

Annex H

THE GENETIC EFFECTS OF RADIATION

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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 mutations⁹ and may, indeed, clarify these; for example, it remains possible that further investigations of genes and chromosomes¹⁰ 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 fulfilling 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 heal 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.²⁰ 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,³¹⁻³² following earlier experimenters.³⁴⁻³⁶ Muller³⁷ 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, Oakberg³⁸ 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 corn⁵² 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 conditions⁵⁹ 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 plants⁶⁰ 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 Giles⁶¹ 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 calculated⁶¹ 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.⁶⁵ 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's⁷⁰ 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 Philips⁷⁵ and of Russell^{69,76} illustrates the difficulty. Because chromosome structural changes occur naturally at much lower frequencies even than apparent gene mutations^{77,80,104} 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 identifiable 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 Szilard⁷⁸ 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 strains¹⁷⁴ and between sexes⁸⁰ and dependence upon age⁸⁰ 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).

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 mutations⁸³ 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.

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 Schull¹⁹⁰ are the most extensive, and that by Bök⁸⁷ 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 Bök shows an entirely different picture of viability, although in a very small sample; the total deaths, including prenatal and up to age 30, in Bök'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 Bööck. (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 Turpin⁹¹ 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 induc-

tion 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 effects 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 oogonia show a mutability similar to that of spermatogonia while late oocytes 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. Muller¹⁰³ 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 species¹⁰⁴ 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 Haldane¹⁰⁵ 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 Penrose⁹³ 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 con-

dition 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 hypothetical 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,

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

If we require that $\chi^2 \gg 4$ 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,

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

In terms of D and D_2 :

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

For example, in the study of Neel and Schull,¹¹¹ the progeny of irradiated parents numbered 3.3×10^4 and the progeny 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 $1/2$, 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

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

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

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

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

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

A number of completed surveys, irrespective of the significance of their results, all show decreases in s when the mother is irradiated from which values of k of the order of $-1 \times 10^{-4}/\text{rad}$ 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

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

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 Penrose⁹³ 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 $\frac{\sum_i m_{0i}}{\sum_i k_i} = \bar{D}_2$.

This procedure can be used to estimate a \bar{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 \bar{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 \bar{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 Penrose¹⁴⁰ 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 Turpin¹²⁰ 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

$$\frac{-3.36 \times 10^{-4} \times 6}{-6 \times 10^{-5}} \doteq 30 \text{ rad} \quad \left/ \begin{array}{l} \text{From age 0} \\ \text{to age 30 years.} \end{array} \right.$$

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;^{121,124}

(4) The study of other variates such as birth rank¹⁸⁸ 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 man¹²⁶ 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 Schull¹¹¹ 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 premeiotic 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 mouse¹⁰⁷ and *Drosophila*.† The DNA content of human cells is about 6/5 that of mouse cells, according to Vendrely.²⁰ Hence, upon the stated hypothesis, it might be expected that roughly one recessive lethal per 250 rad would be induced in human sperm by irradiation. Again by analogy with both the mouse and *Drosophila*, which behave alike, it might be expected that in spermatogonia only about one quarter as many gene mutations would occur. However, in *Drosophila* it has been estimated that the total rate of mutation to appreciably deleterious alleles is about four times the recessive lethal rate.¹⁰⁸ In the assumptions made so far, it has been possible to rely upon common quantitative behaviour of two diverse species. But the induced mutation rates for single loci of mice, as well as the total recessive lethal rate, are greater than those of *Drosophila* by a factor of 20,

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

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

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

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 grounds¹³³ 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 Wallace¹³⁴ 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 mutant 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 elimina-

tion: 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 $k_i D$, where D is the genetically significant dose of radiation to the population. By a theorem originally due to Haldane⁸⁴ there must on the average be $k_i D$ 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 $k_i p_i D$ and the whole contribution of the dose D to the future social burden is $\sum k_i p_i D$ 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_{21} by $k_i D_{21} = m_i$ and for all mutations or a large class of them a mean doubling dose \bar{D}_2 can be defined by the equation $k \bar{D}_2 = m$ where $k = \sum k_i$, $m = \sum m_i$. It is unfortunate that in man we do not know any individual k_i or D_{21} . 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_1 due to a given condition denoted by i , whose occurrence is related to the presence of adverse genes? (b) Of the genetic burden b_1 , what fraction f_1 is due to recurrent mutation? (c) By what fraction g_1 will this be increased immediately or in the future by a given fractional change c_1 in the natural mutation rate m_1 ? If the change c_1 is caused by a genetically significant dose D to the population,

$$c_1 m_1 = k_1 D \text{ or } c_1 = D/D_{21}$$

For all conditions or a large class of them the total genetic burden may be written $b = \sum_1 b_1$, that due to recurrent mutation $fb = \sum_1 f_1 b_1$ and that due to a given dose D as $\sum_1 g_1 f_1 b_1$. If it is assumed that $g_1 = c_1$, this may be written as

$$D \sum_1 \frac{f_1 b_1}{D_{21}}$$

It may be assumed that b_1 and f_1 are independent of D_{21} . Then the increased burden may be written

$$D/\bar{D}_2 \sum_1 f_1 b_1 \text{ which may be written } (D/\bar{D}_2) f b$$

$$\text{where } f = \sum_1 f_1 b_1 / \sum_1 b_1$$

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

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

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_1 or f_1 , 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_1 is relatively well known but p_1 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_1 are known but most p_1 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. Penrose¹⁴⁰ 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,¹³⁰ 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 Stevenson¹⁴⁴ 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 Ireland¹⁴⁴ 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 thalassaemia 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 $\frac{1}{4}$ to $\frac{1}{2}$ 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/\bar{D}_2 per cent and $4D/\bar{D}_2$ 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

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

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, life-span 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,^{149,155} half of it associated with maternal genotype, and in the case of intelligence as $\frac{1}{2}$, or perhaps as high as $\frac{3}{4}$.¹⁶⁰ 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's¹⁴⁹ and Karn and Penrose's¹⁵¹ 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. Mather¹⁵² 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 Robertson¹⁵³ 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^{157,166}) support this conclusion. By comparing irradiated and unirradiated populations, Clayton and Robertson further showed that some $10^5 r$ would have been needed to produce an increment equal to the natural variance. With selective neutrality such a genetic variance in the natural population is perfectly compatible with an established equilibrium between mutation and a degree of inbreeding due to limited effective population size. For a character of greater selective importance the genetic variance displayed by the population would exceed the increment per generation by a correspondingly smaller factor. Haldane¹⁵⁴ 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. Robertson¹⁵⁵ 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 Fisher¹⁵⁶). 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. Lerner¹⁵³ 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^{157,166} 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.¹⁵⁷ 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 polygenic 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 birthweight¹⁵¹ fit the classical expectation, but that those concerning intelligence¹⁶¹ 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 calculations¹⁵² 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 Russell¹⁴² 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.¹⁹³

Fertility

104. The most direct expression of the effect of undesirable mutations is through the net reproduction per generation or fertility differentials. Penrose⁹³ has suggested that, in man, some 50 per cent of the zygotes of each generation fail to contribute to the next one by reproduction, and has suggested, by analogy with other metrical characters, that some half of this might be of genetic origin. Penrose also points out that, on the same analogy, much of the infertility might well be due to the presence of conditionally deleterious alleles which are not primarily maintained by mutation and are essentially unaffected by changes in mutation rate. However, one may compare such a rate of elimination with an estimate of the total rate of mutation to unconditionally deleterious alleles such as was derived in paragraph 74 above.

105. Applying a representative doubling dose of 30 rad to the estimate of paragraph 74, the natural rate of mutation to deleterious alleles would amount to some $\frac{1}{8}$ (i.e., approximately 30/250) per haploid gamete or $\frac{1}{4}$ per diploid zygote. At equilibrium, these could be eliminated by $\frac{1}{4}$ of zygotes failing to reproduce. These estimates of mutation are therefore consistent with that of Penrose concerning fertility, and with the assumption of genetic equilibrium, which suggests the possibility that at present $\frac{1}{4}$ of all zygotes fail to contribute to the next generation because of the presence of deleterious alleles maintained by recurrent mutation. Taking this to be an upper estimate, indefinite application of a doubling dose to each generation might eventually extend the fraction of non-contributing zygotes from $\frac{1}{2}$ to $\frac{3}{4}$ and require a doubling of average family size for a previously constant population to maintain itself. This appears to be well within human capacity. If it be further supposed that the mixture of dominants and recessives concerned has an average persistence in the population of 10-100

generations, then exposure of one generation to 10 or 100 times the doubling dose would impose the equivalent of the same load for a period of 10 or 100 generations. Such doses are of the magnitude 300-3000 rad, and in a range which is such as to render further considerations of genetic problems redundant. It therefore seems probable that the human race has ample breeding capacity to survive the genetic consequences of any foreseeable radiation exposure.

Pool of recessive mutants

106. Examination of the offspring of consanguineous marriages can give information concerning the total of deleterious recessive mutant alleles in a population, and Morton, Crow and Muller⁸⁸ 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
<i>Autosomal dominants (direct observation)</i>	
Epiloia.....	8 x 10 ⁻⁶
Achondroplasia.....	45 x 10 ⁻⁶
Aniridia.....	5 x 10 ⁻⁶
Retinoblastoma.....	4-23 x 10 ⁻⁶
Partial albinism with deafness.....	4 x 10 ⁻⁶
Microphthalmos.....	5 x 10 ⁻⁶
Neurofibromatosis.....	1.3-2.5 x 10 ⁻⁴
Average of 7 loci.....	4 x 10 ⁻⁵
<i>Rare dominant</i>	
Porcupine.....	<10 ⁻⁹ ^a
<i>Sex-linked recessives (direct)</i>	
Hemophilia.....	3 x 10 ⁻⁵
Duchenne's type muscular dystrophy.....	4-10 x 10 ⁻⁵
<i>Autosomal recessives (indirect)</i>	
Albinism.....	2.8 x 10 ⁻⁵
Ichthyosis congenita.....	1.1 x 10 ⁻⁵
Total colour blindness.....	2.8 x 10 ⁻⁵
Infantile amaurotic idiocy.....	1.1 x 10 ⁻⁵
Amyotonia congenita.....	2.0 x 10 ⁻⁵
True microcephaly.....	4.9 x 10 ⁻⁵
Phenylketonuria.....	2.5 x 10 ⁻⁵
Average of 7 loci.....	2.4 x 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	
<i>D. melanogaster</i>		
Average for 9 sex-linked recessive visibles in XXY female.....	3 x 10 ^{-5a}	Muller, Valencia and Valencia ¹⁷¹
Average for 4 autosomal recessive visibles in Oregon-R females..	2.5 x 10 ⁻⁶	Glass and Ritterhof ¹⁷²
Average for 4 autosomal recessive visibles in Oregon-R males....	4.5 x 10 ⁻⁵	Glass and Ritterhof ¹⁷²
Average for about 12 sex-linked recessive visibles in Oregon-R females.....	2.4 x 10 ⁻⁶	Glass and Ritterhof ¹⁷²
White eye.....	0.7-3.7 x 10 ⁻⁵	Bonnier and Luning ¹⁷³
8 sex-linked recessive visibles in mutable Florida stock.....	3 x 10 ⁻⁵	Demerec ¹⁷⁴
<i>Mice</i>		
Average of 7 autosomal recessive visibles in male	ca. 7 x 10 ⁻⁶	Russell ⁷⁶ , Carter <i>et al.</i> ⁷⁵
<i>Bacteria</i>		
Average of about 30 biochemical back-mutations.	4.5 x 10 ⁻⁹	Glover in Demerec <i>et al.</i> ⁵³
Range of above... 10 ⁻¹¹ to 4 x 10 ⁻⁸		Glover in Demerec <i>et al.</i> ⁵³

^a But approximately 5 x 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	
<i>D. melanogaster</i>		
Sex-linked recessive lethals:		
young sperm.....	1.0 x 10 ⁻⁸	{ Spencer and Stern ³² Uphoff and Stern ⁸¹
aged sperm.....	2.0 x 10 ⁻⁸	{ Caspari and Stern ³³ Uphoff and Stern ⁸¹
range for various wild type stocks.....	0.7-11 x 10 ⁻⁸	Demerec ¹⁷⁴
mutable Florida stock	1.1 x 10 ⁻²	Demerec ¹⁷⁴
XXY females.....	7.0 x 10 ⁻³	Muller <i>et al.</i> ¹⁷¹
	1.8 x 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
<i>D. melanogaster</i>		
Average of 9 recessive visible autosomals in oocytes, oogonia	1.4 x 10 ⁻⁸	Muller, Valencia and Valencia ¹⁷¹
Average of 9 recessive visible autosomals:		
spermatogonia..	1.5 x 10 ⁻⁵	Alexander ⁷⁰
mature sperm...	6 x 10 ⁻⁸	Alexander ⁷⁰
mature sperm...	4.4 x 10 ⁻⁸	Patterson ¹⁷⁵
mature sperm...	5.2 x 10 ⁻⁸	Demerec ¹⁷⁶
White eye mature sperm.....	0.8-1.2 x 10 ⁻⁷	Bonnier and Luning ¹⁷³
<i>D. virilis</i>		
Average of 7 sex-linked recessive visibles:		
mature sperm...	7.6 x 10 ⁻⁸	Girvin ¹⁷⁷
<i>E. coli</i>		
Average of about 30 biochemical back-mutations.....	2.7 x 10 ⁻¹⁰	Glover in Demerec <i>et al.</i> ⁵³
<i>Mice</i>		
Average of 7 recessive visible autosomals: spermatogonia..	2.5 x 10 ⁻⁷	Russell ⁷⁶

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

	Mutations/r	
<i>D. melanogaster</i>		
Sex-linked recessive lethals in		
aged sperm.....	2.3 x 10 ⁻⁵	Uphoff and Stern ⁸¹
young sperm.....	2.8 x 10 ⁻⁵	Uphoff and Stern ⁸¹

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

Experiment	Reference	Number of irradiated parents	Dose range in rads	Results						Remarks		
				Abortions		Stillbirths		Congenital malformations* (live births)			Sex-ratio (live births)	
				Irrad.	Control	Irrad.	Control	Irrad.	Control	Irrad.	Control	
Survey of pregnancies in Hiroshima and Nagasaki	Neel and Schull ¹¹	approx. 27,000 ♀ approx. 14,000 ♂	8-200 8-200			546	408	300	294			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 $k = -5.5 \times 10^{-4}$ /rad for irradiated mothers; among earlier births k was -8×10^{-6} and significant. Slight non-significant increase for irradiated fathers in earlier births. ¹²
				33,181	31,559	33,527	31,904	regression lines based upon several doses; for raw data see Ref. 111, Chapter VII.				
Survey of offspring of French patients	Turpin, Lejeune and Rethore ^{117, 108}	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			
Follow-up on progeny of women treated for sterility	Kaplan ¹¹⁹	311 ♀	ca. 60	91	513	2	513	3	513	191	409	No control as yet. Very low sex-ratio significantly different from 0.515, $k \sim -8 \times 10^{-4}$ /rad.
				513	513	513	513					
Surveys of children of American radiologists	Crow ¹⁰⁶	654 ♂	Unknown accumulation of many small doses	Abortions and Stillbirths		Congenital malformations		Sex-ratio				No data on malformations or sex-ratio. Inquiry by questionnaire.
				Irrad.	Control	Irrad.	Control	Irrad.	Control			
				1,653	215	1,348	215					
	Macht and Lawrence ¹²⁰	5,461 ♂	many small doses	766	548	328	216	2,090	1,766			Non-significant increase in stillbirths 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 Maurer¹⁰⁸ and by Murphy and Goldstein¹⁰⁷ respectively revealed⁷ $\frac{1}{229}$ 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..... <i>B. lact. aerog.</i>	2 x 10 ⁻¹⁵	
<i>E. coli</i>	2.3 x 10 ⁻¹⁵	
(compare T2 bacteriophage)		3 x 10 ⁻¹⁶ per particle)
Microbes..... <i>Penicillium</i>		1.5 x 10 ⁻¹³ per spore
<i>Aspergillus</i>		1.9 x 10 ⁻¹² per spore
Yeast		6.2 x 10 ⁻¹⁵
<i>Drosophila</i>Salivary glands ♂	2.6 x 10 ⁻¹¹	
♀	2.8 x 10 ⁻¹¹	
Diploid cells (limb)		1.7 x 10 ⁻¹³
Rat.....Diploid cells	0.6-1.0 x 10 ⁻¹²	
Mouse.....Submaxillary glands (diploid)	0.7-1.4 x 10 ⁻¹²	
Man.....B.M.	8.7 x 10 ⁻¹³	
Leukocytes	8.6 x 10 ⁻¹³	
RBC	7.0 x 10 ⁻¹³	
Liver	1.0 x 10 ⁻¹³	
Kidney	8.7 x 10 ⁻¹³	

^a For a further extensive table, see ref. 21.

TABLE VIII. CALCULATED DOUBLING DOSES IN ORGANISMS OTHER THAN MAN¹⁷⁸

Organism	Loci	Conditions of irradiated cell	Doubling dose (rad)	Ref.
<i>Zea mays</i>	4 recessive visibles	Pollen	28	179
<i>Oenothera, Prunus</i>	Self-incompatibility	Pollen	60	180, 181
<i>Drosophila</i>	Sex-linked lethals	spermatozoa	50	31-33
		aged spermatozoa	140	31-33
		oocytes 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	At birth
Stevenson ¹⁴⁴	Rare heterozygotes.....	1.36 x 10 ⁻²	1.9 x 10 ⁻²
	Rare homozygotes.....	1.0 x 10 ⁻³	2.1 x 10 ⁻³
	Rare sex-linked.....	1.6 x 10 ⁻⁴	4 x 10 ⁻⁴
	Common traits of hard interpretation...	1.0 x 10 ⁻²	1.5 x 10 ⁻²
	TOTAL	2.7 x 10 ⁻²	3.6 x 10 ⁻²
U.S.A. Panel ¹⁴⁵	Tangible defects of genetic origin (1/2 total).....		2 x 10 ⁻²
Kemp ^{139, 191}	Physical malformations and defects.....		< 1 x 10 ⁻²
	Severe hereditary afflictions.....		< 2-3 x 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 haemangiomas	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 hypercholesteremia	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 with- } out spina bifida or rachischisis	360	—
Occipital meningocele.....		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) ..	+ ∞ ^a	Intermediate finite value	Near and possibly even above present selective optimum; ¹⁵⁸ far below social optimum
Life-span	+ ∞ ^a	Unknown: perhaps + ∞ ^a	Below social optimum: probably below selective optimum

^a " + ∞ " 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 Penrose¹⁵¹ and Fraccaro¹⁸⁴ 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.

$$\text{Let } S = S_0 \exp - w^2/2\sigma_3^2$$

$$N = N_0 \exp - 1/2 \left(\frac{w - m'}{\sigma_4} \right)^2$$

Then the curve determining survival is

$$\frac{S}{N} = \frac{S_0}{N_0} \exp - \frac{1}{2\sigma_1^2} \left(w + \frac{m'\sigma_3^2}{\sigma_4^2 - \sigma_3^2} \right)^2 \exp \frac{1}{2} \left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2} \right)$$

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

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

$$\bar{k} = \frac{\sigma_4 N_0}{\sigma_3 S_0 + \sigma_4 N_0}$$

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

and at this point

$$\left(\frac{S}{N} \right)_{opt} = \frac{S_0}{N_0} \exp - 1/2 \left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2} \right)$$

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

$$\text{where } k_{min} = \frac{N_0/S_0 \exp - 1/2 \left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2} \right)}{1 + N_0/S_0 \exp - 1/2 \left(\frac{m'^2}{\sigma_4^2 - \sigma_3^2} \right)}$$

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

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

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

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

Comparison of r 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

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

and

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

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 Robson¹⁸⁵ and by Penrose¹⁴⁹ 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. <i>The biological effects of atomic radiation</i> 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. <i>The hazards to man of nuclear and allied radiations</i> 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. <i>Preliminary report on modern methods for the evaluation of the biological effects of small doses of external radiation or absorbed radioactive materials</i> 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.) <i>Researches on the effects of the H-bomb explosion at Bikini Atoll 1954 on animal industry and sericulture in Japan</i> 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. (Part 2.) <i>The radioactive contamination of agricultural crops in Japan</i> 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. (Part 3.) <i>A preliminary report of recommendations on the modern methods of estimating the biological activity of small radiation dose</i> Several current hematological findings in Japan are summarized and discussed. (Part 4.) <i>The airborne radioactivity in Japan</i> 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. (Part 5.) <i>Report on the systematic observations of the atmospheric radioactivity in Japan</i> 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. (Part 6.) <i>On the distribution of naturally radioactive nuclides in Japanese islands</i> Surveys of the distribution of naturally radioactive nuclides in Japanese waters and minerals are reviewed and summarized.	10 13 3 28 56 27

Document Number	Country and Title	Approximate No. of pages
A/AC.82/G/R.	JAPAN (continued)	
	(Part 7.) <i>Radiochemical analysis of radioactive fall-out observed in Japan</i>	24
	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.	
	(Part 8.) <i>Fission products in water area and aquatic organisms</i>	24
	Describes fall-out distribution and uptake generally, with special reference to water and aquatic organisms and to the problem of Sr ⁹⁰ .	
5.	MEXICO. <i>First report on the studies of radioactive fall-out</i>	15
	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.	
6.	UNION OF SOUTH AFRICA. <i>Preliminary report on radioactive fall-out</i>	2
	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.	
7.	UNITED STATES. <i>Radioactive fall-out through September 1955</i>	13
	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.	
8.	CHINA. <i>Reports by the Atomic Energy Council of the Executive Yuan of the Republic of China</i>	8
	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.	
9.	CANADA. <i>Report on waste disposal system at the Chalk River Plant of Atomic Energy of Canada Limited</i>	15
	Describes procedures and results of ground dispersal of radioactive wastes from a natural uranium heavy water-moderated reactor.	
10.	<i>The Canadian programme for the investigation of the genetic effects of ionizing radiation</i>	15
	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).	
11.	UNITED STATES. <i>Pathologic effects of atomic radiation</i>	100
	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.	
12.	CANADA. <i>Levels of strontium-90 in Canada</i>	7
	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 μc/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.	
13.	NEW ZEALAND. <i>Note by New Zealand</i>	12
	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.	
14.	NORWAY. <i>Report of three parts</i>	9
	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 .	
14/Add.1	<i>Addendum to Part 1</i>	7

Document Number	Country and Title	Approximate No. of pages
A/AC.82/G/R.		
15.	SWEDEN. <i>Report of fifteen parts</i> 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	<i>Corrigendum to parts 1 and 9</i>	2
15/Corr.2	<i>Corrigendum to part 9</i>	1
16.	FRANCE. <i>Report of three parts</i> 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	<i>Addendum to above report</i>	20
17.	CZECHOSLOVAKIA. <i>Natural radioactivity of water, air and soil in the Czechoslovak Republic</i> 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. <i>Report concerning the request for information on natural radiation background</i> Describes counters used for monitoring radiation background and gives results (cpm) from January 1955 to June 1956.	10
19.	AUSTRIA. <i>Information prepared by the Austrian Government relating to the effects of atomic radiation</i> 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. <i>The radiological dose to persons in the United Kingdom due to debris from nuclear test explosions prior to January 1956</i> 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	<i>Corrigendum to above report</i>	2
21.	UNITED STATES. <i>Project Sunshine Bulletin No. 12</i> 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.	<i>Summary of analytical results from the Hasl Strontium Program to June 1956</i> 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. <i>Preliminary report on possible methods of estimating the biological effects of small doses of radiation</i> 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. <i>The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki</i> 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

<i>Document Number</i>	<i>Country and Title</i>	<i>Approximate No. of pages</i>
A/AC.82/G/R.		
25.	HUNGARY. <i>Unusual radioactivity observed in the atmospheric precipitation in Debrecen (Hungary) between 22 April-31 December 1952</i> Describes methods and discusses results of measurements of total beta activity of fall-out at Debrecen, April-December 1952.	13
26.	BELGIUM. <i>Report consisting of five parts</i> 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 <i>Institut du cancer</i> 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. <i>Letter from the "Service fédéral de l'hygiène publique", Bern</i> Gives brief description of studies on atomic radiations conducted in Switzerland.	6
28.	ARGENTINA. <i>Information summary on the preliminary work carried out in Argentina for the measurement and study of radioactive fall-out</i> Gives summary description of methods tried in Argentina for measurement of total fall-out radioactivity and airborne radioactivity.	2
29.	AUSTRALIA. <i>(Report consisting of six parts, as follows:)</i> <i>(Part I.) Human genetics</i> 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). <i>(Part II.) Plant genetics</i> Gives plan of research to be organized. <i>(Part III.) Radio-biological unit in the University of Adelaide</i> To be established. <i>(Part IV.) Natural radiation background and environmental contamination</i> Describes future organization of investigations on natural radiation background and contamination; radioactivity of food will be determined. <i>(Part V.) Occupational exposure in Australia</i> 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). <i>(Part VI.) Health and safety precautions in uranium mining and milling in Australia</i> Describes health and safety precautions in uranium mining and milling.	17
30.	UNITED KINGDOM. <i>Radio-strontium fall-out in biological materials in Britain</i> 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. <i>Replies to the questions put by the United Nations Scientific Committee on the Effects of Atomic Radiation</i> 1. Levels of natural radiation background. 2. Summarizes long-term research in biology and medicine under the direction of <i>Langendorff</i> (genetic effects, restorations, physicochemical effects); <i>Rajewski</i> (effects of natural radioactivity, accumulation of nuclides in tissues); <i>Marquardt</i> (research on natural mutation rates and their modification by irradiations); <i>Other institutes</i> (pathological and physicochemical effect). No details given—refers to scientific publications.	6
32.	INDIA. <i>Procedure used in India for collection of fall-out samples and some data on fall-out recorded in 1956</i> 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.	<i>External radiation dose received by the inhabitants of monozite areas of Travancore-Cochin, India</i> Contains results of a survey to measure the radiation level of the Indian State of Travancore. The radiation level due to gamma-rays at about three feet above the ground level ranges from 6,000 to 100 mrad/year, approximately. The main contributors are thorium and its decay products.	9

Document Number	Country and Title	Approximate No. of pages
A/AC.82/G/R.		
34 and Add.1	BRAZIL. <i>On the intensity levels of natural radioactivity in certain selected areas of Brazil</i> 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	<i>Corrigendum to above report.</i>	6
35.	WORLD METEOROLOGICAL ORGANIZATION. <i>Summary of comments of WMO on procedures for collection and analysis of atmospheric radioactivity data</i> 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. <i>Measurements of long-range fall-out in Rio de Janeiro</i> 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. <i>On the methods of indicating the changes produced in the organism by small doses of ionizing radiation</i> 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. <i>Absorption curve of fall-out products</i> 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. <i>Content of natural radioactive substances in the atmosphere and in water in the territory of the Union of Soviet Socialist Republics</i> 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.	<i>Study of the atmospheric content of strontium-90 and other long-lived fissions products</i> 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.	<i>On the behaviour of radioactive fission products in soils, their absorption by plants and their accumulation in crops</i> Report of two parts: <i>Part I.</i> —Experiments of absorption and desorption by soil of fission products and especially of isotopes such as $\text{Sr}^{90} + \text{Y}^{90}$, Cs^{137} , $\text{Zr}^{95} + \text{Nb}^{95}$ and $\text{Ru}^{106} + \text{Rh}^{106}$ are described. Theoretical analysis is also described. It was observed that $\text{Sr}^{90} + \text{Y}^{90}$ 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 $\text{Sr}^{90} + \text{Y}^{90}$. 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. <i>Part II.</i> —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. <i>First studies on radioactive fall-out</i> Revised form of UN document A/AC.82/G/R.5.	15
43.	JAPAN. <i>The effect of momentary X-ray exposure in a small dose upon the peripheral blood picture</i> 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.	<i>Hematological effects of single exposure to small doses of X-ray</i> 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.	<i>Morphological changes of platelets in chronic radiation injuries</i> 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. <i>Preliminary report on environmental iodine-131 measurement in sheep and cattle thyroids in Cairo, Egypt</i> 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. <i>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</i> 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.	<i>Programme of scientific research on the effects of ionizing radiations on the health of present and future generations</i> 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.	<i>Summaries of papers presented at the Conference on the remote consequences of injuries caused by the action of ionizing radiation</i> 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.	<i>Contributions to the study of the metabolism of caesium, strontium and a mixture of beta-emitters in cows</i>	20

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The metabolism of Cs¹³⁷, 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 P³² (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 K⁴⁰). 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

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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—*

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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.

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These annexes were:

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

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	Some problems in the estimation of spontaneous mutation rates in animals and man—James V. Neel.	
59.	NETHERLANDS. <i>Radioactive fall-out measurements in the Netherlands</i> 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.	6
60.	UNITED KINGDOM. <i>Genetic research in the United Kingdom</i> 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.	6
60/Add.1	<i>Suggestions for research in radiation genetics</i> General considerations are reviewed and a list of suggested programmes of research in the fields (i) to (iii) is appended.	3
61.	JAPAN. <i>Current and proposed programmes of research and investigation related to radiation genetics in Japan</i> A brief survey of current and planned research in Japan relevant to radiation genetics, covering both human surveys and experimental work.	16
61/Add.1	<i>Table 1 (2) to above report:</i> <i>Experimental data with beta radiation</i>	
62.	<i>Radiochemical analysis of Sr⁹⁰ and Cs¹³⁷</i> 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.	6
63.	<i>Review of the recent researches on the biological effects of ionizing radiation in Japan</i> 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.	14
64.	UNITED STATES. <i>Shortening of life in the offspring of male mice exposed to neutron radiation from an atomic bomb</i> 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.	12
65.	<i>Gamma-ray sensitivity of spermatogonia of the mouse</i> Relates the depletion of spermatogenic cells to killing of spermatogonia, the re-population being related to the maturation of surviving cells.	3
66.	<i>Some delayed effects of low doses of ionizing radiations in small laboratory animals</i> A quantitative study of the life span, the incidence of leukemia, tumours (lung, liver, ovary), and lens opacities as a response to low dosages (less than 100 rads).	7
67.	<i>Effects of low-level radiation (1 to 3 r) on mitotic rate of grasshopper neuroblasts</i> A study of the inhibitions of mitotic rate and of its possible relationship with the alteration of chromosome structure.	4

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68.	<i>Effects of low doses of X-rays on embryonic development in the mouse</i> Effects of 25 r applied during different stages of embryonic development on skeletal malformations appearing in the young.	6
69.	SWEDEN. <i>Does there exist mutational adaptation to chronic irradiation?</i> An account of an experiment in which a population of <i>Drosophila</i> 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. <i>Radiological data in Japan</i> 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	<i>Corrigendum to above document</i>	5
71.	UNITED STATES. <i>Occupational radiation exposures in Atomic Energy projects</i> A series of five tables concerning yearly exposures from 1947 to 1955 from external and internal radiation sources.	9
72.	<i>Worldwide effects of atomic weapons</i> (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.	<i>Maximum permissible radiation exposures to man</i> 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.	<i>Gonadal dose produced by the medical use of X-rays</i> 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.	<i>Summary of current and proposed programmes of research in the U.S.A. related to radiation genetics</i> 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. <i>Principal calcium contributors in national diets in relation to effects of atomic radiation from Sr⁹⁰</i> 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. <i>Principal calcium contributors in national diets in relation to effects of atomic radiation from strontium-90</i> This paper replaces the preliminary note circulated as UN document A/AC.82/-G/R.76.	8
77.	NORWAY AND SWEDEN. <i>Radioactive fall-out over the Scandinavian peninsula between July and December 1956</i> 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. <i>Information in eight parts on human genetics submitted by Belgium</i> 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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	(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 cholesterol content of the suprarenals of the rat following irradiation of normal and hypophysectomised animals.	11
79.	SWEDEN. <i>A suggested procedure for the collection of radioactive fall-out</i> 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. <i>A geological, radiometric and botanic survey of the region "Los Chañores" in the province of Mendoza of Argentine Republic</i> Radiometric data on the above-mentioned region are shown on the attachment to the document.	4
81.	<i>Measurements of the cosmic ray intensity in three latitudes of Argentine Republic</i> Data on the intensity of the cosmic rays in three points of observation at different latitudes in Argentina.	5
81/Corr.1	<i>Corrigendum to above report</i>	2
82.	<i>On the absorption of the nucleonic component of the cosmic radiation at -15° geomagnetic latitude</i>	1
83.	<i>Mutations in barley seeds induced by acute treatments by gamma rays of cobalt-60</i> 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	<i>Addendum to above report</i>	1
84.	<i>Mutations in barley induced by formaldehyde</i> A report of experiments on the induction of mutations at a number of loci in barley by formaldehyde.	1
85.	<i>Spontaneous mutations in barley</i> A report of experiments on spontaneous mutations at a number of loci in barley.	2
86.	<i>A study of radioactive fall-out in Argentine Republic</i> 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.	<i>A research programme in Argentina on the genetic influence in the plants of the ionizing and ultra-violet radiation</i> 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.	<i>Programme of physical oceanography for the International Geophysical Year</i>	33
89.	<i>Information on the general programme to be developed in Argentina on items of interest to the Scientific Committee on the Effects of Atomic Radiation</i> A brief general survey of Argentina research activities related to the effects and levels of ionizing radiations.	2
90.	NETHERLANDS. <i>Chemical steps involved in the production of mutations and chromosome aberration by X-radiation and certain chemicals in Drosophila</i> A survey of comparative studies of X-ray and chemical mutagenesis in <i>Drosophila</i> , 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. <i>Strontium-90 in man</i> 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. <i>Radioactive fall-out in Norway</i> Contains information on methods and results of measurements of fall-out in Norway.	19
93.	<i>Summary of analytical results from the HASL Strontium Program July through December 1956</i> 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.	<i>Environmental radon concentrations—An interim report</i> 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.	<i>The radium content of soil, water, food and humans—Reported values</i>	6
96.	<i>Marine biology—Effects of radiation—A selected bibliography</i> Twenty-four references concerning investigation on the distribution and metabolism of fission products in marine organisms.	2
97.	<i>Sea disposal operation</i> 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	<i>Corrigendum to the above report</i>	1
98.	CANADA. <i>Radiochemical procedures for strontium and yttrium</i> 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.	<i>Levels of strontium-90 in Canada up to December 1956</i> 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. <i>The determination of long-lived fall-out in rainwater</i> Describes radiochemical procedures for the determination of Sr ⁸⁹ , Sr ⁹⁰ , Cs ¹³⁷ and Ce ¹⁴⁴ activities in the rainwater.	
101.	DENMARK. <i>Measurement of activity of airborne dust. Measurements of fall-out deposited on the ground</i> 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. <i>Radiological data. Demographic data.</i> 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. <i>Modification of immunological phenomena and pathogenic action of infectious agents after irradiation of the host</i> 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.	<i>Some data, estimates and reflections on congenital and hereditary anomalies in the population of Northern Ireland</i> 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.	<i>Leukemia and aplastic anaemia in patients irradiated for ankylosing spondylitis</i> The incidence of leukemia and of aplastic anaemia was investigated in patients	135

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	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. <i>Information on radiological data</i> Summary tables on radiological data in Norway with an extensive set of data on X-ray and natural radiation exposures.	44
106/Add.1	<i>Addendum to above report</i>	2
107.	NEW ZEALAND. <i>New Zealand report to U.N. Scientific Committee on Atomic Radiation: Effects of atomic radiation measured in New Zealand to 31 July 1957</i> A set of notes on the current status of various programmes in New Zealand within the field of interest on the Scientific Committee on the Effects of Atomic Radiation, including preliminary measurement of radioactive fall-out, C ¹⁴ airborne activity, natural and artificial radioactivity, and occupational gonad exposures.	6
108.	UNITED STATES. <i>Current research findings on radioactive fall-out</i> General survey of the fall-out problem, especially Sr ⁹⁰ distribution and uptake in the human body.	18
109.	<i>Dosages from natural radioactivity and cosmic rays</i>	2
110.	NETHERLANDS. <i>Four reports on quantitative determination of radioactivity</i> A group of tables containing figures for the radiation doses from natural and man-made sources in the Netherlands.	48
111.	NORWAY. <i>On the deposition of nuclear bomb debris in relation to air concentration</i> Studies the relation between the deposition of fall-out and the airborne activity. It appears that in 1956-1957 the fall-out in the Oslo area was roughly proportional to the product of precipitation and airborne activity at ground level.	16
112.	<i>Radioactive fall-out in Norway up to August 1957</i> Gives the results of measurement of fall-out materials in air, precipitation, water and other samples. Measurement of airborne activity at high altitudes are included. Sr ⁹⁰ values are computed from total beta activity, a small number of samples having been checked by chemical analysis. Samples of water, milk and urine have been analysed for iodine-131.	22
113.	<i>Radiochemical analysis of fall-out in Norway</i> Describes the methods used in Norway for determination of Sr ⁹⁰ , Cs ¹³⁷ and I ¹³¹ and contains data of Sr ⁹⁰ and Cs ¹³⁷ activities in water and milk and of I ¹³¹ in milk, in the period February-June 1957.	10
114.	UNITED KINGDOM. <i>The relative hazards of Sr⁹⁰ and Ra²²⁶</i> Methods for calculations of the doses received by soft tissue cavities in bone containing Sr ⁹⁰ and Ra ²²⁶ are presented. Non-uniformity factors are given for the dose from Sr ⁹⁰ . Calculation of the maximum permissible body burden for radium on the basis of a given maximum permissible dose-rate to bone gives a wide range of values, depending on the assumptions made. In the case of radio-strontium, the range of possible values is less. It is suggested that radium be no longer taken as the basis for the calculation of maximum permissible body burden of Sr ⁹⁰ .	26
115.	<i>Shortening of life by chronic irradiation: the experimental facts</i> 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.	7
116.	BELGIUM. <i>Report on health protection in uranium mining operations in Katanga</i>	7

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A/AC.82/G/R.		
117.	INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION AND INTERNATIONAL COMMISSION ON RADIOLOGICAL UNITS AND MEASUREMENTS. <i>Exposure of man to ionizing radiation arising from medical procedures</i> 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. <i>Report on measurements of fall-out in Poland</i> Continuous measurements of global beta activity of fall-out are reported for four stations in Poland.	4
119.	BELGIUM. <i>Effect of a lethal dose of radiation on the amount of reducing steroids in the blood of the rat</i> 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.	<i>Action of hydrogen peroxide on the growth of young barley plants</i> 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.	<i>Action of cystamine and glutathione on X-ray irradiated barley seed</i> 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.	<i>Action of X-rays on the growth of internodal cells of the alga Chara Vulgaris L.</i> Irradiation of internodal cells of <i>alga Chara Vulgaris L.</i> 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. <i>Radioactivity of people and foods</i> 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.	<i>Atmospheric radioactivity along the 80th meridian, 1956</i> 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.	<i>Radioactive contamination of certain areas in the Pacific Ocean from nuclear tests</i> 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. <i>Radiostrontium in soil, grass, milk and bone in the United Kingdom: 1956 results</i> 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. <i>Calcium and potassium content of foodstuffs in the Argentine Republic</i> 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. <i>Ionizing radiation and the socially handicapped</i> 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. <i>Dose from unsealed radio-nuclides</i> Calculations based upon information on shipments of radioisotopes show that the gonad dose to age 30 from unsealed radio-nuclides during 1956 in Canada is about 0.5 per cent of the dose from the natural radiation sources. The main dose arises from iodine-131.	11

Document Number	Country and Title	Approximate No. of pages
A/AC.82/G/R		
130.	UNITED STATES. <i>The nature of radioactive fall-out and its effects on man</i> 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	<i>Index to above report.</i>	51
131.	<i>Radioactive strontium fall-out</i> General survey of the fall-out problem, especially strontium-90 distribution and uptake in the human body.	26
132.	UNITED KINGDOM. <i>The determination of long-lived fall-out in rainwater</i> 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. <i>Excerpt from a letter dated 6 November 1957 received from the Secretary-General of the WMO—Interim international reference precipitation gauge</i> 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. <i>Report on genetics 1950-57—A brief report on the research work done in the field of genetics in Italy</i> Extensive notes reporting relevant research work in the field of genetics carried out in Italy during the period 1950-1957.	47
135.	JAPAN. <i>Analysis of Sr⁹⁰, Cs¹³⁷ and Pu²³⁹ in fall-out and contaminated materials</i> 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.	<i>Primary estimate of the dose given to the lungs by the airborne radioactivity originated by the nuclear bomb tests</i> 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	<i>Corrigendum to above report</i>	1
137.	<i>A measure of future strontium-90 level from earth surface to human bone</i> 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 skeletal dose and maximum permissible level of ground deposit are then calculated.	14
138.	<i>Supplemental review of the recent researches on the alleviation of radiation hazards</i> 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	<i>Corrigendum to above report</i>	1
139.	<i>Experimental studies on the development of leukemia in mice with frequent administrations of small doses of some radioactive isotopes (P³², Sr⁸⁹, Ce¹⁴⁴)</i> The development of leukemia is described in three strains of mice in which the disease has not been observed under control conditions. Nine cases of leukemia have been observed among forty-six animals surviving twenty-one weeks and longer following the first of repeated administrations of P ³² at three dose levels (0.1, 0.3, and 0.5 µc/gm). Latent periods varied with total dose administered. Larger doses were more effective than small doses. The leukemia was primarily of the myeloid type. 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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	JAPAN (<i>continued</i>)	
	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	<i>Corrigendum to above report</i>	1
140.	<i>Experimental studies on radiation injury by colloidal radioisotope-liver injury by colloidal radioactive chromic phosphate CrP³²O₄</i>	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 O 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	<i>Corrigendum to above report</i>	1
141.	<i>Radiological data in Japan II—Concentrations of Sr⁹⁰, Cs¹³⁷, Pu²³⁹ and others in various materials on earth's surface</i>	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	<i>Corrigendum to above report</i>	2
141/Add.1	<i>Addendum to above report</i>	3
142.	UNITED STATES. <i>Radioactive fall-out</i>	18
	General survey of the fall-out problem, especially Sr ⁹⁰ distribution and uptake in the human body.	
143.	UNITED KINGDOM. <i>The world-wide deposition of long-lived fission products from nuclear test explosions</i>	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. <i>Radioactive fall-out up to November 1957</i>	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. <i>Uptake of strontium and caesium by plants grown in soils of different texture and different calcium and potassium content</i>	5
146.	<i>The radioactive fall-out in Sweden up to 1.7.1957</i>	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.	<i>Gamma radiation from some Swedish foodstuffs</i>	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.	<i>Progress report on the metabolism of fission products in ruminants</i>	3
	The excretion of radioactive fission products (Sr ⁹⁰ and I ¹³¹) in milk after per oral administration is measured.	
149.	<i>A method for monthly collection of radioactive fall-out</i>	7
	Describes a collecting procedure using anion and cation exchange resins.	
150.	<i>The computation of infinite plane 30-year doses from radioactive fall-out</i>	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.	<i>The control of irradiation of populations from natural and artificial sources</i>	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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A/AC.82/G/R		
152.	UNITED KINGDOM. <i>The analysis of low level gamma-ray activity by scintillation spectrometry</i> The application of gamma-ray spectrometry enables measurement of the gamma-activity of 10 ⁻¹¹ curies or less.	9
153.	UNITED STATES. <i>The Chicago Sunshine method: Absolute assay of strontium-90 in biological materials, soils, waters and air filters</i> 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. <i>Normal calcium content of San Juan wines</i>	8
155.	BELGIUM. <i>Recent research on the chemical protectors and particularly on cysteamine-cystamine. (Document in English)</i> Discusses the possible mechanisms of action of chemical radioprotectors particularly of those above-mentioned.	9
156.	<i>Effect of X-rays on the growth of internodal cells of the alga Chara vulgaris L</i> 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. <i>Radioactive fall-out from the atmosphere in the Argentine Republic during 1957</i> Includes tables of results for first three-quarters of 1957. Total activity and strontium-90 content is measured.	18
158.	BELGIUM. <i>The action of various drugs on the suprarenal response of the rat to total body X-irradiation. (Document in English)</i> Describes strict difference in action of radioprotectors (cysteamine) or narcotic drugs (morphine and barbiturate) in preventing adrenal changes of irradiated animals.	8
159.	<i>Nervous control of the reaction of anterior hypophysis to X-irradiation as studied in grafted and newborn rats. (Document in English.)</i> 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. <i>Draft of Chapter F prepared by the delegation of the USSR to the Scientific Committee on the Effects of Atomic Radiation</i>	18
161.	JAPAN. <i>A sensitive method for detecting the effect of radiation upon the human body</i> 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. <i>UNESCO/FAO/WHO report on sea and ocean disposal of radioactive wastes, including appendices A, B and C</i> Summarizes contributions made by different authorities. <i>Appendix A:</i> 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. <i>Appendix B:</i> 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. <i>Appendix C:</i> Abstracts of eight other contributions to the report on sea and ocean disposal of radioactive wastes.	118
163.	USSR. <i>Data on the radioactive strontium fall-out on the territory of the USSR as to the end of 1955</i>	1

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A/AC.82/G/R		
164.	MEXICO. <i>Third report on the studies on radioactive fall-out</i> 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. <i>General considerations regarding calcium availability in the broad soil groups of the world in relation to the uptake of radiostrontium</i> 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. <i>Measurements on the radiation fields in the Monazite areas of Kerala in India</i> 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. <i>Measurements of Cs¹³⁷ in human beings in the United Kingdom 1956/1957</i> Describes the method of determining the Cs ¹³⁷ content in the human body using gamma-ray spectrometry. The average present value is $34.0 \pm 7.6 \mu\mu\text{c}$ per g potassium.	5
168.	JAPAN. <i>An enumeration of future Sr⁹⁰ concentration in foods and bone</i> Gives amendments and corrections to the report A/AC.82/G/R.137 based upon new available data.	6
169.	BRAZIL. <i>On the nature of long-range fall-out. (Document in English.)</i> Describes one surprisingly high value of daily collected fall-out activity due to a single big and highly active particle.	4
169/Corr.1	<i>Corrigendum to above report</i>	1
170.	UNITED KINGDOM. <i>The disposal of radioactive waste to the sea during 1956 by the United Kingdom Atomic Energy Authority</i> 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.	<i>A summary of the biological investigations of the discharges of aqueous radioactive waste to the sea from Windscale Works, Sellafield, Cumberland</i> 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. <i>The estimation of the amount of Sr⁹⁰ deposition and the external infinite gamma dose in Japan due to man-made radioactivity</i>	10
173.	SWEDEN. <i>Transfer of strontium-90 from mother to foetus at various stages of gestation in mice</i> 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.	<i>The recovery phenomenon after irradiation in Drosophila melanogaster</i> 1. <i>Recovery or differential sensitivity to X-rays</i> 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	<i>The recovery phenomenon after irradiation in Drosophila melanogaster</i> 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	<i>The recovery phenomenon after irradiation in Drosophila melanogaster</i> Chromosomes breakage <i>per se</i> or their rejoining by recovery seems to have no genetic consequences.	5

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SWEDEN (continued)		
175.	<i>Reports on scientific observations and experiments relevant to the effects of ionizing radiation upon man and his environment already under way in Sweden</i>	4
175/Add.1	<i>Report on experiments on the influence of selection pressure on irradiated populations of Drosophila melanogaster</i> 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	<i>Studies on the mutagenic effect of X-rays</i> Summarizes the results of the work on radiation-induced chromosome breakage under various conditions (K. G. Luning).	3
175/Add.3	<i>Does there exist mutational adaptation to chronic irradiation?</i> 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	<i>Some results and previews of research in Sweden relevant to human radiation genetics</i> 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	<i>Summary of papers of Lars Ehrenberg and co-workers with regards to the questions of the U.N. Radiation Committee</i> Summary of papers of L. Ehrenberg and co-workers on genetic effects of radiation.	7
175/Add.6	<i>Studies on the effects of irradiation on plant material carried out during recent years at the Institute for Physiologic Botany of Uppsala University</i>	2
175/Add.7	<i>Swedish mutation research in plants</i>	1
175/Add.8	<i>Dr. Gunnar Östergren and co-workers</i> Study on experimentally induced chromosome fragmentation (G. Östergren).	1
175/Add.9	<i>Investigations carried out by Dr. C. A. Larson (human genetics)</i>	1
176.	<i>Some notes on skin doses and bone marrow doses in mass miniature radiography</i>	2
177.	<i>Investigations into the health and blood picture of Swedish women living in houses representing different levels of ionizing radiation</i> 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.	<i>Other haemopoetic functions: Read-off methods in radio-haematological control</i> Proposes a statistical method of evaluating total white-cells count as a control test of radiation damage.	11
179.	FRANCE. <i>Atomic Energy Commission. Centre of Nuclear Studies at Saclay, Gif-sur-Yvette (Seine et Oise), France. Measurement of environmental activity: Methods and results</i> Gives results of measurements of both natural and artificial radioactivity in the environment.	7
179/Corr.1	<i>Corrigendum to above report</i>	1
180.	<i>Biological methods available for use in the quantitative detection of ionizing radiations</i> Surveys and evaluates the biological methods usable for the quantitative estimation of absorbed dose.	43
181.	SWEDEN. <i>Bone and radiostrontium</i> 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.	<i>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.</i>	3
183.	THE NETHERLANDS. <i>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</i> Report on the amount of radioactivity, its world-wide spreading and its biological risk as a consequence of test explosions.	48
184.	<i>Radioactive fall-out measurements in the Netherlands until December 31, 1957</i>	8
184/Corr.1	<i>Corrigendum to above report</i>	1

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185.	NEW ZEALAND. <i>Report on some aspects of radiation protection work in New Zealand</i> 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. <i>Doses received by the genital organs of children during X-ray examinations</i> Suggests the improvement of the radiological techniques and certain protective measures for decreasing the gonad dose from radiography.	15
187.	MEXICO. <i>Summary of radioactive fall-out data recorded in Mexico</i>	1
188.	BRAZIL. <i>Summary—strontium-90 analysis in dry milk and human urine</i>	2
189.	<i>On the composition of long-range fall-out particles</i> 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.	<i>On the uptake of M_sThI in naturally contaminated areas</i> 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. <i>Radioactive fall-out in Egypt: December 1956-February 1957</i>	5
192.	<i>Radioactive fall-out in Egypt: March-December 1957</i>	7
193.	<i>Some somatic changes observed in <i>Culex Molestus Forskal 1775</i></i> 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. <i>Gonad doses in radiodiagnosis</i> Summarizes the systematic study on the gonad dose due to diagnostic examination by means of X-rays.	64
195.	ITALY. <i>Data on radioactive fall-out collected in Italy (1956, 1957, 1958)</i>	6
196.	USSR. <i>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</i>	14
197.	<i>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</i>	17
198.	<i>Contamination of the biosphere in the vicinity of Leningrad by the products of nuclear explosions</i> 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.	<i>Study of the strontium-90 content of the atmosphere, soil, foodstuffs and human bones in the USSR</i> 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.	<i>Uptake of radioactive strontium by plants and its accumulation in various agricultural crops</i> 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.	<i>Some results of a study of the bone system after injury by radioactive strontium</i> 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 (<i>continued</i>)		
	the initial stages after contamination are marked pretumorous changes; their histological characteristic and their pathogenetic significance are discussed.	
202.	<i>Blastomogenic effects of strontium-90</i> 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.	<i>The radiation hazards of explosions of pure hydrogen and ordinary atomic bombs</i> 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.	<i>Towards an assessment of the hazard from radioactive fall-out</i> 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.	<i>Nature of the initial effect of radiation on the hereditary structures</i> A survey of the present knowledge of the nature of the primary mechanisms through which ionizing radiation damages the hereditary structures.	40
206.	<i>Radiation and human heredity</i> 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.	<i>The effect of radiation on the histological structure of monkey testes</i> 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.	<i>The cytogenetic effects of radiation exposure on spermatogenesis in monkeys</i> 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 <i>Drosophila</i> after exposure to the same dose, being 65 per cent and 1.6 per cent after 500 r respectively.	18
209.	BELGIUM. <i>Radioactive fall-out measured at the CEN during 1955-1956 and 1957</i> Describes methods and results of fall-out measurements in the period 1955-1957.	9
210.	<i>Average dose received by the personnel of CEN, MOL, from 1954 to 1957</i> 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. <i>Study of the gonad dose during systematic X-ray examinations (Preliminary note dealing only with the irradiation of male gonads)</i> 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.	<i>Determination of the absorbed dose/exposure dose ratio in bone and muscle by the equivalent-gases method. Principle of the method and preliminary results</i> 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.

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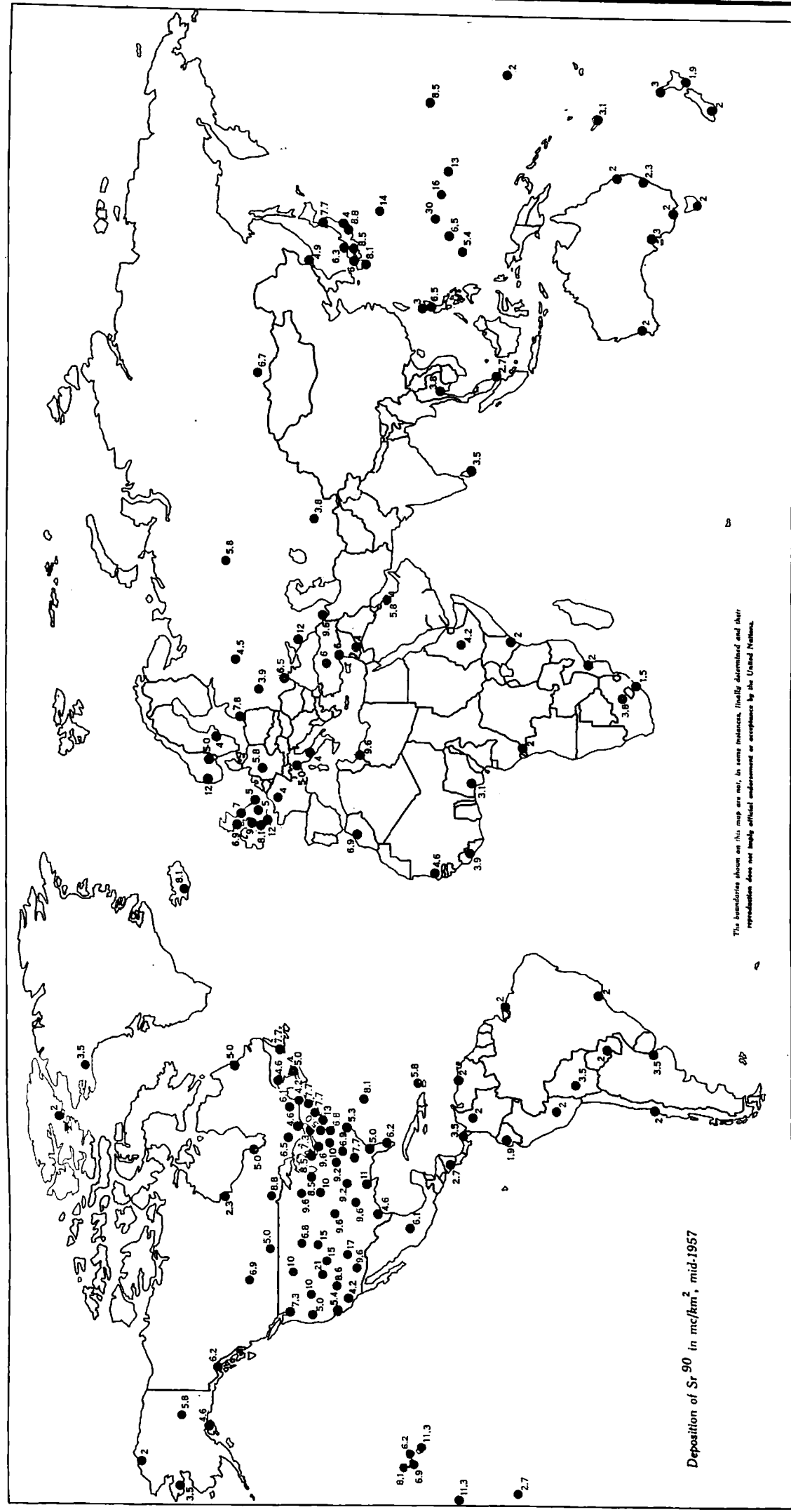
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Deposition of Sr⁹⁰ in mc/km², mid-1957

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