of recessive traits at birth in the population studied by Stevenson (*loc. cit.*) and have a combined frequency of 0.09 per cent of all live births. The second and larger proportion (category III (b); table XIII (*b*)) of category III is difficult to define and limit. Six examples of serious, "constitutional," diseases are listed in the table, but it is difficult to know where to draw the line thereafter. In different communities the frequencies will vary considerably. It is impossible to estimate frequencies without making some arbitrary decisions as to what will be included; as an example, admission to hospital might be made a criterion. Furthermore, the frequencies depend on the ages to which people live in populations, as in the cases of diabetes and the primary presenile psychoses. Finally, there are environmental factors of importance which vary in different populations. In sum, at least 1.5 per cent of those liveborn will suffer from one or another of this group of disorders.

91. It must be emphasized that the list of traits, trait frequencies and categories outlined above and in tables XI-XIII:

(*a*) Represents only tangible or detectable genetic damage, which in principle, although in practice with great difficulty only, can be assessed by "counting heads";

(*b*) Includes only defects of such severity as to be at least very inconvenient to their possessors;

(*c*) Is certainly an incomplete list, even of such conditions;

(*d*) Ignores maternal/foetal incompatibility and mongolism; in the latter the genetical component appears to be weak, and in the former the relative frequency of the alleles, which is the most important factor in determining proportions of affected infants, would probably not be affected appreciably by increased mutation rates;

(*e*) Excludes a group of individually rare or mild traits which mostly appear to be determined by simple, irregular, dominant genes and are listed in table XIV.

Nevertheless, the list gives rise to the expectation that some 4 per cent of the liveborn suffer or will suffer from defects predominantly of genetic origin. Certain comments are pertinent to this estimate:

(1) Any present over-all estimate of total genetic damage must of necessity be minimal. However, even though more sophisticated methods of detection can be expected to increase the present estimates, it is unlikely that in the near future more than a very small number of new specific traits will be discovered, relative to the total so far known. (See also paragraph 104 below.)

(2) The present estimates refer to those born alive. In addition, approximately another ¼ to ½ per cent of foetuses alive after the twenty-eighth week of pregnancy are born dead mainly by reason of detectable developmental defects which may be of genetic origin.

(3) In about half of the affected liveborn, the defect will be detectable at or soon after birth, but in the other half the expression of the genotype will only be apparent in later childhood or in adult life.

92. The division of the 4 per cent affected live-births into categories as outlined above may be summarized as follows:

Category I: About 1 per cent of defects due to single mutants of classical type (majority not recognizable at birth);

Category II: About 1 per cent showing no consistent familial pattern compatible with a simple genetic hypothesis and often having an environmental component in their aetiology (majority recognizable at birth);

Category III: About 1.6 per cent either (*a*) show trait frequencies too high to be maintained by mutation pressure, or (*b*) determine constitutional illnesses whose frequency is also unexpectedly high in relation to their severity.

This division into categories is of great importance for predicting the results of increased exposures of populations to ionizing radiations. The supply of recognizably disadvantageous mutant alleles in a population may be maintained either by recurrent mutations balanced by selection or by selective advantage among individuals in whom the disadvantage is not expressed; that is, by a balance between opposing selective forces. A reasonably small increase in mutation rate cannot be expected to affect greatly the pattern of gene elimination and so should cause at equilibrium an equal fractional increase in the genetic damage due to alleles maintained in the first manner (corresponding to traits in category I above, together with an unknown fraction of those in categories II and III), but a much smaller increase in the genetic damage due to alleles mentioned in the second manner (corresponding to an unknown fraction of the traits in categories II and III above). It follows that permanent exposure of a population to an extra genetically significant dose D per generation may be expected eventually to give rise to an increase in the incidence of live births who are or will be affected of between $D/\overline{D}_2$ per cent and $4D/\overline{D}_2$ per cent where D_2 is the representative dose. If the increased irradiation were to occur in only one generation to a population of fixed breeding size P, it follows, by a principle of detailed balancing, that the calculated total number of affected live births is expected to lie between

$$\frac{D}{\overline{D}_2} \times \frac{P}{100} \text{ and } \frac{D}{\overline{D}_2} \times \frac{4P}{100}$$

93. It must be borne in mind that the mutant alleles concerned in the above estimates range all the way from severe dominant to true recessive, and the time during which the genetic damage either climbs to equilibrium or completes its expression after exposure of a single generation varies in turn from one or two to many tens of generations. Thus, in the case of irradiation of the present population, the damage may well become expressed under social and technological conditions which

cannot even be imagined today, and which may grossly affect the relation between gene elimination and its social consequences. Some geneticists therefore question the utility of assessment of a hazard so far in the future.[145]

94. In conclusion, it must be emphasized that even for this most tangible kind of genetic damage, far more work is needed on family studies, on sib-correlations, incidence in consanguineous marriages, twin studies etc., so as to establish more accurately the genetic nature of the traits listed here and other conditions. If Governments wish to know the genetic health of their peoples it will be necessary for them to support the necessary work. It has been argued that, at present, populations under review by single institutes of human genetics cannot conveniently exceed 3×10^6.[11] However, the problems related to both the scale and scope of such work involve questions of general medical education and co-operation as well as legal and administrative aspects which merit the attention both of Governments and public health authorities. For example, a number of human geneticists feel that the present *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death* is inadequate in its present scope and form for scientific purposes in the classification of congenital conditions.

Biometrical characters

95. Many important characteristics of man, among which specific mention must be made of intelligence, lifespan and birthweight, vary continuously in natural populations about some mean which is often close to a selectively optimal value. Where this is true, selection may act on the phenotype quite largely by reducing the variance, rather than by shifting the mean; to that extent, it is normalizing or stabilizing selection.[148] Such quantitative variation is often influenced by many genes in combination whose separate effects cannot be distinguished, in contrast to those exhibiting specific qualitative effects and discussed above. These genes can only be studied statistically, principally through that part of the variance of the character for which they are responsible. This variance may be of considerable importance as a social burden or loss of population fitness. Discussion of the consequences of possible shifts in the mean of such characters will be deferred to paragraph 99 below.

96. The genetic component of the variance has been tentatively estimated in the case of birthweight by Penrose and by Robson as some 40 per cent,[149,185] half of it associated with maternal genotype, and in the case of intelligence as ½, or perhaps as high as ¾.[150] In each of these cases, the more extreme phenotypes of the distribution are observed to be associated with a loss in viability or reproductive fitness and with social burden. Thus on the basis of Penrose's[149] and Karn and Penrose's[151] work it can be estimated (see appendix) that the genetic component of this variance was associated with the occurrence of some 1.6 per cent of stillbirths and neo-natal deaths among males. Mather[152] has calculated that on an intelligence quotient scale normalized to mean 100 and standard deviation 15, 2.3 per cent of children will fall below intelligence quotient 70, and a doubling of the heritable component of variance, assuming no shift in the mean, would increase this number by a factor which may lie between 2.2 and 2.9; this calculation depends upon the assumption of a Gaussian distribution of the measured variable at the tails of the distribution, where the assumption is itself least sure and confers greatest uncertainty. Mather's calculation is a useful guide to the upper limit of the social burden expected to be conferred by radiation-induced genetic changes in the variance of intelligence (but see footnote to paragraph 102 below).

Relationship of genetic component of variance to mutation

97. The relationships of selection, genetic variability and mutation in a character of relatively low selective importance (bristle number) have been studied by several authors in *Drosophila*. In particular, Clayton and Robertson[153] have been able to show that the natural additive genetic variance in an outbred population, from which their experimental flies were originally drawn, exceeded the spontaneous increase in genetic variance per generation by a factor of 1,000, and observations by Paxman (quoted by Mather[157,196]) support this conclusion. By comparing irradiated and unirradiated populations, Clayton and Robertson further showed that some 10^5r would have been needed to produce an increment equal to the natural variance. With selective neutrality such a genetic variance in the natural population is perfectly compatible with an established equilibrium between mutation and a degree of inbreeding due to limited effective population size. For a character of greater selective importance the genetic variance displayed by the population would exceed the increment per generation by a correspondingly smaller factor. Haldane[154] has pointed out that, in the cited case of birthweight, selection removes 10 per cent of the observable variation per generation. If this selection makes no distinction between variation of genetic and of environmental origin, it poses the question: How is the genetic component of variance maintained?

98. Robertson[155] has recently discussed the theoretical consequences of selection for optimal central phenotype. It appears that this process cannot of itself maintain genetic variability, even though heterozygotes have intermediate values of the character (see Fisher[156]). The genetic variation must therefore be maintained either by the selective advantage, in some circumstances, of the heterozygotes as such (i.e., the majority of the genes are individually heterotic) or by mutation. Lerner[133] has argued for expecting heterosis among genes of this kind, his argument being based partly upon an anticipation of improved buffering or canalization in the developmental processes of heterozygotes and partly upon experimental evidence (of which, however, a considerable fraction is drawn from *Drosophila*) and general experience of inbreeding. Paxman[157,196] has, on the other hand, failed to find evidence of such heterosis, despite a search for it. Thus evidence of the necessary heterosis is by no means conclusive and further data are much needed. At the same time, the high rate of selective elimination does not seem compatible with replacement by mutation at the low rates observed in experiment. This difficulty may well, however, be less than it seems, because where many genes of similar effect contribute to the variation of a character, only a portion of the total genetic variability present in the population is manifest as variation actually observable by difference among the phenotypes of the individuals. In a polygenic system, alleles at different loci can exert their actions in opposite directions and thus balance out one another's effects, so that some of the variation lies hidden as balanced differences within the genotypes of the individuals.[197] The proportion of the total variability so hidden increases directly with the

number of genes in the system, and it may go up even higher if the genes are linked. The hidden variability is released by recombination of the genes which balance one another, to become exposed as phenotypic differences, and this rather than mutation is the immediate source of replenishment of the observable variation eliminated by natural selection. Ultimately replenishment must depend on mutation: but, by virtue of the reservoir of hidden variability, the accumulation of new variation from mutation need balance loss through selection only in the long term. Thus the rate of selective elimination observed at any given time need not provide a reliable indication of the rate at which new variation is arising by mutation. Furthermore, the selective elimination of any fraction of the observable variation represents the loss of a much smaller fraction of the total genetic variability. Thus with birthweight, 10 per cent of the observable variation is eliminated in each generation, but this loss could represent as low a fraction as 1 per cent of the total genetic variability for this character in the population if it depended on the simultaneous action of no more than 10 polygenes. Mutational increments quite low in relation to the total variability might thus suffice to maintain the plygenic variation of a character against the erosion of selection. This is a matter on which more data are needed; but pending their appearance it would seem conservative to suppose that $\frac{1}{10}$ of the genetic variability of most quantitative characters is the greatest fraction which it is necessary to envisage as replenished by mutation in each generation, and the fraction may indeed generally be very much smaller than this. The Committee emphasizes, however, that there is at present no satisfactory experimental basis for determining whether this fraction is large or small even in experimental species, much less in man. Clearly, further data are much needed in this whole area.

Shifts in mean values of metrical characters

99. Besides contributing to the variance of a metrical character, genetic factors may impose a social burden by affecting the position of its mean. Three quantities must be considered: the population mean, the selective optimum and the social optimum. The three may all differ, as is illustrated in table XV for the characters mentioned in paragraph 95.

100. The great majority of well-studied single-locus mutants in experimental organisms are hypomorphic;[159,160] that is, they appear to lead to a reduction in the function or character most immediately affected. There is good *a priori* reason to expect this, as random interference with a complex machine will more often be destructive than constructive. In consequence it might be expected that most mutations and mutant alleles would act so as to diminish the population mean relative to the selective optimum. However, it must be questioned whether there are sufficient grounds for extrapolating this view to polygenes affecting quantitative characters. Provided that the changes are not so large that they excessively disrupt the organism's general control of the developmental channels concerned, is it not just as reasonable to suppose that a particular organ of social import—for example, the brain—may in fact benefit from hypomorphic changes in most other organs, due to a compensating diversion of resources, so that many such changes would be hypermorphic for it? Among the characters of table XV, it is of interest that the facts concerning birthweight[151] fit the classical expectation, but that those concerning intelligence[161] possibly do not.

101. In the case of birthweight, it can be calculated (see appendix) that the difference by which Karn and Penrose observed the selective optimum to exceed the population mean in males is associated with 0.4 times as many deaths at or near birth as the total variance and about 0.7 times as many as the estimated genetic component of variance. What proportion of this deviation is genetic in origin is not known, but it is clear from the arguments outlined above that recurrent mutation could easily be the principal cause; if so, continued application of a doubling dose to every generation might eventually bring about an increased incidence of some 1.2 per cent in the deaths at or near birth. This selection acts so as to diminish the difference between the mean and the selective optimum by about 7 per cent per generation.[154] If it does not distinguish between genetic and environmental components of the difference, the genetic effects of an altered mutation rate upon the mean must be expected to be spread over some ten generations, and any shift to a new equilibrium value will take a comparable period of time.

102. The case of intelligence is somewhat different. Here the social optimum lies far away from the selective optimum, and it is not simple even to decide what must be computed to assess the social implications of a given change. Moreover, the genetic picture is complicated by a high degree of phenotypic assortative mating.[158] For the purposes of this report Mather's calculations[152] based on United Kingdom figures have been available. Mather based his calculations concerning the effect of increased variance upon an unchanged mean but he also considered a situation in which increased mutation was associated also with a falling mean, such that the effects mediated through mean and variance were roughly comparable in magnitude. However, there is no indication in the figures at present available for the United Kingdom that the population mean lies below the selective optimum; this gives rise to a presumption that increased mutation might not depress the mean appreciably. It seems important to try to find out if this situation is true and, if so, whether it is peculiar to the somewhat special demographic situation in the United Kingdom or is more general, since it raises a question as to how such a position might arise and be maintained.[158] In the meantime, it seems premature to attempt here any assessment of the expected effects of increased mutation rate upon mean intelligence. The social consequence of hereditary shifts in intelligence probably occur mainly as a result of shift in the numbers at the extremes of the I.Q. distribution (of which only changes at the lower end are numerically cited in para. 96 above);* a change in variance will in any event affect these more markedly than an equal change in the mean. Part of the difficulty in discussing shifts of the mean intelligence as measured by intelligence quotient may lie in the need to consider small intelligence quotient differences; it is possible that present tests of intelligence are not sufficiently well-developed and free from bias associated with other variables to serve as suitable material for close quantitative analysis. The problem of further progress in this field may thus depend upon developments in pure human biology. In any

* An increase in variance without change in mean also causes an increase in the classes of highest I.Q. upon which it has been claimed that much of human progress depends. Any judgement concerning the relative value of this increase is a social one; it has therefore not been computed here and no attempt has been made in this report to offset its value against the social burden represented by a calculated increase in the numbers of individuals with I.Q. <70. It must be borne in mind that there is some reason to believe that the distribution of variance due to new mutations would not be symmetrical, and that most of the increase would be in the direction of lowered intelligence.

over-all discussion of intelligence, it is necessary to bear in mind that it is affected not only as a biometrical character by many genes with small interacting effects, but by known specific loci, radiation-induced mutations at which will almost always cause serious harm to any individual in whom the mutant alleles are expressed.

103. In the case of the life-span, the data of Russell[162] on the progeny of male mice irradiated by fast neutrons suggest the existence of the kind of effect which would be expected from classical hypomorphic mutations; that is, the occurrence of radiation-induced mutations to a series of weakly dominant alleles which collectively cause a shortening of the life span. However, the magnitude of any corresponding effect which might be expected in man is entirely unknown. It might seem at first sight as if increased variance in life span would confer little or no increased social burden, but be selectively neutral as long as it affected only groups beyond the age of child-bearing. However, if the mechanism of shortening were related to an effective contraction of time-span of the physiological processes, the reproductive period might be adversely affected, and the selective optimum for life-span might then be very long. It is essential that the work of Russell be confirmed and extended in order to have an adequate experimental basis in other organisms for consideration of the possible implications for man. Russell's experiments are in line with effects observed in irradiated mammalian tissue culture cells and other organisms, among which the survivors frequently carry slightly deleterious dominant alleles,[18,194] as well as with observed correlations between the life-spans of related individuals suggestive of genetic influences.[163]

Fertility

104. The most direct expression of the effect of undesirable mutations is through the net reproduction per generation or fertility differentials. Penrose[93] has suggested that, in man, some 50 per cent of the zygotes of each generation fail to contribute to the next one by reproduction, and has suggested, by analogy with other metrical characters, that some half of this might be of genetic origin. Penrose also points out that, on the same analogy, much of the infertility might well be due to the presence of conditionally deleterious alleles which are not primarily maintained by mutation and are essentially unaffected by changes in mutation rate. However, one may compare such a rate of elimination with an estimate of the total rate of mutation to unconditionally deleterious alleles such as was derived in paragraph 74 above.

105. Applying a representative doubling dose of 30 rad to the estimate of paragraph 74, the natural rate of mutation to deleterious alleles would amount to some ⅛ (i.e., approximately 30/250) per haploid gamete or ¼ per diploid zygote. At equilibrium, these could be eliminated by ¼ of zygotes failing to reproduce. These estimates of mutation are therefore consistent with that of Penrose concerning fertility, and with the assumption of genetic equilibrium, which suggests the possibility that at present ¼ of all zygotes fail to contribute to the next generation because of the presence of deleterious alleles maintained by recurrent mutation. Taking this to be an upper estimate, indefinite application of a doubling dose to each generation might eventually extend the fraction of non-contributing zygotes from ½ to ¾ and require a doubling of average family size for a previously constant population to maintain itself. This appears to be well within human capacity. If it be further supposed that the mixture of dominants and recessives concerned has an average persistence in the population of 10-100 generations, then exposure of one generation to 10 or 100 times the doubling dose would impose the equivalent of the same load for a period of 10 or 100 generations. Such doses are of the magnitude 300-3000 rad, and in a range which is such as to render further considerations of genetic problems redundant. It therefore seems probable that the human race has ample breeding capacity to survive the genetic consequences of any foreseeable radiation exposure.

Pool of recessive mutants

106. Examination of the offspring of consanguineous marriages can give information concerning the total of deleterious recessive mutant alleles in a population, and Morton, Crow and Muller[88] have recently shown how the results of statistical surveys of this kind can be expressed in the form of a number of lethal equivalents per member of the population. In the absence of a figure operationally equivalent to the total number of genes per individual, this information does not relate directly to the social burden upon the population nor, without assuming an average dominance, can it be related to the natural mutation rate. The number of lethal equivalents per head is, however, in its own right, a most important parameter describing the genetic state of a population, derivable from a purely demographic type of information. Governments would do well to investigate it in their populations.

107. It is also possible in principle to compare the number of lethal equivalents, derived from vital statistical information, with the number of recessive deleterious genes found in the direct intensive surveys of smaller numbers of consanguineous marriages. Ideally, such studies should cover the whole period during which identical alleles are together and so liable to give rise to an effect through homozygosity; thus not only the number and viability but also the fertility of the progeny of consanguineous marriages should be investigated; a preliminary study of this kind has been initiated by Fraser.[193] Such a comparison could be of great importance as indicating what fraction of the total recessive deleterious pool we know about, through recognizable specific effects. At the present time the evidence of both kinds is very scanty. By direct examination of a north Swedish population, Böök has estimated that about three recessive deleterious genes are carried per individual.[87] However, using the criteria of Stevenson, this figure would be only 0.8-1.7.[144] Stevenson, himself, in a somewhat smaller sample, has found 0.5-0.9.[144] It is not possible to estimate accurately what is the reproductive fitness of the afflicted individuals, relative to the general population, but it is reasonable to suppose that the average would lie between 20 per cent and 80 per cent. Probably, therefore, the best direct intensive investigations today show up about 0.2-0.8 post-natal lethal equivalents per individual in the general population. Following Morton, Crow and Muller's analysis of the work of Sutter and Tabah,[85,86] but excluding stillbirths and neo-natal deaths, it is likely that a total of some 2-2.8 post-natal lethal equivalents per individual are present in their population. This suggests that present recognition encompasses somewhere between 7 per cent and 40 per cent of the total deleterious recessive damage which arises. These numerical figures reflect the strictness of the particular criterion employed by Stevenson in his use of the term "recessive".

108. The specific genetic conditions whose incidence is reported by Stevenson are divided into dominant and

recessive conditions; a most striking feature of the data is that the total incidence of rare dominant conditions exceeds that of recessives by a factor of 10. If a correction is applied for those recessive conditions not at present recognized, using the figures derived in the preceding paragraph, the ratio of total incidence of recessive conditions to total incidence of dominant conditions shifts from 0.1 to between 0.25 and 1.4 and the total incidence is increased by a factor of between 1.2 and 2.3. The calculation is now relatively insensitive to the exact criterion of recessivity employed, provided that it is the same throughout. It perhaps serves to give some idea of the limits of confidence which can be placed upon current estimates of the genetic social burden due to specific recognizable conditions.

109. It is of some interest to compare the ratio of the observed rates of elimination of deleterious recessive and dominant alleles, corrected as in the previous paragraph, with that to be expected from equilibrium with forward mutations. In mice, the ratio of recessive to dominant lethals occurring naturally appears to be about 2.5:1 or 3:1.[107,164] (It is very different for *Drosophila*, perhaps as low as 0.1:1, but if *Drosophila* has much less complex genes than mouse or man, it may be a poor guide.) If the ratio of natural rates is similar in man and mouse, the corrected ratio of elimination rates, between 0.5:1 and 2.8:1, is in reasonable agreement with it, but suggests that the recessive alleles might, if anything, tend to be on the average slightly deleterious rather than advantageous in the heterozygous state.

TABLE I. MEASURED OR CALCULATED VALUES OF NATURAL MUTATION RATES IN MAN[111, 169]

Trait studied	*Mutants per tested gamete*
Autosomal dominants (direct observation)	
Epiloia	8×10^{-6}
Achondroplasia	45×10^{-6}
Aniridia	5×10^{-6}
Retinoblastoma	$4–23 \times 10^{-6}$
Partial albinism with deafness	4×10^{-6}
Microphthalmos	5×10^{-6}
Neurofibromatosis	$1.3–2.5 \times 10^{-4}$
Average of 7 loci	4×10^{-5}
Rare dominant	
Porcupine	$<10^{-9}$ [a]
Sex-linked recessives (direct)	
Hemophilia	3×10^{-5}
Duchenne's type muscular dystrophy	$4–10 \times 10^{-5}$
Autosomal recessives (indirect)	
Albinism	2.8×10^{-5}
Ichthyosis congenita	1.1×10^{-5}
Total colour blindness	2.8×10^{-5}
Infantile amaurotic idiocy	1.1×10^{-5}
Amyotonia congenita	2.0×10^{-5}
True microcephaly	4.9×10^{-5}
Phenylketonuria	2.5×10^{-5}
Average of 7 loci	2.4×10^{-5}

[a] Very rough estimate; see ref. 83.

TABLE II. MEASURED OR CALCULATED VALUES OF NATURAL MUTATION RATES AT SINGLE LOCI OF ORGANISMS OTHER THAN MAN

Mutants studied	*Mutants per tested gamete*	
D. melanogaster		
Average for 9 sex-linked recessive visibles in XXY female	3×10^{-5} [a]	Muller, Valencia and Valencia[171]
Average for 4 autosomal recessive visibles in Oregon-R females	2.5×10^{-6}	Glass and Ritterhof[172]
Average for 4 autosomal recessive visibles in Oregon-R males	4.5×10^{-5}	Glass and Ritterhof[172]
Average for about 12 sex-linked recessive visibles in Oregon-R females	2.4×10^{-6}	Glass and Ritterhof[172]
White eye	$0.7–3.7 \times 10^{-5}$	Bonnier and Lüning[173]
8 sex-linked recessive visibles in mutable Florida stock	3×10^{-5}	Demerec[174]
Mice		
Average of 7 autosomal recessive visibles in male	ca. 7×10^{-6}	Russell[76], Carter *et al.*[75]
Bacteria		
Average of about 30 biochemical back-mutations.	4.5×10^{-9}	Glover in Demerec *et al.*[53]
Range of above	10^{-11} to 4×10^{-8}	Glover in Demerec *et al.*[53]

[a] But approximately 5×10^{-6} if allowance is made for the fact that the rate of sex-linked recessive lethals was abnormally high in this experiment. *Drosophila* rates vary very widely with stage of life, cell-development, etc.

TABLE III. MEASURED OR CALCULATED VALUES OF TOTAL NATURAL MUTATION RATES FOR CLASSES OF LOCI IN ORGANISMS OTHER THAN MAN

Class of mutants studied	*Mutants per tested gamete*	
D. melanogaster		
Sex-linked recessive lethals:		
young sperm	1.0×10^{-3}	Spencer and Stern[32]; Uphoff and Stern[31]
aged sperm	2.0×10^{-3}	Caspari and Stern[33]; Uphoff and Stern[31]
range for various wild type stocks	$0.7–11 \times 10^{-3}$	Demerec[174]
mutable Florida stock	1.1×10^{-2}	Demerec[174]
XXY females	7.0×10^{-3}	Muller *et al.*[171]
	1.8×10^{-3}	Muller[108]

TABLE IV. RATES OF RADIATION-INDUCED MUTATIONS AT SINGLE LOCI IN ORGANISMS OTHER THAN MAN

Loci studied	*Mutations/locus/r*	*Source*
D. melanogaster		
Average of 9 recessive visible autosomals in oocytes, oogonia	1.4×10^{-8}	Muller, Valencia and Valencia[171]
Average of 9 recessive visible autosomals:		
spermatogonia	1.5×10^{-5}	Alexander[70]
mature sperm	6×10^{-8}	Alexander[70]
mature sperm	4.4×10^{-8}	Patterson[175]
mature sperm	5.2×10^{-8}	Demerec[176]
White eye mature sperm	$0.8–1.2 \times 10^{-7}$	Bonnier and Lüning[173]
D. virilis		
Average of 7 sex-linked recessive visibles:		
mature sperm	7.6×10^{-8}	Girvin[177]
E. coli		
Average of about 30 biochemical back-mutations	2.7×10^{-10}	Glover in Demerec *et al.*[53]
Mice		
Average of 7 recessive visible autosomals:		
spermatogonia	2.5×10^{-7}	Russell[76]

TABLE V. TOTAL RATES OF RADIATION-INDUCED MUTATIONS IN CLASSES OF LOCI IN ORGANISMS OTHER THAN MAN

	Mutations/r	
D. melanogaster		
Sex-linked recessive lethals in		
aged sperm	2.3×10^{-5}	Uphoff and Stern[31]
young sperm	2.8×10^{-5}	Uphoff and Stern[31]

TABLE VI. SURVEYS OF HUMAN POPULATIONS FOR PURPOSES OF RADIATION GENETICS

Experiment	Reference	Number of irradiated parents	Dose range in rads	Results: Abortions Irrad.	Abortions Control	Still-births Irrad.	Still-births Control	Congenital malformations[a] (live births) Irrad.	Congenital malformations[a] (live births) Control	Sex-ratio (live births) Irrad.	Sex-ratio (live births) Control	Remarks
Survey of pregnancies in Hiroshima and Nagasaki	Neel and Schull[111]	approx. 27,000 ♀	8–200			546	408	300	294	regression lines based upon several doses: for raw data see Ref. 111, Chapter VII.		Observations include sex-ratio, frequency of stillbirths and neonatal deaths, birthweight, occurrence of congenital malformations, and, for a random 30% sample reexamined at age 9 months, certain bodily measurements and the occurrence of additional malformations not apparent at birth. Non-significant decrease in sex-ratio $k = -5.5 \times 10^{-5}$/rad for irradiated mothers: among earlier births[123] k was -8×10^{-5} and significant. Slight non-significant increase for irradiated fathers in earlier births[123].
		approx. 14,000 ♂	8–200			33,181	31,559	33,527	31,904			
Survey of offspring of French patients	Turpin, Lejeune and Rethore[117, 165]	289 ♂	4–450[b]	47	46	8	7	9	8	225	358	Diminution of sex-ratio for irradiated mothers significant compared to irradiated fathers ($\chi^2 = 4.2$), not significant compared to controls. k between 6×10^{-5}/rad and 12×10^{-5}/rad. No account taken of age and parity. Inquiry by questionnaire.
				452	742	405	696	405	696	405	696	
		97 ♀	40–450[b]	26	18	7	5	5	1	63	130	
				162	254	136	236	136	236	136	236	
Follow-up on progeny of women treated for sterility	Kaplan[119]	311 ♀	ca. 60	91		2		3		191		No control as yet. Very low sex-ratio significantly different from 0.515, $k \backsim -8 \times 10^{-4}$/rad.
				513		513		513		409		
Surveys of children of American radiologists	Crow[166]	654 ♂	Unknown accumulation of many small doses	Abortions and Still-births Irrad. 274	Control 215							No data on malformations or sex-ratio. Inquiry by questionnaire.
				1,653	1,348							
	Macht and Lawrence[126]	5,461 ♂		766	548			328	216	2,090	1,766	Non-significant increase in still-births and abortions. Significant increase in malformations ($\chi^2 = 6.7$) includes many very slight malformations or other diseases, but remains significant if restricted to cardiac malformations only. Inquiry by questionnaire.
				5,461	4,484			5,461	4,484	4,127	3,390	

[a] Earlier literature surveys by Maurer[168] and by Murphy and Goldstein[167] respectively revealed $\frac{7}{229}$ and $\frac{7}{417}$ malformations among mothers who had received heavy doses, but without controls.

[b] Taking the gonad dose to be 1/3 the skin dose.

TABLE VII. CONTENT OF DNA IN VARIOUS TYPES OF CELLS[20a]

Organism and cell types		gm DNA-phosphorus per cell	gm DNA per cell
Bacteria	*B. lact. aerog.*	2×10^{-15}	
	E. coli	2.3×10^{-15}	
	(compare T2 bacteriophage		3×10^{-16} per particle)
Microbes	*Penicillium*		1.5×10^{-13} per spore
	Aspergillus		1.9×10^{-12} per spore
	Yeast		6.2×10^{-15}
Drosophila	Salivary glands ♂	2.6×10^{-11}	
	♀	2.8×10^{-11}	
	Diploid cells (limb)		1.7×10^{-13}
Rat	Diploid cells	$0.6–1.0 \times 10^{-12}$	
Mouse	Submaxillary glands (diploid)	$0.7–1.4 \times 10^{-12}$	
Man	B.M.	8.7×10^{-13}	
	Leukocytes	8.6×10^{-13}	
	RBC	7.0×10^{-13}	
	Liver	1.0×10^{-13}	
	Kidney	8.7×10^{-13}	

[a] For a further extensive table, see ref. 21.

TABLE VIII. CALCULATED DOUBLING DOSES IN ORGANISMS OTHER THAN MAN[178]

Organism	Loci	Conditions of irradiated cell	Doubling dose (rad)	Ref.
Zea mays	4 recessive visibles	Pollen	28	179
Oenothera, Prunus	Self-incompatibility	Pollen	60	180, 181
Drosophila	Sex-linked lethals	spermatozoa	50	31–33
		aged spermatozoa	140	31–33
		oöcytes and oögonia	390	171
Mouse	7 recessive autosomal visibles	spermatogonia	30	76, 69, 75
	Dominant lethals	through spermiogenesis except time of peak sensitivity	<50	164
	Sex-ratio[a]	spermatogonia	50	125

[a] Approximate calculation for natural rate corresponding to age of mice used in 76, 69, 75.

TABLE IX. COMPARISON OF APPROACHES TO QUANTITATIVE ASSESSMENT OF MUTATIONAL DAMAGE

Fertility of carriers of the unexpressed mutant allele	Knowledge of p_i	Knowledge of f_i	Relative effect of mutation upon frequency of condition
Higher than average	$p_i = 1$	Small but unknown	Small
Lower than average	Small but unknown	$f_i = 1$	Large

TABLE X. SOME OVER-ALL ESTIMATES OF SOCIAL BURDEN

Author	Class of traits	Incidence: In population	Incidence: At birth
Stevenson[144]	Rare heterozygotes	1.36×10^{-2}	1.9×10^{-2}
	Rare homozygotes	1.0×10^{-3}	2.1×10^{-3}
	Rare sex-linked	1.6×10^{-4}	4×10^{-4}
	Common traits of hard interpretation	1.0×10^{-2}	1.5×10^{-2}
	TOTAL	2.7×10^{-2}	3.6×10^{-2}
U.S.A. Panel[145]	Tangible defects of genetic origin (1/2 total)		2×10^{-2}
Kemp[139, 191]	Physical malformations and defects		$< 1 \times 10^{-2}$
	Severe hereditary afflictions		$<2\text{-}3 \times 10^{-2}$

TABLE XI. LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY I
(A) AUTOSOMAL DOMINANT TRAITS

Trait	*Remarks*	*Phenotype frequency per million*	
		Births	*Living*
Achondroplasia	Chondrodystrophy 'Foetalis'	28	*28*
Arachnodactyly	Marfan's syndrome	60	*26*
Brachydactyly (major)	Hands and feet affected—mean stature reduced	6	*6*
Ectrodactyly	Including all types of 'split hand'	30	*20*
Multiple exostoses	Only a minority are troublesome	400	*400*
Osteitis deformans		30	*25*
Osteogenesis imperfecta	Fragilitas ossium. Several types, all irregular dominant—genetical relationship not known	60	*25*
Cranio-facial, cranio-cleidal, mandibulo-facial dysostoses	A series of separate disorders individually uncommon	30	*20*
Hypertelorism		20	*8*
Ataxia	Dominant hereditary ataxias—a group of which Friedrich's is the best defined	200	*110*
Epiloia	Tuberose sclerosis (9 living sporadic cases in N.I.)	30	*7*
Huntingdon's chorea	(Three families in N. Ireland known)	10	*8*
Hydrocephaly internal obstructive	Includes stenosis of and forking of aqueduct of Sylvius—probably each due to irregular dominant gene	1,230	*25*
Peroneal muscular atrophy	Charcot-Marie-Tooth disease	40	*24*
Spastic diplegia		100	*20*
Dystrophia myotonica		40	*24*
Muscular dystrophy, limb girdle	Faces affected	25	*14*
Myositis ossificans		20	*10*
Deaf mutism (Deafness total hereditary)	Estimated 3 per cent of all hereditary deaf mutism due to dominant genes	46	*46*
Deafness perception	Early onset dominant type	12	*12*
Deafness and cataract	Severe early onset deafness and cataract	6	*6*
Deafness	Absence of or atresia of external auditory meatus	12	*12*
Neurofibromatosis	Von Recklinghausen's disease	300	*200*
Polyposis of colon, multiple		100	*55*
Alopecia areata		700	*700*
Anhidrotic syndrome	Anhidrotic "ectodermal" Dysplasia	34	*5*
Cephalo-facial haemangiomatosis	Naevoid Amentia	30	*7*
Epidermolysis bullosa		100	*40*
Pityriasis rubra pilaris		20	*20*
Telangiectasis haemorrhagica		100	*12*
Tylosis palmaris et plantaris		35	*35*
Urticaria pigmentosum		90	*90*
Xanthoma tuberosum multiplex	Cutaneous xanthomatosis and essential hypercholesteraemia	40	25
Willebrand's disease	Haemophilia—like syndrome	25	*8*
Polycythaemia vera		45	*20*
Spherocytosis	Acholuric jaundice	60	*25*
Thrombocytopenia chronic recurrent		60	*45*
Porphyria	Dominant type genotype detectable but seldom causes illness	200	*130*
Diabetes (insipidus)		40	*20*
Cystic disease of lungs	(Included here "congenital" bronchiectasis)	*500*	400
Megacolon	Hirschsprung's disease	100	*10*
Aniridia	Dominant very irregular degree of manifestation and probably several dominant mutants can cause	60	60
Cataracts "congenital"	Types detected at birth or early—probably several different types	160	*150*
Cataracts, senile and pre-senile		2,000	*2,000*
Choroidal sclerosis	Several types varying in severity and depending largely on location for disability caused	500	*500*
Colobomata	Common—vary from slight iris defect to big defects of iris choroid and retina involving macula	250	*200*
Corneal dystrophies	Several types of very variable severity	140	*140*
Fundal dystrophies		150	*150*
Glaucomas, infantile and juvenile		100	*100*
Hypermetropia	Can only be arbitrarily accepted as a segregating trait at about 10	100	*100*
Keratoconus		20	*20*
Macular dystrophies	At least two dominant types occur	100	*100*
Nystagmus	Familial idiopathic non-albinotic usually lateral	700	*700*
Retinitis pigmentosa	Relatively mild regular dominant type	150	*150*
Retinoblastoma		*58*	14
Subluxation of the lens	Primary and not part of Marfan's syndrome	6	*6*
Optic atrophy		7	*7*
TOTAL		9,555	7,100

TABLE XI. LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY I (continued)

(B) AUTOSOMAL RECESSIVE TRAITS

Trait	*Remarks*	*Phenotype frequency per million*	
		Births	*Living*
Albinism	Usual type with ocular signs. More than one mutant (?allele), can cause	130	*130*
Alkaptonuria		5	*3*
Methaemoglobinaemia		5	*5*
Phenylpyruvic acid amentia	Phenylketonuria	100	*30*
Porphyria congenital	Recessive light sensitive type	50	*5*
Galactosuria		50	*2*
Gargoylism		20	*4*
Amaurotic idiocy	Warran-Tay-Sachs disease. Various types with different ages of onset. Different loci mutants? Alleles?	50	*5*
Hepato-lenticular degeneration	Wilson's disease	10	*3*
Lawrence-Moon-Biedl syndrome		40	*6*
Microcephaly, true	Microcephalic imbecility	40	*21*
Ataxia		40	*20*
Choreo-athetosis		70	*15*
Myoclonic epilepsy		50	*6*
Spastic diplegia	Spastic diplegia familial often with oligophrenia	50	*18*
Muscular dystrophy limb girdle type	Face not affected	30	*16*
Poikilodermia		10	*3*
Epidermolysis bullosa dystrophica		20	*6*
Ichthyosis congenita	May be more than one type	*10*	—
Anophthalmos		100	*50*
Corneal dystrophies	Severe recessive type	5	*5*
Glaucomas	More than one recessive type with buphthalmos	15	*15*
Macular dystrophies	Juvenile and adult types	10	*10*
Microphthalmos	Pure type as distinct from those associated with other eye defects. Mental deficiency often associated.	100	*100*
Myopia, high	Segregating traits overlapping with ordinary refraction variations 3–6 types with other associated defects included here, e.g. with microphakia and spherophakia	150	*150*
Optic atrophy	Very early onset type	50	*50*
Retinitis pigmentosa	Probably several independent mutants contribute	60	60
TOTAL		1,260	738

(C) SEX-LINKED RECESSIVE TRAITS

Trait	*Remarks*	*Phenotype frequency per million*	
		Births	*Living*
Diabetes insipidus		50	*5*
Haemophilia		100	*66*
Christmas disease		10	*4*
Ichthyosis vulgaris		6	*6*
Muscular dystrophy	Duchenne's type	*176*	*24*
Megalocornea	? Only sex limited	20	*20*
Optic atrophy	Leber's type— ? really sex linked	15	*10*
Retinitis pigmentosa		20	*20*
TOTAL		397	155

(D) SUMMARY OF TRAITS OF CATEGORY I

Inheritance mechanism	*Frequency per million*	
	Births	*Living*
Autosomal dominant	9,555	7,100
Autosomal recessive	1,260	738
Sex-linked recessive	397	155
TOTAL	11,212	7,993

TABLE XII. LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY II

Trait	*Remarks*	*Phenotype frequency per million* Births	Living
Absence of limbs or parts of limbs	Congenital endogenous amputations	200	80
Cleft palate and hare lip, together or separately	Not including these anomalies occurring as parts of syndromes or associated with other gross defects	970	700
Congenital dislocation of hip	Mostly limited in effects to females	900	900
Osteonecrosis	Includes osteochondritis dissecans and local, e.g. diseases of Kienbock, Kohler, Perthe and Schlatter	200	200
Radio-ulnar defects	Varying degrees of absence and deformity, radius usually primary and determining also hand defects	205	205
Talipes-equino-varus	Excluding, where recognized, those with neurological determining causes and when part of severe syndromes e.g. anencephalus	800	700
Vertebrae, defects and fusions	A large group including Klippel—Fiel syndrome, Sprengel's anomaly etc.	400	200
Psoriasis	Not known if all of one origin-varying age of onset, duration of attacks and severity	3,000	3,000
Ichthyosis vulgaris		1,100	1,100
Deafness, otosclerotic		200	200
Anencephalus	i.e. The live born with these defects usually dying shortly after birth, with and without spina bifida or rachischisis	360	—
Occipital meningocoele		80	—
Hydrocephalus (Arnold-Chiari)		300	—
Lumbo-sacral spina bifida		800	100
Other central nervous system malformations		320	—
Cardiac malformations		1,200	400
Digestive tract malformations		630	100
Urogenital tract malformations		200	40
TOTAL TRAIT FREQUENCY		9,825	8,725

TABLE XIII. (A) LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY III

Trait	*Remarks*	*Phenotype frequency per million* Births	Living
Deafness total from birth	97 per cent of all genetic deafness at birth. A number of independent mutants involved. Relative fertility of homozygote about 1/3	264	264
Fibrocystic disease of pancreas	A generalized disorder of external secretory glands. For practical purposes, relative fertility of homozygote is zero	600	15
TOTAL TRAIT FREQUENCY		864	279

TABLE XIII. (B) LIST OF SPECIFIC TRAITS, WITH ESTIMATED INCIDENCES: CATEGORY III (*continued*)

Trait	*Remarks*	*Phenotype frequency per million* Births	Living
Anaemia, pernicious	Addison's anaemia	1,300	1,000
Diabetes mellitus		4,000	3,000
Exophthalmic goitre	Graves's or Basedow's disease	1,700	1,500
Manic depressive reactions	Based on severity requiring hospital admissions	4,000	2,500
Schizophrenia	Based on severity requiring hospital admissions	1,300	1,100
Epilepsy	Secondary to disease or injury	2,500	1,200
TOTAL PHENOTYPE FREQUENCY		14,800	10,300

TABLE XIV. DOMINANT CONDITIONS IDENTIFIED IN THE NORTHERN IRELAND POPULATION BUT NOT INCLUDED IN CATEGORIES I AND II FOR THE REASONS STATED

A. BECAUSE THEIR EFFECTS ARE SLIGHT (*most are common*)

Hand defects: Brachydactyly thumbs, brachydactyly 1st finger, brachydactyly 1st, 3rd, and 4th fingers; camptodactyly; clinodactyly; polydactyly (not part of syndrome) of radial side and of ulnar side (more common) of hands; syndactyly and symphalangism mostly 3rd and 4th finger (hundreds of cases of the above types are known but have not been sought out for special investigation); Dupuytren's contracture familial.

Foot defects: Garber's toe deformity; hallux valgus (familial cases may be associated with metatarsal anomalies); hammer toes (many are familial); syndactyly and symphalangism.

Other skeletal: Diaphyseal achalasia, epiphysitis punctata.

Teeth anomalies (Other than parts of syndromes): Defective or absent enamel (various types); opalescent dentine; additional teeth (many types); absence of permanent incisors and pre-molars; some such anomalies are present in about 1.3 per cent of the population.

Skin and hair anomalies: Adenoma, cystic multiple benign; cysts, epidermoid; dermatomyomat multiple; anonychia and hypoplasia of nails; leukonychia totalis; pachyonychia congenita; hair, white patches; hair kinky; hair woolly; hydroa aestivale; porokeratosis

Eye anomalies: Eyelids—spasm, absence of tarsal plates, uncomplicated ptosis; absence fistula of lacrymal ducts; retina, opaque fibres; strabismus convergent and divergent (primary).

Miscellaneous: Pelger's anomaly, elliptocytosis.

Ear anomalies: Cat's ears, microtia; pre-helicine pits; lobule pits; accessory auricles.

B. BECAUSE EVEN IF THE EFFECTS ARE SEVERE, THE ANOMALIES ARE PROBABLY PRESENT IN LESS THAN FIVE PERSONS PER MILLION

Skeletal: Osteo-petrosis (Albers-Schönberg); phocomelia; ankylosing spondylosis; polyostotic fibrous dysplasia (Albright's disease); multiple enchondroma; fibula absence or defect; oxycephaly; acrocephaly; syndactyly.

Skin: Ichthyosiform congenital erythrodermia; keratosis follicularis spinulosa (Darier's disease); monilethrix; urticaria pigmentosa; tylosis palmaris et plantaris; pili torti; mal de Meleda; lipodystrophy progressiva without gargoylism.

Miscellaneous: Milroy's disease; periodic paralysis; dominant microcytic anaemia; Waardenberg's syndrome; anotia.

TABLE XV. CLASSES OF BIOMETRICAL CHARACTER

Character	*Presumed position of social optimum*	*Position of selective optimum*	*Position of population mean*
Birthweight	At selective optimum	Intermediate finite value	Below selective optimum[151]
Intelligence (measured as intelligence quotient)	$+\infty$ [a]	Intermediate finite value	Near and possibly even above present selective optimum:[158] far below social optimum
Life-span	$+\infty$ [a]	Unknown: perhaps $+\infty$ [a]	Below social optimum: probably below selective optimum

[a] "$+\infty$" implies positive and indefinitely large, always greater than the population mean.

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Appendix

Calculations concerning survival at or near birth and the distribution of birth-weights

110. Both Karn and Penrose[151] and Fraccaro[184] have found in samples of several thousand births that the distributions both of survivors S and non-survivors N through birth and the subsequent 30 days are Gaussian. Under these conditions the influence of the mean and variance of the over-all birth-weight distribution upon survival at or near birth can, at least approximately, be treated algebraically. Suppose birth-weight w to be measured from the birth-weight at which S is maximal.

Let $S = S_o \exp - w^2/2\sigma_3^2$

$$N = N_o \exp - 1/2\left(\frac{w - m'}{\sigma_4}\right)^2$$

Then the curve determining survival is

$$\frac{S}{N} =$$

$$\frac{S_o}{N_o} \exp - \frac{1}{2\sigma_1^2}\left(w + \frac{m'\sigma_3^2}{\sigma_4^2 - \sigma_3^2}\right)^2 \quad \exp \frac{1}{2}\left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2}\right)$$

where $\frac{1}{\sigma_1^2} = \frac{1}{\sigma_3^2} - \frac{1}{\sigma_4^2}$

and the over-all survival is $1 - \bar{k}$ where

$$\bar{k} = \frac{\sigma_4 N_o}{\sigma_3 S_o + \sigma_4 N_o}$$

Moreover, optimal survival is at $\omega_{opt} = \frac{-m'\sigma_3^2}{\sigma_4^2 - \sigma_3^2}$

and at this point

$$\left(\frac{S}{N}\right)_{opt} = \frac{S_o}{N_o} \exp - 1/2\left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2}\right)$$

Then the survival at $\omega = \omega_{opt}$ is $1 - k_{min}$

where $$k_{min} = \frac{N_o/S_o \exp - 1/2\left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2}\right)}{1 + N_o/S_o \exp - 1/2\left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2}\right)}$$

It is desirable to express the relation between k_{min} and $\bar{k}$ in terms of (1) the variance σ_2^2 of the over-all distribution of birth-weights

$$T(W) = S(W)+N(W)$$

(2) the difference m between the mean of the over-all distribution of birth-weights and the birth-weight for optimal survival, and

(3) the variance σ_1^2 which determines the shape of the birth-weight-survival relation.

In terms of the parameters describing S(W) and N(W)

$$m = m' (\sigma_3^2/(\sigma_4^2 - \sigma_3^2) + \bar{k})$$

$$\sigma_2^2 = \sigma_3^2 (1 - \bar{k}) + \sigma_4^2\bar{k} + m'^2 \bar{k} (1 - \bar{k})$$

If it is assumed that $\bar{k}$ is small by comparison with unity, it is possible to write

$$r = \frac{k}{k_{min}} = \frac{\sigma_4}{\sigma_3} \exp 1/2 \left(\frac{m^2}{\sigma_4^2 - \sigma_3^2}\right) + 0 (\bar{k})$$

and so since $\sigma_2^2 = \sigma_3^2 + 0(\bar{k})$ and σ_4^2 can be eliminated in terms of σ_1^2 and σ_3^2

$$r \doteqdot \frac{\sigma_1}{(\sigma_1^2 - \sigma_2^2)\ 1/2} \exp 1/2 \left(\frac{m^2}{\sigma_1^2 - \sigma_2^2}\right) \ldots\ldots (1)$$

Comparison of [1] as observed by Karn and Penrose with values calculated from the above formula and the parameters of their experiments gives

	r_{obs}	r_{calc}
Males	2.07	2.23
Females	2.21	2.36

111. On the basis of equ. (1) it is possible to estimate the consequences of small shifts in the mean or variance of the distribution of birth-weights, assuming that the survival curve (k_{min}, σ_1) remains constant, by the relations

$$\frac{dr}{r} \Big/ \frac{d\,\sigma_2^2}{\sigma_2^2} = 1/2 \left(\frac{\sigma_2^2}{\sigma_1^2 - \sigma_2^2}\right) + 1/2 \left(\frac{m^2\,\sigma_2^2}{(\sigma_1^2 - \sigma_2^2)^2}\right)$$

and

$$\frac{dr}{r} \Big/ \frac{dm}{m} = \left(\frac{m^2}{\sigma_1^2 - \sigma_2^2}\right)$$

Calculated numerical changes in r and in $\bar{k}$ for 1 per cent changes in variance and in departure of mean from optimal birth-weight are given in table XVI calculated from the data of Karn and Penrose and Fraccaro.

112. It has been estimated by Robson[185] and by Penrose[149] that some 40 per cent of the variance of birth-weight in a United Kingdom sample was due to genetic factors, either of the mother or of the foetus. Possibly only a small fraction of this is maintained by recurrent mutation. The other extreme possibility is that recurrent mutation maintains the whole of the genetic component of the variance σ_2^2. In that event a 10 per cent change in mutation rate might lead to a 4 per cent change in σ_2^2 and so to changes in survival at and near birth amounting to 0.2–0.7 per cent. If the representative doubling dose for the polygenes concerned were to be 30 rad, this would then correspond approximately to the genetical influence of natural sources of irradiation upon survival at or near birth.

113. The part played by genetic factors in maintaining the difference between the mean birth-weight and that for optimal survival is not known, but the most extreme possibility is again that recurrent mutation may be responsible for the whole of m. In that event a similar change in mutation rate might lead to changes in survival at or near birth amounting to 0.2–0.8 per cent. These calculated upper limits apply to regions in which the total loss of infants at or near birth is in the range 4–7 per cent. They are illustrative of the need to resolve the underlying and more fundamental problem of the part played by mutation in maintaining the current distribution of birth-weights against the pressure of selection acting through this phenotype.

TABLE XVI. CALCULATED CONSEQUENCES OF CHANGES IN THE PARAMETERS GOVERNING BIRTH-WEIGHT DISTRIBUTION

Survey Sample		*Changes due to 1 per cent change in σ_2^2*		*Changes due to 1 per cent change in m*	
		Fractional change in r (per cent)	*Absolute change in $\bar{k}$ (per cent)*	*Fractional change in r (per cent)*	*Absolute change in $\bar{k}$ (per cent)*
Karn and Penrose[151]	Males	1.5	0.072	0.50	0.024
	Females	1.3	0.053	0.84	0.034
Fraccaro[184]	Males	1.6	0.11	0.72	0.048
	Females	2.9	0.18	1.2	0.076

Annex I

LIST OF REPORTS SUBMITTED TO THE COMMITTEE

1. This annex lists reports received by the Committee from Governments, specialized agencies, the International Commission on Radiological Protection and the International Commission on Radiological Units and Measurements. Abstracts have been inserted where appropriate.

2. All those reports are included of which a sufficient number of copies for distribution in the A/AC.82/G/R. document series were received before 1 March 1958.

3. The list also includes reports received after 1 March 1958, preliminary copies of which were submitted to the Committee prior to that date.

Document Number	*Country and Title*	*Approximate No. of pages*
A/AC.82/G/R.		
1.	UNITED STATES OF AMERICA. *The biological effects of atomic radiation* Summarizes general survey in which committees of experts covered the following subjects: genetics; pathology; meteorology; oceanography and fisheries; agriculture and food supplies; disposal and disposers of radioactive wastes.	108
2.	UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND. *The hazards to man of nuclear and allied radiations* General report covers both somatic and genetic hazards associated with radiation, present and foreseeable levels of exposure, and an assessment of the hazards in terms of associated actual and permissible levels.	128
3.	BELGIUM. *Preliminary report on modern methods for the evaluation of the biological effects of small doses of external radiation or absorbed radioactive materials* Concludes that the most hopeful measurements are those of: 1. DNases and cathepsins in plasma and urine. 2. DNA synthesis in vitro by bone marrow or biopsy specimens. 3. Platelet counts. 4. Antibody synthesis. and that the Committee should re-emphasize the need of appropriate fundamental research in radiobiology.	25
4.	JAPAN. (Report consisting of eight parts, as follows:) (*Part 1.*) *Researches on the effects of the H-bomb explosion at Bikini Atoll 1954 on animal industry and sericulture in Japan* Gives negative results of analysis by absorption method of radioactivity in milk, eggs and agricultural products following the Bikini explosions of May 1954. Related experimental feedings of animals with radioactive ashes were analysed chemically.	10
	(*Part 2.*) *The radioactive contamination of agricultural crops in Japan* Gives results of soil and crop analyses for total radioactivity before and after May 1954 Bikini explosions, after subtraction of K^{40} content, and with some radiochemical analysis. Radioactivity after the explosion was detected in soil, crops and other vegetation which are distributed all over Japan. The possible route of contamination is discussed.	13
	(*Part 3.*) *A preliminary report of recommendations on the modern methods of estimating the biological activity of small radiation dose* Several current hematological findings in Japan are summarized and discussed.	3
	(*Part 4.*) *The airborne radioactivity in Japan* Analyses of airborne radioactivity by filter and by electrical precipitator are described and compared. Results of analyses 1954–1956 show poor correlation between peaks of contamination and trajectories of high-level air masses.	28
	(*Part 5.*) *Report on the systematic observations of the atmospheric radioactivity in Japan* Describes methods of collection and analysis of fall-out in dust, rain and snow, and of airborne radioactivity, as used in a wide survey at meteorological stations. Results from April 1954-March 1956 are summarized and discussed and the cumulative depositions of Sr^{90} is calculated.	56
	(*Part 6.*) *On the distribution of naturally radioactive nuclides in Japanese islands* Surveys of the distribution of naturally radioactive nuclides in Japanese waters and minerals are reviewed and summarized.	27

Document Number	Country and Title	Approximate No. of pages
A/AC.82/G/R.		
	JAPAN *(continued)*	
	(*Part 7.*) *Radiochemical analysis of radioactive fall-out observed in Japan* Present methods and results of radiochemical analyses of ash from the fishing boat No. 5 fukuryu Maru and of rainwater and soil samples in Japan.	24
	(*Part 8.*) *Fission products in water area and aquatic organisms* Describes fall-out distribution and uptake generally, with special reference to water and aquatic organisms and to the problem of Sr^{90}.	24
5.	MEXICO. *First report on the studies of radioactive fall-out* Gives full description and comparisons of sticky paper and pot methods, preliminary results May-July 1956 for total beta activity and intended expansion of programme.	15
6.	UNION OF SOUTH AFRICA. *Preliminary report on radioactive fall-out* The preliminary result of the measurement of total beta activity of fall-out by porcelain dish method is described and results are given for January-June 1956. Sr^{90} deposition was estimated by chemical analysis.	2
7.	UNITED STATES. *Radioactive fall-out through September 1955* Summarizes analysis of daily samples obtained up to end of September 1955 from twenty-six stations in United States and sixty-two elsewhere by gummed film method calibrated against collection in high walled pots (see document A/AC.82/INF.1). Cumulative deposition of mixed fission products, integral gamma doses and Sr^{90} deposits are calculated and compared with other findings, including Sr^{90} content of soils and milk.	13
8.	CHINA. *Reports by the Atomic Energy Council of the Executive Yuan of the Republic of China* Briefly notes the radium content of certain Chinese and other waters and the occurrence of radioactive sailfish and dolphin in seas off Taiwan, June 1954.	8
9.	CANADA. *Report on waste disposal system at the Chalk River Plant of Atomic Energy of Canada Limited* Describes procedures and results of ground dispersal of radioactive wastes from a natural uranium heavy water-moderated reactor.	15
10.	*The Canadian programme for the investigation of the genetic effects of ionizing radiation* Describes a proposal to modify the system of recording of the national vital statistics so as to render useful for genetic analysis the information contained in certificates of births, marriages and deaths (see also document A/AC.82/G/R. 58/Add. 1, annex 12).	15
11.	UNITED STATES. *Pathologic effects of atomic radiation* Present knowledge of the pathological (non-hereditary) effects of radiation is surveyed extensively by a committee. Includes separate sections by sub-committees or individual members on: acute and long-term hematological effects; toxicity of internal emitters; acute and chronic effects of radioactive particles on the respiratory tract; delayed effects of ionizing radiations from external sources; effects of radiation on the embryo and foetus; radiation in a disturbed environment; effects of irradiation of the nervous system; radiation effects on endocrine organs.	100
12.	CANADA. *Levels of strontium-90 in Canada* Gives figures for Sr^{90} and Sr^{89} in milk powder at seven stations, November 1955-May 1956. The Sr^{90} level averages 4.8 $\mu\mu$c/gm Ca. Cumulative total beta activity and calculated Sr^{90} content of fall-out analysed by United States AEC from gummed papers, are summarized annually for 1953 to 1955. Independent Canadian measurements by methods which are not described differ from these by factors 2-5.	7
13.	NEW ZEALAND. *Note by New Zealand* Gives brief notes in reply to the questions contained in individual paragraphs of annexes to letter PO 131/224 of 9 April 1956 (annexes derived from A/AC.82/R.10). Other sections describe: measurements of radioactivity (only radon found) collected from air at Wellington by filter and by electrostatic precipitator February 1953-May 1956, also by an impactor method in 1953 and in rainwater on certain dates November 1955-May 1956; results of measurements of total beta activities of fall-out by sticky paper method May-July 1956.	12
14.	NORWAY. *Report of three parts* Suggests taurine biochemistry and lens opacities as biological indicators for low doses. Gives notes on disposal of small amounts of radioactive wastes. Describes and gives results of analyses by pot method in 1956 of total beta activity due to fall-out on ground, in air, in drinking water and accumulated in snow falls. Includes some analyses for Sr^{90}.	9
14/Add.1	*Addendum to Part 1*	7

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15.	SWEDEN. *Report of fifteen parts* The fifteen sections cover: consumption of the doses to the gonads of the population from various sources; thorough survey of natural radioactivity including estimates of weekly dose-rates; measurements of gamma radiation from the human body; measurements of fall-out (1953-1956) including total beta activity, gamma ray spectrum and migration of Sr^{90} into soils, plants and grazing animals, content of certain isotopes as well as research upon certain related physical quantities; considerations of occupational (medical) exposures. Methods used are extensively described throughout.	330
15/Corr.1	*Corrigendum to parts 1 and 9*	2
15/Corr.2	*Corrigendum to part 9*	1
16.	FRANCE. *Report of three parts* The report includes three main parts: 1. Methods of measuring: the radioactivity produced by nuclear explosions and nuclear industry; natural or artificial radioactivity in living beings; the atmospheric radon. 2. Reports on measurements relative to: natural radioactivity of rocks; radioactivity of soil and water; natural and artificial radioactivity of air, water and soil; occupational radiation exposure. 3. Studies on genetic effects of radiations and on the descendants of patients treated with pelvic radiotherapy.	106
16/Add.1	*Addendum to above report*	20
17.	CZECHOSLOVAKIA. *Natural radioactivity of water, air and soil in the Czechoslovak Republic* Briefly draws attention to deviations from reciprocity and to the partial reversibility of many radiation induced phenomena, to the possible use of organisms in a state of abiosis as integral dose-indicators, to certain specially radiosensitive organisms and responses, and to questions of threshold. An extensive survey reviews many studies of natural radioactivity.	37
18.	KOREA, REPUBLIC OF. *Report concerning the request for information on natural radiation background* Describes counters used for monitoring radiation background and gives results (cpm) from January 1955 to June 1956.	10
19.	AUSTRIA. *Information prepared by the Austrian Government relating to the effects of atomic radiation* Describes radioactive warm springs at Bad Gastein, giving activity levels in water and air. Outlines wide scope of biological and instrumental research at Gastein Institute.	2
20.	UNITED KINGDOM. *The radiological dose to persons in the United Kingdom due to debris from nuclear test explosions prior to January 1956* Summarizes measurements of total beta activity and Sr^{90} content of fall-out at ground stations, in rainwater and in the air over the United Kingdom during 1952-1955. Includes calculations of time-integrated gamma ray doses.	28
20/Corr.1	*Corrigendum to above report*	2
21.	UNITED STATES. *Project Sunshine Bulletin No. 12* Presents and discusses results of Sr^{90} analyses since 1 December 1955. Includes Sr^{90} concentration in human and animal bones, animal products, vegetation, soil, precipitation, other water, and air.	59
22.	*Summary of analytical results from the Hasl Strontium Program to June 1956* Summarizes the data of research on Sr^{90} conducted by Hasl since 1951. Includes the Sr^{90} content in fall-out, soil, vegetation, human and animal bones, human urine, milk, cheese, drinking water, and fish. Fall-out measurements and samples cover not only United States of America but also several other countries.	9
23.	ARGENTINA. *Preliminary report on possible methods of estimating the biological effects of small doses of radiation* Among biological effects of small doses of radiation, emphasizes especially: measurement of DNA synthesis using P^{32} and C^{14} radio-autography, histochemical and electron microscopic examination of changes in lymphocytes and other components of peripheral blood.	13
24.	UNITED STATES. *The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki* Gives full account of survey of pregnancies in Nagasaki and Hiroshima from 1948 to 1954: sex ratio, congenital malformations, still births, birthweights, neo-natal deaths, certain anthropometric measurements at nine months, and autopsies were compared with parental irradiation histories. No significant correlations were found.	380

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25.	HUNGARY. *Unusual radioactivity observed in the atmospheric precipitation in Debrecen (Hungary) between 22 April-31 December 1952* Describes methods and discusses results of measurements of total beta activity of fall-out at Debrecen, April-December 1952.	13
26.	BELGIUM. *Report consisting of five parts* 1. Gives results of clinical observations of patients treated with X-rays, Ra or I^{131} and of persons occupationally exposed. 2. Gives results of studies relating to: the medical and physical control of persons occupationally exposed; the absorbing materials; and the radioactive contamination of the atmosphere. 3. Considers preventive or curative methods of syndromes of acute irradiation. States results of doses received by the occupationally exposed personnel of the *Institut du cancer* of Louvain, Belgium, and of hematological examinations of them. 4. Describes methods for measuring the radioactivity in rain and surface waters. Gives results of measurements of radioactivity in rainwaters. 5. Describes method for measuring the radioactivity of atmospheric dust by continuous filtering of air.	50
27.	SWITZERLAND. *Letter from the "Service fédéral de l'hygiène publique", Bern* Gives brief description of studies on atomic radiations conducted in Switzerland.	6
28.	ARGENTINA. *Information summary on the preliminary work carried out in Argentina for the measurement and study of radioactive fall-out* Gives summary description of methods tried in Argentina for measurement of total fall-out radioactivity and airborne radioactivity.	2
29.	AUSTRALIA. (*Report consisting of six parts, as follows:*) (*Part I.*) *Human genetics* Report gives recommendation as to the kind of human mutations which could be scored: several dominant autosomal genes should be investigated (gives list of such genetical abnormalities). (*Part II.*) *Plant genetics* Gives plan of research to be organized. (*Part III.*) *Radio-biological unit in the University of Adelaide* To be established. (*Part IV.*) *Natural radiation background and environmental contamination* Describes future organization of investigations on natural radiation background and contamination; radioactivity of food will be determined. (*Part V.*) *Occupational exposure in Australia* Describes monitoring system in application since 1940 and summarizes observations done by the use of film badges (gives statement of per cent of personnel having received a specified per cent of the permissible dosage). (*Part VI.*) *Health and safety precautions in uranium mining and milling in Australia* Describes health and safety precautions in uranium mining and milling.	17
30.	UNITED KINGDOM. *Radio-strontium fall-out in biological materials in Britain* Describes methods for determination of Sr^{90} in soils and material of the biological cycle; gives results of measurement effected in England up to spring 1956.	46
31.	FEDERAL REPUBLIC OF GERMANY. *Replies to the questions put by the United Nations Scientific Committee on the Effects of Atomic Radiation* 1. Levels of natural radiation background. 2. Summarizes long-term research in biology and medicine under the direction of *Langendorff* (genetic effects, restorations, physicochemical effects); *Rajewski* (effects of natural radioactivity, accumulation of nuclides in tissues); *Marquardt* (research on natural mutation rates and their modification by irradiations); *Other institutes* (pathological and physicochemical effect). No details given—refers to scientific publications.	6
32.	INDIA. *Procedure used in India for collection of fall-out samples and some data on fall-out recorded in 1956* Describes methods for measurements of airborne activity by filtration, and of deposited fall-out with daily and monthly collection. The information includes tables giving results.	12
33.	*External radiation dose received by the inhabitants of monozite areas of Travancore-Cochin, India* Contains results of a survey to measure the radiation level of the Indian State of Travancore. The radiation level due to gamma-rays at about three feet above the ground level ranges from 6,000 to 100 mrad/year, approximately. The main contributors are thorium and its decay products.	9

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34 and Add.1	BRAZIL. *On the intensity levels of natural radioactivity in certain selected areas of Brazil* States that Brazil has areas of intensive natural background where thorium sands are present. Gives description of a survey on four sample areas which were selected with regard to: (*a*) The geological structure and genesis of their active deposits; (*b*) The extension, configuration and intensity of their radiometric levels; (*c*) The extent and variety of possible biological observations and experiments.	46
34/Corr.1	*Corrigendum to above report.*	6
35.	WORLD METEOROLOGICAL ORGANIZATION. *Summary of comments of WMO on procedures for collection and analysis of atmospheric radioactivity data* Comments on measurements of fall-out and airborne activity; stresses the importance of co-operation between meteorologists in selecting sites wherefrom to obtain samples.	5
36.	BRAZIL. *Measurements of long-range fall-out in Rio de Janeiro* Gives information on measurements of airborne activity done in Rio de Janeiro, including tables showing decay curves of activity of samples and concentration of fission products in air during the period May-July 1956.	13
37.	UNION OF SOVIET SOCIALIST REPUBLICS. *On the methods of indicating the changes produced in the organism by small doses of ionizing radiation* Gives an enumeration of many methods which might be used as tests for small dosages; but these are based on certain symptoms which have not yet been worked out to give a quantitative response, i.e. vegetative-visceral symptoms, nervous symptoms (like the increase in threshold of gustatory and olfactory sensitivity, etc.), skin vascular reactions, electroencephalogram. Blood symptoms are also described (alterations of thrombocytes and lack of a leucocytosis response to the injection of Vit. B-12). Certain "immunological" symptoms are quoted, like the bactericidal properties of saliva and of skin.	13
38.	BRAZIL. *Absorption curve of fall-out products* Is connected with document A/AC.82/G/R.36; gives absorption curve for fission product of an airborne activity sample obtained by filtration.	5
39.	USSR. *Content of natural radioactive substances in the atmosphere and in water in the territory of the Union of Soviet Socialist Republics* Studies content of natural radioactive substances in the atmosphere and in waters; geochemical considerations on mechanism of contamination of waters and description of radio-hydrogeological methods. Gives methods of measurement of airborne activity and results, and includes tables giving content of natural radioactive products in air and waters.	23
40.	*Study of the atmospheric content of strontium-90 and other long-lived fissions products* Gives measurements of airborne fission products (Sr^{90}, Cs^{137}, Ce^{144} and Ru^{106}); methods for collection of samples and their radiochemical analysis; results and comments.	8
41.	*On the behaviour of radioactive fission products in soils, their absorption by plants and their accumulation in crops* Report of two parts: *Part I.*—Experiments of absorption and desorption by soil of fission products and especially of isotopes such as $Sr^{90} + Y^{90}$, Cs^{137}, $Zr^{95} + Nb^{95}$ and $Ru^{106} + Rh^{106}$ are described. Theoretical analysis is also described. It was observed that $Sr^{90} + Y^{90}$ is absorbed through ion exchange reaction, and is completely or almost completely displaced from the absorbed state under the action of a neutral salt such as $CaCl_2$. Radioactive equilibrium between Sr^{90} and Y^{90} is destroyed during the interaction with soil. Displacement of absorbed radiocesium is greatly affected by the potassium ions, but not highly affected by $NaNO_3$ or $CaCl_2$ compared with $Sr^{90} + Y^{90}$. Zirconium and ruthenium absorbed by soil exhibit a much lower susceptibility to desorption into neutral salt solution, though their absorption is less complete. The disturbance of the equilibrium occurs also by absorption or desorption. *Part II.*—The results of experiments on uptake of fission products by several agricultural plants are described. In water culture, the bulk of radioactive isotopes of cesium and strontium is held in the above-ground organ of plant, while Zr, Rh and Ce are mainly retained in the root system. Sr and Cs are likely to accumulate in reproductive organs of plants in larger quantities than Zr, Ru and Ce. The plant uptake is affected by the concentration of hydrogen ions in the solution. Plants' uptake of fission products from soils is considerably smaller than from aqueous solution, and	176

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	cesium was found to be less absorbable from soil, compared with other isotopes, while cesium is among the fission products most strongly absorbed by plants in water culture. These facts can be explained by the absorptive and desorptive capacity of the isotopes of the soil. The properties of soil as well as the application of lime, potassium or mineral fertilizers greatly affect the plant uptake. When a solution of fission products was applied to leaves of a plant, radio-isotopes were observed to pass to other organs. Radiocesium was the most transmovable among the isotopes tested.	
42.	MEXICO. *First studies on radioactive fall-out* Revised form of UN document A/AC.82/G/R.5.	15
43.	JAPAN. *The effect of momentary X-ray exposure in a small dose upon the peripheral blood picture* Decrease in lymphocyte number after single 60 mr exposure in humans. Decrease in lymphocyte count varies from 10 to 50 per cent—the maximum drop occurs thirty minutes after irradiation, and may be followed by an increase in lymphocyte count.	8
44.	*Hematological effects of single exposure to small doses of X-ray* Hematological effects during routine chest examinations. Dosages up to 3r. Most constantly observed are: increase in neutral red bodies and Demel's granules in lymphocytes and late decrease in mitochondrial index of lymphocytes during the four-hour period following the irradiation. The cytochemical identification of these various granules and their biological significance should be established unequivocally.	17
45.	*Morphological changes of platelets in chronic radiation injuries* Platelet morphology in chronic irradiation injury in rabbits (chronic 0.115 r/day or 0.231r/day), X-ray workers (dosage not evaluated) and persons exposed to atomic bomb within 4 km from epicentre (nine years after the exposure). Even if platelet count is normal, area index (proportional to average area) is increased markedly, and may remain so nine years after irradiation and is not necessarily related to low platelet count. Other morphological changes are also shown. This observation should be repeated by other groups.	19
46.	EGYPT. *Preliminary report on environmental iodine-131 measurement in sheep and cattle thyroids in Cairo, Egypt* Contains measurement of radioactivity of I^{131} deposited in thyroids of sheep and cattle which were brought from all over Egypt, Sudan and north coast of Libya. Sampling was made during the period from May to October 1956.	11
47.	USSR. *Preliminary data on the effects of atomic bomb explosions on the concentration of artificial radioactivity in the lower levels of the atmosphere and in the soil* Contains description of methods of measurement of radioactive products in the air at ground level and high altitude and gives results of observations. Also contains the following conclusions: (1) The existing technique for detecting the presence of artificial radioactivity in the lower atmosphere and the technique for determining the integral activity of aerosols deposited on the earth's surface makes it possible to estimate the level of contamination of the soil by radiostrontium (strontium-90). (2) The accumulation of radiostrontium in the soil in various areas of USSR territory is attributable partly to the explosion of atomic bombs in USA and partly to explosions set off in USSR. The lower limit of activity of the strontium-90 which has accumulated in the past two years (1954–1955) is as high as about 30 millicuries per km^2 in certain towns (cf., for example, Adler). (3) Since radiostrontium is readily caught up in the biological cycle, suitable projects must be put in hand to determine the permissible levels of contamination of the soil with radiostrontium (strontium-90) and other biologically dangerous isotopes.	21
48.	*Programme of scientific research on the effects of ionizing radiations on the health of present and future generations* Describes a programme of research intending to study the effects of radiation at dosages 1 or 2 orders of magnitude above background intensity, of contamination of the air and soil and life in areas of high natural radioactivity.	6
49.	*Summaries of papers presented at the Conference on the remote consequences of injuries caused by the action of ionizing radiation* Mostly concerned with effects of various radionuclides and external radiation on different mammalian populations (Hematology, carcinogenesis, fertility mostly studied). Twenty-two papers are summarized.	74
50.	*Contributions to the study of the metabolism of caesium, strontium and a mixture of beta-emitters in cows*	20

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The metabolism of Cs^{137}, $Sr^{89,90}$ and a number of mixed beta-emitters has been studied in cows (milk, urine, faeces, tissues).

Strontium: about 10 per cent given is absorbed in intestine and 1.45 per cent is retained in bones, and twenty times less in the soft tissues. The rest is excreted by milk or urine.

Caesium: about 25 per cent given is absorbed in intestine—one fifth of this is retained in muscle and less than one tenth of this amount in other organs or skeleton; the rest is eliminated in the milk or urine.

51. UNITED KINGDOM. *The genetically significant radiation dose from the diagnosis use of X-rays in England and Wales—A preliminary survey* — 11

Contains an analysis of number of X-ray diagnostic examinations performed per annum in England and Wales, and a subdivision obtained from five selected hospitals into types of examinations, and into age and sex of the patients examined. In addition, an assessment is made of the minimum dose received by the gonads in each type of examination, and the probability of reproduction as a function of age. The results show that it is unlikely that the genetically significant radiation dose received by the population of England and Wales from X-ray diagnosis amounts to less than 22 per cent of that received from natural sources and it may well be several times greater than this figure. Most of this radiation is received in a few types of examinations, undergone by relatively few patients, and by foetal gonads in examinations during pregnancy.

52. ROMANIA. *Organization and results in radiobiological research work in the Romanian People's Republic* — 5

Describes the following:

(1) and (2) Protective effects of narcosis during irradiation only.

(3) After 325 r, up to eleven days narcosis increases biological effects (does not state what criteria of biological effect).

(4) Hibernation (25° C) protects. Hibernation between 18°-25° C enhances effect. Does not state if this is during or after irradiation.

(5) Hematological tests after 350 r.

(6) Caffeine or aktedron during irradiation enhance effect; caffeine or aktedron after irradiation diminish effect.

Suggests roentgenotherapy under conditions of protection (narcosis). Gives programme for radiobiology research in 1956-1957.

53. USSR. Report consisting of two articles: — 10

Part 1. *The effects of ionizing radiations on the electrical activity of the brain*

(*a*) Grigorev's research work states: gamma-rays depress electrical action of human brain. Does not confirm Eldrid-Trowbridge, who do not find effect on monkey.

(*b*) Describes effects of beta-rays of P^{32} (0.05 mc/kg up to 1 mc/kg) on electroencephalogram of dogs. This was followed by radiation sickness (if dose > 0.5 mc/kg) and by hematological effects. A special implantation method of the electrodes is used. Injection of 0.09 mc/kg gives change in amplitude five minutes after the injection (reduction in amplitude). After 0.5 mc/kg lowering of electrical activity lasts for several days. For dosages above 0.1 mc, part of the repression of brain activity is probably a result of the radiation sickness induced by such high dosages.

Part 9. *On the beta-radiation activity of human blood*

Report on radioactivity of human blood: 100 cc of normal blood have a radioactivity of 1.7 to $3.64.10^{-10}$ curies (due to K^{40}). Permits the determination of K content of whole blood. Same values are found in different pathological conditions. No data on people working with radioactive material.

54. UNITED STATES. *Some effects of ionizing radiation on human beings* — 106

A report on the Marshallese and Americans accidentally exposed to radiation from fall-out and a discussion of radiation injury in the human being. Gives general and clinical symptomatology in relation to the estimated dosage and to internally deposited radionuclides.

55. *Background radiation—A literature search* — 43

The results of literature search about background radiations dosage to human beings are described and classified into three categories:

(1) Cosmic radiation; (2) terrestrial radiation sources; and (3) radiation from internal emitter. The cosmic radiation is important for the evaluation of natural background, since it is estimated very roughly to contribute about a quarter of total background dosage to the human population at sea level and high latitude. However, its intensity varies with various factors, such as altitude, geomagnetic latitude, barometric pressure,

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temperature etc. Facts directly related to biological effects of cosmic rays are also reviewed.

Radiations from naturally-occurring radioactive isotopes form another important part of the natural background. The contribution which comes from land is mainly due to K^{40}, Ra^{226}, Th^{232} and U^{238} and the decay products of the last three nuclides. The radium concentrations in surface water and public water supplies in various districts are tabulated. The atmospheric concentration of Rn and Tn is greatly dependent on the locality, atmospheric condition and degree of ventilation, if indoor.

The population dose due to the natural background radiation is difficult to evaluate in general, because of the statistical nature and varying conditions involved in nations.

56. *Operation Troll* — 37

Operation Troll was conducted to survey the radioactivity in sea water and marine life in the Pacific area during the period from February to May 1955. The general conclusions obtained are as follows:

1. Sea water and plankton samples show the existence of widespread low-level activity in the Pacific Ocean. Water activity ranged from 0-570 d/min/litre and plankton from 3-140 d/min/g wet weight.
2. There is some concentration of the activity in the main current streams, such as the North Equatorial Current. The highest activity was off the coast of Luzon, averaging 190 d/min/litre down to 600 m (1 April 1955).
3. Analyses of fish indicate no activity approaching the maximum permissible level for foods. The highest activity in tuna fish was 3.5 d/min/g ash, less than 1 per cent of the permissible level.
4. Measurements of plankton activity offer a sensitive indication of activity in the ocean.
5. Similar operations would be valuable in assessing the activity from future tests and in gathering valuable data for oceanographic studies.

57. *Gonadal dose in roentgen examinations—A literature search* — 6

Contains results of literature research which show the estimated contribution of gonadal dose by standard medical roentgenographic procedures. Contribution to the gonadal dose of certain examinations, such as examinations of teeth, skull, chest and extremities, is relatively insignificant, when compared to the case of pelvic and abdominal examinations. It should be noticed that the dose to the foetal gonad is important genetically.

58. WORLD HEALTH ORGANIZATION. *Effect of radiation on human heredity*— — 148

Report of a Study Group (Copenhagen, 7-11 August 1956).

1. Document A: Reply to a question raised by the United Nations Scientific Committee on the Effects of Atomic Radiation.
2. Report of the study group concerning general questions and recommendations for future progress and research.
3. Annexes 2-9 and 11-12 of the above report, being papers presented by various members of the group.

These annexes were:

Types of mutation at known gene loci and possibility of hitherto unrecognized mutations being induced. Irradiation of animal populations: results and work needed—T. C. Carter.

Some of the problems accompanying an increase of mutation rates in Mendelian populations—Bruce Wallace.

Exposure of man to ionizing radiations, with special reference to possible genetic hazards—R. M. Sievert.

Detection of induced mutations in offspring of irradiated parents—J. Lejeune.

Gonad doses from diagnostic and therapeutic radiology—W. M. Court Brown.

Mutation in man—L. S. Penrose.

Possible areas with sufficiently different background-radiation levels to permit detection of differences in mutation rates of "marker" genes—A. R. Gopal-Ayengar.

Comparisons of mutation rates at single loci in man—A. C. Stevenson.

Effect of inbreeding levels of populations on incidence of hereditary traits due to induced recessive mutations—N. Freire-Maia.

Detection of genetic trends in public health—Harold B. Newcombe.

58/Add.1 Annexes 1 and 10 of the above report of the WHO Study Group on the effect of radiation on human heredity. — 47

These annexes were:

Damage from point mutations in relation to radiation dose and biological conditions —H. J. Muller.

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	WORLD HEALTH ORGANIZATION *(continued)*	
	Some problems in the estimation of spontaneous mutation rates in animals and man—James V. Neel.	
59.	NETHERLANDS. *Radioactive fall-out measurements in the Netherlands*	6
	Describes methods used for collecting samples of airborne radioactivity and of deposited fall-out, and methods of measurement. Includes tables of results for 1955 and 1956; calculation of gamma doses and quantity of strontium-90 computed from total activity.	
60.	UNITED KINGDOM. *Genetic research in the United Kingdom*	6
	Relevant programmes of genetic research in the United Kingdom and their investigators concerned are listed under the headings: (i) Fundamental research upon mechanisms; (ii) Population structure; (iii) Quantitative data on human mutation.	
60/Add.1	*Suggestions for research in radiation genetics*	3
	General considerations are reviewed and a list of suggested programmes of research in the fields (i) to (iii) is appended.	
61.	JAPAN. *Current and proposed programmes of research and investigation related to radiation genetics in Japan*	16
	A brief survey of current and planned research in Japan relevant to radiation genetics, covering both human surveys and experimental work.	
61/Add.1	*Table 1 (2) to above report:* *Experimental data with beta radiation*	2
62.	*Radiochemical analysis of Sr^{90} and Cs^{137}*	6
	Discusses methods of radiochemical analysis of Sr^{90} and Cs^{137}, including separation of strontium by precipitation and by ion exchange. Experiments for determining the best conditions for ion exchange separations are reported.	
63.	*Review of the recent researches on the biological effects of ionizing radiation in Japan*	14
	Contains brief abstracts of fifty-five papers from the Japanese literature dealing with (1) research on biological indicators of the effects of ionizing radiation in small and large doses, and (2) research on counter measures to alleviate radiation injury. Classical and more modern morphological, histochemical and biochemical methods of observation were used for the assessment of radiation damage. Most studies were performed on mammals. It is emphasized that it is very difficult to obtain reliable biological indicators of damage by small doses and that haematological methods are still the most suitable in man.	
64.	UNITED STATES. *Shortening of life in the offspring of male mice exposed to neutron radiation from an atomic bomb*	12
	Length of life in the offspring of male mice exposed to moderate doses of acute neutron radiation from a nuclear detonation is shortened by 0.61 days for each rep received by the father over the dose range tested. This figure excludes death before weaning age. The 95 per cent confidence limits are 0.14 and 1.07 days per rep. Extrapolating to a proportional shortening of life in man gives twenty days per rep received by the father as the point estimate and five and thirty-five days as the 95 per cent confidence limits. The offspring were obtained from matings made from nineteen to twenty-three days after irradiation and, therefore, represent the effect of irradiation on germ cells in a post-spermatogonial and sensitive stage of gametogenesis. It is probable that irradiation of spermatogonia (the stage that is important from the point of view of human hazards) would give a somewhat smaller effect. However, since the present data show an effect on the offspring which is as large as the shortening of life in the exposed individuals themselves, it seems likely that, even when allowance is made for the conditions of human radiation exposure, shortening of life in the immediate descendants will turn out to be of a magnitude that will warrant serious consideration as a genetic hazard in man.	
65.	*Gamma-ray sensitivity of spermatogonia of the mouse*	3
	Relates the depletion of spermatogenic cells to killing of spermatogonia, the repopulation being related to the maturation of surviving cells.	
66.	*Some delayed effects of low doses of ionizing radiations in small laboratory animals*	7
	A quantitative study of the life span, the incidence of leukemia, tumours (lung, liver, overy), and lens opacities as a response to low dosages (less than 100 rads).	
67.	*Effects of low-level radiation (1 to 3 r) on mitotic rate of grasshopper neuroblasts*	4
	A study of the inhibitions of mitotic rate and of its possible relationship with the alteration of chromosome structure.	

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	UNITED STATES *(continued)*	
68.	*Effects of low doses of X-rays on embryonic development in the mouse* Effects of 25 r applied during different stages of embryonic development on skeletal malformations appearing in the young.	6
69.	SWEDEN. *Does there exist mutational adaptation to chronic irradiation?* An account of an experiment in which a population of Drosophila heavily irradiated for many generations was compared with a control unirradiated population in respect of radiation-induced mutability. No significant differences were found.	7
70.	JAPAN. *Radiological data in Japan* The report is a compilation of data on radiation exposures in Japan. Data are arranged as suggested by the Scientific Committee at its October 1956 meeting.	58
70/Corr.1	*Corrigendum to above document*	5
71.	UNITED STATES. *Occupational radiation exposures in Atomic Energy projects* A series of five tables concerning yearly exposures from 1947 to 1955 from external and internal radiation sources.	9
72.	*Worldwide effects of atomic weapons* (A comprehensive preliminary report on the Sr^{90} problem up to 1953). A preliminary report discussing the various aspects of long-range contamination due to the detonation of large numbers of nuclear devices. An improved methodology for assessing the human hazard is developed, and an extensive experimental programme is proposed.	96
73.	*Maximum permissible radiation exposures to man* A preliminary statement of the U.S. National Committee on Radiation Protection and Measurement. The recommendations given by the Committee in National Bureau of Standards Handbook 59 have been revised and the maximum permissible dose-levels have been lowered. The concept of "accumulated" dose for occupational conditions differs from the ICRP recommendations of 1956. For the whole population an annual additional exposure of 2.5 times the exposure from natural radiation sources is allowed.	6
74.	*Gonadal dose produced by the medical use of X-rays* A survey of diagnostic X-ray exposure with an attempt to estimate the genetically significant dose in the United States. The estimate has been made under the assumption that patients undergoing X-ray examinations have a normal child expectancy. The authors have assumed that the genetically significant dose can then be evaluated as approximately equal to the average gonad dose for patients below the age of 30. Using exposure data which are considered fairly representative of American practice they arrive at 130-140 mrem/year and 50 mrem/year as being the most probable and the minimum figure respectively.	105
75.	*Summary of current and proposed programmes of research in the U.S.A. related to radiation genetics* A survey by investigator and title of current and proposed programmes of research in the United States related to radiation genetics.	10
76.	FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS. *Principal calcium contributors in national diets in relation to effects of atomic radiation from Sr^{90}* Gives a general idea of foods contributing to the calcium uptake of human beings in various parts of the world in relation to the different food habits of these people. Data still quite preliminary.	4
76/Rev.1	FAO. *Principal calcium contributors in national diets in relation to effects of atomic radiation from strontium-90* This paper replaces the preliminary note circulated as UN document A/AC.82/-G/R.76.	8
77.	NORWAY AND SWEDEN. *Radioactive fall-out over the Scandinavian peninsula between July and December 1956* In this report, fall-out and rain precipitation figures over the Scandinavian peninsula are discussed. Accumulated monthly fall-out is reported for the period July-December 1956.	6
78.	BELGIUM. *Information in eight parts on human genetics submitted by Belgium* Contains the Belgian memorandum on human genetics prepared for the Geneva meeting in April 1957 and a preliminary report on radioactive regions of Katanga (Belgian Congo). Besides this several reprints of Belgian contributions to radiobiology are presented. The topics included are: (1) Steroid metabolism in irradiated rat. (2) Endocrine response of irradiated animals studied by intraocular grafting.	

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	BELGIUM *(continued)*	
	(3) Doses and hazards due to medical radiology. (4) Metabolism and toxicity of cystamine in the rat. Part 1. Current uncertainties in the field of human genetics. Part 2. A preliminary survey of vegetation and its radioactive content in the Katanga area.	1
	Part 3. Influence of irradiation on the blood level of 17-hydroxy-corticosteroids during the 24 hours following irradiation.	5
	Part 4. Skin and depth doses during diagnostic X-ray procedures.	14
	Part 5. General discussion of the need for methods of effective dose reduction in diagnostic X-ray procedures.	11
	Part 6. Chemical protection (*a*) metabolism of cystamine Part 7. (*b*) the effectiveness and toxicity of cystamine.	11
	Part 8. Experiments on the ascorbic acid and cholestrol content of the supra-renals of the rat following irradiation of normal and hypophysectomised animals.	11
79.	SWEDEN. *A suggested procedure for the collection of radioactive fall-out* Proposes new method for evaluation of the external thirty-year dose due to the deposition of gamma-emitting isotopes, based upon a single beta measurement for each sample and one caesium ratio chemical determination in a pooled sample. A second part of the report describes a collecting procedure using ion exchange resins.	19
80.	ARGENTINA. *A geological, radiometric and botanic survey of the region "Los Chañores" in the province of Mendoza of Argentine Republic* Radiometric data on the above-mentioned region are shown on the attachment to the document.	4
81.	*Measurements of the cosmic ray intensity in three latitudes of Argentine Republic* Data on the intensity of the cosmic rays in three points of observation at different latitudes in Argentina.	5
81/Corr.1	*Corrigendum to above report*	2
82.	*On the absorption of the nucleonic component of the cosmic radiation at −15° geomagnetic latitude*	1
83.	*Mutations in barley seeds induced by acute treatments by gamma rays of cobalt-60* A report of experiments on the induction of mutations at a number of loci in barley by irradiation of seeds with gamma-rays of Co^{60} at 10 r/min.	2
83/Add.1	*Addendum to above report*	1
84.	*Mutations in barley induced by formaldehyde* A report of experiments on the induction of mutations at a number of loci in barley by formaldehyde.	1
85.	*Spontaneous mutations in barley* A report of experiments on spontaneous mutations at a number of loci in barley.	2
86.	*A study of radioactive fall-out in Argentine Republic* Describes the methods used in Argentina for fall-out collection and measurement. Value for strontium-90 and total beta activity are given for the first two months of 1957.	5
87.	*A research programme in Argentina on the genetic influence in the plants of the ionizing and ultra-violet radiation* A brief summary of projected research in Argentina on the genetic effects of ionizing and ultra-violet irradiations of plants, comprising both surveys of areas of high natural background and a broad range of laboratory experiments.	2
88.	*Programme of physical oceanography for the International Geophysical Year*	33
89.	*Information on the general programme to be developed in Argentina on items of interest to the Scientific Committee on the Effects of Atomic Radiation* A brief general survey of Argentina research activities related to the effects and levels of ionizing radiations.	2
90.	NETHERLANDS. *Chemical steps involved in the production of mutations and chromosome aberration by X-radiation and certain chemicals in Drosophila* A survey of comparative studies of X-ray and chemical mutagenesis in Drosophila, made in an attempt to throw light on possible intermediate chemical steps in the induction of chromosome breaks or mutations by ionizing radiation.	6
91.	UNITED STATES. *Strontium-90 in man* Radiochemical analyses of strontium-90 in human bone have been reported. The	7

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	values are in accord with the predicted levels based on fall-out measurements and fractionation through the food-chains.	
92.	NORWAY. *Radioactive fall-out in Norway* Contains information on methods and results of measurements of fall-out in Norway.	19
93.	*Summary of analytical results from the HASL Strontium Program July through December 1956* Summarizes data on samples collected by the U.S.A. fall-out network since September 1955 up to September 1956. In addition, it summarizes the data of the samples collected for the strontium programme during the period July-December 1956.	43
94.	*Environmental radon concentrations—An interim report* Preliminary data showing ambient concentrations of radon in the metropolitan New York area are presented. An attempt has been made to define the variability of concentration of radon in the general atmosphere with location, time, and weather conditions. Samples have been analysed from the outdoor air, inside of buildings, and above and below the surface of the ground. Comparisons with the data obtained by other investigators are also shown.	8
95.	*The radium content of soil, water, food and humans—Reported values*	6
96.	*Marine biology—Effects of radiation—A selected bibliography* Twenty-four references concerning investigation on the distribution and metabolism of fission products in marine organisms.	2
97.	*Sea disposal operation* Some atomic energy activities in the United States have been disposing of radioactive wastes at selected ocean disposal sites since as early as 1946. It is the purpose of this report to describe the extent of these disposal operations including a summary of types of packaging used and of places where the wastes are dumped. The status of related oceanographic research (1956) is briefly touched upon.	14
97/Corr.1	*Corrigendum to the above report*	1
98.	CANADA. *Radiochemical procedures for strontium and yttrium* A detailed ion exchange procedure is given for the determination of radiostrontium in different samples. Methods are described for the treatment of various organic materials.	25
99.	*Levels of strontium-90 in Canada up to December 1956* Reports the results of radiochemical analysis for strontium-90 activity in milk and milk products and human bone. Natural strontium content determinations in milk and bone are also reported.	15
100.	UNITED KINGDOM. *The determination of long-lived fall-out in rainwater* Describes radiochemical procedures for the determination of Sr^{89}, Sr^{90}, Cs^{137} and Ce^{144} activities in the rainwater.	
101.	DENMARK. *Measurement of activity of airborne dust. Measurements of fall-out deposited on the ground* Results of daily measured radioactivity in air (electrostatic filter method) and in precipitations (collection of rainwater) in Copenhagen for the period 1956.	3
102.	AUSTRIA. *Radiological data. Demographic data.* Contains data on RBE dose rate in the gonad due to both natural and artificial sources. Demographic data on the whole population and of special groups are given.	6
103.	UNITED KINGDOM. *Modification of immunological phenomena and pathogenic action of infectious agents after irradiation of the host* Evidence is given that whole body irradiation before the repeated injection of antigen both diminishes the peak-concentration of antibody and delays in time the appearance of the peak. The lowest efficient dose was 25r. The tolerance of heterogenous skin grafts or bone marrow cells has been also shown after irradiation; the duration of inhibition of immune response is proportional to dose received.	2
104.	*Some data, estimates and reflections on congenital and hereditary anomalies in the population of Northern Ireland* Presents an extremely detailed and thorough medico-genetic survey of the population of Northern Ireland using data accumulated over a number of years, together with very pertinent analyses of the data, the problem of genetic disability and its relation to radiation effects.	42
105.	*Leukemia and aplastic anaemia in patients irradiated for ankylosing spondylitis* The incidence of leukemia and of aplastic anaemia was investigated in patients	135

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UNITED KINGDOM *(continued)*

treated in Britain for ankylosing spondylitis by means of ionizing radiations during the years 1935-1954.

Relationship between radiation dose and incidence of leukemia was evaluated. The answers suggest the adoption of working hypothesis that for low doses the incidence of leukemia bears a simple proportional relationship to the dose of radiation, and that there is no threshold dose for the induction of the disease. The dose to the whole bone marrow which would have doubled the expected incidence of leukemia may lie within 30 to 50 r for irradiation with X-rays.

106. NORWAY. *Information on radiological data* — 44

Summary tables on radiological data in Norway with an extensive set of data on X-ray and natural radiation exposures.

106/Add.1 *Addendum to above report* — 2

107. NEW ZEALAND. *New Zealand report to U.N. Scientific Committee on Atomic Radiation: Effects of atomic radiation measured in New Zealand to 31 July 1957* — 6

A set of notes on the current status of various programmes in New Zealand within the field of interest on the Scientific Committee on the Effects of Atomic Radiation, including preliminary measurement of radioactive fall-out, C^{14} airborne activity, natural and artificial radioactivity, and occupational gonad exposures.

108. UNITED STATES. *Current research findings on radioactive fall-out* — 18

General survey of the fall-out problem, especially Sr^{90} distribution and uptake in the human body.

109. *Dosages from natural radioactivity and cosmic rays* — 2

110. NETHERLANDS. *Four reports on quantitative determination of radioactivity* — 48

A group of tables containing figures for the radiation doses from natural and man-made sources in the Netherlands.

111. NORWAY. *On the deposition of nuclear bomb debris in relation to air concentration* — 16

Studies the relation between the deposition of fall-out and the airborne activity. It appears that in 1956-1957 the fall-out in the Oslo area was roughly proportional to the product of precipitation and airborne activity at ground level.

112. *Radioactive fall-out in Norway up to August 1957* — 22

Gives the results of measurement of fall-out materials in air, precipitation, water and other samples. Measurement of airborne activity at high altitudes are included. Sr^{90} values are computed from total beta activity, a small number of samples having been checked by chemical analysis. Samples of water, milk and urine have been analysed for iodine-131.

113. *Radiochemical analysis of fall-out in Norway* — 10

Describes the methods used in Norway for determination of Sr^{90}, Cs^{137} and I^{131} and contains data of Sr^{90} and Cs^{137} activities in water and milk and of I^{131} in milk, in the period February-June 1957.

114. UNITED KINGDOM. *The relative hazards of Sr^{90} and Ra^{226}* — 26

Methods for calculations of the doses received by soft tissue cavities in bone containing Sr^{90} and Ra^{226} are presented. Non-uniformity factors are given for the dose from Sr^{90}. Calculation of the maximum permissible body burden for radium on the basis of a given maximum permissible dose-rate to bone gives a wide range of values, depending on the assumptions made. In the case of radio-strontium, the range of possible values is less. It is suggested that radium be no longer taken as the basis for the calculation of maximum permissible body burden of Sr^{90}.

115. *Shortening of life by chronic irradiation: the experimental facts* — 7

A survey of all published experimental results relating to shortening of life-span of mice due to chronic irradiation.

The comparison of effects between gamma-rays of cobalt-60 and fast neutrons is made; the R.B.E. factor used for fast neutrons was 13.

A good agreement of experimental results has been found indicating that chronic irradiation both with gamma-rays and neutrons shortens the life of mice in a reproducible manner. No statistically significant data were found below the weekly dose of 10r.

The possibility of extrapolation and the possible dose-effect relationship is discussed.

116. BELGIUM. *Report on health protection in uranium mining operations in Katanga* — 7

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117.	INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION AND INTERNATIONAL COMMISSION ON RADIOLOGICAL UNITS AND MEASUREMENTS. *Exposure of man to ionizing radiation arising from medical procedures* Gives a survey of the present exposure of the gonads due to X-ray diagnostic procedures. Some 85 per cent of the diagnostic dose arises from six to seven types of examinations, which are discussed separately. Estimates of the genetically significant dose are given for some countries. It is recommended that the basic studies be extended and that more detailed analysis be obtained through sampling procedures rather than through the systematic recording of the radiation received by every member of the population. Methods for dose reduction are discussed.	60
118.	POLAND. *Report on measurements of fall-out in Poland* Continuous measurements of global beta activity of fall-out are reported for four stations in Poland.	4
119.	BELGIUM. *Effect of a lethal dose of radiation on the amount of reducing steroids in the blood of the rat* Indicates that lethal irradiation shows, in the blood, an increase of reducing steroids. This reaction presents a maximum which is not necessarily linked to the variations of the ascorbic acid and of the cholesterol in the suprarenals.	4
120.	*Action of hydrogen peroxide on the growth of young barley plants* The growth of coleoptiles of young barley plants treated with hydrogen peroxide is affected in the same way as when the plants are irradiated with X-rays.	3
121.	*Action of cystamine and glutathione on X-ray irradiated barley seed* The cystamine and glutathione diminish the effects of X-rays on barley grains; mitosis are still possible after doses which would inhibit them in the absence of these agents.	3
122.	*Action of X-rays on the growth of internodal cells of the alga Chara Vulgaris L.* Irradiation of internodal cells of *alga Chara Vulgaris L.* increases the elongation of these cells for doses up to 150 kr; above this dosage elongation is inhibited (c.f. document A/AC.82/G/R.156).	4
123.	UNITED STATES. *Radioactivity of people and foods* Potassium and caesium activities measured with whole body counters are reported. The amount of caesium-137 now present in the population of the United States shows no marked dependence on geographical location.	32
124.	*Atmospheric radioactivity along the 80th meridian, 1956* Radioactivity levels at the various sites during 1956 are reported for three different collecting systems: air filters, cloth screens and gummed films. Extremely wide variations in the gross radioactivity of fission products in the air have been noted, with the highest levels occurring in the Northern hemisphere. Preliminary results of radiochemical analyses of a few filter collections are included.	13
125.	*Radioactive contamination of certain areas in the Pacific Ocean from nuclear tests* Contains a summary of the data on contamination levels in some areas of the Pacific Ocean and results from medical surveys of Marshall Islands inhabitants. Data on gross beta activity, individual isotope contamination and external gamma-exposure are included.	51
126.	UNITED KINGDOM. *Radiostrontium in soil, grass, milk and bone in the United Kingdom: 1956 results* Results of strontium-90 analysis of soil, grass and animal bone for twelve stations in the United Kingdom are given. Human bone specimens obtained in 1956 have also been measured.	28
127.	ARGENTINA. *Calcium and potassium content of foodstuffs in the Argentine Republic* Describes the methods and results of K and Ca analysis of food in Argentina. It shows that 80 per cent of the dietary Ca is provided by milk.	17
128.	UNITED KINGDOM. *Ionizing radiation and the socially handicapped* Collects available data and calculations concerning the numbers in various classes of handicapped individuals in the United Kingdom and the relationships of these numbers to genetic factors, mutation rates and radiation levels.	9
129.	CANADA. *Dose from unsealed radio-nuclides* Calculations based upon information on shipments of radioisotopes show that the gonad dose to age 30 from unsealed radio-nuclides during 1956 in Canada is about 0.5 per cent of the dose from the natural radiation sources. The main dose arises from iodine-131.	11

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130.	UNITED STATES. *The nature of radioactive fall-out and its effects on man* An extremely diverse and extensive collection of information and expert opinion given as public testimony before a governmental committee, and presented without further evaluation.	2,000
130/Add.1	*Index to above report.*	51
131.	*Radioactive strontium fall-out* General survey of the fall-out problem, especially strontium-90 distribution and uptake in the human body.	26
132.	UNITED KINGDOM. *The determination of long-lived fall-out in rainwater* A method is described for the determination of long-lived isotopes in samples of rain water. Some attention is paid to the development of the method, including details of the checks to ensure radiochemical purity of the final sources used for counting.	21
133.	WORLD METEOROLOGICAL ORGANIZATION. *Excerpt from a letter dated 6 November 1957 received from the Secretary-General of the WMO—Interim international reference precipitation gauge* Brief report of the discussion held by the Executive Committee Panel on Atomic Energy and by the Commission for Instruments and Methods of Observations of the WMO on subjects related to the effects of atomic radiation.	7
134.	ITALY. *Report on genetics 1950-57—A brief report on the research work done in the field of genetics in Italy* Extensive notes reporting relevant research work in the field of genetics carried out in Italy during the period 1950-1957.	47
135.	JAPAN. *Analysis of Sr^{90}, Cs^{137} and Pu^{239} in fall-out and contaminated materials* The report gives radiochemical procedures for Sr^{90}, Cs^{137} and Pu^{239} from air filter ash. The counting equipment is described briefly.	7
136.	*Primary estimate of the dose given to the lungs by the airborne radioactivity originated by the nuclear bomb tests* The report gives method and results of measurement of airborne radioactivity for Tokyo from 1955 to 1957. Values are obtained for gross alpha and beta activity and radiochemically determined concentrations of strontium-90 and plutonium-239. A method for computation of the dose to the lungs is described. The mean dose during 1955-1957 was of the order of magnitude of 10^{-2} rem/year.	7
136/Corr.1	*Corrigendum to above report*	1
137.	*A measure of future strontium-90 level from earth surface to human bone* Calculation of the future strontium-90 level is made on the basis of present data on cumulative ground deposit and food contamination. The cumulative ground deposit (mc/km^2) is calculated assuming that: 1. The total amount of fission products from future tests is known. 2. 20 per cent of airborne strontium-90 falls to the earth's surface every year. 3. The distribution of fall-out is homogeneous. The metabolism of strontium-90 through the food channel and food habit factor related to calcium and strontium source are taken into consideration. The future human skeletonal dose and maximum permissible level of ground deposit are then calculated.	14
138.	*Supplemental review of the recent researches on the alleviation of radiation hazards* This is an addition to G/R 63 and gives abstracts of new developments of radiobiology in Japan. Work on protection by amino acids, cysteamine and some new derivatives of this last compound is reported. Work on the therapeutic effect of a protein diet and of adrenochrome preparation is also reported.	3
138/Corr.1	*Corrigendum to above report*	1
139.	*Experimental studies on the development of leukemia in mice with frequent administrations of small doses of some radioactive isotopes (P^{32}, Sr^{89}, Ce^{144})* The development of leukemia is described in three strains of mice in which the disease has not been observed under control conditions. Nine cases of leukemia have been observed among forty-six animals surviving twenty-one weeks and longer following the first of repeated administrations of P^{32} at three dose levels (0.1, 0.3, and 0.5 $\mu c/gm$). Latent periods varied with total dose administered. Larger doses were more effective than small doses. The leukemia was primarily of the myeloid type. Radiostrontium (Sr^{90}) and radio-cerium (Ce^{144}) were much less and practically ineffective in producing this disease in these animals. Sarcoma of bone was found in strontium-treated animals. It is concluded that leukemia is the result of severe damage	9

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	to the haematopoietic tissues in the bone marrow and lymph nodes. There are many tables and figures, including results of radiochemical analyses of various bones at various intervals following injection.	
139/Corr.1	*Corrigendum to above report*	1
140.	*Experimental studies on radiation injury by colloidal radioisotope-liver injury by colloidal radioactive chromic phosphate $CrP^{32}0_4$*	6
	Describes morphological observations on the liver of rats which were injected intravenously with various concentrations of colloidal suspensions (particle size 0.1-1.0 micron) of radioactive chromium phosphate ($CrP^{32}0_4$). Even with high doses (7.5 μc/gm) liver injury did not become manifest until twenty days after injection and correspondingly later with lower doses. Changes in the liver are described but not illustrated. They are greater in the liver than in other organs containing reticulo-endothelial cells. The lesions are said to resemble those of virus hepatitis. Large doses of chromium phosphate also produce lesions in the bone marrow with concomitant changes in the peripheral blood.	
140/Corr.1	*Corrigendum to above report*	1
141.	*Radiological data in Japan II—Concentrations of Sr^{90}, Cs^{137}, Pu^{239} and others in various materials on earth's surface*	17
	Contains data on concentration of Sr^{90} in rainwater, soil, foodstuffs and human bone in Japan obtained by radiochemical analysis in some cases and by computation from the total beta activity in other cases. Besides Sr^{90}, data on Cs^{137}, Pu^{239}, Zn^{65}, Fe^{55} and Cd^{113} are also included.	
141/Corr.1	*Corrigendum to above report*	2
141/Add.1	*Addendum to above report*	3
142.	UNITED STATES. *Radioactive fall-out*	18
	General survey of the fall-out problem, especially Sr^{90} distribution and uptake in the human body.	
143.	UNITED KINGDOM. *The world-wide deposition of long-lived fission products from nuclear test explosions*	28
	A network of six stations in the United Kingdom and thirteen in other parts of the world has been set up for rainwater collection. Samples are analysed for Sr^{89}, Sr^{90}, Ce^{137} and Ce^{144}. This report contains an account of the results obtained so far, and some discussion of the present and future levels of Sr^{90} in United Kingdom soil.	
144.	NORWAY. *Radioactive fall-out up to November 1957*	24
	A review is given of the monitoring in Norway of airborne activity and fall-out of radioactive dust; also radioactive contamination in drinking water is reported.	
145.	SWEDEN. *Uptake of strontium and caesium by plants grown in soils of different texture and different calcium and potassium content*	5
146.	*The radioactive fall-out in Sweden up to 1.7.1957*	12
	Additional data to the report G/R.15 for the period up to June 1957 are given. The total beta activity, accumulated Sr^{90} and Cs^{137} amount and Sr^{90} content in soil are measured.	
147.	*Gamma radiation from some Swedish foodstuffs*	9
	Significant increase of gamma radiation from milk, beef, cattle-bone and vegetables was found during the period 1952-1956. No increase of gamma radiation from children in the corresponding period could be observed.	
148.	*Progress report on the metabolism of fission products in ruminants*	3
	The excretion of radioactive fission products (Sr^{90} and I^{131}) in milk after per oral administration is measured.	
149.	*A method for monthly collection of radioactive fall-out*	7
	Describes a collecting procedure using anion and cation exchange resins.	
150.	*The computation of infinite plane 30-year doses from radioactive fall-out*	12
	Proposes new method for evaluation of the external 30-year dose due to the deposition of gamma emitting isotopes, based upon a single beta measurement for each sample and one Cs^{137} ratio chemical determination in a pooled sample.	
151.	*The control of irradiation of populations from natural and artificial sources*	3
	Describes an automatic system for continuous indication and recording of very low radiation level. Suggests the use of such instrument for public control purposes.	

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152.	UNITED KINGDOM. *The analysis of low level gamma-ray activity by scintillation spectrometry* The application of gamma-ray spectrometry enables measurement of the gamma-activity of 10^{-11} curies or less.	9
153.	UNITED STATES. *The Chicago Sunshine method: Absolute assay of strontium-90 in biological materials, soils, waters and air filters* Contains a survey of Chicago sunshine research programme on the distribution of strontium-90 in the biosphere. Methods of sample treatment, counting and evaluation of data are reported. Detailed description of analytical chemical procedures is added.	59
154.	ARGENTINA. *Normal calcium content of San Juan wines*	8
155.	BELGIUM. *Recent research on the chemical protectors and particularly on cysteamine-cystamine. (Document in English)* Discusses the possible mechanisms of action of chemical radioprotectors particularly of those above-mentioned.	9
156.	*Effect of X-rays on the growth of internodal cells of the alga Chara vulgaris L* A complicated dose-effect relationship is shown when non-dividing internodal cells are irradiated and their growth tested (cf. document A/AC.82/G/R.122).	4
157.	ARGENTINA. *Radioactive fall-out from the atmosphere in the Argentine Republic during 1957* Includes tables of results for first three-quarters of 1957. Total activity and strontium-90 content is measured.	18
158.	BELGIUM. *The action of various drugs on the suprarenal response of the rat to total body X-irradiation. (Document in English)* Describes strict difference in action of radioprotectors (cysteamine) or narcotic drugs (morphine and barbiturate) in preventing adrenal changes of irradiated animals.	8
159.	*Nervous control of the reaction of anterior hypophysis to X-irradiation as studied in grafted and newborn rats. (Document in English.)* Indicates that the changes of suprarenals after irradiation are consequence of a neuro-humoral chain reaction. The reaction of adrenals seems to have negligible importance in the pathogenesis of radiation disease.	13
160.	USSR. *Draft of Chapter F prepared by the delegation of the USSR to the Scientific Committee on the Effects of Atomic Radiation*	18
161.	JAPAN. *A sensitive method for detecting the effect of radiation upon the human body* Discovers a new extremely sensitive biological indicator of the effect of ionizing radiation. The acute dose of 50 mr and even less results in significant changes of the phosphene threshold of the eye. Approximately linear relationship between the effect and the logarithm of the dose from 1 mr to 50 mr is derived. Summation of the effect of repeated exposure is found.	16
162.	UNESCO/FAO/WHO. *UNESCO/FAO/WHO report on sea and ocean disposal of radioactive wastes, including appendices A, B and C* Summarizes contributions made by different authorities. *Appendix A*: R. Revelle and M. B. Schaefer. General considerations concerning the ocean as a receptacle for artificially radioactive materials. Contains general account of the processes in the oceans and indicates the necessity of research on certain basic problems which would enable the prediction of the consequences of the disposal of large quantity of radioactive material to the sea. Recommends measures of an international character in order to assure safe liquidation of atomic wastes. *Appendix B*: Report prepared by FAO and WHO. Discusses the following questions: 1. The geochemical cycle of various elements between the water and the sediments. 2. The affinities of the various species of organisms in the oceans for different elements which have radioactive isotopes. 3. The possible rate and distance of vertical and horizontal transport of radioactive isotopes by marine organisms. 4. The distribution, abundance and rate of growth of the populations in the oceans. *Appendix C*: Abstracts of eight other contributions to the report on sea and ocean disposal of radioactive wastes.	118
163.	USSR. *Data on the radioactive strontium fall-out on the territory of the USSR as to the end of 1955*	1

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A/AC.82/G/R		
164.	MEXICO. *Third report on the studies on radioactive fall-out* Presents fall-out data for thirteen stations in Mexico covering the period from March to October 1957. Computes approximate figures for infinite gamma dose and Sr^{90} precipitation. Gives preliminary results of Sr^{90} and Cs^{137} content in milk.	25
165.	FAO. *General considerations regarding calcium availability in the broad soil groups of the world in relation to the uptake of radiostrontium* Classifies soil groups with low calcium level. Recommends the investigations of the factors influencing Sr^{90} uptake by plants growing on such soils.	6
166.	INDIA. *Measurements on the radiation fields in the Monazite areas of Kerala in India* Presents results of measurements in the monazite area with high thorium content. As this area is one of the most densely populated areas in the world, the study of the relation between high level radiation background and eventual biological effect would be of great value. The average dose is 1500 mrad per year, exceeding three times the maximum permissible dose recommended by NCRP (USA).	6
167.	UNITED KINGDOM. *Measurements of Cs^{137} in human beings in the United Kingdom 1956/1957* Describes the method of determining the Cs^{137} content in the human body using gamma-ray spectrometry. The average present value is $34.0 \pm 7.6 \mu\mu c$ per g potassium.	5
168.	JAPAN. *An enumeration of future Sr^{90} concentration in foods and bone* Gives amendments and corrections to the report A/AC.82/G/R.137 based upon new available data.	6
169.	BRAZIL. *On the nature of long-range fall-out.* (*Document in English.*) Describes one surprisingly high value of daily collected fall-out activity due to a single big and highly active particle.	4
169/Corr.1	*Corrigendum to above report*	1
170.	UNITED KINGDOM. *The disposal of radioactive waste to the sea during 1956 by the United Kingdom Atomic Energy Authority* Summarizes the discharges of liquid radioactive wastes to the coastal sea from Windscale Works during 1956. The results of monitoring indicate that the average activity of the samples remains well below the permissible level.	3
171.	*A summary of the biological investigations of the discharges of aqueous radioactive waste to the sea from Windscale Works, Sellafield, Cumberland* Summarizes the results of preliminary hydrographic and biological studies and of regular monitoring of the marine environment in the period 1952-1956. About 2,500 curies of radioactive wastes monthly has been discharged during this period. Due to the favourable local conditions, the upper limit for safe liquidation is determined to be more than 45,000 curies per month.	12
172.	JAPAN. *The estimation of the amount of Sr^{90} deposition and the external infinite gamma dose in Japan due to man-made radioactivity*	10
173.	SWEDEN. *Transfer of strontium-90 from mother to foetus at various stages of gestation in mice* Shows that no significant fixation of Sr^{90} by the foetus can be detected before the fifteenth day of gestation. The increase of radioactivity corresponds to the intensity of ossification processes.	2
174.	*The recovery phenomenon after irradiation in Drosophila melanogaster* *1. Recovery or differential sensitivity to X-rays* Experimental results—lower rate of chromosome aberrations induced by X-ray if irradiated in anoxia in comparison with irradiation in air-support the hypothesis of recovery.	29
174/Add.1	*The recovery phenomenon after irradiation in Drosophila melanogaster* Indicates that both the spontaneous recovery and the differential sensitivity in spermatogenesis in Drosophila are responsible for the changes in the rate of chromosome breaks under different conditions of irradiation.	8
174/Add.2	*The recovery phenomenon after irradiation in Drosophila melanogaster* Chromosomes breakage *per se* or their rejoining by recovery seems to have no genetic consequences.	5

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	SWEDEN *(continued)*	
175.	*Reports on scientific observations and experiments relevant to the effects of ionizing radiation upon man and his environment already under way in Sweden*	4
175/Add.1	*Report on experiments on the influence of selection pressure on irradiated populations of Drosophila melanogaster* Attempts to determine the influence of high selection pressure in a population on the spread of radiation-induced genetic changes. No results are as yet available.	3 3
175/Add.2	*Studies on the mutagenic effect of X-rays* Summarizes the results of the work on radiation-induced chromosome breakage under various conditions (K. G. Lüning).	
175/Add.3	*Does there exist mutational adaptation to chronic irradiation?* The results do not confirm the assumption that under the increased radiation-background mutational adaptation occurs due to incorporation in the population of mutational isoalleles with lower mutability.	8
175/Add.4	*Some results and previews of research in Sweden relevant to human radiation genetics* Summarizes the present state of knowledge and recommends: 1. Large-scale international investigation of genetic consequences in females who have been controlled by means of X-rays due to congenital dislocation of the hip. 2. The study of genetic effects of radiation on human cell cultures.	10
175/Add.5	*Summary of papers of Lars Ehrenberg and co-workers with regards to the questions of the U.N. Radiation Committee* Summary of papers of L. Ehrenberg and co-workers on genetic effects of radiation.	7
175/Add.6	*Studies on the effects of irradiation on plant material carried out during recent years at the Institute for Physiologic Botany of Uppsala University*	2
175/Add.7	*Swedish mutation research in plants*	
175/Add.8	*Dr. Gunnar Östergren and co-workers* Study on experimentally induced chromosome fragmentation (G. Östergren).	1
175/Add.9	*Investigations carried out by Dr. C. A. Larson (human genetics)*	1
176.	*Some notes on skin doses and bone marrow doses in mass miniature radiography*	2
177.	*Investigations into the health and blood picture of Swedish women living in houses representing different levels of ionizing radiation* No difference was found either in general health-state or in blood picture among the various groups of individuals (over 2,000 women) living in different types of dwelling.	37
178.	*Other haemopoetic functions: Read-off methods in radio-haematological control* Proposes a statistical method of evaluating total white-cells count as a control test of radiation damage.	11
179.	FRANCE. *Atomic Energy Commission. Centre of Nuclear Studies at Saclay, Gif-sur-Yvette (Seine et Oise), France. Measurement of environmental activity: Methods and results* Gives results of measurements of both natural and artificial radioactivity in the environment.	7
179/Corr.1	*Corrigendum to above report*	1
180.	*Biological methods available for use in the quantitative detection of ionizing radiations* Surveys and evaluates the biological methods usable for the quantitative estimation of absorbed dose.	43
181.	SWEDEN. *Bone and radiostrontium* The local radiation dose to the bone tissue and to the bone marrow after administration of bone-seeking isotopes is discussed. The figures are compared with the maximum permissible body burden.	4
182.	*Radiation doses to the gonads of patients in Swedish roentgen diagnostics. Summary of studies on magnitude and variation of the gonad doses together with dose reducing measures.*	3
183.	THE NETHERLANDS. *Report of the Committee of the Royal Netherlands Academy of Sciences concerning the dangers which may arise from the dissemination of radioactive products through nuclear test explosions* Report on the amount of radioactivity, its world-wide spreading and its biological risk as a consequence of test explosions.	48
184.	*Radioactive fall-out measurements in the Netherlands until December 31, 1957*	8
184/Corr.1	*Corrigendum to above report*	1

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185.	NEW ZEALAND. *Report on some aspects of radiation protection work in New Zealand* Contains: 1. Description of radiation protection measures in New Zealand. 2. Results of routine monitoring of radiation workers. 3. Preliminary results of statistical study on genetically significant gonad dose from X-ray diagnosis.	21
186.	FRANCE. *Doses received by the genital organs of children during X-ray examinations* Suggests the improvement of the radiological techniques and certain protective measures for decreasing the gonad dose from radiography.	15
187.	MEXICO. *Summary of radioactive fall-out data recorded in Mexico*	1
188.	BRAZIL. *Summary—strontium-90 analysis in dry milk and human urine*	2
189.	*On the composition of long-range fall-out particles* A single fall-out particle of large dimensions and relatively high activity was found by daily monitoring of fall-out. A detailed investigation of the nature and activity of this particle is presented.	7
190.	*On the uptake of MsThI in naturally contaminated areas* Gives preliminary results of an investigation on the uptake of natural radioisotopes by plants and animals in thorium-bearing area.	3
191.	UNITED ARAB REPUBLIC. *Radioactive fall-out in Egypt: December 1956-February 1957*	5
192.	*Radioactive fall-out in Egypt: March-December 1957*	7
193.	*Some somatic changes observed in Culex Molestus Forskal 1775* Shows differences in the uptake of P^{32} in dependence upon the development stage and sex. The explanation of sex-difference is discussed.	6
194.	FRANCE. *Gonad doses in radiodiagnosis* Summarizes the systematic study on the gonad dose due to diagnostic examination by means of X-rays.	64
195.	ITALY. *Data on radioactive fall-out collected in Italy (1956, 1957, 1958)*	6
196.	USSR. *Draft chapter on "Genetic Effects of Radiation" for the report to be transmitted by the Scientific Committee on the Effects of Atomic Radiation to the General Assembly in 1958*	14
197.	*Draft chapter on "Conclusions and Recommendations" for the report to be transmitted by the Scientific Committee on the Effects of Atomic Radiation to the General Assembly in 1958*	17
198.	*Contamination of the biosphere in the vicinity of Leningrad by the products of nuclear explosions* Contains the description of methods used for monitoring the fall-out deposition. Results for the period 1953-1957 are given. Data on specific activity of water from the river Neva, the sea and the water supply system are also included. Accumulated radioactivity on the ground and external dose from radioactive deposit are then computed. Special attention is given to the contamination of the biosphere by Sr^{90}. Data are based on Hunter and Ballou's calculation.	28
199.	*Study of the strontium-90 content of the atmosphere, soil, foodstuffs and human bones in the USSR* The strontium-90 content of the air, soil, milk and cereals in various districts of the USSR was determined by radiochemical analysis. Preliminary results on the Sr^{90} content in bones from children in the Moscow district give the average value of 2.3 S.U. in the second half of 1957. A few data on Cs^{137} concentration in the air are attached.	24
200.	*Uptake of radioactive strontium by plants and its accumulation in various agricultural crops* Detailed analysis of Sr^{90} uptake by plants in relation to their biological characteristic (plant species, vegetative period) and the properties of the soil. Both factors can influence to a large extent the incorporation of Sr^{90} during the biological cycle.	27
201.	*Some results of a study of the bone system after injury by radioactive strontium* Reviews the experimental results obtained in the studies on the effect of bone-seeking radioisotopes. The progressive pathological changes leading to the development of bone tumours are described. The disturbances in the osteogenetic processes during	14

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	USSR *(continued)*	
	the initial stages after contamination are marked pretumorous changes; their histological characteristic and their pathogenetic significance are discussed.	
202.	*Blastomogenic effects of strontium-90* Summarizes and evaluates the results so far published on the cancerogenic effect of strontium-90 in bone. In particular, the minimum and optimum tumour-producing doses, the latent period and the distribution of strontium-90 are discussed. The connexion between the blastomogenic effect and the development of leukemia is briefly mentioned.	10
203.	*The radiation hazards of explosions of pure hydrogen and ordinary atomic bombs* Compares the hazards of the long-lived radioactive substances dispersed throughout the world after the explosion of a fission and a pure fusion bomb. Radiation doses to the gonads and bones are calculated and the number of persons affected (hereditary diseases and leukemia) then computed. The conclusion is drawn that a pure fusion bomb cannot be regarded as less dangerous to mankind than a fission bomb.	27
204.	*Towards an assessment of the hazard from radioactive fall-out* An attempt to assess the various forms of hazard involved in the contamination of the earth's surface with long-lived radioactive fission products. The particular importance of strontium-90 is stressed. Effects of small doses of radiation and the concept of maximum permissible dose are discussed.	32
205.	*Nature of the initial effect of radiation on the hereditary structures* A survey of the present knowledge of the nature of the primary mechanisms through which ionizing radiation damages the hereditary structures.	40
206.	*Radiation and human heredity* Emphasizes the importance of the basic scientific principles of radiation genetics for the assessment of radiation-induced changes in human heredity. The natural mutation rate for various hereditary abnormalities is compared with the observations so far available on irradiated human population. The comparison of natural and induced mutagenesis both in experimental organisms and in men is the basis on which the doubling dose for man was estimated as approximately 10 r. The lack of exact knowledge and the urgent need for it is stressed.	22
207.	*The effect of radiation on the histological structure of monkey testes* Presents the results of histological analysis of monkey testes two years after exposure to a dose of 150-450r. While the recovery process proceeds rapidly and is apparently complete in animals irradiated after the attainment of sexual maturity, harmful disturbances have been found in young animals even two years after exposure.	25
208.	*The cytogenetic effects of radiation exposure on spermatogenesis in monkeys* Presents the results of cytological analysis of monkey testes two years after exposure to a dose of 150-450r. Extensive damage to the spermatogenesis was found. The frequency of chromosome re-arrangements in mammals considerably exceeds that in Drosophila after exposure to the same dose, being 65 per cent and 1.6 per cent after 500 r respectively.	18
209.	BELGIUM. *Radioactive fall-out measured at the CEN during 1955-1956 and 1957* Describes methods and results of fall-out measurements in the period 1955-1957.	9
210.	*Average dose received by the personnel of CEN, MOL, from 1954 to 1957* Summarizes the results of monitoring the professional exposure in nuclear energy education centre in Belgium. Film strip enables the differentiation of the proportion of the exposure between beta, gamma and neutron radiation. Only average doses of the personnel are given.	3
211.	FRANCE. *Study of the gonad dose during systematic X-ray examinations (Preliminary note dealing only with the irradiation of male gonads)* Measurement of the gonad dose resulting in males from systematic standardized X-ray examination of the chest indicate that the exposure is very low. An average of 9 mrem for a period of 30 years is computed. The dose to the lungs is discussed with relation to the increase in frequency of lung cancer.	6
212.	*Determination of the absorbed dose/exposure dose ratio in bone and muscle by the equivalent-gases method. Principle of the method and preliminary results* Describes the method for determination of the dose absorbed in various tissues using ionization chambers filled with gas mixtures of equivalent density.	22

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FRANCE *(continued)*

213. *Recovery following the action of ionizing radiation* 26

The authors first discuss the problem of recovery which they consider hypothetically. They attempt to show that it is a phenomenon which, although appearing very complex at first glance, can be simplified by relating the recovery to a definite effect.

They contribute a series of experiments showing that recovery is a very general phenomenon, common to all living things, and related to the metabolic activity of living matter.

They report a new method of experimental analysis which greatly facilitates interpretation of the results. They believe that the study of recovery should be developed on a much larger scale.

Appendix

LIST OF SCIENTIFIC EXPERTS

The scientific experts who have taken part in the preparation of the report while attending Committee sessions as members of national delegations are listed below. The Committee must also express its appreciation to the many individual scientists not directly connected with national delegations whose voluntary co-operation and good will contributed in no small measure to the preparation of the report.

ARGENTINA:
- Dr. C. Nuñez *(Representative)*
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- Professor E. Favret
- Dr. N. Nussis
- Dr. J. A. Olarte

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- Mr. D. J. Stevens *(Representative)*
- Dr. A. R. W. Wilson

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- Mr. R. Boulenger
- Dr. M. Errera
- Professor F. Twisselman

BRAZIL:
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- Professor V. Sobek
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- Professor G. Bonnier
- Professor T. O. Caspersson
- Professor C. A. T. Gustafsson
- Dr. A. G. A. Nelson

* Now in the United Arab Republic.

UNION OF SOVIET SOCIALIST REPUBLICS:

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Professor K. K. Aglintsev
Professor B. M. Isaev
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Dr. W. G. Marley
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