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

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

UNITED NATIONS
New York, 1962

NOTE

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

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

ANNEX C

THE HEREDITARY EFFECTS OF RADIATION

CONTENTS

I. Introduction

1. In its consideration of the hereditary effects of ionizing radiation upon man this report, as did that of 1958,[1] centres its attention on the possible consequences of the increases in the level of radiation to which human populations are currently exposed.

2. The Committee's 1958 report presented a comprehensive outline of the genetic hazard of ionizing radiation; the available evidence in man and other organisms was reviewed thoroughly and a variety of approaches was used to elucidate the problem. At the same time it was emphasized that current knowledge was insufficient to complete this task with more than partial success.

3. Since that time several significant developments have been made in radiation genetics and in related disciplines. In particular, progress has been very rapid in the area of human cyto-genetics; considerable attention is now being focused on the induction of gross chromosome aberrations as a serious genetic hazard. In addition, remarkable advances have been made through investigations with mice. These have indicated the existence of previously undetected intricacies in the dose-mutation relationship.

4. Developments such as these have been of great help in understanding the basic problems of radiation genetics. At the same time they have re-emphasized its complexities. The present annex gives particular attention to the effect which these recent advances have had on our ability to estimate the extent of hereditary damage which may be induced in populations by ionizing radiation. In stressing current problems, the report does not enumerate but is nevertheless based on a vast amount of information which has been accumulated over many years in the field of radiation genetics. For an account of earlier data and well-established genetic concepts, reference should be made to the previous report. However, to make this annex self-contained, this older information is summarized at relevant places.

5. All organisms are subject to hereditary diseases and defects. In man, estimates of the size of this burden of undesirable traits are based on the frequencies of:

(*a*) Abortions, still births and neonatal deaths;

(*b*) Infertility;

(*c*) Hereditary diseases and defects;

(*d*) Detrimental deviations from normal in continuously varying traits such as intelligence, life-span and resistance to disease.

6. Deleterious genetic traits are a direct consequence of the presence of specific basic faults in the genetic constitution of affected individuals. These faults may be either undesirable alleles or chromosome aberrations. However, the prevalence of deleterious hereditary traits in a population does not, in itself, provide a complete picture of the amount of genetic damage present. In some instances the fault is partially or completely masked in the heterozygote. In other instances, its phenotypic expression is so different in the homozygous and heterozygous states that it is impossible to express the total detriment to populations in simple terms. Furthermore, environment, in the form either of the remainder of the genotype or of external conditions, frequently has a great influence on the manner in which the fault is expressed.

7. There is no doubt that any increase in the frequency of radiation-induced mutation contributes to the burden of undesirable traits. It is equally evident that the evaluation of this contribution must rely upon an understanding of the genetic structure of a population and the environmental forces to which it is exposed. Moreover, the effect of an increase in the amount of genetic damage, from whatever source, must be considered in terms of a time interval; once inflicted on a population the damage may persist through future generations and may be expressed only intermittently and with varying degrees of severity.

8. There are a number of complementary approaches to the problem of estimating the detrimental hereditary effects of an increase in rate of mutation in human populations. Estimates of genetic hazard can be obtained empirically by the observation of irradiated populations. However, information obtained in this way is meagre, and estimates are more often calculated from what is known about the induction of genetic damage by radiation and from a knowledge of the way in which this damage will be expressed. These more indirect approaches require information on:

(*a*) The magnitude of natural genetic damage within a population as ascertained from a knowledge of the role of heredity in morbidity, mortality, and infertility;

(*b*) The role of recurrent natural mutation in maintaining the prevalence of this genetic damage;

(*c*) The qualitative and quantitative relation between a given dose of irradiation and the corresponding increase in mutation rate.

9. Every approach has its own difficulties and limitations. The direct approach is impeded not only by a meagreness of data but also by the absence of proper controls. Furthermore, in man it is quite impractical, through direct observation, to ascertain the spread of damage over what may be many generations. On the other hand, more indirect approaches require a knowledge of the genetic structures of populations and of genetic mechanisms which we do not fully possess at this time.

10. All approaches often make use of investigations with other organisms because the mechanism by which hereditary information is transmitted is basically the same in all forms of life. Experimental observations in a wide variety of organisms can thus provide a working model of the effects of ionizing radiation on man. However, there may be radical differences in genetic structure between populations because this structure is undoubtedly affected by the environmental conditions under which a population exists. Furthermore, many hereditary defects that are slight but nevertheless of importance to humans are not easily recognized in other species. As a consequence, generalizations based on the results of investigations with experimental organisms entail many uncertainties.

II. The prevalence of naturally-occurring hereditary defects and diseases

11. It is generally accepted that there is a genetic component in much, if not all, illness. This component is frequently too small to be detected; in other instances the evidence for its presence is unequivocal. Nevertheless, the role of genetic factors in the health of human populations has not in the past been considered seriously in vital and health statistics. As a consequence, data on the prevalence of hereditary diseases and defects are now largely restricted to that collected by geneticists for special purposes in limited populations from a small number of countries.

12. An assessment of the hereditary defects and diseases with which a population is afflicted does not necessarily provide a measure of the imposed burden of suffering and hardship on the individual, the family, or society. Such evaluations require, among other things, consideration of the development of medical services and of the cultural values in communities.[2]

Survey of hereditary disabilities

13. In the 1958 report, a detailed examination of data accumulated in Northern Ireland over many years led to a figure of about 4 per cent as the incidence of more readily detected hereditary diseases and defects. That survey has been the most comprehensive undertaken to date, and although limited to a single geographical region, it has provided a useful base on which to formulate overall estimates. New information now permits a revision and reclassification of these. For instance, it is now possible to estimate the frequency of chromosome aberrations and to transfer some conditions, such as Down's syndrome (mongolism), to a different category. The estimate of the incidence of congenital malformations has also been increased. The revised values are summarized below. Disabilities are placed in any of four categories. They are classified according to the role which mutation is believed to play in maintaining their frequency. This subject will be discussed in more detail in section III.

Category Ia

14. This includes harmful traits whose mechanism of inheritance is understood and whose prevalence is determined mainly by the frequency of individual gene, or point, mutations.

15. Several hundred traits determined by single gene substitutions have been identified. A majority of the traits, perhaps 70 per cent, are determined by autosomal dominant genes. Approximately 5 per cent are sex-linked recessive traits, and the remaining 25 per cent are determined by the homozygous expression of autosomal recessive genes.

16. The majority of dominant traits are sufficiently mild in their effects to be transmitted through several generations. In contrast, the detrimental recessive traits now recognized in man are very severe in their effects and, with few exceptions, are lethal in the genetic sense. As a result, although about 70 per cent of well-established specific traits are determined by dominant

genes, in perhaps 90 per cent of persons who show monomeric traits, these defects are determined by dominant genes. In terms of gene frequency, however, genes for recessive harmful traits must far outnumber those for dominant harmful traits in a given population. Furthermore, many hundreds of traits are encountered in man for each of which a recessive mode of inheritance is suggested, but each is so uncommon that adequate evidence for this is lacking. It seems likely that many of these traits are in fact the homozygous expressions of recessive genes and that they contribute in total more than any other class to the frequency of detrimental traits in populations.

17. Traits listed in this category are at present estimated to affect about 1 per cent of all live-born.

Category Ib

18. Harmful traits which are determined by cytologically demonstrable chromosome aberrations are included in this category. Their frequency is maintained mainly by recurrent mutation.

19. There is direct evidence that congenital and other physical defects are sometimes due to chromosome aberrations. This important information has been acquired as a consequence of improved techniques in human cytogenetics. Because most research in this area is new, the subject will be considered here in some detail.

20. As with those traits caused by the action of specific alleles, there is often considerable variation in the clinical severity of defects caused by chromosome aberrations. For this reason, all the clinical aspects of some specific defects remain to be described. Different degrees of mosaicism may be partly responsible for this variation in expression. Many associations of physical impairment with chromosome aberrations are now being reported and it must be suspected that some of these associations are due to chance. Reasonably well-established associations are presented in table I, others, necessitating further confirmation, in table II. All the disabilities noted in tables I and II are congenital, but some diseases of somatic origin are known to be associated with chromosome aberration. Two of these are granulocytic chronic leukaemia[3] and Waldenström's macroglobulinaemia.[4] Such diseases are discussed in annex D.

21. The fact that some well known defects occur as a consequence of anomalies in the number of autosomes was discovered in 1959, when it was demonstrated that Down's syndrome is associated with trisomy of one of the small acrocentric chromosomes (number 21 under the Denver Convention).[5,6] There are two other well-established instances of trisomy syndromes. One involves a member of the 17-18 group,[7] the other a member of the 13-15 group.[8] All three kinds of trisomy are associated with mental retardation.

22. Some detrimental traits are attributable to anomalies in the number of sex chromosomes. This was established when it was shown that a condition known as Klinefelter's syndrome can be caused by an XXY constitution.[9] Related clinical symptoms have now been attributed to XXXY,[10] XXXXY[11] and XXYY[12] karyotypes. Turner's syndrome has been associated with an XO constitution.[13] Females with XXX and XXXX karyotypes have also been described.[14,15]

23. Defects attributable to the presence of chromosome rearrangements have also been detected. Some individuals with Down's syndrome are known to have a forty-six chromosome complement in which part of an extra chromosome 21 is translocated to another autosome.[16-18] Other disabilities that have been associated with translocations or other types of aberration are listed in table II.

24. Defective traits caused by chromosome aberrations are sometimes, as might be expected, inherited through successive generations. A chromosome rearrangement which permits Down's syndrome to be transmitted by phenotypically normal females with a translocation in the balanced state has been demonstrated repeatedly.[17-20] Cases have also been reported of translocation-carrying phenotypically normal males whose children exhibit Down's syndrome.[20,21] Other balanced and unbalanced karyotypes have been noted in parental and child generations (table II). There are indications of differential transmission of aberrant chromosomal types in the two sexes.[22]

25. Mental retardation is one of the common consequences of gross chromosomal aberration. Relevant data have been obtained through the procedure of nuclear sexing of buccal mucosa to detect sex-chromosome anomalies. This procedure reveals deeply staining chromatin bodies within nuclei. The number of these Barr bodies per cell is, in general, one fewer than the number of X chromosomes present; the cells of a normal male are chromatin negative, whereas those of a normal female contain one Barr body. In five surveys, the combined frequency of chromatin-positive individuals among males attending special schools for the mentally backward was 8.77/1,000 (29/3,306).[23-27] Five surveys of male inmates of institutions for mental defectives indicated a frequency of 9.51/1,000 (70/7,358) chromatin-positive cases.[28-32] Two surveys of female inmates of institutions for mental defectives showed a combined frequency of 4.46/1,000 (12/2,689) females with double sex-chromatin bodies and one chromatin-negative female.[31] These figures may be compared with those found in the general population (para. 28 below).

26. Sterility is a frequent consequence of chromosome aberration. Males with sex-chromosome abnormalities are almost always sterile.[33] A study of men attending an infertility clinic showed that about 3 per cent of the patients were chromatin-positive.[34] Among sixty-eight women with a presumptive diagnosis of primary amenorrhoea, 28 per cent were found to have sex-chromosome anomalies.[35]

27. Some cases of still birth and abortion are attributable to chromosome aberration. In a survey for sex-chromosome anomalies in still-born children by nuclear sexing, none of fifty-two females was found to be abnormal, but two of forty-nine males were chromatin-positive.[36] In two instances of miscarriage the embryos have been shown to be triploid.[37,38] Here it was possible to culture material from foetal remnants.

28. A general picture of the prevalence of defective traits caused by gross chromosome anomalies is beginning to emerge despite the newness of this field of research. Some specific traits are extremely rare. However, the frequency of Down's syndrome is about 1.5 per 1,000 total births in Europe, North America, and Japan.[39-41] Comparative figures from other parts of the world are rather scanty. Current data on the frequency of sex-chromosome abnormalities have recently been summarized.[33] Cases of Klinefelter's syndrome (XXY), or at least karyotypes containing a Y and more than one

X, are relatively common, whereas cases of Turner's syndrome (XO) are rare. Three surveys by nuclear sexing of buccal mucosa, have been made among consecutive live-born. A frequency of 2.65/1,000 (18/6,801) chromatin-positive males was found in the combined data. Chromosome studies of seven of the anomalous cases showed that four were XY/XXY mosaics and three had an XXY complement. The frequency of abnormal nuclear sex among females was 0.90/1,000 (6/6,642).[36,42,43]

29. It is now estimated that about 1 per cent of all live-born have some harmful trait determined by chromosome aberrations sufficiently gross to be detected by present techniques. Many of these individuals are mosaics. Rather more than half of the aberrations are anomalies in chromosome number. The rest are intra-chromosome changes, translocations or combinations of these with numerical changes. Only a small fraction of these aberrations are transmitted to subsequent generations. It is likely, however, that estimates of the frequency of transmissible chromosome aberrations would be greater with more refined techniques since these aberrations, being less gross, are more difficult to detect.

Category II

30. This category includes developmental malformations whose mechanism of inheritance is ill understood. Environment is influential in the aetiology of these traits. Drugs, certain infections, and radiation are known to be teratogenic at critical stages of organogenesis, and maternal (intra-uterine) environmental factors are also known to have a great influence on prevalence. The role of mutation in maintaining the frequency of these traits has not yet been ascertained. They often show some familial concentration, but this fact does not necessarily prove the existence of a genetic component.

31. Some of these malformations may be caused by chromosome aberrations. However, no cytological evidence of this has been found in many of the more commonly-occurring malformations.[44-46] It is of course possible that chromosome changes too small to be identified by current techniques are responsible. Alternatively, complex genotypes and unusual environments may be causal factors; it has been suggested that a fraction of congenital malformations are caused by an insufficient degree of such heterozygosity as is necessary to ensure normal development.[40,47] However, it is difficult to distinguish between conditions due to individual recessive genes of low penetrance and any that may arise because of a deficiency of heterozygosity at a multiplicity of loci.

32. Many of these traits are detectable at birth. The frequency of live-born so affected is now estimated to be about 1.5 per cent, but is higher if still births are included. At the age of five years, an additional 1 per cent of affected children can be detected.[40,48]

Category III

33. In this category have been placed serious "constitutional" disorders in which the mechanism and contribution of inheritance are ill understood.

34. Included here are mental illnesses such as schizophrenia and manic depressive reactions as well as disorders such as diabetes mellitus, pernicious anaemia and some affecting the thyroid gland.

35. There is general agreement about the existence of a major genetic component in these traits and, on occasion, a simple mode of inheritance has been postulated for some of them. However, their frequency in the face of strong selection and their distribution in families are difficult to reconcile with a monomeric hypothesis. As a consequence, simple modes of inheritance are not usually assumed.[49] Each of these traits is common and prevalent over most of the world. They were collectively estimated in the 1958 report to affect at least 1.5 of all adults, but this estimate is very uncertain.

Category IV

36. This category includes harmful traits which are determined at single loci, but it is highly unlikely that the frequency of the alleles is substantially influenced by mutation.

37. The frequency of these traits tends to be high in localized areas of the world. This high frequency is a consequence of the fact that each of the traits exists as a part of a system of balanced polymorphism; selection pressures maintain the related genotypes in a state of balance. Included in this category are sickle-cell anaemia and thalassaemia. Many other traits, such as fibrocystic disease of the pancreas, probably belong here. On the other hand, a change in environment at some time in the future might remove some traits from the category. Except in certain localized areas in the world, the prevalence of these traits as currently recognized is extremely low. The subject of balanced polymorphism will be discussed in greater detail in a later section (paras. 47-52).

ROLE OF HEREDITY IN PREMATURE DEATH

38. Abortions, still births and neonatal deaths present special problems in a survey of hereditary defects; not only is the frequency of these defects greatly affected by environmental factors, but the role of heredity in their cause is difficult to ascertain because they are not transmitted to the next generation. In consequence, with the exception of those cases known to be caused by gross chromosome aberration, these defects are not considered in categories I-IV. Nevertheless, breeding experiments in animals have shown that simple genetic mechanisms contribute to their incidence. In other instances the additive effects of several genes with slight individual effects may be responsible.

LETHAL AND DETRIMENTAL EQUIVALENTS

39. All the genetic damage within a population is not expressed phenotypically in any one generation. To a large extent, this is because many detrimental traits are partially, if not completely, recessive; complete expression occurs only in the homozygote. The amount of this recessive damage is an important measure of the genetic health of a population. It can be estimated indirectly from a knowledge of the increase in mortality and morbidity observed in the progeny of consanguineous marriages; in these circumstances the hidden genetic damage can be described in terms of lethal and detrimental equivalents. A lethal equivalent has been defined as a group of mutant genes of such number that, if dispersed in different individuals, it will cause one death on the average.[50] This death occurs with homozygosity. In the same manner, genes leading to visible recessive defects can be defined in terms of detrimental equivalents.[51]

40. The procedure outlined above is a powerful tool with which to estimate the amount of recessive genetic damage within a population. However, lethal and detri-

mental equivalents do not represent genes determining any special category of recessive detrimental traits; when expressed phenotypically in the homozygote, the traits may fall in any of the lists of defects in paragraphs 13 to 38. Furthermore, an estimate of the frequency of equivalents does not provide any direct measure of that fraction of genetic damage within a population which is expressed in the heterozygous condition. Nor does a knowledge of the size of the pool of recessive lethal and detrimental genes, by itself, indicate the mechanism by which these genes are maintained in a population.

41. Estimates of lethal equivalents obtained from available surveys are presented in table III. The surveys are of very unequal scope and reliability, the one carried out in Japan being by far the most extensive. In spite of inconsistencies in the results, including some between the two cities in Japan, it seems reasonable to conclude that individuals in human populations carry from two to four lethal equivalents which are expressed, in homozygotes, before the age of twenty to thirty. In addition, each individual carries approximately the same number of detrimental equivalents.

III. The role of mutation in supporting the prevalence of hereditary disabilities

42. Mutation may be broadly defined as any change imposed in the genetic constitution of a cell. In the present annex, mutation is considered in terms of the two fundamental units of heredity, the gene and the chromosome. Natural mutations are generally referred to as spontaneous though in fact it is understood that there are causal factors over which we do not usually have any direct control. One of these factors is undoubtedly naturally-occurring ionizing radiation. Other physical and chemical variations that occur in nature, and the gene complement itself, probably influence mutability.

43. Two mechanisms are involved in maintaining the prevalence of detrimental hereditary traits within a population. One of these is recurrent mutation. The other is direct transmission of the basic genetic faults through successive generations. The role of transmission is generally expressed in terms of genetic fitness of the relevant genotypes, i.e., the number of their progeny which reach maturity. The importance of mutations in human populations cannot be considered independently of genetic fitness because reliable estimates of specific natural mutation rates and of the over-all contribution of mutation to ill health are frequently dependent on accurate information about this fitness.

Relative genetic fitness

44. The relationship between mutation, genetic fitness, and the prevalence of hereditary disabilities is concisely expressed by the principle which holds that each mutation, whether fully lethal or slightly detrimental, will on the average, result in the death of a descendant or in a failure to reproduce.[52, 53] The more genetically unfit of these mutations, as for instance dominant lethals, will be eliminated quickly, and occasionally without provoking any suffering or undue hardship on the population. Mutations which have less drastic effects on fitness will usually be transmitted through many generations and their phenotypic effects will be expressed in correspondingly more descendants.

45. Genetic damage can affect the phenotype of individuals in either the homozygous or heterozygous states. It is known that few dominant diseases and defects are completely dominant and it is becoming increasingly clear that many recessive traits may not be, in fact, completely recessive. This partial dominance can reflect on the genetic fitness of heterozygotes. The effect that even a minor change in heterozygotic fitness may have on the estimated mutation rate required to maintain the frequency of a defect at a constant level can be illustrated with a trait such as phenylketonuria. This trait occurs with a frequency of 25×10^{-6} in the population of England and the genetic fitness of the homozygote is nearly zero.[54] Under the assumption that the heterozygote has the same fitness as the homozygous normal, a mutation rate of 25×10^{-6} per locus per generation is required to maintain the gene at its present level in the population. If, however, the fitness of the heterozygote is 1 per cent, 2 per cent, or 5 per cent lower, as has been suggested, then the corresponding mutation rates would be three, five and eleven times the previously mentioned rates.[50, 51, 53] In contrast, if a slight heterozygous advantage is assumed, a very different estimate is obtained; with only a 0.1 per cent or 0.2 per cent advantage in fitness, the estimated mutation rate would be only 4/5 or 3/5 that of the original rate.[39] With an advantage of 0.5 per cent, mutation would not be required to compensate for the loss of genes due to deleterious homozygotes; in fact, the gene frequency would increase to a higher level.

46. Genetic fitness of heterozygotes cannot be treated as an invariable property of the two alleles under consideration. Rather, fitness can be influenced not only by the remainder of the genotype, as in the intricate situation involved in populations carrying genes for both thalassaemia and glucose-6-phosphate dehydrogenase deficiency,[55] but also by the external environment. For such reasons an individual estimate of fitness may be valid for the immediate future but less valid when applied over several generations.

47. One of the advances in human population genetics has been the discovery of several balanced polymorphic systems (category IV). The term polymorphism, as used here, describes "the occurrence in the same habitat of two or more discontinuous forms of a species maintained by a balance of selective forces, as opposed to maintenance by recurrent mutation".[56] Such systems arise when a gene confers reduced genetic fitness in some circumstances and increased fitness in others. The increase in fitness may be a consequence of a shift in the macro- or micro-environment or it may be a consequence of heterozygosity as contrasted with homozygosity. The role of mutation in supporting the frequency of polymorphic traits is minor. To predict the over-all consequences of an increased mutation rate it is therefore essential to know the extent to which balanced polymorphic systems contribute to the burden of detrimental hereditary traits. It is also essential to know what fraction of new mutants are equivalent to alleles that are already part of a polymorphic system.

48. The existence of balanced polymorphism is suspected when excessively high mutation rates must be postulated to maintain the frequency of a detrimental trait under the assumption that the heterozygote is neutral. An example of heterozygous advantage in genetic fitness is provided by sickle-cell anaemia, a trait which is fatal in the homozygote. The distribution of the sickle-cell trait has been investigated over large areas of the world and is very uneven; the trait is completely absent in a number of populations, yet the homozygote

has a frequency of 3 to 4 per cent in some populations of Asia and Africa.[57] It has now been demonstrated that heterozygous individuals have an increased resistance to malignant tertian malaria and a consequent selective advantage in a malarial environment.[57, 58] It is likely that other serious haemoglobinopathies, including thalassaemia, are maintained by a similar mechanism. Current world-wide measures to eradicate malaria will have the effect of reducing the genetic fitness of heterozygotes. As a consequence, a reduction in gene frequency is to be expected. However, the rate of reduction will be slow and the trait will continue to be carried for many generations. It has been suggested that the inexplicably high frequencies of some detrimental traits are a consequence of relatively greater genetic fitness of heterozygous carriers at some time or place in the past.[59]

49. The frequency with which balanced polymorphic systems occur in human populations has yet to be determined. Relevant to this problem are two contrasting but not mutually exclusive hypotheses that have been proposed for the construction of extreme models of gene behaviour. One has been termed the classical, the other the balance hypothesis.[59] Under the classical hypothesis, it is assumed that genetic variability is maintained by recurrent mutation. Furthermore, it is assumed that almost all mutations are unconditionally deleterious and subject to selective elimination; heterozygous advantage is restricted to a small number of loci although it may contribute greatly to existing genetic variability. The balance hypothesis, on the other hand, assumes that genetic variability is to a large extent maintained by heterozygous advantage; mutation may not be unconditionally deleterious and a certain level of heterozygosity is essential to high fitness.

50. Using the concepts of lethal and detrimental equivalents, it is possible to deduce the relative importance of these two models. It has been calculated that an inbreeding depression of such a high degree as has been detected experimentally cannot be expected from systems of balanced polymorphism; this has led to the conclusion that most hereditary defects revealed by inbreeding are maintained by recurrent mutation.[60] A similar conclusion has also been reached from different evidence; an analysis of the frequencies and modes of inheritance of deafmutism, limb-girdle muscular dystrophy and low grade mental defects has suggested that the mean genetic fitness of a population would be impossibly low if the prevalence of these and other traits were not maintained by mutation.[51] On the other hand, in a recent study of two Japanese populations, the detected inbreeding depression was so slight as to indicate that the role of balanced polymorphic systems in maintaining the prevalence of hereditary effects is greater in those populations than in others previously studied.[61]

51. Investigations with irradiated experimental organisms have also produced conflicting evidence,[62–67] a fact which may well reflect the importance of strain differences and environment in the phenotypic expression of genotypes. It is also possible that a variation in frequency of gross chromosomal aberrations with different doses of radiation contributes to differences between results.

52. In the absence of complete information about the role of balanced polymorphic systems it is usually assumed that most of the genetic damage within populations is mutation-maintained; this avoids the risk of underestimating radiation damage. Even if this assumption is incorrect, it is possible that most new mutant alleles at loci involved in polymorphic systems are unconditionally harmful in contrast to those alleles which support the polymorphic systems in nature. In these circumstances it is important to know the average reduction in fitness of the heterozygote, since this value determines the number of generations over which a temporary increase in mutation rate would be felt by a population. It also determines to some extent the magnitude of the total damage. There is no general information about this value in man. In *Drosophila*, extensive studies have indicated that the average reduction in fitness of heterozygous lethals and semi-lethals is about 2 per cent.[50, 68] It would probably be larger in poor environmental conditions.[69, 70]

Natural mutation rates at individual loci in man

53. The frequency of mutation at a locus can only be studied when the mutation determines a specific detectable trait. Mutation is always an uncommon event; a freshly-arisen specific mutation seldom occurs with a frequency of more than one in fifty thousand gametes. It follows that very large populations must be studied to obtain a reliable estimate of this rate.

54. In many respects man is a very suitable organism for the observation of mutation rates because large free-living populations can be defined and close relatives are easily identified. Furthermore, the high efficiency of medical diagnostic procedures renders relatively easy the identification of many traits in man that might be missed in experimental animals. For these reasons, more estimates of natural mutation rates are available for man than for most species other than micro-organisms. There are, however, difficulties in relating traits to specific mutant alleles in man. These difficulties do not arise as frequently in animals, because planned breeding and genetic analysis can be employed.

55. Some of these problems are specific to dominant, some to sex-linked, some to recessive gene mutations, and some are common to all three. Those common to all three derive from the following circumstances:

(*a*) Certain mutant gene traits are mimicked by phenocopies. These are identical or nearly identical traits determined not by the genotype but by abnormal development in the embryo of foetus *in utero*. However, careful clinical study often serves to distinguish such phenocopies, as for example in the case of certain cataracts, and in cases of congenital deafness;

(*b*) Certain traits which are difficult if not impossible to distinguish clinically, are sometimes determined by mutations on different chromosomes. For example, ichthyosis vulgaris is determined by an autosomal dominant gene and also by a recessive gene on the X-chromosome;

(*c*) Some clinically identical traits seem to be inherited as if they were autosomal dominant at some times and recessive at other times. Examples are achondroplasia and a number of degenerations of the choroid in the eye. This variation may be a consequence of mutations to different alleles at the same locus, of mutations at different loci on the same chromosome, or of mutations at loci on different autosomes;

(*d*) Some traits, though apparently inherited in the same manner, show differences between families which suggest that the causal mutations are different in kind. Although different loci may be involved in these cases, it is conventional to express mutation rate in terms of a

single locus. Such difficulties lead to over-estimates of mutation rates.

56. Precision in the estimation of the mutation rates of genes determining harmful traits in man depends upon the completeness of ascertainment of the character in a large defined population. High precision can only be achieved where the medical and social services for the population are well organized. Even so, complete ascertainment is virtually impossible and can never be assumed as certain. Incompleteness of ascertainment tends to result in under-estimation of mutation frequency.

57. In generalizations of the mutation rates per locus in man one further factor must be considered. If the mutation rate of a gene is very low the trait may arise too infrequently to be recognized as of genetic origin, or even if so recognized, it may not attract study because of the great difficulty of collecting a sufficient number of cases. In consequence, only those traits occurring with a sufficiently high frequency to give a reliable estimate of mutation rate are selected for investigation.

Autosomal dominant traits

58. A direct method is applicable for estimating rates of mutation to dominant traits. This method attempts to identify all cases of a certain trait in the offspring of parents not affected by the trait. If it is assumed that the gene is fully manifested, then each case must represent a mutation in the germ cells of one parent. As each birth results from two gametes, the mutation rate per gamete is one-half the frequency per birth. This method can seldom be employed and can be fallacious if unrecognized phenocopies occur.

59. An indirect method can also be used. This method assumes that an equilibrium has been reached in which the frequency of the trait is more or less constant. At this equilibrium, the number of fresh mutations arising in the population in each generation is approximately balanced by the number of mutations eliminated by selection. The equilibrium equation is $\mu = \frac{1}{2}(1\text{-}f)\,x$, where μ is the mutation rate per gamete per generation, x is the trait frequency in the population, and f is the relative fertility of the individuals bearing the trait. In such an equilibrium the value of f is of great importance. It is, however, difficult to estimate with accuracy. If f is zero then the condition is not recognized as genetic in origin. On the other hand, relative fertility of the affected individuals can be estimated only if it is as low as 85 per cent. As a result, estimates of mutation rate tend to be made for traits with a value of f between 0.0 and 0.8. A number of estimates are listed in table IV.

Sex-linked traits

60. Estimates of the recessive mutation rate at loci on the X-chromosome must be made by an indirect method. The equilibrium equation is $\mu = \frac{1}{3}(1\text{-}f)\,x$. In this case, it is assumed that the fertility of heterozygous females is the same as that of homozygous normal females in the population.

61. The most reliable estimates of mutation rates for a sex-linked recessive gene are those for Duchenne-type muscular dystrophy. However, there is some evidence that even this trait is clinically heterogeneous. In consequence, current estimates may represent the sum of mutations at more than one locus.

62. No reliable estimates of the mutation rate for haemophilia A have been made since haemophilia B (Christmas disease) was identified as a separate entity. The proportion of haemophilia types A and B varies in different countries. Possibly the older estimates of the mutation rate for haemophilia, if reduced by about one-tenth, serve as reasonable estimates for the locus determining haemophilia A. However, the trait can be so mild that ascertainment is almost certainly incomplete. This tends to produce under-estimates of the true mutation rate. Some estimates are presented in table V.

Autosomal recessive traits

63. Only indirect estimates of autosomal recessive mutation rates can be made and these are of very uncertain reliability. The equilibrium equation is $\mu = (1\text{-}f)\,x$. In man, the value of f is zero or extremely low for the great majority of recessive homozygotes. Exceptions are albinism and some forms of recessive deaf-mutism. Even with these conditions, however, the value of f is not over 0.5. If f has a value of zero then the estimate of mutation rate corresponds to the trait frequency. Here, however, there are many difficulties. It is assumed, as for sex-linked genes, that the fertility of the heterozygote is the same as the average in the population. However, a high proportion of all mutant genes in the population are in heterozygotes. For this reason any selection in favour of or against the heterozygote has a much greater effect on the prevalence of a trait at equilibrium than has the loss due to homozygosis. Furthermore, a shift in the environment can upset the population equilibrium by affecting the genetic fitness of the different genotypes. When this happens, many generations may pass before equilibrium is restored. Again, changes in marriage customs can affect the frequency of different genotypes. A decline in the amount of inbreeding has been noted in Europe during the last century or two; such a circumstance is likely to lead to estimates that are too low.[71] Some estimates of autosomal recessive mutation rates are presented in table VI.

64. In spite of all the reservations, there is a large group of grossly harmful mutations, autosomal dominant, recessive, and sex-linked recessive, whose estimated mutation rates cluster around 10×10^{-6} per generation. However, this clustering may be conditioned largely by the selection of traits for study.

Natural mutation rates at individual loci in experimental animals

65. With experimental animals it is possible to estimate natural mutation rates with methods that involve test matings. In the mouse, the rates of natural visible mutation have been estimated at seven loci. These loci are identified by recessive visible alleles namely: *a* (non-agouti), *b* (brown), *c* (chinchilla), *d* (dilution), *p* (pink-eye), *s* (piebald spotting), and *se* (short ear). The loci are distributed on five of the twenty chromosomes. There is linkage between *d* and *se* and between *c* and *p*. These alleles were selected for various radiation studies and should not be considered a random sample. The over-all mean mutation rate is estimated to be about 7.3×10^{-6} per locus per gamete (table X).

66. Estimated values of natural mutation rates at specific loci in *Drosophila* were discussed in the previous report and in a recent review.[72]

Naturally-occurring chromosome aberrations in man

67. Man has a relatively stable karyotype; the diploid chromosome number is forty-six.[73,74] Nevertheless,

with the development of improved techniques in mammalian cytology, examples of aberrations already well known in plants and insects are being accumulated. The detection of chromosome anomalies in man is aided by the relative ease with which associated abnormal phenotypes can be recognized. On the other hand, cytogenetic techniques are not yet far enough advanced to permit the detection of less obvious aberrations. Those which are not now detectable include reciprocal translocations of nearly equal size, inversions and either small duplications or small deletions having a length less than 10 per cent that of the affected chromosome. Other aberrations may be undetected because they are lethal at a very early stage in embryo development.[33]

68. The most common of detected aberrations are trisomies of the smaller autosomes and either monosomy or polysomy of the sex chromosomes. It seems likely that monosomy and trisomy of autosomes other than that producing Down's syndrome, are rare or usually lethal.[75] Triploidy has been detected,[37,38,76] and translocations and other aberrations are frequently reported (tables I and II).

69. Whole-chromosome anomalies may be a consequence of either chromosome loss or "non-disjunction". Monosomy can result from either process, but polysomy is attributable only to non-disjunction. It seems likely that the majority of whole-chromosome aberrations occur in meiotic divisions of a parent or in early cleavage divisions of the zygote. Little is yet known about the relative importance of non-disjunction and chromosome loss during meiosis. However, there is considerable evidence that one or both of these processes frequently occurs in mitotic divisions following fertilization. This evidence is supplied by the existence of mosaics[76-82] and of exceptional twins.[83] The occurrence of whole-chromosome anomalies during mitosis may be more frequent than present data suggest; mosaicism is not likely to be detected when it does not originate in early cleavage divisions. Moreover, selection pressures may eliminate one of the stem lines. The possibility that the processes leading to mosaicism tend to recur in a cell line is suggested by the fact that two or three types of cells are sometimes present in the growth from a single biopsy of bone marrow or even of skin.[84]

70. For one reason or another, most individuals with detrimental traits caused by gross chromosome aberrations fail to produce progeny. Exceptions so far recognized are those phenotypically normal persons with balanced translocations. The general incidence of such translocations is, however, low. As a consequence, the incidence of gross chromosome aberrations in a population tends to correspond with their mutation rate. For estimates of frequency, see paragraphs 28 and 29 above.

Naturally-occurring chromosome aberrations in experimental organisms

71. In the mouse, non-disjunction of sex chromosomes has been shown to occur in meiotic divisions. However, non-disjunction in the first meiotic division is rare in the male and possibly non-existent in the female. In contrast to man, XO karyotypes occur much more frequently than do XXY karyotypes.[85] There is evidence that XO individuals most often result from the loss of the paternal sex chromosome some time between sperm entry into the vitellus and the first cleavage. This evidence is based on the observation that when $X^{M}O$ and $X^{M}X^{P}Y$ mice are scored simultaneously (the superscripts M and P designate maternal and paternal derivations of the X chromosome) the relative frequencies are 0.7 per cent and 0.02 per cent, and on the fact that primary XO's are not randomly distributed.[86,87] Deficiencies and monosomies that would have been detected in extensive experiments on certain genetically marked autosomes in the mouse have so far not been found.[85,88] Spontaneous translocation has been observed in the rat.[89]

72. In *Drosophila*, maternal non-disjunction and meiotic loss of whole chromosomes from dividing cells both operate to produce abnormal eggs. This information has been deduced from the fact that the frequency of eggs with two X chromosomes is less than that of eggs with no X chromosomes. The frequency of abnormal eggs that arise as a result of non-disjunction has been estimated at 0.08 per cent and the frequency of those arising as a result of meiotic loss of the X chromosome at about 0.12 per cent. This produces an XO:XXY ratio of about 4:1.[90] There is also a considerable rate of non-disjunction of sex chromosomes in males; the ratio of scored $X^{M}O$ to $X^{M}X^{P}Y^{P}$ individuals is 2.8:1.[91] Monosomy and trisomy of the small fourth chromosome occurs spontaneously but non-disjunction or loss of the second and third chromosomes has not been detected by genetic or cytological methods of analysis. It is probable that these events occur but that monosomy or trisomy of long autosomes leads to elimination in embryonic stages.[90] An early study showed that aging of females by itself has no effect on the natural rate of non-disjunction, although the frequency of non-disjunction following irradiation of virgin females increases through the first ten days.[92] More recent studies have confirmed that maternal age *per se* has no appreciable effect on the frequency of spontaneous non-disjunction.[93] In view of the recognized increase in frequency of Down's syndrome with advancing maternal age[39] and similar observations on the two other autosomal trisomies,[94] this observation shows the difficulty of comparing natural chromosomal mutation rates of flies and man.

Factors affecting the frequency of natural mutation

73. It has long been observed that the frequencies with which natural mutations are found may vary in different circumstances. This variation provides an opportunity to identify and study individual causal or influencing factors. In man, some of these factors can be detected because a relatively long childhood and reproductive span permit the factors to work over a prolonged period of time.

74. With some hereditary diseases and defects it has been observed that mutant frequency among offspring increases with parental age. Such conditions are epiloia, neurofibromatosis and retinoblastoma. This effect of time suggests a simple dependency of mutation frequency on the accumulated dose of the causal factor. Here, by implication, some cumulative influence is involved.[39] In other conditions, such as Down's syndrome, an increase in mutant frequency accompanies rising maternal age but not rising paternal age. Again, a contrasting situation holds with achondroplasia, where the increase in the occurrence of the anomaly is associated only with rising paternal age. Each of these latter examples suggests the presence of influencing factors which are not common to both sexes. Thus, when paternal but not maternal age affects mutant frequency, a dependence of mutation on frequency of cell division in gametogenesis may be involved.

75. A number of factors are known to affect natural mutation frequency in experimental organisms. One of the most studied of these is sex; the spontaneous mutation rate to sex-linked recessive lethals is apparently lower in females than in males of *Drosophila*.[95, 96] An effect of sex on mutation frequency in the silkworm has been noted. Here locus specificity is a factor; at one locus the frequency of mutation is higher in the male, at another it is lower.[97] In the mouse, the data on seven loci under detailed study provide some indication that mutation frequency is lower in females than in males (table X). Females have yielded one mutant among 98,828 offspring. In contrast, males have yielded thirty-two mutants among 544,897 young. However, in man, a study of mutation to the sex-linked trait, Duchenne-type muscular dystrophy, has provided no evidence of a sex difference.[98]

76. Genetic constitution can also affect the frequency with which naturally-occurring mutations are found. A number of specific genes in *Drosophila* have long been known to modify the natural mutation rate by a factor of ten or more over at least a segment of the entire genome.[99] A difference between two geographical races in the frequency with which sex-linked lethals are produced has been demonstrated.[100] In addition, there is no doubt that the mutation rate varies with different loci. The mutability of a gene is also affected by its position in the chromosome.[327, 328]

77. In man, tendencies towards diverse chromosome aberrations in the same individual and towards familial occurrence of diverse chromosome aberrations have been noted. For example, cases of Down's syndrome (trisomy 21) and Klinefelter's syndrome (XXY) in the same individual have been described.[101–105] Associations of XXY with a translocation between chromosomes 14 and 15[106] and of XXX with trisomy 18[107] have been reported. Trisomy for the 13-15 group and an XO constitution has been noted in two sisters.[108] Trisomy 21 has been reported in the progeny of a female carrying an autosomal translocation.[109] Such clustering of gross chromosome aberrations has led to the suggestion that the cells of some individuals may be labile in this respect,[21] or that the occurrence of a first aberration predisposes the chromosomes of a cell towards a second.[84]

78. There is evidence that natural mutations occur at different rates in cells in different stages of gametogenesis. Relevant investigations in *Drosophila* have recently been reviewed.[72] Some loci are more mutable in the germ line than in the soma, while for others the reverse applies.[110]

79. No doubt other as yet unrecognized influencing factors exist. For instance, a significant increase in the frequency of sex-linked recessive lethal mutations has been reported in each of two strains of *Drosophila* as a consequence of space flight.[111] Similar circumstances are also reported to result in an increased frequency of chromosome anomalies (non-disjunction) in germ cells of *Drosophila*.[112] The intensity of cosmic radiation during flight was insufficient to account for these phenomena, and an influence of some other factors must be suspected.

80. It has been hypothesized that the genetic response of a species to the factors influencing mutation rate is itself modified through selection. This concept presupposes the existence of an optimum mutation rate for survival of a species;[113–115] if the mutation rate is too high the species may be crushed under a heavy mutational load and if it is too low the species may not be able to adapt to environmental changes. This concept has been formulated as a mathematical model by introducing what is called the principle of minimum genetic load.[116] A species must adapt itself to progressive changes in the environment and the ability to do so comes from genetic variation, the ultimate source of which is mutation. The importance of new mutation for the future adaptation of the human species is problematical.

IV. The induction of mutation by radiation

81. For obvious reasons, most of our information on the induction of mutation by radiation comes from experimental organisms. However, there is ample evidence that the mutation process is fundamentally similar in all forms of life and there is no reason to suppose that man is exceptional in this respect.

Factors affecting the frequency of radiation-induced mutation

82. The genetic hazards to populations cannot be determined in the absence of a knowledge of the relationship between frequency of mutation and dose of radiation. It is now well recognized that many factors can influence this relationship. The foundation for our knowledge in this field was laid through investigations with *Drosophila*. More recently, studies with mammals have yielded significant information.

Linearity of the dose-effect relationship and absence of a threshold

83. The assumption of a linear dose-effect relationship down to zero dose, and thus of an absence of threshold for mutagenic effects has been considerably strengthened by the results of investigations with *Drosophila*. Studies of mutations at more than fifty loci which affect minute bristles have indicated that acute doses as low as 5 r have a significant mutagenic effect and that the dose-effect curve is linear from lower to higher doses.[117] A linear relationship in the low dose range down to 5 r has also been found for radiation-induced recessive lethals.[118] However, in germ cell stages such as spermatogonia and oöcytes, where the repair of some of the pre-mutational damage is possible, the effect at low doses may turn out to be somewhat less than expected on a linear basis from the mutation frequency at high doses.[119] A departure from linearity has been found for mutations induced with high doses of acute radiation in mouse spermatogonia. A dose of 1,000 r produced significantly fewer mutations than expected on the basis of linearity with results at lower doses.[120] The view that this effect might be due to cell selection gains some support from the finding that fractionation of the dose gave a higher mutation rate which was consistent with linearity.[121] In *E. coli*, evidence of a linear relationship down to doses as low as 8.5 r has been presented.[122]

The dose-rate effect

84. The rate of delivery of ionizing radiation has now been demonstrated to affect the frequency of mutations induced by a given dose. This has been shown for both mice and insects.

85. In mice, the effect of differences in dose-rate on the frequencies of mutations induced at seven specific loci has been studied.[119, 121, 123–127] It has been observed that (table X):

(*a*) When spermatogonia are exposed to doses of 300-600 r at a rate of 8.5×10^{-3} r/min (90 r/week), the frequency of induced mutations is less by a factor of about four than is the frequency following the same dose delivered at a rate of 90 r/min;

(*b*) There is an even more pronounced dose-rate effect in parallel studies of irradiated oöcytes;

(*c*) The dose-rate effect for spermatogonia is not demonstrably greater when the lower rate of delivery is reduced from 8.5×10^{-3} r/min to 1×10^{-3} r/min;

(*d*) Most of the dose-rate effect in spermatogonia is displayed within the range of 24 r/min and 0.8 r/min, whereas in females the range of effectiveness appears to be greater;

(*e*) As in *Drosophila,* no dose-rate effect is evident in spermatozoa.

86. In *Drosophila* a significant dose-rate effect on lethal mutations in chromosome II has been reported with irradiation of oögonia[128] and spermatogonia.[129] In spermatogonia, a lowering of the intensity from 0.10 r/min to 0.01 r/min at a total dose of 200 r results in a significant reduction in mutation frequency. However, a dose-rate effect for contrasting doses of 2 r/min and 2000 r/min at a total dose of 3,000 r gamma radiation has not been observed. In the silkworm there have been found two different types of dose-rate dependence of mutations affecting egg colour and induced during early larval development.[97] In one type the mutagenic effectiveness of chronic irradiation at 0.15 r/min is lower than that of acute irradiation at 320 r/min, and in the other the mutagenic effectiveness is higher with chronic irradiation than with acute irradiation. The former is observed only in the very young larval stage when primordial cells are prevalent in the gonads, whereas the latter is found when germ cells are irradiated in later stages of development. This latter result, which is opposite to the expected effect of dose rate, may not be a dose-rate effect on the mutation process, for it is suspected that cell selection is reducing the yield of mutants at the high dose rate. In any case, it resembles an effect observed at a high dose rate in the mouse, where a dose of 1,000 r gave fewer mutations than a dose of 600 r.[120] Cell selection was invoked to account for this odd result also. In the chalcid wasp *Dahlbominus* no significant dose-rate effect on mutations affecting eye colour has been found when female larvae receive a total dose of 1,000 r at 1,000 r/min and at 0.17 r/min.[130]

87. Although some of the factors that affect the dose-rate phenomenon have been uncovered, investigation has not yet proceeded far enough to elucidate the mechanism involved. Nevertheless, there is strong evidence that it is the mutation process itself which is affected. Thus, cell selection, which may at times play a role, can, in some specific instances, be eliminated as the causal factor. For example, the effect is observed in those mouse oöcyte follicle stages in which cell-killing by the doses of radiation used is negligible.[119, 121] Furthermore, the amount of spermatogonial killing induced by radiation is approximately constant over a range of dose rates in which the dose-rate effect on mutation is evident.[125, 131, 132] If the mechanism for the dose-rate effect does indeed involve the mutation process itself, then it seems likely that some kind of "repair" of pre-mutational damage must be taking place at the lower dose rates.[119] It has been suggested[133] that many of the mutations observed at the seven loci under study may be a consequence of multi-hit chromosomal aberrations which would be expected to occur with reduced frequency at low dose rates.[134, 135] However, there are several lines of evidence, including the shape of the dose-effect curve, that suggest that, although multi-hit aberrations are easily induced by radiation in mouse spermatozoa, the specific-locus mutations induced in mouse spermatogonia are almost never associated with such multi-hit effects. Most mutations in *Drosophila* spermatogonia also appear not to be a result of multi-hit aberrations. This evidence supports the view that the specific-locus mutations induced in spermatogonia of the mouse are point mutations or extremely small deficiencies,[88, 136, 137] and that it is repair of the pre-mutational damage associated with this type of mutation that is involved in the dose-rate effect.[127] Current investigations in other organisms confirm the existence of processes of natural repair or elimination of pre-mutational (primary) damage at low dose rates. The subject of repair will be discussed in detail in the next section.

"Repair" of pre-mutational damage

88. Studies of a variety of organisms have indicated that the process of induction of mutation is not irreversibly fixed at the time of irradiation, but that there is a limited interval between the absorption of radiation energy and the completion of the mutation process during which, depending on the physiological state of the cells, modification of pre-mutational damage is possible. Repair of broken chromosomes by restitutional unions of the breakage ends has been known for a long time and has been studied in some detail. The subject has recently been reviewed.[138] Though there are some reasons to think that restitution and recovery from pre-mutational damage are separate though analogous phenomena, this distinction has not been established by experimental means.

89. In *Paramecium,* post-irradiation treatments are known to alter the extent of recessive damage from a given radiation exposure, provided they are applied before a certain critical stage has been reached in the subsequent division cycle. Moreover, in cells not receiving post-irradiation treatment, the effect of irradiation is increased the later it is administered prior to that critical stage.[139–141] It was shown earlier that a large fraction of the mutational effect of exposure of bacterial cells to ionizing radiation can be reduced by post-irradiation treatment with chemical reagents in certain circumstances.[142] A similar pattern of results has been observed when investigators have worked with UV instead of ionizing radiation.[143–150] It now appears that all these results are consistent with the hypothesis that the terminal event for fixation of some major part of the potential mutation corresponds to the first post-irradiation replication of DNA.[144, 147, 148, 151]

90. Recent data obtained with *Drosophila* show that modification of pre-mutational damage is possible in spermatids, meiotic stages, and late spermatogonia.[152–157] In cells with peak sensitivity, spermatids and spermatocytes, post-treatment with cyanide following exposure to X-rays at a high dose rate may lead to either an increase or a decrease in radiation-induced mutation frequency. Inhibition of oxidative respiration by means of post-treatment with nitrogen causes an increase in mutation frequency in spermatids, meiotic stages, and spermatogonia. On the other hand, fractionation of a dose given at an intensity of 55 r/sec results in a decrease of the mutation frequency in exactly those stages where cyanide is effective. Inhibition of protein synthesis by means of pre-treatment with either chloramphenicol or ribonuclease leads to a significant reduction in the frequency of mutation in spermatids, and in the case of chloramphenicol

col, in the earlier stages as well. Since a ring-shaped X chromosome has been used in such experiments, the reported changes refer to lethal gene mutations and possibly to small deletions. These results have been explained by assuming that, in analogy to the findings in *Paramecium*, two contrasting processes are involved, one associated with the rate of disappearance of pre-mutational damage, the other with the time or rate required for its fixation.[141] Thus, the enhancement of mutation frequency after post-treatment with nitrogen is thought to result from an inhibition of the metabolic repair process. On the other hand, the reduced mutation frequency observed after pre-treatment with both chloramphenicol and ribonuclease suggests that inhibition of protein synthesis prolongs the time-span available for repair of pre-mutational damage. Although it is not known at present what process is involved in fixation of pre-mutational damage in spermatids, the reported findings suggest a correspondence of repair mechanisms in such widely different organisms as *Drosophila* and *Paramecium*.

91. The interaction of oxygen and X-rays in the production of genetic damage, as detected in the progeny of irradiated males of *Drosophila*, has been studied extensively.[158-165] Dose-fractionation experiments, in which part of the dose is delivered in nitrogen and part in air or oxygen, indicate that X-irradiation destroys a protective oxygen-sensitive system. It has been variously postulated that this system acts to reduce the initial amount of damage and that it acts to increase the amount of repair. The system affects both recessive lethals and chromosome aberrations.

92. Table VII summarizes some of the phenomena and material studied both before and since the drafting of the Committee's 1958 report. The similarity of the effects observed is striking, considering the wide range of organisms observed. From these data it can be concluded that a proportion of radiation-induced mutational or pre-mutational changes are subject to natural repair for a finite but relatively brief period after they occur, and that the natural repair process itself is subject to interference by radiation and by metabolic inhibitors. It is important to determine whether this effect is applicable to man, and if so, the single dose-levels or continuous dose-rates at which the natural repair processes are effective, and the critical period of time and the circumstances under which they act. It is emphasized that probably not all pre-mutational damage is reparable and that a linear dose-mutation relationship independent of dose-rate is to be expected at low doses which do not appreciably affect the repair process.

Locus specificity

93. Both the natural and induced rates of mutation have long been known to vary markedly at different loci in various organisms. This observation has now been firmly established in the mouse.[88,136] Among the seven loci under study, the lowest and highest rates for mutations induced in spermatogonia differ by a factor of thirty. This information is based on 174 mutations induced with doses of 300-1,000 r and high-dose rates. Of these, seventy-one mutations were induced at locus *s*, ninety-nine were induced among the four loci, *b*, *c*, *d* and *p*, and only four were induced at the two loci, *a* and *se*. Ninety-two of the mutations were analysed for viability of the homozygotes. Seventy-one (77 per cent) were lethal prior to maturity and twenty-one were viable. There was some variability among the seven loci in this respect also. All the twelve mutations at the locus *d* and all thirty-eight at the locus *s* were lethal. In contrast, of those at loci *b*, *c* and *p*, twenty out of thirty-eight were viable.

Sex and stage of gametogenesis

94. The frequency of radiation-induced mutations can be influenced both by sex and by stage of gametogenesis. The cell stages of greatest importance in determining radiation hazards to man are the oöcyte and spermatogonial, and the genetic effect of ionizing radiation on these stages of the germ cells of mammals has received considerable attention.[166-168] The most extensive investigations have been concerned with the mouse.

95. Male mice irradiated with doses as high as 1,000 r maintain their fertility briefly, and then undergo a period of sterility. Near-normal fertility is then resumed. The temporary sterility is a consequence of the fact that certain spermatogonial stages are extremely sensitive to irradiation.[169,170] Cells in these stages have an LD_{50} of 20 to 40 r. However, a few of the early type A spermatogonial cells survive high radiation doses; these cells repopulate the germinal epithelium and are responsible for the resumption of fertility of the irradiated animal. The existence of the sterile period aids in distinguishing between genetic effects induced in spermatogonial and post-spermatogonial stages.

96. Irradiation of female mice with doses as low as 50 r can result in permanent sterility after an initial period of post-irradiation fertility. A dose-rate effect on this induced sterility has been detected.[171] The permanency of induced sterility is attributable to the fact that the majority of oöcytes are in early stages of follicular development, and are extremely sensitive to radiation. Since there is no new formation of oöcytes in the adult mouse ovary, sterility sets in when the supply of radioresistant oöcytes in older follicles is exhausted.

97. It has been possible to distinguish two kinds of radiation-induced cell death in different types of germ cells in mouse gonads. Most spermatogonia die immediately after irradiation, while spermatocytes show no response until they reach the meiotic divisions. In both cell types, chromosome damage in the classical sense of aneuploidy can, at most, account for only a small part of the cell loss.[172] A similar situation has been found in the rat-kangaroo.[173] These studies suggest that chromosomal damage is a minor cause of cell death in spermatogonia irradiated with moderate doses. The subject of the radiosensitivity of the gonads is treated more fully in annex D.

98. Peak sensitivity to the induction of dominant lethals and recessive visibles in the mouse has been found in spermatids and spermatocytes[174-178] for the male, and metaphase primary oöcytes for the female.[179] With an acute dose of 300 r of X-rays, the mean frequency for mutations at specific loci following irradiation of post-spermatogonial stages is twice that induced in spermatogonia.[178] It has also been shown that exposure of adult females to an acute dose of 200 r of X-rays results in more mutations than a similar exposure of 17½ day old foetuses. In males the induced-mutation frequency has also been observed to be higher in adults than in foetuses, but the difference is not statistically significant.[175]

99. The ratios of induced mutation frequencies at the seven loci under study in mice differs with irradiation of spermatogonial and post-spermatogonial stages.[88,136] Deficiencies large enough to involve both the *d* and *se* loci (with cross-over value of 0.16 per cent) are common among the mutations induced in post-spermatogonial

cells, but irradiation of spermatogonia yields such deletions only with extremely low frequency, if at all. Such deficiencies are, however, induced in oöcytes. It thus seems that mutations contributed to progeny as a result of spermatogonial irradiation differ systematically from those due to post-spermatogonial and oöcyte irradiation.

100. In *Drosophila*, the influence of sex and stage of gametogenesis in radiation-induced mutations is well documented.[72,180,181,329] The lowest and highest frequencies of induced mutation for a given radiation dose vary by a factor of fifteen. Spermatogonia and oögonia are the least sensitive; oöcytes are somewhat more sensitive than oögonia. In contrast, spermatocytes and spermatids are several times more sensitive than spermatogonia. Spermatozoa vary in sensitivity depending on their stage of maturity. The difference in radio-sensitivity between *Drosophila* sperm and spermatids is attributable both to differences in O_2-tension[164,182-186] and to changes associated with protein synthesis.[153-155]

Species specificity

101. Species differ widely in their genetic sensitivity to radiation. The induced rate of mutation at the seven loci studied in mice is about fifteen times that for a comparable group of loci in *Drosophila*.[187] Comparisons of dominant lethals in mammals and *Drosophila*[188] and of chromosome mutation in plants[189] have likewise indicated the existence of species specificity. Radio-sensitivity in different species of rodents has been determined in terms of the number of chromosome rearrangements in the nuclei of spermatogonia exposed to a low acute dose of 4 r.[190,191] Such measurements are difficult to make because the frequency of chromosome breakage varies greatly in different cell stages, a fact which can lead to the confounding of species and cell-stage differences. Nevertheless, the percentage of cells with rearrangements has been reported to vary from 2.6 in guinea pigs to 0.6 in rats, 0.2 in mice, and 0.1 in rabbits. A comparison of the cytogenetic radio-sensitivity of germ cells of the monkey and mouse at doses from 50 to 400 r has suggested that sensitivity of monkeys is twice that of mice.[168,192]

Induced chromosome aberrations

102. Because some serious hereditary defects in man have recently been found to be associated with chromosome aberrations, the role of ionizing radiation in producing these anomalies will be considered in detail. The fact that radiation can cause extensive chromosome changes has been known for many years; investigations in plants[193] and in animals[90] have been reviewed in detail. Actually, it is not always possible to make a sharp distinction between gene mutation and chromosome aberration. Minute chromosome aberrations often cannot be distinguished from gene mutations. Furthermore, rearrangements of chromosome segments sometimes involve "position effects" in which the phenotypic expression of genes is altered.[85]

Observations on experimental organisms

103. One of the most suitable organisms for studies of induced chromosomal changes is *Drosophila;* in this organism small chromosome changes can be detected cytologically by examination of salivary gland chromosomes. Furthermore, detailed information on the linear sequence of specific loci is available. Although observations made with this organism cannot be used for direct extrapolation to man, they nevertheless serve as a useful guide to those effects which might be expected. They are briefly summarized here.

104. Most of the *Drosophila* information has been obtained through irradiation of spermatozoa. Aberrations are detected in either the first or subsequent generations following irradiation. Cytological as well as genetic techniques can be used for this purpose.

105. Viable aberrations resulting from chromosome breakage include duplications, deficiencies, and intra- or inter-chromosome rearrangements. The ability of individuals with deficiencies or duplications to survive this aneuploidy depends upon the length and genic content of the segments involved. Both duplications and deficiencies upset genic balance, and tend to lower viability and to be transmitted as recessive lethals. Viable intra- and inter-chromosome rearrangements include inversions and transpositions of segments within chromosomes, as well as translocations between chromosomes. These aberrations do not involve aneuploidy, and affected individuals are phenotypically normal if "position effect" is not involved. However, their progeny may be genetically normal, or again contain the balanced rearrangement, or be aneuploid.

106. At low doses, the frequency of individuals with aberrations caused by single breaks tends to increase linearly with dose. In some instances it has been noted that small intercalary deficiencies also increase linearly with dose. The frequency of individuals with aberrations caused by two breaks, such as inversions and translocations, increases more rapidly than the first power of the dose, approaching the second power of the dose at lower levels of treatment.

107. Whole-chromosome aneuploidy in *Drosophila* is also caused by ionizing radiation. The induction of primary non-disjunction was first reported in 1921.[194,195] Using irradiated females of *Drosophila virilis* it has been demonstrated that there is a linear increase in the occurrence of primaryXO males in the dose-range 400-1,200 r, and that the induced rate of occurrence of XO males is approximately 1×10^{-5}/r/egg.[196,197] The rate of occurrence of XO males is approximately fifteen times that of XXY females. The ratio of XO:XXY flies is thus greater than the naturally-occurring ratio which is about 4:1. More recently a similar investigation has been carried out with *Drosophila melanogaster*.[93] With exposure to doses of 600 r, 2,400 r, and 3,600 r, the frequency of non-disjunctional males increased at a rate of approximately $2.5 - 3.0 \times 10^{-5}$/r. Non-disjunctional males were more frequent than non-disjunctional females by about one order of magnitude.

108. In mice, gross chromosomal anomalies are rarely found as a consequence of irradiation of parental premeiotic germ cells. This rarity has sometimes been attributed to failure of transmission rather than to lack of occurrence. However, for at least two types of chromosomal aberrations, reciprocal translocations and deletions, this explanation does not seem to be correct. Translocations induced in post-meiotic stages can be transmitted through subsequent meioses to become heritable traits.[166] Thus, a more likely explanation for the rarity of these aberrations following pre-meiotic irradiation is either that the necessary chromosome breaks do not occur or that the broken parts do not exchange. The same situation exists for deletions. An exhaustive study of what appear to be deletions in the *d-se* region of linkage group II in the mouse has shown that these are produced as a consequence of post-spermatogonial and

oöcyte irradiation, but not of spermatogonial irradiation.[88] Transmission of the induced deletions ranges from poor to normal or near normal. Since transmission is possible, it is apparent that either lack of breakage or rejoining is responsible for the non-appearance of the deletions following spermatogonial irradiation.

109. Some types of chromosomal damage are, however, produced with high frequency by irradiation of spermatogonia. Many abnormal anaphases have been found in spermatogonial cells of monkeys two years after exposure.[198] More recently, cytological evidence of chromosome damage in irradiated spermatocytes has been noted at the first post-irradiation cell division in mice.[172] Those particular types of aberration probably cause cell death before maturation of the gametes. However, a recent report suggests that structural changes induced in pre-meiotic germ cells can occasionally be transmitted to progeny.[199]

110. Data on the induction of whole-chromosome changes in the mouse are at present largely restricted to sex-chromosome changes. Experimental work in this field has developed rapidly in recent years.[85] The availability of useful sex-linked marker genes and improvement in cytological techniques have contributed to this progress. The sex-determining mechanism of man has recently been shown to be much more similar to that of the mouse than it is to that of *Drosophila*.

111. In mice, irradiation of sperm increases the frequency with which paternal sex-chromosomes are lost: 1.3 per cent of progeny suffered such a loss after a dose of 600 r as compared with 0.1 per cent in the control.[200, 201] However, the bulk of spontaneously occurring XO individuals are believed to arise from events following sperm entry into the vitellus.[85, 202, 203] Irradiation of the zygote in the interval between sperm penetration and the first cleavage is particularly effective in inducing loss of a sex chromosome. Thus, 100 r yielded 5 per cent XO individuals as compared with 1 per cent for controls. Both maternal and paternal losses can be induced by radiation, whereas only paternal losses have occurred in the controls. No autosome loss has been detected in these experiments in which four and in some cases five autosomes carried genetic markers. This suggests that such losses, if they occur with an appreciable frequency, are lethal.

112. Extensive investigations of the *in vitro* cytogenetic effects of radiation on mammalian somatic cells have been undertaken. Although from the point of view of heredity the important chromosomes are those of the germ cells, these studies of the radio-sensitivity of somatic cells provide a direct method for determining the effect of radiation on chromosomes. It is to be expected that they will play an important role in the future. Measurements are usually based on the frequencies of aberrations detected at the first post-irradiation cell division because many types of aberration are lost in subsequent divisions. Commonly-used mammals include the Chinese hamster,[204–206] the mouse[207–209] and the monkey.[206]

113. Most of the previously known types of aberrations have been detected in these investigations. Breaks are of the chromatid or chromosome type depending upon whether the chromosomes are effectively double at the time of irradiation. Data on the frequency of breaks are not always in good agreement and it is apparent that one of the influencing factors is the method by which cells are cultured. Nevertheless reproducibility of results is good under standard conditions.

114. As is to be expected, terminal deletions increase linearly with the dose but total breakage occurs more frequently than the first power of the dose.[206] At low doses a measure based on linearity is of practical use but a more accurate measure of damage is the "coefficient of aberration production".[210] Values for chromatid aberrations *in vitro* cultures of epithelioid-type cells of monkeys and Chinese hamsters have been found to be in general agreement with those for *Tradescantia* microspores.[211]

115. With experimental mammals it is possible to compare the *in vitro* and *in vivo* rate of induction of visible chromosome aberrations. Somatic cells cultured *in vitro* frequently have a much higher spontaneous mutation rate than do *in vivo* cells.[211] However, investigations with Chinese hamsters and with monkeys indicate that the radiation-induced aberration rate of epithelioid-type cells cultured *in vitro* is not greatly different from that of rapidly dividing cells *in vivo*.[205, 206]

Observations on human cells

116. No measure of the radiation sensitivity of human germ cells has yet been made. Nor have extensive quantitative measurements been made of chromosomal damage induced in somatic cells of individuals. However, it has been clearly shown that chromosomal aberrations are produced.[46, 212–216] This subject is dealt with in annex D, paragraphs 155 to 158.

117. The effect of ionizing radiation on chromosomes of human cells cultured *in vitro* has received considerable attention in recent years.[206, 217–223] As with experimental mammals, data on the frequency with which breaks occur are not in good agreement. For epithelioid-type cells the observed rate at metaphase is about 0.3/cell/100 r[206, 217] but for "fibroblasts" the rate is about 2/cell/100 r.[218, 220] The frequency of chromosome breaks has been reported to be 0.9/cell/100 r for fibroblast-type cells[220] and 2/cell/100 r for leucocytes in freshly-drawn human blood.[222] The coefficients of aberration production for chromatid breaks in epithelioid-type cells *in vitro* and for chromosome breaks in leucocytes are in remarkably good agreement with those for *Tradescantia* miscrospores and for chromatid breakage in epithelioid-type cells of the monkey and Chinese hamster.[222]

Comparability of radiation-induced and naturally-occurring mutations

118. Mankind has long been exposed to natural radiation and it is to be expected that an increase in the level of exposure would not result in any mutations which have not occurred in the past. Nevertheless, natural radiation is only one of the causes of "spontaneous" mutation and it is therefore possible that there may be differences between the spectra of radiation-induced and naturally-occurring mutations.

119. Evidence concerning the comparability of the two sorts of mutations was presented in the Committee's last report.[224] Most of this information came from studies with lower organisms and suggested that, in general, mutations induced by ionizing radiation are similar in kind to those of natural origin.

120. There is evidence that in *Drosophila* the radiation-induced and natural rates of sex-linked recessive lethal mutations are similarly affected by sex and stage of gametogenesis.[72] Close correspondence between induced and spontaneous mutations is not found, however, in mice.[137] Furthermore, in mice loss of the maternal X chromosome can easily be induced by irradiation but spontaneous maternal loss is very rare.[85] There is also

very good evidence from *E. coli* that the natural mutabilities of loci are sometimes not correlated with their radiation-induced mutabilities.[122]

V. Effects observed in descendants of irradiated populations

Induced mutations in the immediate progeny of irradiated humans

121. Direct observations of the genetic consequences to man of exposure to ionizing radiation are now limited to observations of first-generation offspring. Such surveys can be expected to detect only autosomal dominant or sex-linked gene mutations and chromosome aberrations. Among the difficulties of such inquiries are those of estimating the gonad doses actually received by parents, and the small absolute and relative increases to be expected in the frequency of traits determined by such mutations.

122. In these surveys, the data are usually concerned with such matters as abortion, still birth, neonatal death, congenital malformation, and shifts in the sex-ratio of progeny. Results frequently indicate a detrimental effect of radiation but this is seldom statistically significant. One study detected a significant effect of radiation on the frequency of congenital malformations in the progeny of irradiated individuals but interpretation is hampered by the incomplete response to the questionnaires used.[225] Another similar study failed to show this effect.[226] The most extensive survey was carried out in the Japanese cities of Hiroshima and Nagasaki following the atomic bombings; data were collected on more than 30,000 offspring of irradiated parents and on a comparable control group.[227] Observations were made of still births, neonatal deaths, birth weight and congenital malformations. Analysis of these data failed to detect a significant effect of radiation on either the frequency of early death or congenital malformations. It did, however, detect a significant shift in the sex-ratio of immediate progeny. More recently, an analysis of the same data by an independent investigator has produced statistical significance of radiation effects for some other categories of defects and also for over-all early death of progeny.[228, 229]

123. The comparatively high frequencies of Down's and Klinefelter's syndromes permit the effect of parental irradiation on the incidence of these defects in offspring to be studied with relatively little effort. Three such investigations have already been reported. In one of these the radiation history was obtained of the mothers of eighty-one children with Down's syndrome, ninety-one children with cleft lip and seventy-one children with no defect. A possible association between maternal irradiation and Down's syndrome was indicated.[230] However, results of the other two investigations, one of which involved fifty-one patients with Down's syndrome and fifty-one controls,[231] the other 197 patients and 197 controls,[232] were completely negative.

124. A survey of the incidence of congenital malformations in different regions has indicated that higher incidences are associated with geographical areas with high background radiation.[233] Another survey has reported that the frequency of malformation varies with the geomagnetic latitude to which is related the cosmic-ray energy flux.[234] However, it is difficult to prove that natural radiation is the direct influencing factor.

125. A shift in the proportion of male offspring of irradiated individuals has been considered one of the best available methods for detecting induced genetic damage in humans and for estimating its extent. Six such studies have been reported.[225, 227, 235-238] In interpreting the results, the effect of maternal irradiation is more appropriately considered independently of the effect of paternal irradiation. The effect of maternal irradiation on the proportion of male offspring is summarized in table VIII. A consistent reduction in proportion of male offspring has occurred following maternal irradiation. In terms of the simplest genetic interpretation, this can be attributed to the induction, in irradiated women, of sex-linked recessive mutations having a lethal effect on the foetus. The effect of paternal irradiation is summarized in table IX. These latter data are not amenable to a single interpretation; the proportion of male offspring is apparently increased with higher doses, but, in at least some instances, reduced with low doses. The former effect is interpretable in terms of the induction of dominant sex-linked lethals. However, the validity of such a simple genetic interpretation has been questioned on the grounds that the Y chromosome cannot be considered genetically inert.[239] In addition, the induction of XO and XXY karyotypes may also affect the relative frequency of male and female offspring. Furthermore, explanations based on the assumption that the effect on sex ratio is due to damage to sex chromosomes cannot be accepted without reservation. For instance, the drop in proportion of males which has sometimes been noted could be attributed to autosomal mutations which further increase the existing higher mortality of males. The occasionally erratic control values must also be considered in any interpretation.

Induced mutations in the immediate progeny of irradiated mammals

126. By means of properly controlled experiments it is possible to detect induced dominant mutations in the immediate progeny of irradiated mammals. Current information has been obtained principally from mice. In mammals it is particularly difficult to distinguish between gene mutations and minor chromosomal changes. Reduction in litter size, following irradiation of spermatozoa or oöcytes, is most plausibly explained in terms of the induction of chromosome aberration, although gene mutations may also be involved.

127. Spermatogonial cells and oöcytes are of greatest concern in a consideration of radiation hazards. Oöcytes are not replenished, and it has been shown that there is no significant change in mutation rate with time after irradiation of spermatogonia.[240] Irradiation of spermatogonia has much less effect on litter size than does irradiation of later germ-cell stages. This no doubt reflects a drastic reduction in frequency of gross chromosome aberrations. For instance, individuals with deficiencies involving more than one gene locus are commonly found after irradiation of post-spermatogonial cells but irradiation of spermatogonia yields such deletions only with extremely low frequency, if at all. These aberrations do occur, however, among progeny produced after irradiation of oöcytes.[88, 137]

128. The fact that dominant detrimental mutations are induced and transmitted after irradiation of post-spermatogonial stages has been demonstrated by a shortening of the life span in the offspring of male mice exposed to neutrons.[241] In another study, a significant increase in certain types of skeletal abnormalities was found in the first-generation descendants of irradiated male mice.[242] Evidence that some dominant lethality is transmitted after irradiation of spermatogonia has been provided by

analysis of the cause of litter-size reduction following exposure to 1,200 r.[199] The same data indicate that translocations are occasionally found in progeny following irradiation of spermatogonial cells.

129. The specific-locus method of detecting mutations in mice has yielded further information on the dominance of mutations induced in spermatogonia. About three-quarters of all the induced mutations have been recessive lethals. However, some of these have a visible effect on the heterozygote.[136] In a freely-breeding population these mutations might well produce greater total damage as heterozygotes than as homozygotes.

130. In mice, several studies of the effect of paternal irradiation have not revealed any consistent effect on the sex ratio of offspring.[166, 239, 243] Another comprehensive investigation has shown that although the presence of sex-linked recessive lethals in the second generation progeny of irradiated males can be detected, nevertheless sex-ratio changes do not now provide a reliable method of estimating the genetic hazards of radiation because of the complexity of factors governing this ratio.[244] This complexity has been emphasized by the fact that strain differences in the ratio can be obtained through differential selection for low and high blood pH.[245] In fowl, a significant decrease in the frequency of female progeny resulting after exposure of male birds to 600 r has been noted.[246] In *Drosophila*, most investigations have demonstrated some tendency toward an excess of males among the progeny of irradiated males.[247, 248] A significant shift in this direction has been reported recently.[249] Research on sex-ratio shifts needs to be continued in the hope of laying a firm foundation for the application of this method in analyses of radiation-induced mutation in man.

Polygenic traits

131. The subject of polygenic traits was treated at some length in the 1958 report with special reference to intelligence, life span and birth weight.[250] Attention was drawn to the paucity of information regarding the inheritance of continuously varying, or quantitative, traits. These traits, which are influenced to varying degrees by many genes, present a special problem in the estimation of genetic hazards of ionizing radiation to populations. For example, intelligence is influenced by certain rare genes having major effects and by a multiplicity of genes, each with a small effect. In those instances where a mutation has a drastic effect on the trait, or concomitant effects on some other trait, it is individually identifiable and classed as a qualitative mutation. Mutations resulting in such conditions as phenylketonuria and mongolism belong to this category. Where the effect is less drastic no such identification is possible. Furthermore, the frequency of mutations having minor effects is many times greater than is the frequency of mutations having major effects. Finally, a great deal of genetic variability within these traits is common in a normal population, and phenotype is, in addition, often strongly influenced by the environment. In such circumstances the relative contributions of heredity and environment to the over-all phenotypic variability are difficult to determine. A few traits, such as dermal-ridge count, are relatively unaffected by environment after birth; here a more accurate genetic analysis can be made.[251] However, the role of mutation in supporting the genetic variability of polygenic traits has defied any simple analysis.

132. Because rates of mutation of the individual genes in a polygenic system cannot be studied, most investigators have adopted the procedure of expressing induced mutation in terms of the resulting increase in the genetic component of the variance, with or without reference to the genetic component observed in natural outbred populations. The extent of this increase has, in general, been measured either directly by variance analysis or indirectly by calculation of the capacity of an irradiated population to respond to selection. Pertinent information from experiments concerned with natural and radiation-induced mutation rates is summarized in table XI.

133. Such experiments are of special value in indicating whether the genes determining polygenic traits differ in their pattern of mutability from those individually recognized through discrete changes. Estimates of doubling dose for abdominal and sternopleural bristles in *Drosophila* agree well with those for major genes.[252] On the other hand, the estimated induced rates for polygenes controlling viability are high.[253]

134. Loss of genetic variance per generation in an unselected, random-mating *Drosophila* population of limited size is only a small portion of the natural variability of the species. Polygenic traits are evidently well buffered against the effects of mutation. Thus the radiation damage from an increased rate of polygene mutation, although possibly considerable when summed over many generations, is probably small in its impact on the first few generations. Variability in these traits may be maintained in part by a balance of selective forces, a possibility which further complicates the estimation of radiation-induced mutational damage to polygenic systems in an organism such as man, that cannot be directly experimented on.

135. The learning ability, as measured by a maze test, of a population of rats which were irradiated in each generation has decreased in preliminary experiments.[254] If further experiments exclude other interpretations, these results will support the view that radiation results in the induction of many small but deleterious mutations. Again, a significant accumulation of recessive or sub-lethal mutations affecting ability to survive irradiation has been reported in mice after ten generations of chronic gamma irradiation.[255]

VI. Interpretation

136. The preceding sections of this annex were concerned with the genetic concepts and information now available for estimating the hereditary effects of an increase in the level of ionizing radiation. The present section considers the practical problems involved in formulating reliable estimates from this knowledge.

Direct approach

137. An estimate of the genetic hazards of radiation to man can, in principle, be obtained by a direct comparison of the descendants of irradiated with those of control populations. To be reliable, such surveys must be extensive, since most severe genetic defects tend to be rare. Furthermore, many aspects of genetic well-being must be considered and it is desirable to continue the observations over many generations. These conditions have not been fulfilled in any study to date. All surveys made so far have, in addition, been hampered by problems of dosimetry and the difficulty of obtaining proper controls. In the most extensive of these, that dealing with the populations of Hiroshima and Nagasaki, the investi-

gators were unable to detect a significant effect of radiation on either the frequency of early death or the occurrence of malformations. At least, this negative finding suggests that the human genetic mechanism is not substantially more sensitive to radiation than are those of other organisms that have been investigated. It has been suggested that the acute dose required to double the frequency of mutations causing the defects under study is probably more than 10 r.[227] The Japanese survey detected, as did others of lesser scope, a shift in the proportion of first generation male offspring suggestive of the induction of sex-linked lethal damage in irradiated parents. The precise nature of this damage is not known at present.

Indirect approaches

138. Indirect approaches attempt to predict the genetic consequences of exposure to ionizing radiations through an understanding of basic genetic mechanisms and their reaction to radiation. More specifically, estimates are derived through a knowledge of the prevalence of naturally-occurring hereditary ill health within a population, the role of mutation in supporting this burden, and the relation between the dose of radiation and the mutation rate in man.

The prevalence of hereditary diseases and defects

139. There is probably a genetic component in the aetiology of most diseases. It is now estimated that about 6 per cent of all live-born suffer at some time during their lives from serious disabilities in which this component is either known or suspected to be of major importance. Without doubt the estimate of natural genetic burden will increase with future research. In about one third of these disabilities, those of categories Ia, Ib, and IV, the genetic component is high and the underlying genetic mechanism is understood. Of these defects, about half are associated with what appear to be specific alleles, and about half are associated with gross chromosome anomalies. For the remainder of the defects, the developmental malformations and serious constitutional disorders of categories II and III, neither the size of the genetic component nor its underlying genetic mechanism is known with any assurance. These disabilities are almost certainly heterogeneous in aetiology; some are probably almost completely environmental in origin, but in others genotype may be an important factor. However, even where the importance of genetic constitution is suspected, the basic nature of the fault is not clear; complex constellations of genes, specific alleles of low penetrance, or cytologically undetected chromosome aberrations may be responsible.

140. The amount of recessive damage, that hidden in heterozygotes, has been estimated at 2-4 lethal equivalents and an equal number of detrimental equivalents per individual. When exposed by homozygosis, the lethal equivalents are expressed as an increase in miscarriages, still births and in neonatal, infant, and juvenile deaths. The detrimental equivalents are associated with viable malformations and overlap the previous listing to some extent. A comparable measure of genes producing recessive infertility has not been made. No similar method is yet available for estimating the amount of dominant genetic damage within populations.

The role of spontaneous mutation in maintaining the frequency of hereditary disabilities

141. Various mechanisms by which detrimental traits can be maintained in a population are well recognized. A gene sometimes conferring reduced fitness, but never conferring increased fitness, must be maintained entirely by recurrent mutation. On the other hand, if a gene confers increased selective advantage in some circumstances, mutation may have only a minor influence on its frequency.

142. The extent to which such balanced selective forces are responsible for maintaining hereditary disabilities in human populations is unknown at present. Of the defects listed in section II, only among the specific disabilities now recognized to have a high genetic component is it possible to discriminate between those that are mutation-maintained (categories Ia and Ib) and those that are maintained by a balance of selective forces (category IV). At present, traits of category IV provide but a small fraction of the total amount of serious ill health of known or suspected genetic origin. Suitably designed studies will undoubtedly produce more examples in the future. In the meantime, estimates of the importance of balanced selective forces are dependent on the use of indirect procedures or are based on concepts of the genetic structure of human populations which have yet to be confirmed.

143. When the prevalence of defective traits is maintained by recurrent mutation, the genetic hazards of radiation can be estimated if the factor by which mutation rate will be increased by a given radiation dose is known. However, when the frequency of induced mutations has been determined at only one dose it is necessary to know the spontaneous rates to estimate the hazard. Reliable estimates of spontaneous rates can be made only when the genetic fitness of both homozygote and heterozygote is known. It is possible to measure fitness where dominant traits are concerned. However, with recessive traits it is difficult to determine genetic fitness of heterozygotes; as a consequence, reliable estimates of natural mutation rates are rare. Point mutation rates so far estimated cluster around the value 10×10^{-6} per locus per generation. The total mutation rate for gross chromosomal aberrations is now estimated at about 1 per cent per generation.

Dose-mutation relationship

144. The genetic effects of ionizing radiations cannot be understood without establishing a firm relationship between frequency of induced mutation and the dose of irradiation delivered. Most of the earlier information about this relationship was accumulated from the results of experiments with *Drosophila* sperm. Past research led to the working assumptions that: (*a*) the dose-mutation curve is linear in the low-dose range, (*b*) there is no threshold dose, and (*c*) mutation frequency is not dependent on dose rate over the range under consideration. Much effort has been put into the task of either confirming or disproving these three assumptions. Recent investigations have strengthened the first two, but have disproved the last. It has now been conclusively demonstrated that rate of delivery of radiation can have an effect on the frequency with which mutations are found. In male mice, low dose-rates of ionizing radiation produce one fourth as many mutations as do high dose-rates. In females, this phenomenon is even more pronounced.

145. Recent research has increasingly emphasized the fact that radiation-induced mutation frequency can be drastically affected by circumstances other than dose and dose rates:

(*a*) Radiation-induced mutation rates may vary for genes in the same species and this variation need not

correspond to the variation in natural rates. In mice the induced rates per unit dose in spermatogonia at seven specified loci may vary by a factor of thirty.

(*b*) Rate of radiation-induced mutation per unit dose varies in different species. Furthermore, it has been reported that the frequency of cytologically observed induced chromosome abnormalities in spermatogonia of the guinea pig is nearly thirty times that of the rabbit, a closely related species.

(*c*) It is clearly established that sex and stage of gametogenesis can have a profound influence on both spontaneous and radiation-induced mutation frequencies. The existence of such interactions between radiation effect and the circumstances of its delivery add to the complications of estimating radiation effects in humans. For example, it increases the possibility that errors may be involved in extrapolating from one species to another, from non-gonadal tissues to germ cells, and from one germ-cell stage to another.

The doubling-dose concept in indirect assessments

146. The indirect methods for assessing the hereditary effects of an increase in level of ionizing radiation to which a population is exposed involve the estimation of "doubling dose" and the assumption of linearity of the dose-effect relationship. The doubling dose for a particular mutation is that dose which will increase the mutation rate to double the spontaneous rate. A prediction of the phenotypic effect of an increase in mutation rate can be calculated from the fact that the number of affected persons arising as a consequence of a doubling dose delivered in one generation, is equal to the number of affected persons normally present in any one generation as a result of recurrent mutations of natural origin. This increase in affected individuals will be spread over one or more generations depending on the genetic fitness which specific mutations confer on their carriers. The genetic fitness of the heterozygote is of more importance than that of the homozygote in most cases, because rare mutant genes occur much more frequently in the heterozygous state in a random-breeding population. When genetic fitness of the heterozygote is very low, most of the impact of the new mutations will be felt in the subsequent generation; if fitness is reduced by one-fifth, most of the effect will appear within the first five generations; if reduction in fitness is slight the effect will spread over very many generations. A permanent doubling of the mutation rate eventually results in a permanent doubling of the incidence of those traits normally maintained by recurrent spontaneous mutation. On the assumption of an average reduction of 2 per cent in genetic fitness of heterozygotes, most of the impact of a permanent doubling of mutation rate would be felt in about fifty generations. Where systems of balanced polymorphism are in force, natural mutation is a relatively minor factor in the maintenance of genetic variability and a doubling of the mutation rate would have little effect on the prevalence of the associated traits.

147. The usefulness of the doubling-dose procedure was considered in detail in the 1958 report of the Committee. To a large extent this usefulness stems from the fact that whole classes of mutation can be handled as a unit in the absence of any information about the number of loci involved or their individual mutation rates. Tentative numerical estimates of the doubling dose for man were presented in the 1958 report. It was pointed out at that time that little direct information was available on the sensitivity of human genetic loci to radiation. Estimates of doubling dose were consequently based on several other considerations. These included a simple genetic interpretation of sex-ratio changes in man based on the assumed induction of sex-linked dominant and recessive mutations having a lethal effect *in utero*. Account was also taken of the investigation of seven specific loci in mice and of extensive observations on sex-linked lethal mutation in *Drosophila*. As expected, advances in our knowledge have indicated that this estimate is in need of revision.

148. The usefulness of sex-ratio changes in estimating a doubling dose must be considered doubtful because of inconsistencies in the sex-ratio change in the progeny of irradiated fathers (table IX). Furthermore, there is no significant effect on the sex-ratio in the progeny of irradiated male mice.

149. Recently acquired information has also stressed the fact that, apart from the radiation dose alone, there are a number of specific factors which should be taken into account in calculating the doubling dose. Dose rate, sex, and stage of gametogenesis are all factors which affect the frequency and quality of mutation in both mice and *Drosophila* and it must be suspected that they are effective in man. An example of the influence of rate of dose on the calculated doubling dose can be obtained from table X where the main results of irradiation of spermatogonia and oöcytes of the mouse have been summarized. The most important single comparison is that for males between the dose rates of 80-90 r/min and 8.5×10^{-3} r/min. The former rate provides a doubling dose of 30-40 rad, the latter 100-200 rad. A significant dose-rate effect is also evident for oöcytes, and the doubling doses for acute and chronic irradiation show an even greater spread than in males.

150. It is becoming increasingly evident that the spectrum of mutations in man is too wide to be included in a single category for the purpose of estimating a meaningful representative doubling dose. For instance, the doubling dose for gross chromosome mutations may well differ drastically from that for point mutations. If so, the frequency-distribution of hereditary defects resulting from a specific increase in the level of exposure to radiation would not be parallel to the natural spectrum.

151. In view of the undoubted complexities of the dose-mutation relationship, it is evident that this method of assessing hereditary effects of ionizing radiation can easily yield imprecise estimates. At the same time it is equally evident that none of these recently discovered complexities invalidates the doubling-dose concept itself; they merely emphasize that the method must be applied under carefully defined conditions if accurate estimates are to be obtained. In particular, it is important to discriminate between the genetic hazards of chronic low-level exposures and more acute medical and accidental exposures.

152. The difficulties of obtaining information on the hazards of ionizing radiation would be reduced if the large amount of data collected in other organisms could be applied directly to humans. Differences in species introduce into this procedure uncertainties the extent of which is difficult to estimate. A second approach is through the observation of human cells grown in tissue culture; reproducible results relating to radio-sensitivity of cells can be obtained in this way. However, here also extrapolation of information is at present associated with uncertainties. Nevertheless it is clear that *in vivo* and *in vitro* research in different organisms will ultimately

provide a valuable source of information. Such investigations must be accompanied by an understanding of the genetic structure of human populations and the respective roles of mutation and selection in moulding that structure.

Conclusions

153. Sufficient information is not now available to calculate with a useful degree of accuracy a representative dose which would double the mutation rate (doubling dose). Nor is it yet possible to predict directly the quantitative or qualitative effects of such a dose on populations. Nevertheless, information regarding some aspects of the genetic hazards of ionizing radiation can be obtained by the doubling-dose method. This involves the calculation of separate doubling doses for different dose rates, and, in addition, for different specific categories of defects. The complexity of the calculations is reduced by the fact that differential sensitivity of germ-cell stages within each sex can be largely ignored; as far as the genetic hazards of radiation to man are concerned, the significant germ-cell stages are the spermatogonia and the oöcyte. This is true whether irradiation is chronic or acute.

154. The group of disabilities to which the doubling dose can, at present, be most usefully applied are those severe defects maintained by recurrent point mutation (category Ia). Calculations of the 1958 report suggested that the over-all representative doubling dose for man might well lie between 10 and 100 rad, with 30 rad as the most probable value. This estimate was based on studies which involved acute irradiation and the production of point mutations. In the absence of better evidence, the doubling dose for acute irradiation of males does not require revision. However, there is evidence that this value is lower in females; experiments with mice have shown that oöcytes are somewhat more sensitive to acute (but not to chronic) irradiation than spermatogonia. The doubling dose for the two sexes combined must therefore be lower than that for males and may well be about half this value. For chronic irradiation of males, new information from mouse experiments suggests that the doubling dose is about four times the 1958 value of 30 rad. For chronic low intensity irradiation of females, mutation rates seem to be lower than in males. The combined doubling dose for both sexes cannot exceed twice the value for males and is not likely to be much lower than that value. For these estimates, uncertainty due to species extrapolation and the limited number of loci used in experimental studies probably does not exceed threefold in either direction. A permanent doubling of the mutation rate would ultimately double the prevalence of the serious defects under consideration. These are now estimated to have a prevalence at about 1 per cent.

155. The doubling dose for the defects of category Ib, those due to gross chromosome aberration, cannot now be estimated for lack of data. However, the effect of radiation on the frequency of gross chromosome mutation is amenable to study, and it can be expected that continued research in this field will enable estimates to be made in the near future. A doubling of the mutation rate in one generation would almost certainly double the prevalence of these defects in the next generation. This prevalence is now estimated to be about 1 per cent.

156. It is not possible to estimate the doubling dose for the genetic changes contributing to developmental malformations and serious constitutional disorders of categories II and III. The prevalence of these defects might be doubled by a doubling dose but the increase would probably be much less; environment is suspected to have a strong influence on their aetiology, and unrecognized balancing selective mechanisms may also be effective in maintaining their frequency.

157. Significant progress towards an understanding of the genetic effects of ionizing radiation has been made in the last four years. The Committee emphasizes that: (*a*) all research has confirmed the fact that ionizing radiation produces genetic damage at all doses and dose rates so far tested, and (*b*) further progress in understanding the genetic hazards of radiation will come not only from *ad hoc* research in radiation genetics but from an increase in all types of genetic research in man and in experimental organisms.

TABLE I. CHROMOSOME ABERRATIONS ESTABLISHED IN MAN

	Associated clinical condition	*Chromosome complement*	*Chromosome number*	*First reference*
I.	*Anomalies related to chromosome number*			
	Down's syndrome (mongolism)	Autosomes: Trisomy-21	47	6
	Complex congenital malformations	Trisomy-(17–18)	47	7
	Complex congenital malformations	Trisomy-(13–15)	47	8
	Klinefelter's syndrome	Sex-chromosomes: XXY	47	9
	Klinefelter's syndrome	XXXY	48	10
	Klinefelter's syndrome	XXXXY	49	11
	Turner's syndrome	XO	45	13
	Mild mental defect	XXX	47	14
	Mental defect	XXXX	48	15
II.	*Structural anomalies*			
	Down's syndrome with trisomy-21	21 ~ (13–15)	46	16

TABLE II. DISABILITIES WHICH HAVE BEEN ASSOCIATED WITH ABNORMAL KARYOTYPES, EXCLUDING KNOWN MOSAICS

	Clinical condition	*Chromosome complement*	*Chromosome number*	*Reference*
I.	*Anomalies related to chromosome number*			
	Klinefelter's syndrome	XXYY	48	12
	Klinefelter's-Down's syndrome	XXY, trisomy 21	48	102
	Prenatal death	Triploidy	69	37
	Mental retardation	Trisomy 6(?)	47	256
	Facial anomalies	Trisomy 22(?)	47	257
II.	*Structural anomalies*			
	Polydysspondyly	22 ~ (13–15)	45	258
	Familial mental and speech defect	22 ~ (13–15)	45	109
	Primary amenorrhoea	X + partly deleted X	46	259
	Down's syndrome	21 ~ 22	46	18
	Down's syndrome	21 ~ 21, or trisomy 19 and monosomy 21	46	21
	Convulsive disorder	(1–2) ~ (6–12)	46	260
	Klinefelter's syndrome	XXY and 14~15	46	106
	Congenital abnormality	16 ~ 21, or trisomy 21 and monosomy 16	46	261
	Pseudo-hermaphroditism	21 ~ Y	46	262
	Turner's syndrome	Enlarged X	46	263
	Familial Marfan's syndrome	Enlarged satellite	46	264
	Transmissible hypospadias	Y deletion	46	265
	Gonadal dysgenesis	X or Y deletion	46	266
	Auricular septal defect	2 ~ (6–12)	46	267
	Familial malformation of central nervous system	Enlarged satellite	46	268

TABLE III. LETHAL AND DETRIMENTAL EQUIVALENTS DERIVED FROM STUDIES OF OFFSPRING FROM FIRST-COUSIN MARRIAGES

(*Modified after Newcombe*[209])

		Consanguineous (first cousin only)			*Control*					
Place	*Condition*	*Affected*	*Total*	*Frequency (%)*	*Affected*	*Total*	*Frequency (%)*	*Difference (%)*	*Lethal or detrimental equivalent*	*Reference*
U.S.A.										
	Infant death; juvenile death	637	2,778	22.93	134	837	16.01	6.92 ± 1.50	2.21 ± 0.48	270
	Death under 20 years	113	672	16.82	370	3,184	11.62	5.20 ± 1.55	1.66 ± 0.50	271
	Miscarriage	36	248	14.52	25	194	12.89	1.63 ± 3.29	0.52 ± 1.05	
	Still birth; neonatal death	7	212	3.33	5	196	2.98	0.35 ± 1.73	0.11 ± 0.55	272**
	Infant death; juvenile death	14	205	6.34	1	164	0.61	5.73 ± 1.81	1.83 ± 0.58	
	Abnormality	31	192	6.15	16	163	9.82	6.33 ± 2.91	2.03 ± 0.93	
France										
	Still birth	43	1,043	4.12	84	4,094	2.05	2.07 ± 0.65	0.66 ± 0.21	
	Infant death	87	982	8.86	182	4,010	4.54	4.32 ± 0.96	1.38 ± 0.31	273
	Death from 1 to 30 years	104	886	11.74	227	3,822	5.94	5.80 ± 1.12	1.86 ± 0.36	274
	Abnormality*	169	1,043	16.20	176	4,094	4.30	11.90 ± 1.18	3.81 ± 0.38	
Japan										
	Still birth; neonatal death	125	2,798	4.47	2,091	63,145	3.31	1.16 ± 0.40	0.37 ± 0.13	
	Infant death	54	822	6.57	808	17,331	4.66	1.91 ± 0.88	0.61 ± 0.28	40
	Juvenile death	41	352	11.65	31	567	5.47	6.18 ± 1.96	1.98 ± 0.63	275
	Abnormality*	69	4,845	1.42	651	63,796	1.02	0.40 ± 0.17	0.14 ± 0.05	

* Indicates some overlap with the preceding classes.

** Controls drawn from offspring of sibs of the consanguineous pair.

See also Böök[276] who found no significant difference in the mortality in small samples of offspring of first-cousin and control marriages, but a considerably greater proportion of the cousin offspring having hereditary diseases (16 versus 4 per cent), and having lower than average intelligence (26 versus 15 per cent). Since the individual offspring were observed for varying periods of time the mortality data are not readily presented in the above form. An average of three recessive deleterious genes per person is estimated from these data.

TABLE IV. ESTIMATED MUTATION RATES AT LOCI DETERMINING AUTOSOMAL DOMINANT DISEASES IN MAN

(Modified from Stevenson[277] and Penrose[39])

Trait	*Region*	*Estimated rate/locus/gen. (× 10^{-6})*	*Reference*
Epiloia	England	8	278
Achondroplasia	Denmark	43*	279
	Sweden	68*	280
	Northern Ireland	13	281
Aniridia	Denmark	5	282
	Michigan	4	283
Microphthalmos	Sweden	5	284
Retinoblastoma	England	15	285
	Michigan	23	286
	Northern Ireland	29	287
	Germany, Fed. Rep. of	4**	288
Neurofibromatosis	Michigan	100+	289
Huntington's chorea	Michigan	5	290
Arachnodactyly	Northern Ireland	6	291
Acrocephalosyndactyly	England	3	292

* This estimate probably includes phenocopies.
** This figure is adjusted for presumptive phenocopies.

TABLE V. ESTIMATED MUTATION RATES AT LOCI DETERMINING SEX-LINKED DISEASES IN MAN

(Modified from Stevenson[277])

Trait	*Region*	*Basis of estimation $\mu = 1/3\ (1 - f)\ x$**	*Estimated rate/locus/gen. (× 10^{-6})*	*Reference*
Haemophilia	England	$f = 0.25$ Est $x = 0.8 \times 10^{-4}$	20	293
	Denmark	$f = 0.286$ Est $x = 1.33 \times 10^{-4}$	32	294, 295
	Denmark and Switzerland	$f = 0.333$ $x = 489/4{,}092{,}025$	27	296
Duchenne type muscular dystrophy	Utah, USA	$f = 0$ $x = 18/63{,}000$	95	297
	Northern Ireland	$f = 0$ $x = 48/271{,}896$	59	298
	England	$f = 0$ $x = 16/138{,}403$	39	299
	England	$f = 0$ $x = 15/105{,}310$	47	300
Limb girdle muscular dystrophy	Northern Ireland	**	34	51
Recessive deaf-mutism	Northern Ireland	**	13	51

* μ = Mutation rate/locus/generation.
f = Relative genetic fitness.
x = Frequency of trait in population.
** Estimates made by special methods.[51]

TABLE VI. ESTIMATED MUTATION RATES AT LOCI DETERMINING AUTOSOMAL RECESSIVE DISEASES IN MAN

(Modified from Penrose[39])

Trait	*Region*	*Basis of estimation* ($\mu = (1 - f)\, x^*$)	*Estimated rate/locus/gen.* ($\times 10^{-6}$)	*Reference*
Juvenile amaurotic idiocy	Sweden	$f = 0$ Est $x = 3.8 \times 10^{-5}$	38	301
Albinism	Japan	$f = 0.5$ Est $x = 5.5 \times 10^{-5}$	28	302
Ichthyosis congenita	Japan	$f = 0$ Est $x = 1.1 \times 10^{-5}$	11	302
Total colour blindness	Japan	$f = 0.5$ Est $x = 5.5 \times 10^{-5}$	28	302
Infantile amaurotic idiocy	Japan	$f = 0$ Est $x = 1.1 \times 10^{-5}$	11	302
Amyotonia congenita	Sweden	$f = 0$ $x = 1/44109$	23	280
Epidermolysis bullosa	Sweden	$f = 0$ $x = 2/44109$	45	280
Microcephaly	Japan	$f = 0.02$ Est $x = 5 \times 10^{-5}$	49	303
Phenylketonuria	England	$f = 0$ Est $x = 2.5 \times 10^{-5}$	25	54

* μ = Mutation rate/locus/generation.
f = Relative genetic fitness.
x = Frequency of trait in population.

TABLE VII. STUDIES OF TIME-DISTRIBUTION OF DOSE—MODIFICATION OF PRE-MUTATIONAL DAMAGE AND ASSOCIATED PHENOMENA

Material	*Radiation*	*Mutations*	*Phenomenon*	*Remarks*	*Reference*
Mouse spermatogonia	X, γ	Recessive visibles and lethals at seven selected loci	Fourfold reduction in effect at low dose-rate	Differential viability of cells, radiation quality eliminated	119,124, 127, 132
Mouse oöcytes	X, γ	Recessive visibles and lethals at seven selected loci	More than fourfold reduction at low dose-rate	Inter-cell selection differential viability, radiation quality eliminated	121,123 304
Drosophila oögonia	γ	Sex-linked recessive lethals	Reduced effect at low dose-rate		128
Silkworm, early stages of spermatogonia and oögonia	X, γ	Egg-colour mutants at two specific loci	Reduced effect at low dose-rate	After elimination of cell selection and later stages	97
Dahlbominus, wasp oögonia	γ	Eye-colour mutants in female larvae	No effect at intensity differences of 1,000 r/min and 0.17 r/min	Probably oögonia	130
Drosophila spermatogonia	γ	2nd chromosome recessive lethals	No intensity effect at 2,000 r/min and 2.0 r/min	Total dose 3,000 r	129
Drosophila spermatogonia	γ	2nd chromosome recessive lethals	Reduction at intensity differences from 0.01 r/min to 0.10 r/min	Total dose 200 r	129
Drosophila spermatogonia	X	Sex-linked recessive lethals	Reduced (?) effect of fractionated dose	Shifts in brood pattern of mutation rates cannot be excluded	305
Drosophila spermatogonia	X	Sex-linked recessive lethals in ring-X chromosome	No effect of dose fractionation; enhancement by post-treatment with N_2; reduction by pre-treatment with chloramphenicol	Intensity of radiation for fractionation and N_2 post-treatment 55 r/sec	153,154, 155, 156
Drosophila spermatogonia (?)	X	Sex-linked lethals	Decrease by feeding of larvae with actinomycin D and penicillin	Stage not defined, probably spermatogonia	306, 307

TABLE VII. STUDIES OF TIME-DISTRIBUTION OF DOSE—MODIFICATION OF PRE-MUTATIONAL DAMAGE AND ASSOCIATED PHENOMENA (*continued*)

Material	*Radiation*	*Mutations*	*Phenomenon*	*Remarks*	*Reference*
Drosophila spermatids and spermatocytes	X	Sex-linked recessive lethals in ring-X chromosome	Reduced effect of dose fractionation and of pre-treatment with chloramphenicol and ribonuclease; enhancement by post-treatment with N_2; both increase and decrease by post-treatment with HCN	Gene mutations and possibly small deletions; radiation given at high dose-rates; inhibition of metabolic repair and delay of mutation fixation	152,153, 154,155, 156, 157
Drosophila sperm	X	Sex-linked recessive lethals in ring-X chromosome	Increase by pre-treatment with ribonuclease and chloramphenicol		153, 154
Drosophila sperm	X	Sex-linked recessive lethals; chromosome breaks	Reduced (?) effect of dose-fractionation in absence of O_2	Critical period ~ 40 min; critical dose for breaks	158, 161
Drosophila sperm	X	Chromosome breaks	O_2 affects both breakage and rejoining of chromosome fragments; no saturation of O_2 sensitivity systems	Radiation given in N_2, air, or at 1 At of O_2	163
Drosophila oöcytes	X	Half-translocations, detachment of attached X-chromosomes	O_2 affects both breakage and restitution of breaks	N_2 between X-ray fractions, or as a post-treatment increase half-translocation frequency	308, 309
Habrobracon oöcytes	X	Hatchability of eggs treated in first meiotic metaphase	Post-treatments with N_2 and CO increase radiation damage	Realization of potential radiation damage	310
Drosophila spermatids	X	Translocation	Cyanide post-treatment increases frequency	After both low and high dose-rates; CN delays restitution of breaks, more translocations	152, 311
Paramecium	X, UV, α	Recessive lethals expressed after autogamy	Effect of time between irradiation and chromosome duplication	Effect of various post-treatments (nutrition, metabolic inhibitors)	139, 140
E. coli; *Streptomyces* spores; *Serratia*	UV, X	Biochemical reversions, "EMB colour"	Observe mutation frequency decline, mutation stabilization, mutation fixation, and mutation expression	Pre- and post-treatment with various temperatures, nutritional factors, and metabolic inhibitors, relations to protein, RNA and DNA synthesis	143,144, 145,146, 147,148, 149
Neurospora	UV	Biochemical mutation	Protein synthesis decreases mutation at low UV doses, but increases mutation at high doses	RNA derivatives increase mutation frequency at low doses only	150
Trifolium		Somatic mutations at leaf marking locus	Reducing effect of dose fractionation	Protection by dose of 12.5 r, dependent on O_2-tension and temperature	312
Vicia	X, Neutron	Chromosome breaks	Process of rejoining inhibited by radiation	Repair requires cellular metabolism and protein synthesis	313, 314

TABLE VIII. EFFECT OF IRRADIATION OF MOTHERS ON THE PROPORTION OF MALE OFFSPRING

Country	Control		Dose range rads	Irradiated		Reference
	No. live births	Per cent male		No. live births	Per cent male	
Japan	43,544	52.085	ca. 8	19,610	51.979	227, 315
			ca. 75	3,958	51.440	
			ca. 200	2,268	51.190	
U.S.A.	Control not available		50–200	407	49.1	235
France	355	54.6	200–400	161	44.7	236
	674	50.1	2–10	797	52.2	
Netherlands	225	53.3	300–600	221	48.0	238

TABLE IX. EFFECT OF IRRADIATION OF FATHERS ON THE PROPORTION OF MALE OFFSPRING

Country	Control		Dose range rads	Irradiated		Reference
	No. live births	Per cent male		No. live births	Per cent male	
Japan	43,544	52.085	ca. 8	5,168	51.587	227, 315
			ca. 60	1,226	53.263	
			ca. 200	753	52.722	
	609	51.72	Many doses of unknown amount	4,201	53.64	237
	Average for Japan	51.24				
U.S.A.	3,491	52.42	Many small doses	4,277	51.39	225
France	1,185	51.5	200–400	656	56.1	236
	1,926	52.7	2–20	1,394	46.0	
Netherlands	828	46.6	300–600	635	52.3	238
	657	52.3	1–10	668	53.4	

TABLE X. NATURAL AND INDUCED MUTATION RATES AT SEVEN SPECIFIC LOCI IN ADULT MOUSE SPERMATOGONIA AND OÖCYTES

Source	Details of irradiation		No. of offspring	Mutations in spermatogonia		Reference
	Total Dose (r)	Dose Rate (r/min)		No. of mutations	Mean no. of mutations per locus per gamete ($\times 10^{-5}$)	
X-ray	300	80–90	40,408	25	8.84	119
X-ray	600	80–90	119,326	111	13.29	119
X-ray	1000	80–90	31,815	23	10.33[a]	119
X-ray	600 + 400[b]	80–90	4,904	10	29.13	121
X-ray	600	60–70	10,761	11	14.60	126
Co^{60}	600	24	44,352	33	10.63	121, 316
X-ray	600	9	28,339	14	7.06	317
Cs^{137}	600	0.8	27,840	10	5.13	125
Cs^{137}	300	0.009	58,457	10	2.44	121, 316
Cs^{137}	516	0.009	26,325	5	2.71	121
Cs^{137}	861	0.009	24,281	12	7.06	121
Co^{60}	603[c]	0.007–0.009	10,763	2	2.65	126
Co^{60} and radium	37.5[d]	0.0011–0.0078	63,322	6	1.35	318
Cs^{137}	86	0.001	56,993	6	1.50	121
Control	—	—	544,897	32	0.84	119, 121, 316, 318
				Mutations in oöcytes		
X-ray	400	92–96	12,853	16	17.78	121, 123
Cs^{137}	400	0.8	36,083	13	5.15	304
Co^{60}	600[e]	0.05	10,117	1	1.41	319
Cs^{137}	258	0.009	27,174	2	1.05	121, 123
Control	—	—	98,828	1	0.14	121, 123, 316

[a] For a possible explanation of the low mutation frequency, see paragraph 83 above.
[b] The two fractions were delivered 15 weeks or more apart.
[c] Delivered in 90 12-hr. or 16-hr. days.
[d] Delivered in 5, 25, or 35 16-hr. nights.
[e] Delivered in 12 16-hr. nights.

TABLE XI. POLYGENIC TRAITS: MUTATIONAL DATA

Material and characters	*Treatment*	*Method*	*Results: increase in genetic variance*	*Comments*	*Reference*
Drosophila melanogaster					
Abdominal bristle number.....	(*a*) 1,800 r per generation as adults	Response to selection for high and low lines	3.3×10^{-5} rad Not significant but ≥ 0.006/generation	Natural genetic variance cited as 5 units for abdominals and 1.7 units for sternopleural	320
	(*b*) Nil	(10/25)			
Drosophila melanogaster					
Abdominal bristle number.....	Nil	Analysis of increased variance associated with second chromosome	0.0014/generation		321
Sternopleural bristle number.....	Nil	Ditto	0.0004/generation		
Drosophila melanogaster					
Abdominal bristle number.....	Nil	Analysis of variance associated with second chromosome	0.006/generation		322
Sternopleural bristle number.....	Nil	Ditto	0.002/generation		
Drosophila melanogaster					
Abdominal bristle number.....	?	Regression of variance on dose for large chromosomes	8.7×10^{-5}/rad		
Sternopleural bristle number.....	?	Ditto	3.5×10^{-5}/rad	Details of X-ray treatment and dose not given	
Drosophila melanogaster					
Sternopleural bristle number.....	(*a*) 3,000 r X-rays every generation	Selection for high no. (*a*) Top 15% every generation	$\geq 4.7 \times 10^{-5}$/rad*		323
	(*b*) 3,000 r X-rays every other generation	(*b*) Top 15% every other generation	$\geq 2.5 \times 10^{-5}$/rad*		
Rice					
Heading date.....	6 or 12,000 r X-rays to seeds	Variance analysis 5 generations after irradiation of highly inbred line	1.5×10^{-5}(day)^2/rad	If suppose inbreeding system leaves variance equiv. of 3–5 generations of spontaneous mutation, can calculate spont. rates of $8–10 \times 10^{-3}$(day)^2/generation for heading date and $6–7.5 \times 10^{-2}$(cm)^2/generation for plant height	324
Plant height.....	Ditto	Ditto	8.4×10^{-5}(cm)^2/rad		
Maize					
9 attributes.....	Nil	Analysis of shifts in plot means over 6 generations of selfing doubled monoploids	Average of 4.5×10^{-2} mutations per attribute per gamete	Variance analysis failed to give significant results because of high environmental component	325
Arabidopsis thaliana					
Logarithm of flowering data.....	0–150 kr X-rays to dry seeds		2×10^{-5}/rad	Variance of flowering data in natural populations not known. Controls probably not significantly different from ~ 0.00043; good linearity with dose obtained	326

* Secretariat calculation.

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