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

GENERAL ASSEMBLY

OFFICIAL RECORDS : TWENTY-FIRST SESSION
SUPPLEMENT No. 14 (A/6314)

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Annex C

THE GENETIC RISKS OF IONIZING RADIATION

CONTENTS

I. Introduction

1. The 1958[1] and 1962[2] reports of the Committee surveyed in some detail the subject of the genetic effects of ionizing radiation. The present paper updates those parts of the earlier reviews that require significant revision in the light of recent progress, with particular regard to those results that more or less directly bear on the estimates of risk from radiation for human populations.

2. The present annex is not self-contained and should be read in the context of the earlier reviews made by the Committee, particularly of that contained in its 1962 report. Many problems that were earlier considered in some detail by the Committee will not be reviewed here, since they are not considered to be directly relevant to the question of risk estimates.

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

3. The surveys of naturally-occurring hereditary defects and diseases made by the Committee in its 1958 and 1962 reports are still in large part valid. The present annex will therefore refrain from discussing again the hereditary factors involved in the general morbidity of the population or in the occurrence of congenital malformations, since too little has been recently added to our knowledge both with regard to the extent of their genetic component and to the mechanisms through which that component acts.

4. Likewise, no detailed discussion will be made of those unfavourable traits that are maintained in human populations by mechanisms which, though reasonably well known, are not predominantly mutational. Exposure of a population to radiation is likely only slightly to affect the prevalence of these traits by comparison with those primarily maintained in the population by recurrent mutations. For the purpose of estimating risks, the relevance of a discussion of these traits is therefore, at most, accessory.

5. Finally, the distribution of quantitative traits in human populations also will not be discussed in the present review. Their importance from the point of view of risk estimates cannot be doubted, but our knowledge has not sufficiently progressed to warrant a revision of the rather detailed discussion contained in the 1958 report of the Committee.

Major disabilities due to single gene traits maintained by recurrent mutation

6. In earlier reports, the Committee considered as an individual category those harmful traits whose mechanism of inheritance was understood and whose prevalence in the population was mainly determined by recurrent mutations, excluding those traits that were due to a cytologically detectable chromosome anomaly. This category, apparently due to gene mutations, included autosomal dominant, autosomal recessive and sex-linked traits.

7. In its 1958 report, the Committee accepted a figure of about 1 per cent as the proportion of all live-born infants falling into this category. Subsequent information suggests that this figure is slightly low. Of this 1 per cent, about 70 per cent are believed to be accounted for by approximately fifty dominant traits determined by autosomal genes. The terms "dominant" and "recessive" as used here are conventional in human genetics. Thus the term "dominant" includes traits usually recognized by the heterozygous expression of the mutation, although in the great majority of examples the condition of individuals homozygous for such genes has never been observed.

8. *Dominant autosomal traits.* The relative frequency of the fifty dominant autosomal traits referred to in the previous paragraph is now estimated to be approximately 80 per cent. An analysis of the proportion of sporadic cases at birth (i.e., cases having no affected relatives) among all living cases suffering from these disabilities indicates that about 4 per cent of the cases are due to new mutations arising in parental gametes.[3] The frequency of live-born children carrying new dominant mutations responsible for major disabilities appears therefore to lie around 3×10^{-4} ($0.01 \times 0.80 \times 0.04$).

9. This frequency corresponds to a rate of 1.5×10^{-4} mutations per generation per gamete. The average mutation frequency of the individual loci responsible for those traits is not known, estimates at individual loci being available only for a few of them which are rather more mutable and not likely to be representative of the rest. It is a safe assumption, however, that the fifty traits referred to in paragraph 7 are determined at fifty loci at least, and, for the purpose of the present discussion, this will be assumed to be true. With fifty loci the average mutation rate per locus per generation would be around 3×10^{-6}. This rate is an upper limit to the average mutation rate at all loci at which dominant visible mutations occur, but it seems unlikely that the average mutation rate can be lower than by, at most, one order of magnitude. If this were so, the number of loci involved would be correspondingly higher.

10. Other limitations may result from the possible inclusion of phenocopies and of recessives mimicking dominant phenotypes. Again, however, the cumulative frequency of traits here considered is unlikely to be more than slightly over-estimated by ignoring these complications.

11. Finally, the frequency of sporadic cases among all cases of the traits considered here, though justified by the need to obtain an over-all mutation rate, may be misleading in as much as it may suggest that the traits involved confer a rather small reduction in fitness. It must be realized, however, that the traits on which the estimate rests span the whole range of severity, from epiloia where the mean fitness is very low, to ichthyosis and alopecia areata in which it is almost unimpaired, even though the latter two diseases may be a cause for serious physical or social hardship to some affected individuals.

12. *Sex-linked traits.* The category of traits that can be confidently attributed to mutations at loci lying on the X chromosome includes, according to a recent survey of the literature,[4] some sixty different disabilities. Another study[5] indicates that the number of clearly sex-linked harmful traits that are maintained in the population by recurrent mutation is forty-nine, most of them with very severe effects.

13. A tentative analysis of the distribution of frequencies of these forty-nine traits suggests that the corresponding over-all mutation frequency is approximately 1.3×10^{-4} mutations per gamete per generation. Assuming that each trait is determined at a single locus, the rate per locus per generation is therefore 2.7×10^{-6}, in reasonable agreement with the upper limit of the estimate obtained independently in paragraph 9 for autosomal dominants.

14. It is important to note, however, that only sixteen of the forty-nine sex-linked traits occur at a rate higher than 10^{-6}. While it is likely that our inventory of relatively common traits maintained by high spontaneous mutation rates is almost complete, it is to be expected that we shall continue to recognize an increasingly large number of very rare traits caused by X-linked mutations. It follows, therefore, that, as in the case of autosomal dominants, the average rate per locus here obtained applies only to those loci that have been sampled so far, and that it would be misleading to assume that they are representative of the spontaneous rates per locus over the rest of the genome.

15. *Autosomal recessive traits.* Recessive traits in man are usually much more severe in their effects (homozygous expressions) than those due to dominant genes where, in general, only the heterozygous expressions are observed. Special methods are now available by means of which it is possible to recognize with a high degree of probability individuals heterozygous for recessive genes, at least when the corresponding gene frequencies in the population are sufficiently high. Many recessive gene traits, probably the great majority, are so uncommon that they are very seldom seen or their genesis recognized. Finally, although recessive detrimental traits are less common, the corresponding gene frequencies, on the average, must be very much higher than those of genes whose expression is easily recognizable in heterozygotes.

Over-all rate of spontaneous mutation

16. The estimation of the rate of spontaneous mutation over the whole genome in man can be approached in several independent ways. Most of them make use of information obtained from studies of the sex-ratio and are based on the hypothesis that differences in the values of the ratio at birth and during various stages of intrauterine life may result from the elimination of various stages of development of males hemizygous for recessive lethals on the X chromosome. The assumption is obviously very crude, as it ignores the physiological factors involved in the differential survival of foetuses of either sex, and the complications due to non-disjunction, to loss or to structural rearrangements of sex chromosomes which are now well documented in man. The sex-ratio might also be affected to some extent by sex-limited autosomal mutations. Accepting the assumption that the sex-ratio is largely controlled by the occurrence of sex-linked recessive mutations and using data on the sex-ratio of dead foetuses, the rate of mutation over the whole X chromosome has been estimated to be 6.8×10^{-3} per generation for mutations expressed between the twenty-eighth week of pregnancy and birth.[6] The same method applied to different data yields similar estimates.[7, 8]

17. Other data were analysed by a more refined method[9] based on the assumption that lethal recessive mutations on the X chromosome accumulate with the age of the mother. A negative correlation between the sex-ratio of live-born children and maternal age is therefore expected and makes it possible to estimate the rate of accumulation of mutants with time. This study also presents several limitations, because the effect of birth order and paternal age cannot in these data be separated from that of the age of mothers, and because maternal age may be correlated with maternal factors differentially affecting foetuses of either sex. The method also fails to remove the bias due to the possible correlation between maternal age and the occurrence of chromosome losses that might alter the sex-ratio at birth. Besides, very large samples are needed to achieve a sufficient resolving power, because the rate of accumulation of mutations in oöcytes is expected to be low if at least part of the mutations that occur spontaneously are due to copying errors, whose frequency of occurrence is more dependent on the rate of cell multiplication than on time alone.

18. The study yielded an estimate of $(2 \pm 0.75) \times 10^{-3}$ mutations per generation per X chromosome in female gametes. Neglecting the theoretical limitations that were outlined above, the estimate applies to recessive lethals acting between conception and birth.

19. Some of the limitations that weaken the validity of the previous methods are removed by studying the relationship between the sex-ratio and the age of the maternal grandfather at the birth of the mother.[10] The relationship is believed to be determined by the accumulation with age of recessive lethals that arise during the continued multiplication of spermatogonia. X chromosomes carrying mutations will be transmitted to daughters, and, from them, to 50 per cent of the male offspring that will thus be eliminated. The age of the maternal grandfather is therefore expected to be positively correlated with male mortality *in utero* and therefore with the sex-ratio of aborted foetuses and stillborn, and negatively correlated with the sex-ratio of live-born children.

20. Although it is not possible even with this method to allow for the occurrence of mutations with sex-limited expression and for structural rearrangements of the sex-chromosomes, the three-generation approach has the advantage that the correlation between time and sex-ratio is unlikely to be obscured by maternal physiological factors or by the occurrence of chromosome losses.

21. The method has been applied to a sample of live-born children with inconclusive results.[11, 12] When applied to a sample of some 7,000 dead foetuses,[13] the method showed a significant positive correlation of grandpaternal age with the sex-ratio, once the confounding effects of other concomitant variables, such as the age of the parents, age of the maternal grandmother, birth order and so on were eliminated. It was thus possible to estimate a rate per generation in male gametes of $(3.6 \pm 0.9) \times 10^{-3}$ sex-linked recessive lethals acting between twenty weeks after conception and birth. An earlier survey of the same size based on still-born gave an estimate of 2.5×10^{-3}, in good agreement with the previous one.

22. The rate thus obtained is probably an underestimate of the total rate of mutation, since, judging from *Drosophila* data,[14-16] sex-linked lethals, as opposed to autosomal lethals, are strongly selected against in spermatogonia, most studies indicating a reduction of around 50 per cent. If the same severe selection holds in man, the rate of sex-linked recessive lethals per generation in the viable male gametes is only half that in the genome before meiosis.

23. A certain number of sex-linked mutants must also be acting later in life. Their rate of induction must be lower, however, since the excess male mortality attributable to genetic causes is certainly very small. If, on the other hand, the rate of spontaneous mutation on the X chromosome is higher in spermatogonia than in oöcytes, the estimate of the spontaneous mutation rate over the whole genome will over-estimate the over-all rate representative of both sexes, but not by a factor of more than two. Although not all the reservations that may be advanced have been reviewed here, as a first approximation the estimate just given, corrected for germinal selection, may be taken as the total rate of induction of sex-linked recessive lethals. Assuming that the X chromosome comprises about 5 per cent of the human genome and that its mutability per unit length is the same as that of the rest of the genome, the total rate of recessive mutations over the whole genome is approximately 14 per cent per gamete per generation.

24. The total rate of mutation as estimated above, divided by the rate of mutation per locus per generation, gives an estimate of the size of the genome in terms of number of loci at which detectable mutations may arise. The average rate of recessive mutations per locus per generation is not known but is likely to lie between 2×10^{-5} and 0.2×10^{-5}, indicating that the genome may contain anywhere between 7,000 and 70,000 loci. A figure that has frequently been used—10,000 loci—was derived from *Drosophila* data by considering the ratio between the over-all rate of induction of sex-linked lethals by radiation and the average rate per locus.[17] For purposes of computation, the figure of 20,000 loci in man will be used in the rest of this review.

25. The significance of an over-all mutation rate in terms of individual or collective hardship is very difficult to assess. While sex-linked recessive lethal genes are promptly eliminated in the hemizygous state *in*

utero, fully recessive mutations arising on autosomes are eliminated mainly in homozygotes and these, because of the low levels of inbreeding prevailing in most human populations, are rarely observed. As was mentioned in an earlier section, strictly recessive mutations that occur spontaneously in man have usually a very severe effect in the homozygote.

26. Evidence from *Drosophila*,[18-21] however, suggests that newly arising mutations on the average are not completely recessive but find a varying measure of phenotypic expression in heterozygotes as well and, in fact, range from fully dominant to completely recessive. Their phenotype is usually harmful, and the mutations are thus eliminated at a rate between 1 and 7 per cent per generation. No such figures are available for any other species, and the *Drosophila* estimate can only be applied to man with the greatest caution.

27. The manner in which mutants are eliminated through heterozygotes in man is also unknown. A number of mechanisms[22] can be thought of, such as loss of embryos and foetuses *in utero*, premature deaths and reduction of fecundity due to physical or mental defects of all shades of severity, and that ill-defined but significant entity known as the genetic component of morbidity. At present, it is not possible to determine to what extent any of these mechanisms contributes to the elimination; in particular, it is unknown what fraction of the elimination takes place through losses assessable in socially meaningful terms.

28. On the other hand, the very concept of unconditional harmfulness entailed by the assumption that mutant genes are eliminated in the heterozygous state has been questioned[23] because a number of genes, both in man and in experimental animals, are known to be advantageous in the heterozygous state, at least in some environments, even though they are detrimental or lethal in homozygotes. The existence of such genes is a matter of experimental observation, but it seems unlikely that they represent more than a small fraction of the newly arisen mutants.

29. Since the phenotypic expression of any gene depends on the expression of the other components of the genome, it could also be argued that, with such a large number of mutants as arise spontaneously in each generation, their interactions with the rest of the genome should be taken into account before reaching conclusions regarding how and when they are eliminated. This cannot at present be done with the available experimental data. Until evidence to the contrary accumulates, however, it is reasonable to assume that the net effect can be neglected, as positive and negative interactions presumably tend to cancel each other.

30. If the rate of elimination observed in *Drosophila* is accepted as valid for man—and there is no denying the tentativeness of such an assumption—and if, as a first approximation, the rate of elimination of new mutations is assumed to be between 1 and 7 per cent per generation, the total number of detrimental genes carried, on the average, by human gametes can be estimated to be between two and fourteen ($0.14/0.07 = 2$; $0.14/0.01 = 14$).

31. Some indirect support for this estimate comes from the study of the offspring of consanguineous marriages in man.[24] Consanguinity of the parents increases the likelihood of their offspring being homozygous for a fraction of the genome, including lethal and detrimental genes. The amount of detriment thus observed in the offspring is directly related to the number of detrimental genes carried by the parents on the one hand, and on the degree of consanguinity on the other. As discussed in earlier reports of the Committee, the relationship between detriment and degree of consanguinity, when established on an adequate sample of consanguineous marriages, makes it possible to estimate the number of genes, or rather of lethal equivalents, in the population which, in the homozygous state, give rise to the type of detriment that is being studied. The estimates vary from one sample to another. A recent review[25] of the available data sets three as a likely upper limit to the mean number of lethal equivalents per gamete acting after birth.

32. The estimate based on the three-generation approach refers to the whole of the newly arisen mutational detriment. The estimate derived from consanguinity studies, on the other hand, is a measure of the detriment carried by the population, as expressed in homozygotes after birth. Estimates of the corresponding damage expressed before birth have so far been so erratic[25, 26] as to preclude conclusions regarding the importance of its contribution to the total detriment, although there is reason to believe from results of animal experiments that it may be far from negligible. Considering that, as discussed in the previous paragraph, the damage estimated on the basis of consanguinity data and the damage quite independently assessed through sex-linked lethals are not entirely the same, and taking into account the errors involved in either estimate, the two approaches appear to lead to reasonably consistent results. Too much weight should not be attached to their closeness, however, because the estimates in both cases are dependent, in different ways, on a large number of assumptions.

33. It must also be mentioned that the damage estimated through consanguinity studies may only in part be due to balance between recurrent mutation and selective elimination through heterozygotes. Even if, as was mentioned in paragraph 28, mutations conferring selective advantage to heterozygotes were much rarer in the population than the others, they could contribute more to the detriment expressed in the homozygous state.[27]

34. The method of assessment of genetic detriment through consanguinity studies was originally expected to yield quantitative information on the respective role of either mechanism in maintaining the detriment in human populations. So far, however, the results of human surveys have been inconsistent. Besides, the approach through which the role of the alternative mechanism can be assessed has recently been challenged on the ground that some of the assumptions on which it rests are unjustified.[28] The estimate based on the three-generation approach can only be regarded as applying to mutational damage. Comparison with that obtained from consanguinity studies suggests that the latter may include a large mutational component.

35. Even consanguinity studies do not provide information about the manner in which genes are eliminated at the levels of inbreeding commonly prevailing in human populations. The damage revealed by these studies is, by definition, due to detrimental genes acting in the homozygous state. There is no way at present to guess at what period of life this damage is being expressed, although it seems unlikely that it can be expressed earlier than in homozygotes.

36. This section has shown that estimates of the over-all spontaneous mutation frequency in man may be derived mainly from human sources, but the degree of confidence in these is still limited by deficiencies both of theory and of the empirical data. However, there is merit in making as much use of human information as possible, and the methods themselves are potentially capable of improvement. It may be noted that the only figure obtained in this section which is used in estimating risks is the estimate of the total number of mutable gene loci in the human genome. Although this figure is based on human data alone, the uncertainty of the assumptions that are used in obtaining it must be clearly borne in mind.

CONSTITUTIONAL CHROMOSOME ANOMALIES

Introduction

37. Despite the considerable advances that have been made in recent years in the field of human cytogenetics and that require a revision of the points discussed by the Committee in its 1962 report, it is still too early to achieve a balanced inventory of the chromosomal anomalies prevailing in the human species. This is not only due to the fact that it is often impossible to establish a close correlation between a clinical pattern and the chromosome anomaly that is observed, but also to the fact that it is difficult to identify certain pairs of chromosomes[a] and that still relatively few subjects have been studied. Nevertheless, several specific syndromes can now be characterized by the chromosome anomalies associated with them.

38. It is customary to consider separately autosomal and sex-chromosome anomalies and, within each of these, changes in the number of chromosomes and structural rearrangements. Among the autosomal anomalies, four syndromes are especially frequent. These are trisomy 21 (i.e., Down's syndrome associated with trisomy of one of the two pairs of chromosomes of the G group which is conventionally called No. 21); trisomy 18 (i.e., of a No. 18 chromosome in the E group) and trisomy 13 (i.e., of one of the 13-15 or D group chromosomes. Conventionally the extra chromosome is assumed to be a No. 13). The fourth syndrome is due to deletion of part of the short arm of chromosome 5 (*cri du chat* syndrome).[b]

39. In addition to these four common anomalies, the occurrence of other types of autosomal alterations has been described:[30-34]

(*a*) An extra chromosome (e.g. 21) from which a portion is deleted, so that a completely trisomic state is not present.

(*b*) Deletions, particularly involving the short arm or the long arm of chromosome 18.

(*c*) Isochromosomes.

(*d*) Ring chromosomes.

(*e*) Translocations of two general types:

(i) Those in which essentially all of one chromosome is exchanged to another, with no identifiable reciprocal product. This produces a chromosome number of 45 in the individual, without phenotypic change. This type of translocation always involves one acrocentric chromosome (groups D and G).

(ii) Translocations in which parts of two chromosomes are reciprocally translocated. This does not produce phenotypic changes in the balanced state, but results in severe damage in the unbalanced condition.

(*f*) Mosaicism—a mixture of two cell lines in the same individual. These may include various combinations of monosomic, disomic and trisomic cells (e.g. involving chromosome 21); a mixture of diploid and triploid cells; or a mixture involving any of the types of abnormalities described above.

40. Among sex-chromosome anomalies,[30-32,35-37] three types are particularly frequent, the XO (Turner's syndrome[c]), the XXY (Klinefelter's syndrome[d]) and the XXX[e] complements. The other complements that have been described—XXYY, XYY, XXXY, XXXXY, XXXX, XXXXX—are much rarer. Structural anomalies are also known: ring X (X_R), isochromosome X involving the long or the short arm of the X chromosomes, deletion of the short (X_{DS}) or of the long arm (X_{DL}) of the X chromosome.

41. Several different types of mosaics, associating, for instance, an XO with an XX line or an XY with an XXY line, have been described. Sometimes structural anomalies of the X chromosome are involved, such as XO/XX_R, $XO/X_{iso}X$, etc. (table I). Each type of mosaic determines different phenotypes depending on which line is preponderant. In true hermaphroditism, karyotypes vary from one case to another; both XX and mosaics are known, the latter of the types XX/XXY, XX/XY and XO/XY.

Prevalence of constitutional chromosomal anomalies

Autosomal anomalies

42. *Trisomy 21.* Most autosomal anomalies have been too recently known to make it possible to estimate accurately their individual rates of occurrence. Several investigations, however, have dealt with trisomy 21, the earliest among the anomalies to be defined as a syndrome. The frequency of trisomy 21 seems to be of the same order of magnitude in all areas where it has been estimated,[38, 39] approximately 1.5 per 1,000 live

[a] The international conferences held at Denver and London[29] defined the characteristics of the normal human karyotype and the relevant terminology. At the London conference it was agreed that chromosomes could be classified according to two systems, alphabetical and numerical, as follows:
1-3 (A), 4-5 (B), 6-12 and X (C), 13-15 (D), 16-18 (E), 19-20 (F), 21-22 and Y (G).

[b] The syndromes due to these autosomal anomalies consist of serious mental retardation associated with a constellation of malformations that makes possible the clinical diagnosis of each syndrome. The most frequent malformations are, schematically:

Trisomy 21: Peculiar facial features with palpebral fissures slanted upwards and outwards, epicanthus, short nose with broad base, thick lips, small and malformed ears, small and spherical skull, hands and feet short and broad, muscular hypotonism.

Trisomy 13: Microcephaly, microphthalmia, harelip, ear and heart malformations, polydactyly, characteristic foot deformity, arrhinencephaly.

Trisomy 18: Ear and skull malformations, abnormal position of hands and fingers, cardiac malformations.

Cri du chat syndrome: roundish face, hypoplasia of the lower jaw, hypertelorism and highly characteristic cry, particularly in the first years of life.

[c] Turner's syndrome: gonadal agenesis, absence of secondary sex-characters, small stature and various malformations in phenotypic females with amoenorrhea.

[d] Klinefelter's syndrome: phenotypic males with high stature, gynecomastia, gonadal hypoplasia and sterility.

[e] The XXX syndrome is a chromosomal rather than a clinical entity that has been observed both in seemingly normal and in feeble-minded women without serious genital disorders.

births. Not all cases of trisomy 21 are regular but the frequency of translocated trisomies 21 is difficult to assess because the samples that have been studied in different laboratories (table II) are usually biased, since karyotype analyses are carried out in most cases in children from mothers under thirty years of age when the chances of detecting a translocation are highest. Based on these selected cases, the frequency of D ~ G and G ~ G translocations is 7-12 per cent,[30, 40, 41] but the most reliable estimates cluster around 2 per cent of all trisomies 21.[42, 43, 44] These translocations are usually of the type D ~ G and G ~ G, other types being exceptional. It should be noted that only in one-third of the families where two or more sibs are affected is trisomy 21 accompanied by a detectable translocation.[45] Translocations involving chromosome 21 have recently been estimated to arise at an approximate rate between 2.1×10^{-5} and 2.7×10^{-5} per chromosome 21 per gamete per generation. The expected frequency of translocated chromosome 21 among live-born children would then be approximately 5.4×10^{-5}.[46]

43. Among these translocations, only a minority is inherited from parents carrying the translocations themselves. Only one in four (3/12) is found when data from several authors[41] are pooled. According to a recent survey,[46] 49 per cent of D ~ 21 translocations and 5.6 per cent only of G ~ 21 translocations are inherited from parents. It can be estimated on the basis of current knowledge that *de novo* translocations in trisomy 21 represent from one-half to three-quarters of all these translocations. The frequency of mosaics of which one cellular line at least is trisomic 21 is low, probably less than 1 per cent,[47] and partial trisomy with deletion of part of a chromosome 21 is exceptional.[48]

44. *Trisomies 18 and 13.* Few statistical data on autosomal trisomies 18 and 13 are available. The first estimates for trisomy 18 give frequencies ranging from 0.2 to 1.6 per 1,000 births.[30, 49-51] For still unknown reasons, a clear predominance of females is apparent—forty-five females as against thirteen males according to a recent survey.[52] Out of sixty-five cases of trisomy 18, sixty regular trisomies have been observed, two translocation trisomies and three mosaics,[52] but the relative proportions of the different chromosomal complements are probably not representative of the actual population frequencies, inasmuch as a bias occurs in the selection of published observations. The same is true for trisomy 13[53] where, out of forty-eight cases, two mosaics, three partial trisomies and three translocation trisomies have been observed. The frequency of trisomy 13 at birth appears to be lower than that of trisomy 18.[51]

45. Cri du chat *syndrome.* No data are yet available on the frequency of this anomaly of which some fifty cases are now known and which consists of deletion of part of the short arm of chromosome 5. Seven cases (including two sibs) have been observed in a population of 1,562 feeble-minded subjects.[54] The frequency of the syndrome is probably higher than that of trisomy 13. The association of the anomaly with a translocation has been described in one case.[55]

46. *Translocations.* It is also difficult to assess the frequency of translocations in the general population, since balanced translocations are phenotypically undetectable and are usually identified through anomalies occurring among the descendants of carrier individuals. Thus, only systematic surveys can give an idea of the frequencies involved. A recent investigation on 438 adults[56, 57] yielded a frequency of five per 1,000 for reciprocal translocations and possibly pericentric inversions, which represent major karyotypic anomalies. Minor variations affecting the size of the short arm of group D and G chromosomes or the location of the centromere of a chromosome 16 are probably fairly frequent (2-3 per cent). It is not proved, however, that those anomalies are associated with any detectable malformation.

Sex-chromosome anomalies

47. The frequencies of sex-chromosome anomalies are better known than those involving autosomes since the number of special stainable bodies (Barr bodies or sex-chromatin) in interphase nuclei makes it possible to know how many X chromosomes are present in a cell. In general, as many bodies are observed in the interphase nucleus as there are X chromosomes less one. Normal male individuals have no sex-chromatin and their cells are called sex-chromatin negative. Cells of normal females have one Barr body which is visible only in a certain percentage (from 20 per cent upwards) of cells called sex-chromatin positive. Cells with three X chromosomes have two Barr bodies and are called double-positive.

48. Sex-chromatin tests therefore make it possible to recognize anomalies involving the number of X chromosomes (XXX, XXY, etc.) and certain mosaics in which normal cells are in sufficient proportion to be detected in a relatively small sample of cells. If the abnormal cell population is a small minority, the mosaic situation will be detected by this means only with great difficulty.

49. In samples from certain selected populations the frequency of sex-chromosome anomalies is higher than in the general population. This is the case with feeble-minded subjects,[36, 56] with sterile subjects,[58] with criminals[59, 60] and with females with stature below normal[61] (table III).

50. A number of surveys have dealt with the frequencies of sex-chromosome anomalies among live-born children. By pooling the data from five of these surveys[62-66] involving altogether over 25,000 children, the following frequencies of subjects with abnormal sex-chromatin are observed: 1.5 per 1,000 females, of whom three-fourths, or 1.2 per 1,000, were double-positive (XXX), 0.3 per 1,000 negative, and 1.7 per 1,000 chromatin-positive males. In eighteen of the 10,725 males who underwent a chromosome examination, twelve were XXY, one was XXXY and five were mosaics XX/XXY.[64] In twelve girls among 10,000 that were investigated, nine proved to be XXX, two were XO, and one was a mosaic $XO/X_{DL}X$ (deletion of part of the long arm). Those figures show the high frequency of mosaics among individuals with sex-chromosome anomalies, a frequency which has been estimated to be about 18 per cent of these anomalies.[36] Finally, Y-chromosome polymorphism is known in man[62] as it is in other organisms, but its significance is not clear.

Conclusions

51. Although more information is needed, it is generally agreed that chromosome anomalies are observed in about ten per 1,000 live new-born infants. Autosomal trisomies and sex-chromosome anomalies

account for about 3.5 per 1,000 each, the rest being accounted for by translocations (table IV). It must be borne in mind, however, that only relatively major anomalies of the karyotype are detectable through present techniques. A sizable number of chromosome anomalies escape cytological diagnosis. On the other hand, attention has recently been drawn[67] to the existence in man of complex structural changes, for example insertions, which can produce genetic imbalance in the children of carriers (duplications, deficiencies). These events do not seem always to be accompanied by detectable morphological differences between the chromosomes of children and those of their parents. Their frequency cannot at present be assessed.

Chromosome anomalies in miscarried foetuses

52. A certain number of spontaneous abortions are associated with chromosome anomalies. Sometimes it is the abnormal chromosome constitution of one of the parents that is responsible[68-71]—mosaics or structural rearrangements, particularly translocations. More frequently, the anomaly concerns the foetus alone—monosomies and trisomies, triploidies—with no apparent anomaly detected in the parents.[72-75] The proportion of chromosome anomalies observed in a number of studies of spontaneous abortions is large: thirty cases out of eighty-two.[76-80] The largest homogeneous survey includes 200 cases.[81,82] Chromosome anomalies were obtained forty-four times: 11 XO, 9 triploids, 7 E-trisomics, 6 D-trisomics, 5 G-trisomics, 2 C-trisomics, 2 tetraploids, 1 B-trisomic and 1 A-trisomic.

53. About one-fourth of all spontaneous abortions therefore appear to be associated with chromosome anomalies, particularly anomalies of the number of chromosomes. The high pre-natal lethality of XO individuals probably explains why the proportion of XO new-born children is much lower than that of XXX or XXY new-born children. Assuming that 15 per cent of all pregnancies result in spontaneous abortions,[83] chromosome anomalies would be responsible for the interruption of about 4 per cent of the pregnancies. The over-all burden of chromosome anomalies would therefore be 5 per cent per generation.

Factors affecting the prevalence of chromosome anomalies in human populations

Modes of transmission

54. Many individuals with constitutional chromosome anomalies have no descendants owing to sterility related to a sex-chromosome anomaly or to some debility associated with an autosomal anomaly. The viability of trisomic subjects, particularly with regard to chromosomes 18 and 13, is severely reduced, so that it must be assumed that the frequency of these anomalies is maintained in the population almost exclusively through recurrent chromosome mutation. Nevertheless, XXX females have been reported to have children; thus, eleven women have had thirty-one children, about half of whom were examined and in whom no anomaly was detected.[35] Recently,[84] two children with Klinefelter's syndrome (XXY) were observed, who were born respectively of an XXX and of an XX/XXX mother, and an XX/XXX girl born of a mother also XX/XXX.[85] This confirms the possibility that sex-chromosome anomalies can be transmitted as has been shown in other organisms, including mice. Among the few children of XXY/XY mosaics, no anomaly related to the parental mosaicism has been observed.[86, 87]

55. Diplo-triplo-21 mosaics have also been observed in six families among the parents of children who were regular trisomics 21. The risk of recurrence of trisomy 21 is all the more difficult to assess in these cases as the respective proportions of the different cell lines are not necessarily the same in the germ line cells as in the somatic cells where they are detected.

56. Another problem regards the transmission of translocations to the descendants of the carriers. The most accurately studied cases are those concerning D ~ 21 translocations. According to certain authors, when the mother carries the anomaly, on the average one-third of her children are normal, one-third carry the balanced translocation and one-third are trisomics 21.[39] Other authors believe that the latter proportion is between one-third and one-tenth.[42] The inconsistency may be due to the different statistical methods employed. When the father is the carrier, on the other hand, the frequency of trisomics 21 among the offspring is much lower, certainly less than 5 per cent,[39] the reason for such a difference in transmission with the sex of the carrier being unknown.

57. In the case of G ~ 21 translocations, the sex of the transmitting parent does not seem to play a role. Therefore 21 ~ 22 translocations will give rise to one-third, one-third, one-third proportions, whereas the offspring of 21 ~ 21 translocations will be trisomics 21 since the lethality of haplo-21 zygotes is probably very high.

58. The frequency of transmission of other types of translocations is less known. A familial observation of a D ~ D translocation showed a 1:1 segregation of the anomaly in the course of three generations.[89] It is not unlikely that the size of the chromosomes involved in the translocation may influence the frequencies of abnormal[90] segregation, but the available data are still insufficient. Interchromosomal effects[91] are an additional cause of aneuploidy among the descendants: the presence of an anomaly, e.g. a translocation, may increase the likelihood of an anomaly of a different type in the offspring; several observations of regular trisomies 21 have been reported in children born of parents carrying translocations of the D ~ D type and sex-chromosome anomalies in children of a parent carrying an autosomal translocation have also been observed.

Mechanisms of induction

59. Still relatively little is known on the mechanisms of induction of chromosome anomalies in man. Anomalies involving the number of chromosomes may be due to non-disjunction or to loss of a chromosome during meiosis. But both loss and non-disjunction may also take place in the zygote.

60. When abnormal segregation or losses of chromosomes occur at the blastomeric stage, they give rise to mosaics consisting of two or more cell lines. The existence of monozygotic twins with different karyotypes argues in favour of such a mechanism.[30] If one of the cells resulting from non-disjunction is unviable (e.g. YO), the complementary cell (XXY) only will give rise to an anomalous homogeneous line.

61. Abnormal gametes may arise at meiosis in translocation carriers. Certain structural anomalies may also take place during meiosis (production of X isochromosomes) but not necessarily so. Other mechanisms have been suggested to account for certain aneuploidies: asynchronous duplication of a single chromosome,[92]

polyspermy or double fertilization, of which several examples have been recently described in the case of XY/XX mosaics.[93-95] The frequency of those accidents, however, is still wholly unknown.

62. In certain cases it is possible to identify the stage at which the accident has occurred. Thus, an $X^M X^P Y$ complement[f] is due to a non-disjunction during the first meiotic division in the male, whereas $X^M X^P X^P$ and XYY are believed to result from non-disjunction at the second division.[35] By means of the markers located on the X chromosome (colour blindness, glucose-6-phosphate-dehydrogenase deficiency, Xg blood group), it is occasionally possible to determine the paternal or maternal origin of an X chromosome. Thus, among the XO subjects studied in one series, the maternal origin of the X chromosome has been ascertained twenty times and its paternal origin once,[96] but because of the difficulty of the technique this cannot be taken as a reliable estimate. Likewise, XXY subjects are known to have arisen as a consequence of non-disjunction occurring during gametogenesis in either parent.[30, 35, 97, 98] Finally, an XXYY subject has been reported to originate from two successive non-disjunctions.[99]

Possible aetiologic factors

63. A certain number of factors are known to induce chromosome anomalies, but their actual effect in man can only be indirectly inferred, since few cytogenetic data on human gametogenesis and the early stages of development of the human embryo are available.

64. *Maternal age* is positively correlated with the occurrence of aneuploids. This is clearly proved in the case of trisomy 21,[38, 39] and is observed also with trisomies 13 and 18 though to a lesser degree,[30] and perhaps in the case of Klinefelter's syndrome (XXY)[100] as well, but apparently not with Turner's syndrome (XO).[101]

65. *Certain viruses* may be responsible for chromosome or chromatid breaks, both *in vivo* and *in vitro*, and also for cases of aneuploidy, sometimes preferentially involving certain chromosome pairs.[102] Attention has been drawn to time fluctuations of certain constitutional chromosome anomalies and to their accumulation in certain limited areas.[38, 103, 104] A correlation has been suggested between an increased frequency of X-chromosome anomalies and of trisomy 21 on the one hand, and an epidemic of rubella in the preceding months on the other, as well as between an increased frequency of trisomy 21 and an outbreak of infectious hepatitis.[105, 106]

66. *Ionizing radiations*, particularly x rays, have been suspected of inducing aneuploidy in man. It does not seem, however, that exposure to radiation is actually recalled more frequently among mothers of trisomics 21 than among mothers of normal children,[107, 108] as had earlier been held,[109] although the results of a recent survey[110] reopen the problem once more. The possible role of parental radiation before conception has again been suggested recently with regard to one case of trisomy 13[111] and in several cases of trisomy 18.[112]

67. Very few cases of chromosome anomalies in human somatic cells have so far been observed after pre-natal irradiation. In a recent observation the anomaly consisted of a mosaic of minute chromosomes, with no apparent structural rearrangements, in a child who had been exposed to radiation in the first weeks of intra-uterine life.[113] Additional studies have also been made in recent years on the effects of both x rays and internally-deposited radio-active isotopes (I^{131}, P^{32}) on chromosomes of human somatic cells. The studies were carried out on blood, skin or aponeurotic cells drawn from subjects exposed to radiation accidentally[114-117] or occupationally,[114, 118-123] or exposed for therapeutic or diagnostic reasons.[113, 114, 121, 124-149]

68. These *in vivo* studies have yielded information on the types of anomalies observed and on their persistence in the organism. Both aneuploidies and polyploidies, frequently due to endo-reduplications, and also structural anomalies have been observed: chromatid and chromosome breaks, acentric fragments, minute chromosomes, di- and polycentric chromosomes, and ring chromosomes. Some of these changes persist for years. Observations have been reported in which the irradiation had taken place more than twenty or thirty years prior to the observation.

69. In other studies, human somatic cells were exposed to radiation *in vitro*.[150-160] *In vitro* irradiation makes it possible to select the quality of the radiation, to estimate more accurately the doses and dose rates received by cultured cells, and to evaluate the number of various types of chromosome rearrangements as a function of the dose. The frequency of deletions has thus been shown to be linearly related to the dose of both x rays and neutrons.[153-157] The frequency of two-hit events (dicentric and ring chromosomes) bears a quadratic relationship with the x-ray dose and a linear relationship with the dose of neutrons (table V).[153, 161, 162]

70. *Conclusion.* The respective role of each of these factors cannot at present be assessed, especially as still other factors that are not mutagenic *stricto sensu* may also play a role. The association of several different chromosome anomalies in certain families or in certain subjects suggests the existence of factors predisposing to these anomalies. An interchromosome effect (paragraph 58) may enter into play in certain cases, while others have been attributed by some authors to the effect of a gene similar to those already known to be responsible for non-disjunction in *Drosophila*. The role of a gene responsible for familial mosaicisms has also been suggested.[85, 163]

III. Experimental data on radio-sensitivity of germ cells *in vivo*

Changes in the number of chromosomes

Changes of ploidy

71. Several attempts have been made to induce changes of entire sets of chromosomes in mammals. Where radiation was used as the inducing agent the attempts have not been successful. Experiments not involving radiation showed that triploid embryos can survive. They were observed at nine and one-half and twelve days gestation in mice and rats, respectively, and at five months of age in human foetuses.[30, 164] In experimental animals, embryos of higher ploidy are eliminated before implantation. If the same phenomenon

[f] X^M and X^P indicate X chromosomes of maternal and paternal origin, respectively.

obtained in man, these embryos would be eliminated during the first week after conception.[g]

72. In contrast to what has been observed in mammalian species, viable triploid animals have been described in *Drosophila*, the parasitic wasp *Habrobracon*,[165] the land isopod *Trichoniscus* and the salamander *Triturus viridescens*.[166] Polyploidy has been observed in the silkworm *Bombyx mori* and the butterfly *Solenobia triquetiella*.[167-172]

Loss or addition of individual chromosomes

73. Animals monosomic for one of the autosomes have rarely been observed. The best known example is that of the fruit fly which can survive the loss of one of the fourth chromosomes, representing a few per cent of the total genome. Mammals monosomic for one of the autosomes have never been observed, and several lines of evidence suggest that monosomics are always lethal before birth, although mosaics may survive.[173]

74. Instances of trisomy have been studied extensively in plants for a quarter of a century.[174] They are known for the fourth chromosome of *Drosophila* and have recently been reported in the mouse by Griffen and Bunker[175] who described three different autosomal trisomics by analysing the male offspring of males, the spermatogonia of which had been irradiated with 350 and 700 R of x rays. Two of the trisomics were sterile and the third semi-sterile. In each case, the extra chromosome was a member of the smaller chromosome classes, and none of the males showed external deviations from the normal phenotype. A phenotypically normal but sterile male trisomic for one of the smallest chromosomes has also been found by Cattanach.[176]

75. Anomalies involving sex-chromosomes are much better known than those involving autosomes. Information on the spontaneous occurrence of the sex-chromosome anomalies in mammals has been reviewed extensively by Russell.[173] The spontaneous occurrence of these anomalies in mice and in *Drosophila* was discussed in the 1962 report (annex C, paragraphs 71 and 72).

76. In experimental animals, the most commonly observed anomalies are of the XO and XXY type, irrespective of whether male or female germ cell stages have been irradiated. XO individuals are observed more frequently than XXY individuals, the reverse being true in man (paragraph 53), because, in addition to non-disjunction, XO individuals can arise through loss of the paternal X or Y chromosome or the maternal X chromosome during germ cell formation as well as during or before the first cleavage of the zygote. By contrast, it is likely that the majority of XXY individuals arise from non-disjunction.

77. Experiments with mice have demonstrated that a considerable increase above the spontaneous frequency of XO and XXY individuals can be obtained by irradiating various germ cell stages as well as early zygotes.[177, 178, 179] Table VI summarizes the data.

78. With regard to the induction of sex-chromosome losses (XO individuals) in mice, the sensitivity is highest in the early zygotes, namely, shortly after sperm entry (completion of second meiotic division) and also in the early pronucleus stage. Sensitivity then becomes relatively low in the mid-pronucleus stage (probably post-DNA synthesis). Male and female germ cells at all stages are much less sensitive than are early zygote stages. Spermatids appear to be the most sensitive germ cells in males.

79. In females, the early prophase stages of the primary oöcyte, which are only present in the ovaries of foetuses and new-born children, are about as sensitive as early spermatocytes. From the point of view of genetic risks, it is the dictyate stage of the oöcyte that is most important. Dictyate oöcytes in various developmental phases are present in the ovaries from shortly after birth until about eight hours before each ovulation. In man, cells at that stage therefore absorb more natural and man-made radiation by several orders of magnitude than any other female cell stage.

80. Oöcytes in the early phases of the dictyate stage are easily killed by exposures as low as 8 R.[180] Genetic effects have therefore not yet been studied for this early stage. Preliminary results on later phases of the dictyate stage (table VI) have shown that the sensitivity of these cells with regard to sex-chromosome losses is on the average of the same order as that of the male germ cell stages.

81. Studies on the induction of sex-chromosome loss in the metaphase of the first meiotic division of the oöcyte are in progress. In view of the results of the induction of dominant lethals (paragraph 108), it is to be expected that radiation-induced sex-chromosome loss in this stage will be high compared to other female germ cell stages.

82. In adult *Drosophila* males, several independent attempts have been made to determine the rate of induction of XO animals.[181-186] The absolute frequencies, however, are dependent upon the age of the males at the time of irradiation and the type of X chromosome carried by the irradiated males. In decreasing order of sensitivity, male germ cells rank as follows: spermatocytes > spermatids > spermatozoa > spermatogonia. Below 1,000 R, the results for spermatocytes are consistent with a linear dose-effect relationship and suggest that the induced rate of XO animals per R is about 2.3×10^{-5}. This figure is remarkably close to that obtained for spermatocytes in mice (table VI).

83. Information on the induction of sex-chromosome loss in spermatogonia of *Drosophila* is scanty. The induced frequencies observed are close to those of the controls. Sensitivity would therefore seem to be much lower than for other stages.

84. With regard to the induction of non-disjunction by irradiation, the peak sensitivity for XO and XXY animals is found in the same stage(s) of spermatogenesis.[181, 186, 187]

85. Experiments with oöcytes in different developmental stages have clearly shown that XO and XXY animals can result from the irradiation of *Drosophila* oöcytes in the prophase of the first meiotic division.[188, 189] The most recent study provides good evidence that the frequency of XO animals increases faster than linearly with dose in the exposure range 500-5,000 R. The dose-effect relationship for the production of XXY animals is more complicated and difficult to interpret.

86. The induced frequency of occurrence of X^M (maternal X) loss in *Drosophila* is 0.58×10^{-5} per roentgen (calculated by taking account of the fact that YO is lethal) at an exposure of 500 R.

[g]

	Pre-implantation period in days	*Major organogenesis period in days*	*Foetal period in days*
Mouse	0-5	6-13	14-20
Man	0-8	9-56	57-270

87. The evidence presented in the preceding paragraphs demonstrates that loss of sex-chromosomes (and most probably of other chromosomes as well) and non-disjunction of these chromosomes can be induced by ionizing radiation in experimental animals. There are no reasons to doubt that chromosome changes of this type can also be induced by radiation in the germ cells of man. In fact, there is already some evidence that this is the case.[110] It is perhaps not coincidental that a similar frequency of induction of sex-chromosome loss is observed in the spermatocytes of *Drosophila* and of the mouse. Results for dictyate oöcytes of the mouse are of the same order of magnitude. Information on the induction of sex-chromosome loss and non-disjunction in dictyate stage oöcytes and spermatogonia is still far from complete. In view of the results obtained with *Drosophila,* one can surmise that the rate of induction of sex-chromosome losses in the spermatogonia of mice and man may also be much lower than the corresponding frequencies obtaining at other stages of spermatogenesis. Special emphasis needs to be given to the fact that the early zygote stages in mice have proved to be extremely sensitive to the induction of chromosome loss by irradiation.

Dominant lethals

Introduction

88. For the purpose of this section "dominant lethals" are defined as those genetic changes, irrespective of their exact nature, that cause embryonic death and early post-natal death in heterozygotes. However, the term has more specifically come to be applied to those embryonic deaths that result from point mutations or chromosome breaks in parental germ cells. All induced changes that affect the germ cells themselves or render the gametes incapable of participating in fertilization are excluded from the dominant lethal category.[164]

89. There should be a clear distinction between dominant lethals arising in mature gametes as compared to those in immature germ cells. In post-meiotic male germ cells, the frequency of dominant lethals rises linearly with dose at low x-ray doses. The damage primarily results from chromosome losses due to single chromosome breaks. If the broken ends of chromosomes remain unrestituted and form acentric fragments and dicentric chromosomes during the development of the zygote, they cause death. At higher doses of irradiation, two-break events lead to structural chromosome anomalies which may also result in zygotic death. However, the main contribution to zygotic mortality is probably from single chromosome breaks.

90. In pre-meiotic male germ cells, most, if not all, of the chromosome breaks which yield acentric and dicentric chromosome combinations will be expected to lead to death of the descendant cells and therefore to be selectively eliminated prior to becoming mature germ cells. On the other hand, most dominant lethals induced by treatment of pre-meiotic cells are the consequence of multiple (two or more) chromosome breaks leading to simple translocations, inversions, etc. In their original form, such changes frequently do not kill either the germ cells carrying them or the resultant zygotes. However, as a result of events at meiosis, they may give rise to genetically unbalanced gametes still capable of fertilization but eventually leading to unviable zygotes.

91. In the mouse, two methods are available to estimate the dominant lethality induced by radiation. The first method measures changes in litter-size of irradiated animals. The second method takes into account the components of pre-natal mortality as observed by dissecting pregnant females about twelve to eighteen days after mating, and counting the number of *corpora lutea* and of dead and living implanted embryos, thus making it possible to estimate the proportion of pre-natal deaths that occur before or after implantation. Not all pre-implantation losses can be attributed to zygotic deaths. They can also be due to (*a*) lack of fertilization: (*b*) lack of fertility of the egg. Similarly, not all zygotic deaths result from dominant lethal action. They may also be due to maternal factors, such as failure of the uterus to respond to the appropriate endocrine stimulus, thus precluding implantation of fertilized eggs.

92. Both methods have been in use since 1932. Litter-size, however, has proved to be an extremely variable character, so that more reliance is now placed on estimates based on pre-natal death data. Litter-size can be affected by many factors, such as the number of implanted embryos in the uterus and the lactation stimulus which in turn is also dependent on the number of sibs in a litter. In experiments with highly inbred animals, litter-size data can be misleading, because the death of an embryo may increase the chances of survival of the remaining embryos by reducing intra-uterine competition.

Male germ cells

93. *Spermatogonia.* As early as 1956, it was found that the irradiation of mouse spermatogonia led to a significant decrease in mean litter-size as measured three weeks after birth.[190, 191] These reductions were observed following acute exposures of 600 and 1,000 R. Even after a single exposure of 300 R, a reduction in litter-size of about 3-4 per cent was found.

94. In more recent years, most data have been obtained through the pre-natal death method. There is, however, no common opinion as to how the measurements of pre-natal death should be used to estimate dominant lethal damage. Therefore in this review, comparing results obtained by different authors[192-197] made it necessary to recalculate their data, as the figures given in their tables were such that comparisons could otherwise only be made for post-implantation deaths. Table VII gives the results of the recalculations and shows that the total rate of induction of dominant lethals increases significantly when spermatogonia are irradiated with acute x-ray exposures of 300 R and higher.

95. The data obtained by the various authors are conflicting with respect to the question whether pre-natal death occurs predominantly before or after implantation.

96. There is evidence that the induction of dominant lethals is dose-rate dependent.[194, 198] Results presented in table VII show that irradiation at 600 R + 600 R acute x rays increases the frequency of dominant lethals significantly,[198] whereas a single dose of chronic radiation does not.[194]

97. With regard to the question of the persistence of irradiation-induced dominant lethal damage in spermatogonia, the results obtained by Sheridan[196] are of particular importance. His data showed that the frequency of dominant lethals, as measured by the proportion of dead implants among total implants, remained constant over a period of at least twenty-four weeks. These results indicate that dominant lethals

once induced in primary spermatogonia may be indefinitely transmitted to the more mature germ cells that originate from these spermatogonia.

98. It is not unlikely that the dominant lethality which is observed over the twenty-four-week period can at least partly be accounted for by translocations induced in primary spermatogonia. Translocations will be dealt with in the section on translocations (paragraphs 114-129).

99. *Other germ cell stages.* The most recent information on sensitivity with regard to the induction of dominant lethals in the male germ cells of mice at other stages is presented in table VIII. Older data have recently been reviewed.[164] In interpreting the data in tables VII and VIII, it must be borne in mind that part of the spermatocytes and spermatogonia could have been killed almost instantaneously by the x-ray doses that were employed, thus leading to sperm depletion. As a consequence, an unknown fraction of the non-implanted eggs may be accounted for by lack of fertilization rather than by the induction of dominant lethals.[164] It is therefore more appropriate to base estimates of dominant lethal damage on post-implantation data.

100. The post-implantation data in table VIII show that spermatids are the most sensitive cells. Spermatozoa in the vas deferens and in the epididymis are more sensitive than those in the testis tubules, whereas part of the spermatocytes are probably as sensitive as spermatozoa, others being less sensitive. Finally, spermatogonia appear to be somewhat less sensitive than spermatocytes.

101. The changes in sensitivity in maturing male germ cells of *Drosophila* are very similar to those observed in mice.[199-205] Dominant lethal induction is highest in spermatids and spermatocytes. Spermatozoa are roughly half as sensitive as spermatids, and, finally, spermatogonia are about half as sensitive as spermatozoa. The pattern of response of male germ cells of the silkworm to the induction of dominant lethals, although less well known, follows essentially the same pattern as observed with *Drosophila*.[206] Studies on various species of insects have provided a powerful tool in programmes to control insect pests by means of radiation-induced sterilization.[207]

102. Induction of dominant lethals in post-meiotic cells has not only been studied in the mouse, but also in guinea pigs, rats and rabbits. The data, summarized in table IX, indicate the variability in sensitivity between mature spermatozoa of different species. It was calculated that the LD_{50}'s due to induced dominant lethals in these species are 730, 430, 380 and 305 R, respectively.[208, 209] However, general conclusions on the relative sensitivity of these species cannot be made since it varies with dose.

103. Dominant lethal induction has also been studied in swine.[210-214] Since in these experiments only the effects on spermatogonia have been studied, these data cannot be compared with those of the species mentioned in the preceding paragraphs.

104. The objective of the studies with swine was to measure the effects of paternal irradiation (300 R x rays) on the first generation offspring. Changes in litter-size at birth, mortality between birth and weaning, and increase of weight within the first 152 days of life were some of the criteria which were used to detect the genetic effects. In these experiments, two different breeds of pigs were used—Duroc and Hampshire. Thus far, 2,315 litters have been examined. In the Duroc breed, radiation caused a slightly significant increase (4.2 per cent) in the litter-size at birth and a rise in the sex-ratio. On the other hand, irradiated Hampshire males sired smaller litters than their unexposed brothers though the difference was not significant. At present the discrepancy between the two breeds cannot be adequately explained.

105. The mortality of new-born pigs was analysed during three periods (0-1 day; 2-6 days; 7-42 days) between birth and weaning. In each of these periods the mortality rate in Duroc pigs was higher in the irradiated than in the non-irradiated series. The irradiated group of the Hampshire breed showed higher mortality only in the first period. In the Duroc breed, total mortality at forty-two days was significantly higher ($P < 0.05$) in the irradiated than in the non-irradiated series. The total mortality rate in the control and irradiated series of the Hampshire breed was not significantly different.

106. In general, mortality was greater in large litters than in small ones. Furthermore, male pigs had higher mortality rates than females, the relationship between sex and mortality being more pronounced in the Duroc than in the Hampshire breed. All data taken together indicate that the results obtained with the Duroc breed are inconsistent with those obtained with the Hampshire breed and make it premature to generalize on the consequences of irradiation of sires in swine.

Female germ cells

107. Information on dominant lethal induction in the different stages of oögenesis in mice and other species is not as extensive as that for spermatogenesis. The earlier data on various mammalian species have been extensively reviewed[164] and show that stages which possibly correspond to the diakinesis stage or to the metaphase stage of the first meiotic division are much more sensitive than those between the early dictyate and the diakinesis stages. In more recent years, the relative sensitivity of mouse oöcytes at different stages has been studied by using the technique of induced ovulation, by means of which it is possible to irradiate oöcytes at different stages throughout the meiotic divisions.[215]

108. The results of these studies are summarized in table X and show that the total rate of induction of dominant lethals reaches its largest values in oöcytes irradiated during the metaphase of the first meiotic division. Anaphase I and metaphase II are less sensitive than metaphase I oöcytes, but still considerably more sensitive than the dictyate and pro-nucleus stages. The same pattern of sensitivity can be demonstrated for induced post-implantation death. For induced pre-implantation death, as defined in table VII, no clear sensitivity pattern can be observed. In practically all stages, pre-natal death occurs predominantly after implantation; in particular, this is evident in the series in which the females had been exposed to 200 R.

109. The data obtained with oöcytes lend themselves to a comparison with those obtained in male germ cells. The best possible comparison is that between the data of Bateman[195] (table VIII) and those of Edwards and Searle[215] (table X), since both experiments were performed at the same exposure of 200 R. Although it is realized that these experiments were carried out by different authors, and that the total rates of induction of dominant lethals can vary because of differences in experimental technique, it seems justified to conclude that metaphase I oöcytes seem decidedly

more sensitive than spermatids. From a comparison between oöcytes in the dictyate stage and spermatogonia, it may be presumed that oöcytes in the dictyate stage are more sensitive than spermatogonia by a factor of ten to twenty. However, this has only been observed at 200 R. At other doses this factor may be completely different, since sensitivity to cell killing and to the induction of genetic damage can vary widely among cells of the spermatogonial population and among cells in the dictyate stage.

110. In insect species, as in mice, it has repeatedly been observed that oöcytes in metaphase I are much more sensitive to dominant lethal induction than during prophase stages (*Drosophila*,[216-218] *Habrobracon*,[219] *Cochliomyia hominivora*[220]). Similarly, studies with the silkworm (*Bombyx mori*) have shown that the frequency of dominant lethals observed after irradiation of oöcytes immediately before metaphase is twenty times higher than the frequency observed after irradiation of oögonia when only lethals which act in the embryonic stage are taken into account. Most lethals induced in the oöcytes were found to be eliminated during embryonic and larval stages, whereas death caused by lethals induced in oögonia was evenly spread over all developmental stages.[221]

Summary and conclusions

111. With regard to dominant lethal induction, it is clear that the sensitivity pattern for the various stages of gametogenesis is strikingly similar in widely different species. In all species studied, the highest frequencies of dominant lethals are observed in spermatids and the lowest frequencies in spermatogonia. Among female germ cell stages, the highest frequencies are found in metaphase oöcytes in the first meiotic division, whereas the lowest frequencies are encountered in dictyate stage oöcytes of mammals and in oögonia of insects. Induced frequencies of dominant lethals in spermatogonia vary widely among species, even within mammals.

112. Experiments with mice, rats and guinea pigs have shown that death due to dominant lethality occurs mainly at about the time of implantation or shortly thereafter. In rabbits, however, dominant lethals act predominantly before implantation of the embryo. Predictions concerning the time of action of dominant lethals in man are difficult to make on the basis of results obtained with other mammals. This is so because man is monotocous, whereas the other mammals are polytocous.[h] Furthermore, there exist differences in nidation and placentation between man and primates on the one hand, and other mammalian species on the other.

113. Results of studies with mice indicated that dominant lethals induced in primary (predefinitive) spermatogonia of the mouse can be transmitted to the immediate offspring of the carriers of these spermatogonia for over a period of at least twenty weeks and possibly much longer.

Translocations

Male germ cells

114. In mice, the presence of translocations is usually ascertained by analysing the F_1 progeny of treated and control animals for heritable semi-sterility. In practice, semi-sterile animals are recognized as those animals of the F_1 progeny which have considerably less than the normal number of F_2 offspring. In addition to the criterion of semi-sterility, most authors confirm the presence of translocations by examining cytologically pre-meiotic and meiotic germ cells of presumed translocation carriers. Table XI surveys the data presently available on translocation induction in spermatogonia of mice.

115. It is highly probable that translocation induction in spermatogonia is an important cause of dominant lethality in zygotes descended from those cells, since in the mouse each spermatocyte (division product of spermatogonia) heterozygous for a translocation will produce one gamete carrying the translocation, one gamete with the normal chromosome complement and two unbalanced gametes carrying duplications and deficiencies. Unbalanced gametes, upon fertilization, give rise to zygotes which usually die at about the time of implantation. However, some zygotes die between implantation and birth, while a few apparently survive to maturity.[222]

116. Experiment 1 in the table shows that irradiation of spermatogonia with two acute exposures of 600 R each results in a significant increase in the percentage of translocations in both female and male F_1 progeny. The pooled data from experiment 1 show that about 4 per cent of mature offspring of the irradiated males carry induced reciprocal translocations. From this percentage it was calculated that the frequency of translocation heterozygotes among spermatogonia was 14.8 per cent.[223] Since radiation was given in two fractions to prevent substantial killing of spermatogonia, the translocation frequency might have been different if the total had been given in one single exposure instead of two.

117. The experiment mentioned above was not only performed to obtain an estimate of the rate of induction of translocations but also to provide information on the total rate of induction of dominant lethals. By studying data both on translocation induction and on dominant lethal induction, it is possible to estimate that about 67 per cent of the total amount of dominant lethality (total amount of pre-natal death) in the 1,200 R experiment can be attributed to translocations, whereas the remaining dominant lethality is thought to be caused by "primary dominant lethal mutations".[198] The situation is different when the haploid post-meiotic germ cells are irradiated. In that case, the contribution of translocations to dominant lethality is much smaller, because in these cells translocations of the aneucentric[i] type will cause death of the zygotes, whereas eucentric translocations will be tolerated.

118. Experiments 1 and 2 in table XI are the only ones that provide information on the effect of dose rate on translocation induction in spermatogonia of mice. As expected, the dose-rate effect is very pronounced[194, 198] (see also paragraph 124).

119. Experiment 3 provides information on translocation induction in spermatogonia following irradiation with an acute exposure of 700 R.[224] The frequency of translocations in this experiment is significantly lower than the frequency in experiment 1, even when the difference in dose is taken into account. Differences in the experimental procedure and in the strains used are mentioned as the possible factors which might account for the observed discrepancy.

[h] Monotocous and polytocous mammals produce respectively one and many young at a birth.

[i] Aneucentric translocations involve the centromere so that there results an acentric and a dicentric chromosome.

120. Results obtained from experiment 6 do not provide evidence in favour of or against the validity of the estimates derived from experiments 1 and 3. The percentages of semi-sterility obtained at the three different doses in experiment 6 do not differ significantly; neither do they differ significantly from the percentage of semi-sterility (4.14) observed in experiment 1. The data of experiment 6, however, must be interpreted with some care, because only an unknown percentage of the semi-sterile F_1 individuals has been analysed cytologically. Since it can be deduced from experiment 6 that not all semi-sterile F_1 animals had cytologically detectable translocations, it might well be that the frequencies obtained from this experiment lead to over-estimates of the rate of induction of translocations by a factor which is unknown and that probably varies with dose.

121. Experiments 4, 5 and 7 in table XI were not primarily designed to detect translocations.[196, 197, 225] The results of these experiments seem to be consistent with those of experiment 1, but accurate estimates of the rate of induction of translocations cannot be obtained from them because of the fairly small number of animals involved and because cytological analyses were not performed.

122. The experiments summarized in the previous paragraphs have shown conclusively that translocations can be induced in pre-meiotic male germ cells. The rate of induction being low, as had already been noted in the 1962 report on the basis of much more limited information, translocations have been recovered only at high doses and dose rates. It must be pointed out that the rates of induction thus obtained refer to those translocations alone that are recoverable through semi-sterility. This procedure may lead to an underestimate of the total rate of induction of translocations.

123. Older data on translocation induction in other stages of spermatogenesis have been reviewed by L. B. Russell.[164] These data, together with the more recent data of Griffen,[226] show that post-meiotic cells are much more sensitive than pre-meiotic cells, and that among the post-meiotic stages the spermatid stage is the most sensitive one. Pooling the data reviewed by Russell and those of Griffen indicates that approximately 25 per cent of the offspring are semi-sterile when post-meiotic cells are irradiated with a dose of about 700 R. It thus seems that post-meiotic cells are about six times as sensitive to the induction of translocation as spermatogonia.[223] On the basis of theoretical considerations, Auerbach and Slizynska[227] conclude that post-meiotic cells are twelve times more sensitive than spermatogonia.

124. Besides genetic studies, cytological studies also have been performed on the induction of translocations. Arsenieva and Bochkara[228] discovered that, when primary spermatocytes are irradiated with 50 R or less, both balanced and unbalanced translocations occur twice as frequently in monkeys (*Macaca mulatta*) as in mice. Other cytological studies provided information on the effect of dose rate on translocation induction in spermatogonia of mice which were exposed to 600 R of x or gamma rays.[292] Frequencies of multivalent configurations (indicative of heterozygosity for reciprocal translocations) in spermatocytes at dose rates of 913, 89 and 9.7 R per minute did not differ significantly, all being 12-13 per cent. At lower dose rates, however, frequencies were much lower, being about 5 per cent at 0.86 R per minute, and falling to only 1.5 per cent at 0.02 R per minute. It therefore seems that, with regard to translocation induction in type A spermatogonia at the dose level of 600 R, high dose-rate irradiation is about eight times as effective as low dose-rate irradiation.

125. The application of the cytological technique has also revealed a marked discrepancy between the translocation frequency in spermatogonia as found in the genetic experiment (600 R + 600 R, paragraph 116), and that observed cytologically in spermatocytes.[220, 290-292] The observed frequency of translocations in the genetic experiment is about half that observed cytologically. It is thought that the observed discrepancy does not result from a failure of translocation heterozygotes to show semi-sterility, but rather from a selective process between meiotic metaphase and fertilization.

126. As far as the genetic experiments are concerned, it is remarkable that the sensitivity pattern for translocation induction in the different stages of spermatogenesis in mice is very similar to that observed in *Drosophila*. Information on the latter species is, however, much more detailed.[205, 230-233] *Drosophila* spermatogonia appear to be less sensitive to translocation induction than mice. For the F_1 male progeny, the frequency of induction of autosomal translocations is around 0.5 per cent (3,280 tested gametes).[231] No translocations were found in an experiment by Oster (2.000 R, 813 tested gametes)[230] and only one in the experiment of McCarthy and Nafei (400 R, 901 tested gametes).[232]

Female germ cells

127. Information on translocation induction in oöcytes of the mouse is very scanty. Irradiation of late oöcytes with 400 R acute x rays, resulted in a frequency of induced heritable partial sterility of about 2 per cent.[164] This figure is not far removed from the figure of 4 per cent semi-sterility which has been obtained for spermatogonia irradiated with 600 R + 600 R (paragraph 116).

128. The observations on the induction of translocations in female germ cells of mice confirm the findings in *Drosophila*, where it has also been found that the frequency of radiation-induced reciprocal translocations in female germ cells is very low.[234-236]

129. The preceding paragraphs on the induction of translocations in germ cells of experimental animals have shown that these anomalies are induced in both male and female germ cells. The studies indicate that the frequency of radiation-induced translocations is higher in spermatogonia than in dictyate oöcytes. At present, only results obtained with spermatogonial irradiation can be used to estimate the rate of induction of translocations in man.

POINT MUTATIONS

Specific locus mutations

130. In its 1962 report, the Committee reviewed extensive data on the induction of recessive mutations at seven specific loci in the mouse. Since then, more data have become available. Both old and new data are listed in table XII. They only refer to specific locus mutations induced in spermatogonia and oöcytes. Ignoring variability between loci, the spontaneous mutation rate at the seven specific loci in male germ cells lies between 0.46×10^{-5} and 1.0×10^{-5} mutations per locus per generation (95 per cent confidence limits).

131. In spermatogonia the rate of induction of specific locus mutations rises linearly with acute exposures

up to 600 R. At higher doses, the yield of mutations falls off. This has been attributed to "selective elimination at high doses of the more mutationally sensitive cells in the spermatogonial population".[237] In spermatogonia, the rate of induction is about 2.2×10^{-7} mutations per locus per roentgen. Owing to the sampling variability of the data and to variations in mutability between loci, the rate of induction may lie anywhere between 0.75×10^{-7} and 5.5×10^{-7} (95 per cent confidence limits). These data were obtained from the mutation rates observed after exposure of spermatogonia to 600 R of acute x rays.

132. Recently, results have been published of a study on mutation rates at a set of six specific loci in the mouse.[238] Only one locus in the new set is common to both sets. So far, only three mutations have been recovered in the new stock, yielding a rate of induction of about 0.5×10^{-7} mutations per locus per roentgen. Because of the small numbers involved, this estimate is affected by a large error. As it stands, the estimate lies below the mean of 2.2×10^{-7} obtained with the seven specific loci stock, but two of those loci had even lower rates.

133. A joint estimate is difficult to obtain, but the data taken together suggest that it may be around 1×10^{-7} mutations per locus per roentgen, with presumable confidence limits ($P = 0.95$) one order of magnitude apart.

134. The spontaneous mutation rate in female germ cells is not well known. With one mutation observed in 98,828 offspring, the confidence limits are very wide. Data on the induction of mutations at seven specific loci are also much scantier in mouse oöcytes than in spermatogonia. The data from high doses of acute x rays lead to an estimate of 4.8×10^{-7} mutations per locus per roentgen with 95 per cent confidence limits 2.5×10^{-7} and 7.7×10^{-7}, suggesting that acute irradiation of oöcytes might yield more mutations than irradiation of spermatogonia. Oöcyte data have not yet been obtained for the new set of six specific loci.

135. The results of experiments on the induction of recessive mutations at specific loci in the mouse and in other species are summarized in table XIII. It is apparent that *Drosophila* stands out as the species least susceptible to mutation induction by radiation, even though the comparison of species can be based only on very small samples of loci.

Over-all rates of mutation

Recessive lethal mutations

136. *Drosophila.* Abrahamson exposed spermatogonia of *Drosophila* males to 8,500 R gamma rays from a caesium source and analysed the induction of second and X-chromosome lethals in these cells.[16] The rate of induction of recessive lethals in the second chromosome turned out to be 12.01 per cent, whereas in the X chromosome it was 2.17 per cent. Since the number of mutations in the very small fourth chromosome is negligible and the third chromosome contains as much genetic material as the second chromosome, it can be estimated that the over-all rate of induction of recessive lethals in the whole genome is equal to 26.19 per cent at an exposure of 8,550 R. From this it follows that the over-all rate of recessive lethals per gamete per roentgen is 3.1×10^{-5}.

137. In Abrahamson's data, the ratio of second chromosome lethals to X-chromosome lethals is 5.5. The second chromosome contains about twice as much genetic material as the X chromosome; therefore it would be expected that the ratio between second and X-chromosome lethals would be roughly 2 instead of 5.5. That the ratio is 5.5 and not about 2 is explained by germinal selection, whereby about half the lethal-carrying spermatogonia are killed by the action of these lethals on the cell's own metabolism. Germinal selection does not occur in post-meiotic cells, because in these cells the ratio of second to X-chromosome lethals is in accordance with what one would expect on the basis of the length of the respective chromosomes.[14-16, 239]

138. In experiments of McSheehy,[240] spermatogonia of larvae or adult males received gamma ray doses in the range 200-800 rads. The dose-effect curve for second chromosome lethals proved to be linear. Taking into account germinal selection and the relative length of the chromosomes, it is possible to derive from McSheehy's data an estimate of the over-all rate of induction of recessive lethals per gamete per rad that is equal to 2.9×10^{-5}. This value is close to that obtained by Abrahamson. The induction of second chromosome lethals in spermatogonia has also been studied by Ytterborn.[241] The over-all frequency of recessive lethals in his experiment is 3.4×10^{-5} per gamete per roentgen. Because of the absence of data for non-irradiated controls, it is not possible to estimate the over-all rate of induction of recessive lethals. The over-all rates obtained by Abrahamson and McSheehy are consistent with the rate of induction of recessive visible mutation at specific loci in the same species.

139. *The mouse.* In 1959, a first attempt was made to calculate the rate of induction of autosomal recessive lethals in mouse spermatogonia by following a method proposed by Haldane.[242] It was found that the efficiency of the method was rather disappointing.[243] The same method has also been used by other authors.[244, 245] The results, however, were inconclusive. In 1961, another method was used to estimate the frequency of recessive lethals per gamete.[193] This attempt was also unsuccessful because, among other things, the presence of inbreeding depression made a proper evaluation of the amount of induced recessive lethals impossible.

140. In an experiment by Lyon *et al.*[198] inbreeding was avoided, and, furthermore, the scale of the experiment as well as the doses were increased. Hybrid F_1 males were given two exposures of 600 R high intensity x rays eight weeks apart. Twelve weeks after the application of the second dose, the males were outcrossed to females from a different stock. F_1 males free of translocations and of other factors likely to interfere with tests for recessive lethality were mated to females derived from a stock different from that used for F_1 females. F_2 females were then backcrossed to F_1 males. The offspring from father-daughter matings was used to analyse the presence of recessive lethals (and visibles) which had originally been induced in the spermatogonia of P_1 males. A control experiment was also carried out in which the males were not irradiated.

141. Evidence on the rate of induction of recessive lethals was obtained from three different sets of data: (*a*) embryonic lethality at fourteen days gestation in first litters of F_2 daughters backcrossed to their sires; (*b*) litter-size at birth and weaning of litters from F_2 daughters allowed to produce three litters; (*c*) fourth litter dissection data of daughters having already produced three litters.

142. The final estimate of the radiation-induced recessive lethality was derived exclusively from the first

and third sets of data. These data showed that embryonic survival in the irradiated series was 96.8 per cent of that in the controls. From this figure, it could be estimated that the rate of induction of recessive lethal mutations was about 29.5×10^{-2} per gamete, or 2.46×10^{-4} per gamete per roentgen. The estimate has a large standard error and only makes it possible to establish an upper 95 per cent confidence limit of 4.3×10^{-4} mutations per gamete per roentgen.

143. A different experimental procedure to estimate the rate of induction of recessive lethals per genome was followed by Lüning.[246] Lüning exposed males of a mouse population to 276 R acute x rays in each of seven consecutive generations and prevented inbreeding by starting every generation with a sufficient number of different pairs. A similar experiment was performed in which the males were not irradiated. The presence of recessive lethals in the third and following generations was analysed by making sib matings in each generation. Any induced recessive lethal was thus expected to become manifest in the offspring of those matings. The analysis was similar to that made by Lyon *et al.*[198] on the progeny of father-daughter matings, information being obtained on embryonic death and on litter-size at birth and at weaning.

144. As in Lyon's experiments, data on embryonic deaths were regarded to be the most reliable. They were obtained from the offspring of the fourth to eighth generation of sib matings. The data were then pooled, making allowance for the different doses of radiation that individual generations had received. To evaluate what percentage of deaths among the offspring of sib matings between control and irradiated individuals could be attributed to dominant mutations, Lüning performed an additional experiment using non-sib crosses in the irradiated and control series. The ratio of embryonic death among the offspring of irradiated sibs and irradiated non-sib crosses, once corrected for the rate of spontaneous recessive lethals, indicated that the embryonic survival in the irradiated population was 98.9 per cent of that in a standard population. Such a survival ratio leads to an estimate of the rate of induction of $0.8\text{-}2.0 \times 10^{-4}$ per roentgen per gamete, a figure remarkably close to that obtained by Lyon *et al.* Here also the error is large, but the upper limit to the rate is 6.4×10^{-4} mutations per gamete per roentgen.

145. Despite their large error, the observed rates of induction of recessive lethals per gamete are, at first sight, apparently lower than might be expected from the estimated average rate of induction at the seven specific loci most extensively studied, if it is assumed that the number of mutable loci in the mouse is the same as information in man and *Drosophila* leads us to expect. However, allowance must be made for only 75 per cent of the mutations induced at the seven loci being lethal. Furthermore, it must be noted that radiation-induced lethality was scored *in utero* in the studies of over-all induction, whereas in the investigation at the seven loci the scoring included lethals acting perinatally and post-natally. Allowing for these two factors alone narrows the gap between the two sets of estimates to the extent that, rather than being inconsistent, they may support each other.

146. If the recent data on five additional loci are taken into account as was done in paragraph 133, where an estimate per locus per roentgen of 1×10^{-7} mutations was suggested, the apparent discrepancy between over-all rates and rates per locus is reduced even further.

Recessive visible mutations

147. The over-all spontaneous rate of mutation to recessive visibles in mice has been estimated to be 7.04×10^{-3} per generation. The confidence limits of this figure are very wide since only one mutation has been observed in 142 tested gametes.[198] The over-all rate of induction of recessive visibles in the same experiment was estimated to be 1.8×10^{-5} mutations per gamete per roentgen. At first sight, such an estimate seems inconsistent with the rates observed at specific loci and with the presumable size of the mouse genome, even when account is taken of the fact that only about 25 per cent of the induced mutations at specific loci are viable. It must be observed, however, that the results of comparisons of the over-all frequency of visible mutations with the frequency of mutations at specific loci are difficult to assess, since ascertainment is practically complete in the case of specific loci and incomplete to an unknown extent in the other.

Dominant visible mutations

148. The over-all spontaneous rate of mutation to dominant visibles in mice appears to be 1.7×10^{-5} per generation with 95 per cent confidence limits of 2×10^{-6} and 6×10^{-5}.[247] The estimate is lower than the spontaneous rate observed in man, but it would be unwise to draw conclusions regarding the mutability of the two species with respect to dominant visibles, as too many traits that would require intensive investigation in the mouse are easily detected in man.

149. The over-all rate of induction of dominant visibles by acute radiation can be estimated on the basis of one experiment to be 4.6×10^{-7} mutations per gamete per roentgen.[198] The over-all rate of induction of recessive visibles as estimated by the same observers (1.8×10^{-5}) appears to be considerably higher, the ratio between the two rates being about 40. Such a ratio is based on few mutations only, but it is highly significant, with approximately 95 per cent confidence limits of 7 and 250.

150. Two extreme hypotheses may be advanced to account for that ratio. According to one hypothesis, the ratio would indicate that the genome is made up of two groups of loci, a smaller one where only dominant mutations arise and a larger one where only recessive mutations arise, and that the average rates of induction per locus are the same in the two groups. Alternatively, one could assume that most or all of the loci can mutate both to dominants and to recessives though at different rates, the rates of induction of dominants being forty times lower than those for recessives. The true explanation probably lies somewhere between these two extreme hypotheses, but both theory and empirical data are inadequate to provide a satisfactory interpretation of the results. The ratio between induced recessive and dominant mutations in *Drosophila* is known to be about 5,[248] a value significantly lower than in the mouse. A larger proportion of the induced mutations appears therefore to be recessive in the mouse than is known in *Drosophila*. The reason for the difference between the two species is not known.

151. In the past few years, Ehling[249-252] has shown that irradiation of pre- and post-meiotic male germ cells of mice can lead to the induction of mutations that give rise to skeletal abnormalities. Since these mutations become manifest in the first generation offspring of the irradiated male parents, it is thought that they represent a type of dominant visible mutation.

152. A rather large number of skeletal malformations were observed, and it was considered quite likely that only a small proportion of the abnormalities were due to freshly induced mutations. To distinguish between the possible causes of abnormality, the malformations were divided according to whether they occurred only once in particular experiments (class 1 abnormality) or more frequently (class 2 abnormality). Most of the class 1 abnormalities were considered to be due to dominant point mutations. In view of what is generally known about mutation frequencies at specific loci, it was thought that under the conditions of these experiments a specific dominant mutation would have been likely to occur at most once in the testing of 3,000 to 4,000 gametes.

153. In experiments in which pre- and post-meiotic germs cells were irradiated with 600 R acute exposure, Ehling observed a significant increase of class 1 abnormalities (scored at four weeks of age). The excess over control of class 1 abnormalities per gamete per roentgen was 3.5×10^{-5} for post-meiotic stages and 2.3×10^{-5} for pre-meiotic stages.

154. Excluding the portion of class 1 abnormalities that may not be mutational in origin, the frequency of dominant mutations affecting the skeleton after single exposure with 600 R is 2.9×10^{-5} mutations per gamete per roentgen for post-meiotic germ cells and 1.1×10^{-5} mutations per gamete per roentgen for pre-meiotic germ cells. Additional data were obtained from two experiments in which spermatogonial cells had been irradiated with a split dose. A total of twenty-three dominant mutations was observed in 1,968 offspring derived from irradiated males, and one mutation was observed in 1,739 offspring derived from unirradiated control males.

155. The ratio between dominant skeletal mutations induced in spermatogonial and post-spermatogonial stages is similar to that found in the specific locus experiments. This observation indirectly supports the notion that a sizable proportion of the skeletal abnormalities may result from point mutations. If they had been predominantly chromosomal aberrations, one would have expected a larger difference between the frequencies in spermatogonial and post-spermatogonial stages. The question whether these dominant mutations are transmissible to the second and later generations after irradiation is still open but under investigation.

Dose-rate effect on specific locus and recessive lethal mutations

Mice

156. *Spermatogonia.* Table XII shows that most of the information on dose-rate effects in the spermatogonia of mice was reviewed by the Committee in its 1962 report. The final results of experiments which had not been fully completed when the 1962 report was adopted do not significantly alter the results available at that time and largely confirm the following conclusions arrived at by the Committee:

(*a*) When spermatogonia are given exposures of 300 to 600 R gamma radiation at a rate of 0.009 R per minute (90 R per week), the frequency of induced specific locus mutations is lower by a factor of about three than when the same doses of x rays are delivered at a rate of 90 R per minute.

(*b*) At 0.8 R per minute (gamma rays) most of the dose-rate effect has already occurred, and the yield does not differ significantly from that observed at 0.009 R per minute (gamma rays).

(*c*) At the rate of 9 R per minute (x rays) the response is intermediate between the responses at 90 R per minute (x rays) and 0.8 R per minute (gamma rays).

(*d*) A reduction of the rate from 0.009 R per minute (gamma rays) to 0.001 R per minute (gamma rays) does not result in a further lowering of the mutation frequency.

157. *Oöcytes.* Data on dose-rate effects in oöcytes are fewer than those obtained in spermatogonia because the early follicle stages of the oöcyte development are easily destroyed at those doses that are necessary to obtain adequate mutation frequencies. The data collected thus far lead to the following conclusions:

(*a*) The dose-rate effect in oöcytes is in the same direction as in spermatogonia but considerably larger. At comparable exposures, the mutation frequency for 90 R per minute x irradiation in oöcytes is substantially higher than for spermatogonia irradiated at the same rate. At a rate of 0.009 R per minute gamma irradiation the opposite is true, the mutation frequency for oöcytes being lower than for spermatogonia.

(*b*) The mutation frequency at 0.8 R per minute (gamma rays) is intermediate between the frequencies at 0.009 (gamma rays) and 90 R per minute (x rays). This finding differs from the results for spermatogonia where mutation frequencies at rates of 0.8 R per minute and 0.009 R per minute are not significantly different.

158. In the course of studies on dose-rate effects in oöcytes,[253] it was shown that the genetic response of old females to irradiation (six to nine months old) was different from that of young females (two to four months old), the mutation frequency after exposure of 400 R (0.8 R per minute) in second litters of old females being considerably higher than the frequency in second litters of young females. No such difference has been found for first litters. No satisfactory explanation for this age effect in females (which has also been observed at a rate of 0.009 R per minute) has yet been given.

159. Since the publication of the 1962 report, the interpretation of the dose-rate effect has not changed. It is believed that the dose-rate response is a direct intracellular effect on the mutation process, although it may be influenced to some extent, and particularly at high doses, by secondary processes such as cell selection or change in cell stage during irradiation. Accepting the evidence that the dose effect operates at the intracellular level, it can be explained in terms of repair of pre-mutational damage. Russell suggests two alternative ways in which the dose rate might affect repair of pre-mutational damage. Firstly, there is more damage to the repair system at high than at low dose-rate irradiation. Secondly, the repair system is saturated by high dose irradiation, because its capacity for repair is limited and it has only a limited time in which it can act. Whatever the correct interpretation of the dose-rate effect may be, it seems evident that there is a threshold dose rate below which the repair system is not affected. This threshold is somewhat higher in spermatogonia than in oöcytes.

Drosophila

160. *Spermatogonia.* In a series of experiments with *Drosophila*, Purdom *et al.*[254-256] investigated the dose-rate effect in spermatogonia. The data indicate the presence of an effect at very low dose rates in a single

experiment, but not in others, and the investigators do not interpret their data as providing conclusive evidence for such an effect at the dose levels studied.

161. Although different dose rates were used in experiments of Oftedal,[257-259] there is no clear evidence of a dose-rate effect for mutation induction. There is, however, strong evidence of a total dose effect at high doses similar to that reported by Russell[237] with x rays and neutrons and by Batchelor *et al.*[260] with neutrons. In experiments with *Drosophila* (table XIV) Oftedal reported a linear increase in mutation frequency at low doses, while the frequency of mutations decreased at higher doses. These results suggest that spermatogonial mutation rates in *Drosophila* may be severely biased by the irradiation technique used. Oftedal, in fact, suggests that acute doses of radiation will kill more of the sensitive cells (that is, the more mutable component) of a heterogeneous spermatogonial population, thus allowing sampling of a less sensitive cell type. The data of Abrahamson *et al.*[261] and McSheehy,[240] measuring recessive lethal induction at doses higher than those used by Oftedal, showed a linear increase in mutation frequency as a function of dose. These results indicate that the less sensitive spermatogonial cells were sampled.

162. *Oögonia.* In adult *Drosophila* females, the oögonial stage is the only one that is maintained for a time long enough to permit the application of chronic radiation doses that extend over several weeks. Results of a pilot study of dose-rate effects in oögonial cells[262] were mentioned in the 1962 report, where it was indicated that 4,000 R Co^{60} gamma rays given at the rate of 7,333 R per minute were significantly more mutagenic by a factor of 2.5 than the same dose applied at the rate of 0.2 R per minute.

163. In subsequent large scale experiments,[263] summarized in table XV, it was found that the results obtained were different depending on (1) the experimental conditions under which the acute or chronic radiation was given and (2) whether the radiation doses were measured physically or biologically. On the basis of more recent results[264, 265] which have not yet been published, Muller favours the view that in *Drosophila* there is no significant difference in the mutagenic effectiveness of gamma rays over the approximate sixty-fold range of rates (0.016 to 1 R per minute) used. It was observed, however, that at high dose rates there was a reduction of effectiveness of about 50 per cent as compared to that at low dose rates.

164. *Oöcytes.* The effect of changes in dose rate on the induction of sex-linked lethals in stage seven oöcytes of *Drosophila* is now being studied by Himoe.[402] Preliminary results show that the yield of mutations is the same whether the oöcytes are irradiated at 330 R/min or 9.4 R/min.

Silkworm (Bombyx mori)

165. Two types of dose-rate effects have been discovered in the silkworm, one being the reverse of the other.[206, 266] In one type (type 1) which occurs in the primordial germ cells (spermatogonia and oögonia) in the gonads of newly hatched larvae, the yield after chronic irradiation (0.1 R per minute) is lower than that after acute irradiation (100 to 300 R per minute). In the other type (type 2), where the effect is found in larvae about eight days old in which the gonial cells are in later developmental stages, the mutagenic effectiveness is higher for chronic irradiation than for acute irradiation. After extensive cytological studies and dose-fractionation investigations (paragraph 176) and neutron studies (paragraph 200), the authors proposed the following hypothesis for the interpretation of the complicated features of the dose-rate effects in the silkworm. At least two mechanisms are involved:

(*a*) A certain part of the radiation-induced pre-mutational damage is subject to repair, and the extent to which this damage will be repaired is primarily dose-rate dependent. This results in the production of higher mutation frequencies following acute irradiation.

(*b*) Because the gonial cell population is changing with time from exclusively primordial germ cells to a mixture of primordial and primary spermatogonial cells, and because the metabolic cycle of many cells in the population is blocked by radiation at a sensitive stage, chronic irradiation can give rise to higher mutation frequencies than acute irradiation. Presumably, the degree and extent of the occurrence of either phenomenon depend largely upon the metabolic activity of the irradiated cells.

The chalcid wasp (Dahlbominus)

166. In contrast to what was mentioned in the 1962 report, more recent information indicates that a small dose-rate effect is detected in oögonia of *Dahlbominus.*[267] Significantly more eye colour mutations are induced with 1,000 R acute irradiation (1,000 R per minute of 2 MVp or 300 kV x rays) than with chronic irradiation (0.08 to 0.17 R per minute gamma rays). The mutational yield following acute irradiation is about one and one-half times that obtained after chronic irradiation. Although these results could be explained as a dose-rate effect, other explanations are possible, for example, differences in radiation quality (paragraph 199).

Conclusions

167. Dose-rate effects have been and are being studied in widely different organisms and in various stages of germ cell development. The above survey is not comprehensive, because it has dealt only with the induced genetic damage that most probably finds its origin in one-hit events (specific locus and recessive lethal mutations) and with the germ cell stages that are most important in the consideration of genetic radiation hazards.

168. Among the several species studied, the mouse is the most closely related to man. In this species, we now have exhaustive and indisputable evidence of a dose-rate effect in spermatogonia and oöcytes. The dose-rate effect is more pronounced in oöcytes than in spermatogonia (see table XII).

169. Dose-rate effects have been reported also in *Bombyx mori*, *Drosophila* and *Dahlbominus.* These effects are not only less pronounced than those obtained in the mouse but also conflicting in nature, and more work is necessary to clarify the situation.

Effects of low doses

170. As early as 1958, on the basis of the dose-rate effect observed in mouse spermatogonia and oöcytes, it was suggested that repair of pre-mutational damage might be affected not only by the dose rate at which the radiation was given but also by the dose itself, it being argued that acute high doses might hamper the repair of pre-mutational damage to a larger extent than would acute low doses. Preliminary results[268, 269] now indicate that in oöcytes the mutation yield after

50 R acute x rays (table XII) is significantly lower than would be expected from the results of irradiation at 400 R, if the dose-effect curve on which the frequency at 400 R lay was a straight line through the origin. This finding is supported by the results of new fractionation experiments in which the total exposure is partitioned into small acute exposures of 50 R separated by intervals of time presumably long enough for the repair process to recover (paragraph 175). These experiments now in progress yield mutation frequencies below those obtained with single, unfractionated exposures.

171. These results from small doses and small dose fractions indicate that the saturation of the repair system or the damage to that system is dose-dependent. It appears that the repair of pre-mutational damage that takes place at low dose rates can also occur to an appreciable extent with acute exposures as high as 50 R.

172. Additional evidence on the effects of small doses on repair mechanisms is provided by the experiments with primary cultures of human and monkey (*Macaca mulatta*) cells in tissue culture.[270-272] Although these data concern chromosome damage rather than point mutations, and somatic cells rather than germ cells, they may be pertinent. Dubinin found that chemicals like cysteamine were able to protect the cells against chromosome damage (most probably due to two or more hit events) resulting from exposures to 25 and 50 R x rays or 50 and 100 R gamma rays. The same chemicals had no protective effect at 12.5 R x rays or at 25 R gamma rays. More evidence that the effectiveness of the repair system is dose-dependent has recently been obtained for the early spermatids of *Drosophila* (paragraph 219).

173. There is now evidence to support what had already been anticipated as soon as the dose-rate effect was discovered, namely that, when acute irradiation is delivered in very small doses, the induced mutation frequency may be as low as that occurring with low dose-rate irradiation. The finding that a substantial repair effect of this kind is occurring in the mouse with acute exposures as high as 50 R indicates that the principle may apply to most of the range of doses usually encountered in human genetic hazards.

The effect of dose fractionation on the induction of point mutations

174. Several lines of evidence indicate that fractionation of the radiation dose sometimes results in a rate of mutation induction that is different from that observed after a single dose. In experiments with spermatogonia of mice, it was observed that the most striking effect of fractionation was found when a total dose of 1,000 R x rays (90 R per minute) was given in two 500 R fractions separated by twenty-four hours (table XVI).[273, 274] Under these circumstances, the mutation frequency in the fractionated series proved to be approximately five times as large as that obtained from the unfractionated series. Some of the other fractionation procedures listed in table XVI also resulted in some increase of the mutation frequency.

175. This effect is presently explained partly in terms of cell-stage synchronization and partly by cell selection. On the other hand, an effect of dose fractionation working in the opposite direction was expected under certain conditions. Thus, since small doses of radiation are now known to produce fewer mutations than would be predicted on the basis of results at large doses (paragraph 170), it was anticipated that a reduced mutation frequency might be obtained when large doses were fractionated into small doses separated by intervals of time sufficiently long for the repair process to recover. There is already some evidence that this is occurring in mice.[269]

176. Fractionation effects similar to those observed in the mouse were reported for spermatogonia and oögonia of the silkworm.[266, 275-277] When a total exposure of 1,000 R was delivered in two or three fractions separated by twelve- or twenty-four-hour intervals, a striking increase in the induced frequency of specific locus mutations was observed in comparison with the unfractionated exposure. The mutation frequencies in the fractionated series were about two times or four to eight times as high as in the unfractionated series, depending on whether the spermatogonia and oögonia were sampled immediately after the hatching of the larvae or seven to nine days later. As in the fractionation experiments with mice, other fractionation procedures increased the mutation frequencies to a lesser extent. The results of the most recent experiments indicate that the depression of repair is due to post-radiation blocking of the cell cycle at the G_2 and/or G_1 phases, in which the amount of repair of the pre-mutational damage is assumed to be small.

177. In *Drosophila*, the effect of dose fractionation has been studied for pre- and post-meiotic male germ cells. Purdom's results of a study on the effect of dose fractionation in spermatogonia were inconclusive.[256]

178. Alexander and Bergendahl[278] reported a fractionation effect for sex-linked recessive lethals in spermatids when irradiation was carried out in the absence of oxygen. Glembodsky *et al.*[279] investigated the effect of acute and fractionated doses of radiation on the induction of sex-linked recessive lethals in spermatids, and no differences were observed. Tates,[280] however, has reported a significant decrease in the frequency of sex-linked recessive lethal mutations in germ cell stages that probably correspond to young spermatids and late spermatocytes when the dose is delivered in five equal fractions, each separated by two-hour intervals, instead of being acute unfractionated.

179. A number of investigators[281-283] have reported that the sex-linked recessive lethal mutation frequency induced in mature sperm of *Drosophila* is the same whether the dose is given in a single exposure or in fractions separated by intervals of days or weeks.

Conclusions

180. The increased mutation frequency observed as a result of dose fractionation occurred only in experiments in which the dose in each fraction was quite high. Therefore, these results would probably apply only to very rare conditions in the exposure of man to ionizing radiation. However, the preliminary evidence on the reduced mutation frequency obtained when a dose is delivered in small fractions may well have many applications in estimating the genetic effects of radiation in man. Quantitative information is needed before these estimates can be made.

The effect of the interval between irradiation and conception

181. In the male mouse, extensive data on spermatogonia have shown no evidence of any significant change in mutation frequency with time after irradiation.

This holds true even to the end of the animal's reproductive life.[237]

182. In contrast to these findings in the male, recently published results from irradiation of female mice with fission neutrons clearly show that the interval between irradiation and conception has a very pronounced effect on the mutation frequency observed in the offspring.[284] In the first seven weeks after irradiation, a period in which two litters are usually conceived, the mutation frequency is high. With a dose of approximately 63 rads, a total of 59 specific locus mutations was observed in 89,301 offspring conceived in that period. After that, no mutations were found in a total of 120,483 offspring. Of all the other biological factors affecting mutation frequency that have been studied, none has produced such a striking effect. There is preliminary evidence (table XII) that the same effect occurs with x rays.

183. The low mutation frequency in the later period comes from oöcytes that were irradiated in immature follicle stages. It is not yet known whether the marked difference in mutation frequencies in the two time intervals is due to a low mutational sensitivity of oöcytes in early follicle stages, to an efficient repair mechanism in these stages, or to cell selection.

184. The extreme lowness of the mutation frequency in the later period is worth emphasizing. In the neutron experiment, the dose was high enough to be highly mutagenic in the early interval after irradiation. Yet in the later period the observed value of the mutation frequency was zero, and even the upper 99 per cent confidence limit of this zero figure was below the spontaneous mutation rate in male mice. (A reliable value for the spontaneous rate in females is not available, although it appears to be lower than that in males).

Conclusions

185. The mutation frequency in female mice is markedly dependent on the interval between irradiation and conception. The frequency is high in the first few weeks after irradiation but then plunges rapidly to an extremely low value. Caution should be used in applying the results to the human female, because the oöcyte stages involved in the two species may not be comparable in their responses. However, there is certainly a possibility of a similar effect and, therefore, an indication that the genetic hazard from the exposure of women may, on the average, be much less than that calculated on the basis of female mouse mutation rates observed after irradiation.

The relative biological effectiveness (RBE) of radiations of different qualities

186. In 1963, the RBE Committee set up by the International Commission on Radiological Protection and the International Commission on Radiation Units and Measurements[285] reviewed the information available at that time on the relative biological effectiveness of different types of radiation with regard to the induction of genetic damage. In general terms, the conclusions of the RBE Committee were that neutrons of various energies were about 2.3 to 7.3 times more effective than x or gamma rays in inducing dominant lethal mutations in spermatozoa of *Drosophila* and the mouse. The actual values depended on the doses and dose rates at which they were determined. RBE values for the induction of sex-linked recessive lethal mutations were of the order of 1.1 to 1.6. The following paragraphs update these conclusions, but the main emphasis is on the recent results obtained with mice, since they have a more direct bearing on the problem of estimation of human risks.

The mouse

Pre-meiotic male germ cells

187. Studies of Russell[237] showed that the rate of induction of specific locus mutations increases with dose when spermatogonia are irradiated with high dose-rate (79 rads per minute) fission neutrons. At doses higher than approximately 100 rads, the mutation frequency is lower than the actual value at 100 rads (table XII). The mutagenic effect of high dose-rate neutrons was compared with that of low dose-rate (0.17 and 0.79 rads per minute) fission neutrons. It was found that there was no dose-rate effect at about 60 rads. However, above 100 rads, high dose-rate irradiation was mutagenically less effective than low dose-rate irradiation. Such a reverse type of dose-rate effect can be explained by assuming that there is a difference in the degree of cell selection under high and low dose-rate irradiation.

188. Comparison of the results of 60 rad neutron irradiation with x irradiation at 90 R per minute indicated an RBE of 5.8 for specific locus mutations. Since the mutagenic effect of 300 R high dose-rate x rays is about 3.3 times larger than the effect of 300 R low dose-rate gamma rays (0.009 R per minute), it follows that an RBE of 19.1 is obtained when the mutagenic effectiveness of neutron irradiation is compared with that of low dose-rate gamma irradiation. Russell arrived at a closely similar RBE value (18.1) on the basis of results of another experiment in which he compared the mutagenic effects of 100 rads of low dose-rate neutron irradiation (0.14 rads per minute), with that of 600 R low dose-rate gamma irradiation (0.13 R per minute).

189. Searle and Phillips reached essentially the same conclusions as Russell with respect to a reversed dose-rate effect at doses above 100 rads (table XII).[260, 286, 288]

190. An analysis of the dose-mutation relationship for very low dose-rate neutron irradiation revealed that it was linear between 0 and 307 rads. The relationship applies to both specific locus mutations and dominant visible mutations. Comparison of the mutagenic effectiveness of 307 rads very low dose-rate neutron radiation with that of 608 rads very low dose-rate gamma radiation led to an estimated RBE of about twenty-three for specific locus mutations and to a figure of twenty for dominant visible mutations.[288]

191. There is little information on the induction in spermatogonia of mutations resulting in dominant lethality. Comparison of litter-size at birth after 307 rads of chronic neutrons compared to 608 rads of chronic gamma rays showed a significantly smaller litter-size in the former.[288]

192. Recent cytological studies have shown that about 21 per cent of the spermatocytes derived from irradiated A type spermatogonia showed multivalent configurations (indicative of translocation heterozygosity) when the spermatogonia were irradiated with 307 rads of low dose-rate neutrons. A percentage of 3.5 was obtained when similar cells were irradiated with 207 rads of higher dose-rate neutrons.[289, 290] If the data obtained for low dose-rate neutron irradiation are compared with those for low dose-rate gamma

irradiation (paragraph 124), and if it is, furthermore, assumed that the dose-mutation relationship for low dose-rate neutron and gamma induction of translocations is linear, then fast neutrons may be as much as forty times as effective as gamma rays from this point of view.

Post-meiotic male germ cells

193. Recently Searle *et al.*[286] obtained some information on the induction of dominant lethal mutations in spermatozoa which had been exposed to 0.7 MeV neutrons at 0.01 rads per minute. The biological effectiveness of these neutrons was calculated by comparing them with x rays on the basis of induced dominant lethality as estimated through live embryos/*corpora lutea* ratios in the control and in the irradiated series. At about 50 per cent induced dominant lethality (100 rads for neutrons, 600 R for x rays), neutrons turned out to be 5.8 times more effective than x rays. Searle's results confirm the results of Russell's studies[293] on the relative effectiveness of neutrons from a nuclear detonation and from a cyclotron. Both Searle and Russell observed that neutron irradiation induced more mutations in spermatids than in spermatozoa. This had been found in earlier studies with x irradiation.

194. The RBE values obtained by Searle and Russell are fairly close to those published by Pomerantseva.[294, 295] The post-meiotic germ cells in her experiments were irradiated with fast neutron (1 MeV) doses from 17 to 228 rads (4.3 to 11.6 rads per minute). Using pre- and post-implantation death as criteria for dominant lethal induction, Pomerantseva estimated that fast neutrons were five to six times more effective than Co^{60} gamma irradiation and four times more so than x rays.

195. Pomerantseva also studied the RBE of 660 MeV protons and observed that this type of radiation was about half as effective as x rays and 0.65 times as effective as Co^{60} gamma irradiation. As a result of studies with rats, Plotnikova *et al.*[296] found that the RBE of 500 MeV protons for dominant lethals in spermatozoa was 0.6 to 0.7 when compared to 180 KeV x rays.

Female germ cells

196. Comparison of the effects of high and low dose-rate neutron irradiation of oöcytes with a dose of approximately 60 rads showed that high dose-rate irradiation is significantly more mutagenic than low dose-rate irradiation.[284] However, the dose-rate effect for neutrons is smaller than that for gamma rays. At high dose rates, the published data on mutation frequency in oöcytes indicate an RBE similar to that obtained for spermatogonia.[284]

Drosophila

197. Abeleva and Lapkin[297, 298] irradiated spermatozoa and spermatids of *Drosophila* with doses of 600, 1,200 and 2,400 rads fast neutrons (55 rads per minute), on the one hand, and 1,200 and 2,400 rads acute x rays on the other. The relative biological effectiveness of neutrons, compared to x rays, as measured by the induction of dominant lethals, was 2.4 to 2.8 for spermatozoa and 1.3 to 1.5 for spermatids. If one takes into account the fact that RBE values vary with dose, dose rate and energy spectrum of the neutrons, the RBE values obtained by Abeleva and Lapkin are in good agreement with those mentioned in the review of the RBE Committee. The same applies to the results of Abeleva and Lapkin's studies on the induction by neutrons of sex-linked recessive lethals in spermatozoa and spermatids. For this category of genetic effects, the RBE for neutrons compared to gamma rays is 1 to 1.5.

198. The finding that the RBE value for spermatids is lower than for spermatozoa is presumably due to the fact that spermatids have a higher sensitivity than spermatozoa to the induction of genetic damage by x rays in the presence of oxygen.[299] Dauch *et al.*[300] observed that, for spermatozoa sampled on the second day after irradiation, the RBE for fast neutrons, as measured by the induction of both recessive lethals and translocations, was considerably higher than in sperm sampled during the first day after radiation exposure. This difference can be ascribed to a difference in oxygen tension between the two stages, because Sobels[301] was able to show that the higher sensitivity to x irradiation of fully mature spermatozoa compared to that of almost mature sperm cells is a consequence of a higher degree of oxygenation in fully mature spermatozoa.

199. With 660 MeV protons, Rappoport *et al.*[302] obtained a linear yield of sex-linked recessive lethals in spermatozoa at doses between 500 and 12,000 rads and a rate of induction of 2×10^{-5} mutations per rad. The data suggest that the RBE of 660 MeV protons compared with gamma rays is approximately one. The early studies of Edington[303] and Edington and Randolph[304] on the induction of sex-linked recessive lethals in spermatozoa had shown that the RBE of x rays compared to gamma rays was approximately 1.1 or 1.4 depending on the dose level at which it was estimated. The fact that high dose-rate x rays are mutagenically more effective than high dose-rate gamma rays has more recently been confirmed by Seeley *et al.*[305] for sex-linked recessive lethals in spermatozoa and by Purdom and McSheehy[255] for IInd chromosome lethals in spermatozoa and spermatogonia.

Silkworm

200. The relative biological effectiveness of 14 MeV neutrons, fission neutrons and gamma rays was determined for specific locus mutations induced in early (type 1 dose-rate effect) and late gonia (type 2 dose-rate effect).[306-309] Since mutation frequencies were found to increase faster than linearly with dose regardless of the type of radiation applied, it is impossible to describe the difference in mutagenicity of these types of radiation by one single RBE value over the whole dose range. Therefore the authors estimated the RBE values at a fixed mutation frequency. The RBE values of 14 MeV neutrons in comparison to gamma rays are the following: early spermatogonia (0.8 pe-locus; 1.0 re-locus); late spermatogonia (3.2; 2.1); early oögonia (1.2; 1.2) and late oögonia (1.7; 2.8). For 1.5 MeV fission neutrons, these values are: early spermatogonia (1.7; 1.9); late spermatogonia (4.2; 3.5); early oögonia (2.1; 2.4) and late oögonia (3.8; 3.0). These RBE values make it possible to rank the three types of radiation according to their relative efficiency of mutation induction as follows: gamma rays, 14 MeV neutrons and fission neutrons.

Dahlbominus *and* Mormoniella

201. In experiments on the induction of specific locus mutations in early and late oöcytes of *Dahlbominus* by 750 rads of 14 MeV neutrons and 750 rads

of gamma rays, Baldwin[310] observed that high dose-rate neutrons were mutagenically more effective than high dose-rate gamma rays, but not significantly so. The relative mutagenic effect of neutrons and gamma rays in early and late oöcytes was the same.

202. The induction of specific locus mutations in oöcytes of *Mormoniella* has been studied by Kayhart[311] who compared the relative mutagenic effectiveness of thermal neutrons, fast neutrons and x rays. The RBE for thermal neutrons could not be estimated, but the RBE for fast neutrons was seventeen to twenty-one in the low dose range (45 to 70 rads) and two to four at higher dose levels (240 to 1,400 rads).

Conclusions

203. All evidence confirms that neutron irradiation is mutagenically more effective than x or gamma irradiation. There are indications that the relative mutagenic effectiveness of neutrons increases with their linear energy transfer. Results of studies with such widely different species as the mouse and the silkworm indicate that RBE values for neutrons are almost always in the range of one to six. An RBE value for the mouse of about twenty was obtained when the mutagenic effects of low dose-rate neutrons or of low doses (60 rads) of high dose-rate neutrons were compared with low dose-rate gamma radiation. It has been established that RBE values can change with doses and dose rates, and it is also known that the RBE values may be different for germ cell stages and types of genetic damage.

Repair of pre-mutational damage

204. Since dose-rate effects and some fractionation effects are usually interpreted on the basis of repair of mutational damage, it seems appropriate to review some of the recent advances in this field.

Paramecium

205. Kimball's extensive studies[312-314] with *Paramecium* showed (*a*) that various post-irradiation treatments can reduce the amount of x-ray induced mutation but only when applied before the first chromosome duplication that follows irradiation, thus demonstrating the existence of reparable pre-mutational damage; (*b*) that the mutation yield is inversely related to the length of the interval between irradiation and chromosome duplication. By sufficiently prolonging the time interval between irradiation and DNA synthesis, up to 60 per cent of the maximum mutation yield can be eliminated. Irradiation damage produced during post-duplication (G_2 phase) and early prophase is subject to most effective repair, and probably almost all of the initial lesions produced during these phases are potentially reparable; (*c*) that the reduction in mutation yield, and therefore the amount of repair, depends on growth conditions and on the presence of metabolic inhibitors, suggesting that an enzymatic process is responsible for the observed reduction.

206. The hypothesis that enzymes are involved in repair of pre-mutational damage in *Paramecium* is made probable by the observation that the mutation yield is increased when the time between irradiation and DNA synthesis is decreased. If there is little time between irradiation and DNA synthesis, there is less opportunity for repair to occur, and, as a consequence, most of the pre-mutational damage will be irreversibly fixed at the time of chromosome duplication.

207. Kimball's investigations into the nature of the initial radiation damage led him to conclude that there were at least two different kinds of pre-mutational damage, one producing permanent alterations (i.e., mutations) through misrepair, the other through misreplication. The results obtained with *Paramecium* suggest that misrepair is less efficient than misreplication.[313] since the longer the time between irradiation and replication, the lower the yield of mutations. Thus, potential mutagenic lesions tend to disappear without producing mutations prior to replication but tend to be converted to mutation at replication. Studies of the pre-mutational lesions that cause mutations by misreplication revealed that these lesions usually affected both conserved strands of the DNA and therefore all progeny of such cells.[313, 315]

208. Repair processes have also been observed for mutations induced by 2,537Å ultra-violet radiation, by alpha particles,[316, 317] by nitrogen mustard, and by tri-ethylene melamine (TEM).[318] At least with TEM mutations, however, the pre-mutational damage that is repaired differs from that due to x rays, since most TEM-induced mutations, unlike those induced by x rays, affect only a half or a quarter of the progeny of the cell in which a mutation has been induced. From observations on the repair of x-ray and TEM-induced mutations, it appears that *Paramecium aurelia* is capable of repairing more than one kind of pre-mutational damage. The two mutagens, furthermore, differ in that the x-ray damage incurred in the G_2 phase is almost completely repaired,[319] whereas a comparatively high yield of mutations is still obtained after TEM treatment of G_2 cells.[318]

Bacteria

209. Studies of repair in bacteria deal mainly with damage affecting the survival or the growth of the treated cells and, therefore, would not seem to be strictly relevant to the problem of repair of pre-mutational damage. The reason for mentioning some of these studies in this report is that they have thrown considerable light on the molecular and enzymatic mechanisms of repair of ultra-violet or chemically induced damage in the DNA. Since no comparable information is available with regard to ionizing radiation, these results may help us to understand the phenomena resulting from x irradiation.

210. Part of the damage affecting the survival of ultra-violet-irradiated bacteria (or bacteriophages) consists in the formation of thymine dimers and can be repaired through the intervention of two groups of enzymes. The photo-reactivating enzymes have been shown[320, 321] to split the ultra-violet-induced thymine dimers in the DNA into the original separate thymine residues in the presence of light with wave-lengths ranging from about 320 to 450 mμ. Dark-repair enzymes, on the other hand, excise the ultra-violet-induced thymine dimers.[322-325] The excision of dimers is followed by *restitutio ad integrum* of the original DNA molecule through a process of reparative replication that fills the gaps with new material. Unlike the photo-reactivating enzymes, the dark-repair enzymes do not require visible light.

211. Both enzymatic systems are genetically controlled and many radio-sensitive mutants, lacking either the photo-reactivating or the dark-reactivating enzymes, have been isolated. On one occasion, an enzyme capable of initiating dark-repair *in vitro* has been isolated from *Micrococcus lysodeikticus*.[326-328]

212. Investigations into the action of the difunctional alkylating agent mustard gas on the growth and survival of *E. coli* strains, with and without dark-reactivating enzymes, have provided evidence that chemically induced lesions in the DNA can also be repaired.[329] The strain carrying the dark-reactivating enzymes was able to excise (i.e. repair) the inter-strand cross-links between guanine moieties that are induced by mustard gas. The strain which did not have the dark-reactivating enzymes could not remove these inter-strand cross-links in the DNA.

213. Less is known with regard to repair of pre-mutational damage. Witkin *et al.*[330] studied mutation induction in three different strains of bacteria. The first strain (H/r) was used to study the induction of mutations to streptomycin resistance. The second strain (H/r30) was an arginine requiring substrain of the first and was used to study mutations to prototrophy. Neither of these strains carried the photo-reactivating enzyme, whereas the third strain (B/r) did. The mutations studied in the B/r strain were mutations to streptomycin resistance. Mutation induction by ultra-violet in all strains was studied in the absence or presence of post-treatment with photo-reactivating light (wavelength 320 to 450 mμ).

214. It was found that the H/r strain was not capable of repairing potential mutations to streptomycin resistance in the presence of photo-reactivating light. The H/r30 strain, on the other hand, was able to repair potential mutations to prototrophy in the presence of photo-reactivating light. The B/r strain which has the photo-reactivating enzyme was capable of repairing potential mutations to streptomycin resistance in the presence of photo-reactivating light. From these results, it was concluded that ultra-violet light induces two kinds of pre-mutational damage. Repair of the first kind of damage (i.e., potential mutations to streptomycin resistance) can only take place in the presence of the photo-reactivating enzyme and photo-reactivating light. The second type of damage (i.e., potential mutation to phototrophy) requires only photo-reactivating light for its repair.

215. The mechanism of repair of pre-mutational damage in bacterial strains which have or lack the photo-reactivating enzyme is not yet well understood. This applies even more to our knowledge concerning the process of repair of ultra-violet-induced mutations in bacterial strains having or lacking the dark-reactivating enzymes.

216. The examples given above have shown striking parallelism between the error-correcting mechanisms for such different lesions in the genetic material as those induced by ultra-violet and mustard gas. There is no such detailed evidence for the mechanism of the repair processes in bacteria exposed to ionizing radiation. However, it has been demonstrated that bacterial strains show a difference in sensitivity to ionizing radiation depending on whether they are equipped with repair enzymes or not. These results seem to suggest that damage from ionizing radiation may be repaired in a way similar to that observed with ultra-violet or chemically treated bacteria.

Metazoan germ cells

217. In the sections on dose-rate and dose-fractionation effects, it was shown that results of dose rate and dose fractionation on mutation induction could be explained by assuming that the mutation process in metazoan germ cells was subject to repair. The possibility of interfering with repair processes in metazoan germ cells by means of pre- or post-irradiation treatments with metabolic inhibitors has been amply demonstrated in the past decade. The details of the evidence are comprehensively analysed in recent reviews.[314, 331] The main conclusions only will therefore be outlined in this report.

218. Evidence for the operation of repair processes in early spermatids and mature spermatozoa of *Drosophila* has been obtained in studies on the effects of different post-treatments by Sobels *et al.*[229, 301, 331-337] It is remarkable that early spermatids and spermatozoa give an opposite response to the same treatments. This suggests that the metabolic pathways involved in the mutational event are essentially different in these two different stages of sperm development.

219. For early spermatids, post-treatment with cyanide or nitrogen following radiation exposure in air leads to an increase of the frequency of recessive sex-linked lethals in a ring X chromosome.[331-335] Since the formation of peroxides could be ruled out in the cyanide experiments[335] it was concluded that inhibition of respiratory enzymes enhanced the mutation frequency by inhibiting a repair process. Further evidence for the oxygen-dependence of the repair system in early spermatids was provided by the observation that, after inhibition of the repair process by anoxia before and during irradiation, the mutation frequency was markedly lowered by post-treatment with O_2, as compared to that observed with N_2.[299] By applying the same treatments (pre-treatment with N_2, followed by post-treatment with either N_2 or O_2) at three dose levels (1,250, 2,500 and 3,750 R), Watson[338] observed that the absolute reduction of the mutation frequencies in the O_2 post-treated series was the same at all three doses. These results suggest that the repair system can only cope with a limited amount of damage, because at the low dose level repair is considerably more effective than at the high dose level where the system apparently becomes saturated. The repair process in early *Drosophila* spermatids therefore shows a remarkable similarity to that postulated by Russell to explain the effect of dose (paragraph 171) and dose rate (paragraph 159) in the mouse.

220. In contrast to the findings in early spermatids, post-treatment with O_2 of mature spermatozoa irradiated under anoxia, increases the frequency of mutations as compared to that observed after post-treatment with N_2.[299, 336] Post-radiation interaction of radicals with O_2 cannot explain this effect.[301] As in spermatids, the post-radiation reduction of the genetic damage in spermatozoa by N_2 is thought to be mediated by an enzymatic repair process which derives its energy from glycolysis. The modification by O_2 versus that by N_2 shows a remarkable similarity to glycolysis, which is also adversely affected by oxygen, but favoured by anoxic conditions. This idea is supported by the finding that pre-treatment with two specific inhibitors of the glycolytic pathway, i.e. sodium fluoride and iodoacetamide, leads to a considerable increase of the radiation-induced mutation frequency in spermatozoa.[301, 339]

221. A contrasting response of early spermatids and spermatozoa has also been observed after inhibition of protein and/or RNA synthesis, since pre-treatments with chloramphenicol, ribonuclease or actinomycin-D all result in an increase of the radiation-induced mutation frequency in sperm, but in a decrease in early spermatids.[301, 331, 337] It is clear therefore that protein

and/or RNA synthesis also play a part in the mutation process in *Drosophila*. It is not yet possible, however, to state more precisely which specific steps are involved from the induction of premutational damage to mutation fixation.

222. Several lines of evidence indicate that the observed post-radiation modifications in early spermatids and mature spermatozoa cannot be explained by:

(*a*) Shifts in the sampling of germ cells with different radio-sensitivities among groups of flies (or pupae) having received different post-treatments,[301, 336, 338] nor by

(*b*) Selective elimination of cells with recessive lethal mutations or with translocations.[301, 339]

223. Experiments of Tazima *et al.*[340] with silkworm showed that it was possible to increase the yield of specific locus mutations in spermatogonia and oögonia by subjecting these cells to post-irradiation treatments with cyanide, chloramphenicol, nitrogen gas and low temperature.

Quantitative traits

224. The general problems associated with radiation-induced changes in quantitative traits were discussed in great detail by the Committee in its 1958 report. In particular, the Committee analysed the implications of induced changes of the variance and the mean of such traits as birth-weight, intelligence, life span and fertility. The discussion was largely based on data collected in *Drosophila* and in plant material. Further experimental results were reviewed more briefly in the 1962 report.

225. Although more data on *Drosophila* have been obtained in recent years,[341-345] in this report attention will only be given to recent results obtained with vertebrates, on which almost no data were available for inclusion in earlier reports. While the information available on the induced changes in quantitative traits in vertebrates is much less complete than in *Drosophila* and plants, the results reviewed here may have a far greater relevance to the situations likely to obtain in man.

226. *Body-weight.* Touchberry and Verley[346] obtained evidence that body-weight at thirty-two days was increased and growth rate speeded up in the offspring of mice whose ancestors had been irradiated during six generations with doses from 10 to 240 R. Newcombe and McGregor[347] studied radiation-induced changes in body-weight in the offspring of rats whose male ancestors had received gonadal exposures of 600 R of x rays over thirteen successive generations. It was found that rats in the irradiated series tended to be heavier than their controls. The relative incidence of "heavy" as compared with "light" animals (defined as those in the upper and lower halves of the weight distribution for irradiated and control groups combined) was significantly higher in the irradiated than in the control group by factors of 3.4 for males and 2.2 for females. It could be demonstrated that the radiation-induced changes in body-weight were primarily associated with induced hereditary changes and not merely a secondary effect of the radiation-induced reductions in litter-size.

227. *Maze-performing ability* was studied in rats which descended from a population in which males (in one experiment both males and females had been irradiated) had been exposed to 400 to 1,000 R acute x rays during twelve consecutive generations. Newcombe and McGregor,[348] who performed these studies, observed a decline in maze-performing ability in the irradiated series. In the same series, they noticed a 70 per cent increase in "dull" animals (animals with error scores that exceeded the mean by more than one standard deviation) and a 30 per cent decrease in "bright" animals (animals with scores lower than the mean by more than one standard deviation). Contrary to expectations, analysis of the variability of error scores revealed a decreased variability in the irradiated series. By analogy with the author's findings with regard to radiation-induced changes in body-weight, it is assumed that radiation-induced reduction in maze-learning ability could also be explained as being due to hereditary changes and not to differences in litter-size between control and irradiated series. At present, it is difficult to evaluate to what extent maze-performing ability in rats can be equated to a clearly defined component of human intelligence.

228. *Life span.* As early as 1957, Russell[349] obtained evidence of a reduction in life span in the offspring of male mice that had been exposed to 30 to 80 rads of detonation neutrons. Since then, several other workers became interested in this subject, because radiation-induced life-shortening represented a genetic hazard for the human population that had been hitherto unforeseen. Spalding[350] irradiated male mice with 30 to 180 rads acute fission neutrons in one experiment and with 60 to 300 rads gamma rays in another. His results did not indicate any reduction in life span in the offspring from irradiated sires or grandsires. On the contrary, the average life span of all control females was shorter than that of the female offspring from irradiated sires or grandsires. The effect was even more pronounced in the male progeny. The results for neutrons and gamma rays were the same.

229. Frölen[351] observed no shortening of the life span in the first generation offspring of male mice exposed to 500 R acute x rays. The results were the same when the irradiated males received a pre-treatment with cysteamine. The life span of the female offspring of irradiated males was not analysed.

230. Studies were also made concerning the life span of descendants of mice populations which had received irradiation during five or more generations. Spalding and Strang[352] failed to demonstrate any reduction of life span attributable to ancestral irradiation in male and female mice from sires exposed for five, ten and fifteen generations, to 200 R acute x rays per generation. Gowen and Stadler[353] exposed mice to gamma irradiation from mating to death. Each following generation was maintained in the irradiation field from conception to death. Extensive analyses of the life span were made when the strains of mice had completed lives through the sixth generation. The average ancestral radiation doses for each generation were, in order of generation, 370, 680, 820, 980, 1,180 and 1,290 R. The results of these experiments indicated that ancestral irradiations over six generations had little effect.

231. All studies listed above, with the exception of that of Russell, have shown that irradiation has little or no effect on life span in offspring from mice irradiated during one or more generations. Russell's experiment was the only one in which fission neutrons were used to irradiate the most sensitive of the post-meiotic male germ cell stages, these conditions being chosen as likely to increase the probability of obtaining an effect.

232. *Reproductive life* and its modification by irradiation have been studied by Spalding *et al.*[352] They observed that the average period of fertility was longer in the offspring of mice that had been irradiated with 200 R per generation during twenty successive generations than in controls.

233. *Skeletal abnormalities.* Searle[354] studied continuous and quasi-continuous skeletal variation in descendants of sublines of an inbred strain of mice which had been kept in a radiation field for about nine generations, receiving 1 R per night and about 80 R per generation. The study has not yet produced a clear picture, and further studies are indicated.

234. The only other vertebrate species in which the effect of irradiation on a quantitative trait has been studied is the chicken. In these experiments,[355] cocks were irradiated to induce genetic variability in stocks which would otherwise no longer respond to selection for high egg numbers. Irradiation of cocks with 1,000 to 1,500 R acute x rays per generation over a period of seven generations, followed by selection for high egg numbers during six generations, led to a negative result; namely, the response to selection was no different, or perhaps slightly less, in the irradiated lines than in controls.

235. In conclusion, studies on radiation-induced changes of quantitative traits in vertebrates have yielded results that must be considered as still fragmentary. The information available does not make it possible to evaluate how the means and variances of these traits are changed by radiation. It must, however, be noted that the only experiment concerning an intellectual function reveals a decrease in the mean without an increase in the variance. Estimates of risk of induced changes of quantitative traits in man must wait until further results are obtained with vertebrates, particularly with mammals.

Miscellaneous genetic effects

Space-flight results

236. In the context of the present report, results of genetic experiments performed in orbiting spacecraft are not of immediate relevance to risk estimates, since the doses received by man and experimental animals have thus far been extremely low and mostly of the order of tens of millirads. It seems, however, appropriate to mention this subject, because some results suggest that genetic damage is induced during space flights even if the detectable amount of ambient radiation in the spacecraft has been small, indicating that other space-flight parameters, such as vibration, weightlessness and acceleration, may induce genetic effects either by themselves or in combination with the ambient radiation.[356-367]

237. Two lines of research have been followed in studying the influence of space-flight parameters. Firstly, several attempts have and are being made to simulate these parameters in ground tests. Thus far, these model experiments on the ground have mainly focussed on the action of vibration alone and in combination with acceleration or with irradiation. The results have been found to be dependent on the type of vibration, the duration of the treatment, the type of genetic damage under study and on whether the vibration was applied before or after the irradiation.[368-371]

238. In the second line of research, the biological material (human blood cells) was treated by irradiation from a man-made radiation source during the orbital phase of the spaceship mission.[372, 373] The frequencies of single and multiple-break aberrations induced in the blood cells were compared with the frequencies in non-irradiated cells aboard the spaceship and with the frequencies in irradiated and non-irradiated cells that remained on the ground. The in-flight control gave the same result as the control on the ground, indicating that the space flight by itself did not induce aberrations. Comparison of in-flight irradiated cells with those irradiated on the ground on the other hand revealed that, while there was no significant difference with regard to yields of multiple-break aberrations, the frequency of single-break aberrations was significantly higher in the samples irradiated in flight. Apparently, synergism exists for the production of human chromosome aberration between radiation and some space-flight parameters.

239. It is still too early to obtain a complete picture of the interaction of irradiation with space-flight factors, and, so far, there is no common opinion as to whether space-flight factors by themselves are able to induce some kinds of genetic damage. The current findings are important, because they lead us to realize that the magnitude of the genetic and somatic risks encountered in space flights is not only determined by dose, dose rate and quality of the radiation received in those circumstances but also by parameters that are peculiar to space-flight situations.

Effects of internally-deposited radio-active isotopes

240. Increased rates of dominant lethals in male mice have been observed by Lüning *et al.* after injection with Sr^{90}. New and extensive data indicate that the increase of dominant lethals is not observed in matings within the first three weeks after injection, but only from the fourth week onwards. This corresponds to effects on spermatocytes and spermatogonia.[374-376]

241. The genetic effects of C^{14} incorporated into *Drosophila* have been studied by Purdom. Preliminary results suggest that the recessive lethals induced by C^{14} are largely due to the emitted beta radiation and probably not, or to a much lesser extent, to transmutation.[377]

242. Tritiated thymidine and deoxycytidine have been studied for their capability to induce sex-linked recessive lethals in *Drosophila* males.[378, 379] The distribution of the lethals along the X chromosome was different for the two types of radio-active chemicals. Two regional differences have been noted, one of high mutability after tritiated thymidine and one of high mutability after tritiated deoxycytidine.

243. Olivieri and Olivieri[380] studied the mutagenic effect of tritiated thymidine and uridine in *Drosophila* males and found that tritiated uridine increased significantly the frequency of sex-linked recessive lethals in spermatocytes. The mutagenic effect of tritiated uridine was even more pronounced when applied in combination with actinomycin D.

IV. Risk estimates

244. Risk estimates express a probable quantitative relationship between doses of radiation and frequencies of certain effects. In this report, risks of genetic effects will be expressed in terms of expected frequencies of genetic changes (point or chromosome mutations) induced per unit dose or function (e.g.

power) of dose. In earlier reviews of genetic effects by the Committee, risks were expressed in terms of doubling doses, these being the doses required to produce a number of mutations equal to those occurring naturally in one generation. Doubling doses can easily be computed when both the natural incidence and the rate of induction of a certain category of mutations are known. When both figures are available, the doubling dose is a compact way of summarizing the information regarding a given effect in given circumstances. The use of the doubling dose, however, is not necessary in arriving at risk estimates, and for that reason the more direct approach is employed in this report.

245. Risk estimates as defined in paragraph 244 have the advantage that they can be obtained in the non-linear case in which a single doubling dose would have little meaning. They are also absolute estimates which give at once the risk in terms of effects, whereas this type of information is less directly obtained from the doubling dose and involves unnecessary assumptions regarding the proportionality between spontaneous and induced rates. Finally, risk estimates as expressed in this report are consistent with the practice followed by the Committee with regard to the risk of induction of malignancies.

246. It may be pointed out that, while estimates of risks of induction of malignancies in man can be derived from the results of irradiated human populations, this is not possible with regard to genetic risks. As will be discussed below, *in vivo* human data are inadequate to provide estimates of genetic risks. These must be based on results of experiments with animals —mainly mice—and with human somatic cells *in vitro*. While there appears to be no alternative at present to the use of such experimental material, its limitations must be clearly borne in mind and will be stressed throughout the following paragraphs. Because of unavoidable inferences from one species to another or from one type of cell to another, the estimates thus obtained are less reliable than the data from which they are derived.

247. An additional difficulty with genetic risks is encountered in expressing them in meaningful terms. The eventual result of the great majority of genetic changes is, sooner or later, the failure of cells carrying those changes to be transmitted to the following generations. Only in a minority of cases—such as certain dominant traits and certain chromosome anomalies that occur frequently in the population and that are easily detected—can we make assumptions as to the manner in which the damage will be expressed. For most genetic changes even conjectures are not permissible regarding the actual manifestation of the damage throughout generations in terms of individual or collective hardship.

248. The estimates reviewed in the following paragraphs were obtained for acute irradiation of spermatogonia by low LET radiation at high single doses. The consequences of irradiation of oöcytes, and those of exposure to radiation of different quality at different doses and dose rates, will be considered separately.

Point mutations

Total risk of induction

249. Much as the total rate of spontaneous mutation can be derived from an analysis of the excess of female over male new-born children, so the total risk of induction could, in principle, be obtained from the shift of the sex-ratio to be expected in the offspring of irradiated mothers as a consequence of the induction of sex-linked recessive lethal mutations. Such a shift has, in fact, been observed and was used by the Committee in its 1958 report to obtain risk estimates. Further observations were summarized and discussed in the 1962 report, in which the Committee discarded estimates of risk of point mutations based on the sex-ratio shift, because, while the shift undoubtedly was largely due to genetic damage and might have reflected a point mutational component, it was not possible to rule out or separate the possible confounding effect of induced chromosome anomalies, the high frequency of which was not known in 1958.

250. Such a reservation is still valid now, despite new data[381, 382] on the offspring of irradiated mothers which confirm earlier observations, and although no increase in the frequency of sex-chromosome anomalies was noted in a survey[383] of the female offspring of irradiated mothers. The size of the survey was too limited, however, to exclude the possibility that induced anomalies of the sex-chromosomes may account for at least part of the effect on the sex-ratio.

251. A further reason why risk estimates based on the sex-ratio shift are not being made in this report lies in the limitation of the data themselves. The largest and dosimetrically best known material is still that collected among the irradiated populations of Hiroshima and Nagasaki.[384] Doses in the parental populations were between 0 and 200 rads, however, and the observed shift was not significant.

252. Some effect on the sex-ratio may also be expected after paternal irradiation, primarily as a consequence of the induction of sex-linked dominant lethals. The expectation has not been conclusively borne out by observations in man, and experimental studies have shown that in mice the results of paternal irradiation cannot be explained on the sole basis of the induction of sex-linked dominant lethals.[384, 385]

253. No other human data are yet available that would make it possible to obtain risk estimates for the induction of point mutations. As in the 1962 report, it will therefore be necessary to base risk estimates in man on rates of induction observed in the mouse. However, it is no more possible now than it was in 1962 to assess how close the rates of induction in man and in the mouse might be. For want of better data, it will be assumed that rates of induction of mutations are the same in man and in mice, but the arbitrary nature of such an assumption needs to be underlined. The possibility that rates of induction may be higher in man than in mice should not be overlooked.

254. The average rate of induction of mutations at twelve specific loci in mouse spermatogonia exposed in the range 300-600 R acute x rays is estimated to be about 1×10^{-7} per locus per roentgen (paragraph 133). The confidence limits, when this figure is used as an estimate of the average rate for all loci in the mouse, are presumed to be about one order of magnitude apart.

255. The size of the human genome in terms of loci at which detectable mutations arise was estimated in paragraph 24 to be between 7,000 and 70,000. As mentioned earlier, the estimate, although very crude, is in agreement with similar but more precise estimates valid for *Drosophila*. It also agrees with a number of other published estimates of the number of mutable loci in man.

256. If the rate of induction of specific locus mutations assumed to apply to man (paragraph 254), is multiplied by the estimated size of the human genome, the resulting estimate of total risk of point mutation in man is 2×10^{-3} mutations per gamete per roentgen. Taking into account the variability of the data on which it is based, it can be assumed that the approximate confidence limits of the estimates are between one and two orders of magnitude apart. While this range reflects the sampling variability of the estimate, the dubiousness of some of the underlying assumptions must also be borne in mind.

257. It will be recalled that direct estimates of the total rates of induction of lethal recessives in mice have been obtained from two independent sets of experiments and are remarkably close (paragraphs 143, 144). Allowing for the fact that these estimates measure only a known part of the damage measured by experiments at specific loci makes it passible to compare direct estimates of the rate of induction over the whole genome with those obtained indirectly. The direct method gives a lower estimate ($\sim 0.5 \times 10^{-3}$) than the indirect method. The upper confidence limit of the direct estimate (1.6×10^{-3}), however, is well within the range of the indirect one. Such an agreement gives strong support to the estimate discussed in paragraph 256, especially as the direct estimate is based on a smaller number of assumptions.

258. The nature of the damage measured by the total rates of induction is as difficult to assess as is that measured by the total rate of spontaneous mutation which was discussed in paragraphs 25-27. The total rate of induction includes all mutations of every degree of dominance and harmfulness. They will all eventually be eliminated from the population.

259. The mechanisms through which the spontaneous mutational damage could be eliminated were mentioned in paragraph 27. These mechanisms also apply to the induced damage, but the relative contribution of any mechanism to the process of elimination cannot in the current state of our knowledge be assessed. It is therefore not possible to express damage, as measured by the total rate of induction, in terms of individual or collective hardship.

260. If observations made in *Drosophila* can be used as a model for the situation obtaining in man, the induced damage will initially be eliminated at the rate of 4-7 per cent per generation. The rate will, after a few generations, taper off into a rate between 1 and 2 per cent that will persist approximately at the same level until all the induced damage has been removed. Genes will persist in the population for periods of time inversely proportional to their rate of elimination and therefore dependent upon the severity of their expression in heterozygotes. If a population was steadily exposed to a constant amount of radiation per generation for a number of generations, the rate of elimination of the damage would tend to become equal to the rate of induction.

Risk of induction of dominant mutations

261. The difficulty of evaluating the total mutational damage in socially meaningful terms justifies attempts to obtain independent estimates of that part of the damage that can be expected to find its expression in an indisputably injurious way. Experimental data that lead to high estimates of dominant skeletal damage in the mouse were discussed in paragraphs 151-155. While it is too early to evaluate from these data the effects at low doses, the Committee wishes to emphasize that this type of observation may in the future offer a clue to the estimation of risks of induction of dominant mutations in man. In the meantime, dominant damage in man can only be estimated for that portion of the genome that is responsible for a selected group of dominant traits (paragraphs 8-11).

262. When the Committee reviewed genetic effects in 1958 and 1962, it gave estimates of the expected frequency that these traits would reach in the population at equilibrium under conditions of steady irradiation. It is, however, more informative and more consistent with the approach adopted for estimating the over-all mutation rate if the rates of induction after a single exposure are obtained, and this approach will be followed here.

263. For that purpose, the rate of induction per locus per roentgen (1×10^{-7}) as observed at specific loci in the mouse will be used. The rate, however, applies to recessive mutations. It will be recalled (paragraphs 149, 150) that limited mouse data show that the over-all rate of induction of dominant visibles is considerably lower than that of recessive visibles. The interpretation of that phenomenon is difficult, but it cannot be excluded that it may in part reflect a lower average rate of induction of dominant mutations. The rate of induction used therefore can only be considered as an upper limit, for it probably over-estimates the rate of induction of dominants, though by not more than two orders of magnitude (paragraphs 149, 150).

264. As discussed in paragraph 9, the part of the human genome under discussion, namely that responsible for some fifty dominant traits most commonly observed and easily detected, consists of at least fifty loci and is unlikely to consist of as many as 500. Multiplying the assumed number of loci by the rate of induction discussed in the previous paragraph gives a total rate of induction ranging from 5×10^{-5} to 5×10^{-6} mutations per gamete per roentgen depending upon the assumptions concerning the number of loci involved and the proportion of dominant mutations induced.

265. Assuming full penetrance, the damage thus estimated will become apparent in the offspring of irradiated subjects and, because of the reduction of fitness that it entails (paragraph 11), will, on the average, persist in the population for some twenty-five generations. The genes responsible for those traits that more drastically impair fitness will be eliminated in the first generation, whereas the mildest ones will persist for a very long time. Under conditions of steady irradiation for several generations, the frequency of the induced traits in the population would build up to a value equal to the rate of induction.

Effects of cell stage and type of irradiation

266. As mentioned in paragraph 248, all mouse data used for numerical estimates have been derived from experiments in which mouse spermatogonia were irradiated with high, unfractionated doses of acute, low LET radiation. However, it needs to be emphasized that the final yield of mutations has proved to be different when the germ cells of mice are irradiated with (*a*) low doses, (*b*) fractionated doses, (*c*) chronic radiation, and (*d*) high LET radiation.

267. As has been discussed in part III of this annex, experimental results in a number of species show that matters may differ considerably when other germ cells are irradiated. On the basis of results ob-

tained at seven specific loci in the mouse, acute x-ray irradiation of oöcytes at high doses yields more mutations per unit dose than acute irradiation of spermatogonia. Although the rate of induction in oöcytes is known with little precision, data suggest that it may be twice as high as in spermatogonia. When individuals of both sexes are irradiated, the total number of mutations induced will therefore be about 50 per cent higher than if oöcytes had the same sensitivity to radiation as spermatogonia.

268. Preliminary results indicate that in oöcytes the yield of specific locus mutations per unit dose after 50 R acute x rays (paragraph 170) is significantly lower than would be expected from results of irradiation at higher doses. It seems therefore that low doses of radiation are relatively less mutagenic than high doses of radiation, at least in oöcytes. Since human populations are more commonly exposed to low than to high radiation doses, it might well be that the estimates of genetic risks which are presently made will eventually prove to be too high.

269. Experiments with spermatogonia and oöcytes have shown that chronic radiation is mutagenically less effective than acute radiation. Under conditions of chronic irradiation of spermatogonia the yield of mutations per unit dose at rates of about 1 R per minute or less is about one-fourth of that at 90 R per minute (paragraph 156). With oöcytes, the reduction of the mutation yield is even more pronounced (paragraph 157). When both sexes are exposed to low dose-rate x or gamma radiation, the over-all yield of mutations can therefore be expected to be between one-eighth and one-fourth of that expected when the same population is exposed to high dose-rate radiation. Preliminary data indicate that a small dose-rate effect obtains with low doses of neutrons in mice oöcytes but not in spermatogonia (paragraphs 187, 196). More detailed information is needed before this dose-rate phenomenon with neutrons can be taken into account.

270. Results of new fractionation experiments (paragraph 175), in which the total radiation exposure is partitioned into small acute exposures of 50 R, indicate that this type of fractionation procedure yields mutation frequencies which are below those obtained with single, unfractionated procedures. Although mutation frequencies in the fractionated and unfractionated series differ by less than one order of magnitude, it is thought that this effect may be of importance for the estimation of human genetic hazards, because the fractionation procedures used are similar to those used in some medical practices.

271. Results of investigations at seven specific loci in spermatogonia show that low doses (up to about 100 rads) of acute or chronic fast fission neutrons are mutagenically more effective than x and gamma rays, suggesting an RBE of five for acute irradiation and of twenty for chronic irradiation (paragraph 188). Since human populations are usually exposed to low doses given at low dose rates, it seems that in spermatogonia the rate of induction of mutations per unit dose of neutrons may be some twenty times higher than the corresponding rate for x or gamma rays.

272. The final yield of mutations is not only affected by factors associated with radiation procedures but also by biological factors. One of the latter factors has recently been discovered and may have an important bearing on the estimation of genetic risks from irradiation of germ cells of females. Experiments with female mice have shown that the interval between irradiation and conception has a very pronounced effect on the mutation frequency observed in the offspring (paragraph 182). The frequency obtained after irradiation of females with low doses of neutrons is high in the first few weeks after irradiation, but, after that period, drops to a very low value, in fact zero in the sample size studied so far. Similar results have been obtained with x rays. There is a possibility of a similar effect in man and, therefore, an indication that the genetic radiation hazard from the exposure of women may, on the average, be less than that calculated on the basis of female mouse mutation rates obtained in the early time interval after irradiation.

Chromosome anomalies

273. The estimation of risks of induction of chromosome mutations can only be made on grounds as tenuous as those on which the estimates of risks of induced point mutations are based. While with regard to the induction of point mutations detailed and reliable quantitative information from *Drosophila* and from the mouse can be used, no comparable amount of data is available concerning the induction of chromosome anomalies. But the induction of point mutation is not borne out by direct observations in man, and the corresponding quantitative relationships between dose and effect are unknown. To estimate risks of induction of point mutations in man, a very major step is therefore necessarily involved in extrapolating from the experimental animals to our own species.

274. With regard to the induction of chromosome anomalies, on the other hand, there is clear evidence that a number of them can be induced by radiation in human cells *in vitro*. Preliminary observations suggest that some can be radiation-induced *in vivo* in germ cells. However, information on rates of induction *in vivo* in man is absent, and that obtained from human peripheral blood cells irradiated *in vitro* must be supplemented with observations in experimental animals.

275. Inferences regarding the induction of chromosome anomalies in our species based on animal material are especially open to criticism, inasmuch as the radiation sensitivity of chromosomes is known to change from one species to another. Thus, there is some evidence that human somatic cells might be more sensitive to the induction of chromosome anomalies by radiation than those of mice. Likewise, extrapolations from *in vitro* studies of human cells can also be quite misleading because of the known dependency of chromosome sensitivity on a number of factors associated with the stage and metabolism of the irradiated cells.

276. It was shown in part II of the present review that constitutional chromosome anomalies are responsible for a large part of the defects of genetic origin carried by human populations. Most of the anomalies are eliminated either pre- or post-natally in the generation immediately following the one in which they have arisen, and are associated with very severe hardship. Some, however, notably translocations, can be transmitted for a number of generations and are also the cause of serious harm to those who carry them in the unbalanced state.

277. Only for some types of chromosome anomalies can tentative risk estimates be obtained. These will be discussed in the following paragraphs. The estimates apply to a minor fraction of the total spontaneous chromosome damage detectable in the population. No estimate of the over-all risk of induction of chromosome

anomalies can be obtained in the current stage of our knowledge.

Changes in chromosome numbers

278. Experimental results indicate that in *Drosophila* the frequency of sex-chromosome loss rises linearly with dose below 1,000 R (paragraph 82). The rate of induced loss per pre-meiotic cell is very close to that obtained from irradiation of mouse spermatocytes at 200 R—between one and four chromosomes per 100,000 cells per roentgen. A comparable figure for non-disjunction cannot be obtained, because in that case the dose-effect relationship as observed in *Drosophila* is more complicated.

279. The possible importance of the induced sex-chromosome loss in man becomes apparent when it is recalled that XO karyotypes have been identified in 5 per cent of a sample of aborted foetuses and may therefore be responsible for a sizable proportion of spontaneous miscarriages. However, the possibility that at least part of the observed losses may have occurred after fertilization cannot be excluded.

280. No estimate of risk can, in the present stage of our knowledge, be obtained for the induction of losses or additions of autosomes. Some still inconclusive evidence, indicating that they may be induced by radiation in man, was mentioned in paragraph 66.

Translocations

281. Translocations in experimental animals are associated with, and frequently recognized through, the incidence of semi-sterility. In man, semi-sterility is a hardly applicable criterion, since the family-size usually falls very short of the natural fecundity of the species. The importance of translocations in human populations lies, therefore, much more in the suffering that they involve for those who receive them in the unbalanced state than in the effect they may have on the fertility of carriers of balanced translocations.

282. The estimation of risks of induction of translocations in man may be approached either from results obtained in mice or from results obtained in human cells *in vitro*. As discussed in part III (paragraph 116), from the incidence of semi-sterility in mice irradiated with 1,200 R of x rays, the number of induced translocations has been estimated to be approximately 14.8×10^{-2} per pre-meiotic cell. The estimate is based on the assumption that translocations are not further transmitted unless they are balanced, that no selection takes place between normal cells and cells carrying a balanced translocation, and that non-disjunction does not bias the observed frequencies of the translocations that are recovered.

283. In this connexion, it must be borne in mind that some of these assumptions may not strictly apply to man, since in our species the association of translocations with trisomies 21 does occur with a frequency of about 5×10^{-5} of all live-born children (paragraph 42), and the viability of cells carrying balanced translocations may, in fact, be different in mice, since the spontaneous frequency of translocations seems to be lower than in man.

284. The use of cell cultures to estimate the frequency of radiation-induced translocations is also far from being free from objections. For example, it is not possible to determine directly the rate of induction of translocations by radiation, because, even if the karyotype of each scored cell were established, present techniques would not make it possible to detect those translocations that involved small quantities of chromosome material or fragments of equal size. Finally, *in vitro* observations are available only on somatic cells, and it does not necessarily follow that, if the anomalies that were observed *in vitro* occurred in pre-meiotic cells *in vivo*, they would be transmitted to a viable gamete, as is indicated by the fact that haplo-21 zygotes appear not to be viable, whereas haplo-21 somatic cells are.[113]

285. Rather than determine the frequency of translocations *in vitro*, most authors have therefore assessed the frequency of breaks, dicentrics and ring chromosomes. Breaks are events whose frequency rises linearly with dose, whereas the frequency of dicentrics and ring chromosomes, like that of translocations, at least when induced by x rays, is proportional to the square of the dose at low doses and to its 1.5th power at high doses. At very low doses, the effect may be proportional to the first power of the dose.

286. The number of dicentrics and of ring chromosomes obtained through irradiation of blood cells at exposures between 50 and 200 R is 0.52×10^{-5} per cell per roentgen squared of which 0.45×10^{-5} are dicentrics.[187] The rate of 0.27×10^{-5} dicentrics per cell per roentgen squared was also obtained,[386] but it is perhaps less relevant because it is based on observations at exposures ranging between limits too far apart (25 to 1,200 R).

287. If it is assumed that translocations on one side and rings and dicentrics on the other are induced at the same rate, and that rates at high doses increase with the 1.5th power rather than with the square of the dose, the expected translocation rate after 1,200 R based on *in vitro* data is approximately 21×10^{-2} translocations per cell (or 18×10^{-2} if only the results on dicentrics are taken into account). This rate is fairly close to that deduced from semi-sterility data in mouse spermatogonia. Under the same reservations as were formulated for that case, the rate of transmission of translocations through the gametes would be four to six times less.

288. The rate of induction of translocations is known to be highly dependent on the rate of delivery of radiation. The estimates of rates of induction discussed in the previous paragraphs refer to acute irradiation. The actual rates under chronic irradiation may be considerably lower, as indicated by the mouse data discussed in paragraphs 118 and 124.

Deletions

289. Estimates of rates of induction of deletions in human germ cells are not available, but an idea of the possible magnitude of the risk of induction of certain clinically significant deletions can be obtained on the basis of the rates of induction of deletions by radiation in human cells *in vitro*. Induced rates *in vitro* are probably reliable, since they are consistent with scantier observations on peripheral cells of subjects irradiated accidentally *in vivo*.[154]

290. It is not known whether one single break is sufficient to bring about a stable "terminal" deletion or whether, in fact, an additional break is required to make it possible for the telomere to attach itself to the centric fragment. The linear rise of the frequency of terminal deletions *in vitro* (paragraph 69) speaks in favour of the one-hit theory.

291. To obtain estimates of the risk of induction of given syndromes due to terminal deletions, it is necessary to know the size of the fragments whose loss is responsible for each syndrome. As mentioned in paragraphs 39 and 40, the following terminal deletions are known to be associated with clinical syndromes severely detrimental but compatible with survival: deletion of part of the short arm of chromosome 5 (*cri du chat* syndrome), of the short arm and of the long arm of 18, and of the short and of the long arm of the X chromosome. It is not known whether any other deletion, be it terminal or interstitial, is compatible with survival nor to what sort of detriment it may be associated.

292. In the *cri du chat* syndrome, the size of the target, i.e., the length of the segment of chromosome 5 where a break must occur to produce the required deletion, amounts to over 50 per cent of the short arm of this chromosome or to about 1 per cent of the length of the diploid chromosome complement. This has been estimated[387] by studying the variations in length of the residual fragment of the short arm of chromosome 5 in the known cases of *cri du chat* syndrome.

293. Observations[157] on blood cells irradiated *in vitro* have shown that x rays induce 1.1×10^{-3} deletions per cell per roentgen. If a single break were enough to bring about the *cri du chat* syndrome, the deletion would be expected to occur with a frequency of $1.1 \times 10^{-3} \times 10^{-2} = 1.1 \times 10^{-5}$ per cell per roentgen. If two breaks were required, the expected frequency would be lower than the square of this (i.e., 1.2×10^{-10} per cell per roentgen squared).

294. Similar estimates can be obtained for the other deletions mentioned previously. Deletions of part of the short and of the long arm of chromosome 18 compatible with survival involve 0.25 and 1 per cent of the length of the diploid chromosome complement, respectively, leading to estimates of 0.3×10^{-5} and 1.1×10^{-5} deletions per cell per roentgen in the case of single events, and of 0.8×10^{-10} and 1.2×10^{-10} deletions if two breaks are required. Likewise, deletions of the short and of the long arm of the X chromosome, involving 3 and 4 per cent of the complement length, respectively, would occur with probabilities of 3.3×10^{-5} and 4.4×10^{-5} deletions per cell per roentgen if one break was required, and 11.0×10^{-10} and 19.0×10^{-10} deletions per cell per roentgen squared otherwise.

295. Nothing is known about the selection that deletions arising in germ cells might undergo. It is conceivable that a fraction of those that radiation may induce would be eliminated sometime before birth or perhaps before fertilization. Neither human nor experimental data are available which would make it possible to assess the extent of the elimination.

V. Conclusions

296. The estimates given in the preceding paragraphs must be examined in the light of the practical value they have in assessing the detriment that will result from exposure of human populations to any source of radiation. For that purpose, risk estimates must, ideally, be comprehensive, therefore taking into account all major genetic effects of social, rather than merely biological, import. If this did not prove possible, it would still be valuable to know the range in which the over-all risk estimate lay or even an upper limit to the estimate.

297. Even taken together, the estimates given earlier do not meet these requirements. The risk of induction of dominant mutations (paragraphs 261-265) applies to those major and easily recognizable traits that are clearly undesirable from the individual and social points of view. These traits are frequently observed in all known populations. That damage would always be a minor fraction of the over-all damage due to point mutations, though a particularly conspicuous one, both because of its immediate manifestation and its persistence for a number of generations, and because of the nature of the detriment to which the risk estimate applied.

298. An approach to the estimation of damage from induced dominant mutations could in the future result from the application to man of the observed frequencies of skeletal defects in first generation irradiated mice (paragraphs 151-155). However, it is not certain that comparable rates of induction apply at low doses.

299. The over-all risk of induction of all point mutations, which are all assumed to have some degree of dominance and to be eliminated predominantly in heterozygotes (paragraphs 253-260), includes the risk of induction of dominant mutations discussed in paragraph 297. One major practical limitation of the over-all risk estimate is due to the fact that the damage that is thus assessed is expressed in terms of loss of mutants through generations. This loss has a clear biological meaning, and has an undesirable character for the individual and for society. However, we do not know how many of the harmful mutations induced by radiation will at some point be eliminated through, say, loss of a zygote before implantation—an event which is not usually detectable in man—rather than through drastic reduction of fertility, miscarriages or serious genetic defects. But the estimate does, at any rate, provide the required upper limit to the damage due to point mutations.

300. This is, however, only part of the induced damage, since it does not include that due to chromosome anomalies. At present, we have no way of estimating the over-all risk of induction of chromosome anomalies. Their high frequency in human populations makes it likely that such a risk may not be negligible. We only have estimates of the induction of sex-chromosome loss (paragraphs 278-280), of translocations (paragraphs 281-288) and of those deletions that are known to be associated with severe clinical syndromes (paragraphs 289-295). The total damage from induced chromosome anomalies is likely to be higher, but our present knowledge is inadequate even to guess its possible magnitude, while such partial estimates as we have discussed are based on assumptions that make conclusions conjectural or, at best, very tentative indeed.

301. In considering the significance of radiation damage to the genetic material, it may be of interest to compare it with the rate of naturally-occurring genetic changes. It was estimated in the report that, on the average, a total of 140 point mutations arose spontaneously in 1,000 gametes in each generation and that under conditions of acute irradiation at high doses one rad induced a total of two mutations per 1,000 gametes. Thus a dose of one rad per generation would add about one-seventieth to the total number of mutations arising spontaneously per generation. To this point mutational damage must be added that due to chromosome anomalies which occur spontaneously in 1 per cent of live-born children. It is not possible at present to estimate

the over-all rate of induction of these anomalies by radiation, but the rate is expected to be very low at low doses.

302. Since neither a comprehensive estimate of the genetic risk, nor an upper limit to that estimate is available, the assessment of genetic damage from main sources of radiation must still be made by means of comparative risks. This is possible only at low doses and dose rates, in so far as linearity of the dose-effect relationship can be accepted as a computational approximation even for those effects that take place as a consequence of more than one event. No such approximation is allowed at high doses and dose rates, and even comparative risks cannot be determined for them.

TABLE I. MAIN TYPES OF SEX-CHROMOSOME MOSAICS OBSERVED IN MAN[30–32, 35–37]

A. *Without structural anomalies of the X chromosome*	
(1) In Klinefelter's and related syndromes ..	XY/XXY
	XX/XXY
	XXXY/XXXXY
	XXXX/XXXXY
	XXY/XXXXY/XXXXXY
	XO/XY/XXY
(2) In Turner's and related syndromes	XO/XX
	XO/XXX
	XO/XX/XXX
	XO/XYY
(3) In the XXX syndrome	XX/XXX
(4) In other syndromes ...	XO/XY
	XY/XXXY
	XX/XXY/XXYYY
	XX/XY
B. *With structural sex-chromosome anomalies*	
	XO/XX_{DL}
	XX/XX_{DL}
	XX/XX_{DS}
	XO/XX_{DS}
	XO/XX_R and $XO/XX_RX_RX_R$
	$XO/X_{iso}X$ and $XO/X_{iso}X/X_{iso}X_{iso}X$
	$XO/X_{iso}Y/X_{iso}Y/Y_{DL}$
	$XO/XY_{DL}/XXY_{DL}$
	$XO/XY/XY_{DL}$
	$X_{iso}X/X_{iso}X_{iso}Y$

TABLE II. FREQUENCY OF TRANSLOCATIONS AMONG TRISOMICS 21

	Observed cases	*Per cent frequency*	*References*
Heavily biased samples ..	(13/110)	11.8	30
	(18/227)	7.9	40
	(3/41)	7	41
Less biased samples	(5/101)	5	389
	(25/652)	4	30
Samples with little bias ..	(1/58)	1.7	43
	(4/203)	2	390
	(2/96)	2.1	44
	(6/127)	4.7	388

TABLE III. FREQUENCY OF ANOMALIES IN SEX-CHROMOSOME NUMBER IN SELECTED POPULATIONS

	Observed cases	*Frequencies per 1,000*	*References*
Feeble-minded			
Chromatin-positive males..	(29/3,306)	8.77	2
	(70/7,358)	9.51	2
Double-positive females ..	(12/2,689)	4.46	2
Chromatin-negative females	(1/2,689)	0.37	2
Criminals			
Chromatin-positive males..	(15/760)	20	59
XYY males	(7/197)	35	60
Sterile subjects			
Chromatin-positive males..		30	2
Females with sex-chromosome anomalies		280	2
Childless males with sex-chromosome anomalies..	(8/130)	62	58
Females with small stature			
Chromatin-positive females		73	61

TABLE IV. FREQUENCY OF SOME COMMON CHROMOSOME ANOMALIES

	Observed cases	*Frequency per 1,000*	*References*
A. Individual anomalies among live-born children			
Trisomy 21	1,522/1,022,042	1.5	2, 39
Trisomy 13	2/10,345	0.2 (0.021–0.69)[a]	51
Trisomy 18	3/10,345	0.3 (0.058–0.85)	51
Cri du chat syndrome		> 0.2[b]	
Klinefelter's and related syndromes	31/18,147	1.7 (1.16–2.98)	62–66
XXX syndrome	12/10,000	1.2 (0.62–2.1)	64
Turner's syndrome	5/16,920	0.29 (0.095–0.69)	62–66
B. Over-all frequency of anomalies in spontaneous abortions	44/200	220 (165–284)	82
C. Frequency of structural changes in an unselected adult population		5	56, 57

[a] 95 per cent confidence limits.

[b] Higher than frequency of trisomy 13.

TABLE V. RATES OF INDUCTION OF CHROMOSOME ANOMALIES BY ACUTE IRRADIATION OF BLOOD CELLS

		References
X rays		
Chromatid breaks per cell per roentgen	0.26×10^{-2}	154
Chromosome breaks per cell per roentgen	0.24×10^{-2}	154
	0.39×10^{-2}	155
	0.69×10^{-2}	156
Deletions per cell per roentgen	$0.11 \times 10^{-2} \pm 0.012$	157
Dicentrics per cell per roentgen squared	$0.45 \times 10^{-5} \pm 0.07$	157
	$0.27 \times 10^{-5} \pm 0.014$	386
Dicentrics per cell per rad squared	0.09×10^{-5}	156
14 MeV neutrons		
Deletions per cell per rad	$0.23 \times 10^{-2} \pm 0.022$	161
Ring and dicentrics per cell per rad squared	$0.81 \times 10^{-2} \pm 0.06$	161
25 MeV neutrons		
Deletions per cell per rad	0.26×10^{-2}	162
Fission neutrons		
Deletions per cell per rad	0.45×10^{-2}	162

TABLE VI. FREQUENCY OF SPONTANEOUS AND RADIATION-INDUCED SEX-CHROMOSOME ANOMALIES IN MALE AND FEMALE GERM CELL STAGES IN THE MOUSE

Irradiated germ cell stage	*Exposure (R)*	*Animals classified*	*Spontaneous frequency (per cent)*	*Adjusted[b] induced frequency per R per 10^6*			*References*
			X^MO[a]	*Loss[c] of* X^M	*Loss of* X^P *or* Y	XXY	
FEMALE GERM CELLS							
Prophase primary oöcyte (irradiated foetuses and newborn, 13½-20½ days post-conception)	150–250 (weighted mean, 220.5)	2,402		1.51	—	0	179
CONTROLS		785	0.0				
Dictyate (irradiated adults; ovulations 1-32 days post-irradiation)	100–400 (weighted mean, 342.0)	331		3.34	—	0	
MALE GERM CELLS							
Spermatocytes (mating 36-42 days post-irradiation)	200	1,508		—	1.6	0	
Spermatocytes (mating 29-35 days post-irradiation)	200	2,370		—	3.6	0.4	177
Spermatocytes (post-pachytene, 22-28 days post-irradiation)	200	1,752		—	0.7	0	
CONTROLS	—	3,059	0.06				
Spermatids (mating 15-21 days post-irradiation)	200	1,656		—	5.7	—	177
CONTROLS	—	1,299	0.13				
Spermatozoa (vas and epididymis)	600	1,112		—	2.0	—	177
CONTROLS	—	1,285	0.14				
PRONUCLEUS STAGES							
♀ and ♂ early pronucleus	100	422		19.0	23.2	0	177
	100	227		17.6	12.5	0	178
♀ and ♂ mid-pronucleus	100	193		0	0	0	178
	200	70		0	2.1	0	177
CONTROLS	—	822	0.97				177
	—	196	0.51				178

[a] X^MO was the only spontaneous sex-chromosome abnormality observed in controls. OX^P and XXX occur spontaneously with very low frequencies.[173]

[b] Irradiated minus control frequency. In the case of X^M loss, frequency is calculated by taking account of the fact that OY is lethal.

[c] Loss of entire chromosome as well as a few cases of deficiency.

TABLE VII. DOMINANT LETHALS IN SPERMATOGONIA OF MICE

Exposure (R)	Rate of delivery (R/min)	Induced pre-implantation losses[a]	Induced post-implantation losses[b]	Total rate of induction of dominant lethals[c]	Reference
0		—	—	—	196
550	69	—	0.02	0.02	
0		—	—	—	391, 392
300	100	0.06[d]	0	0.04[d]	
0		—	—	—	195
200	100	0.01	0	0.01	
0		—	—		198
600 + 600 8 weeks apart	217	0.01		0.11	
0		—	—		194
1,200	0.017	0.02		0.02	
0		—	—	—	197
275	75	—	0.04	—	
55 × 5[e]	75	—	—	—	

[a] $1 - \frac{\text{implanted embryos/}corpora\ lutea\text{ in irradiated series}}{\text{implanted embryos/}corpora\ lutea\text{ in control series}}$.

[b] $1 - \frac{\text{live embryos/total number of implants in irradiated series}}{\text{live embryos/total number of implants in control series}}$.

[c] $1 - \frac{\text{live embryos/}corpora\ lutea\text{ in irradiated series}}{\text{live embryos/}corpora\ lutea\text{ in control series}}$.

[d] Significantly higher than controls.

[e] 5 R per day for fifty-five consecutive days.

TABLE VIII. INDUCTION OF DOMINANT LETHALS IN GERM CELLS OF MALE MICE

Exposure (R)	Weeks after irradiation	1	2	3	4	5	6	7	8	References
300	Total rate of induction of dominant lethals[a]	0.21	0.15	0.38	0.28	0.28	0.24	0.05	0.04	391, 392
300	Post-implantation death[b]	0.19	0.01	0.27	0.08	0.05	—	—	—	
200	Total rate of induction of dominant lethals[a]	0.23	0.13	0.42	0.30	0.40	0.55	0.44	0.01	195
200	Post-implantation death[b]	0.20	0.12	0.32	0.13	0.21	0.09	0.13	—	

[a] $1 - \frac{\text{live embryos/}corpora\ lutea\text{ in irradiated series}}{\text{live embryos/}corpora\ lutea\text{ in control series}}$. [b] $1 - \frac{\text{live embryos/total number of implants in irradiated series}}{\text{live embryos/total number of implants in control series}}$.

TABLE IX. RATE OF INDUCTION OF DOMINANT LETHALS IN POST-MEIOTIC CELLS OF VARIOUS MAMMALS

Mammal	Exposure (R)	Corpora lutea	Per cent induced pre-implantation losses	Per cent induced post-implantation losses	Total rate of induction of dominant lethals	References
Mouse[a]	0	387	—	—	—	208
	400	248	13	40	48	
	670	178	28	51	65.6	
Mouse[b]	0	1,244	—	—	—	391, 392
	400	1,029	15	21	33	
	500	1,052	16.6	35	45	
	600	1,120	18	41	51	
	700	1,165	23	45	58	
Rat[a]	0	758	—	—	—	208
	400	419	13	49	55	
	670	403	29	61	72	
Guinea pig[c]	0	59	—	—	—	393
	500	95	2	43	44	
Guinea pig[a]	0	69	—	—	—	209
	300	47	—	13	10	
	450	46	—	28	25	
	700	40	—	50	45	
Rabbit[a]	0	203	—	—	—	208
	450	214	65	18	71	
	600	195	63	17	69	
Rabbit[c]	0	32	—	—	—	393
	500	105	49	16	57	

[a] Matings within 3 days after irradiation.
[b] Matings within 4 weeks after irradiation.
[c] Matings immediately after irradiation.

TABLE X. DOMINANT LETHALS IN OÖCYTES OF MICE[215]

Exposure (R)	*Oöcyte stage*	Corpora lutea	*A*	*B*
	Control	668	—	—
100	Dictyate	250	0.20	0.02
100	Late prophase I	217	— 0.07	— 0.09
100	Metaphase I	266	0.43	0.35
100	Anaphase I	184	0.37	0.20
100	Metaphase II	227	0.29	0.22
100	Pronucleus stage before or during DNA synthesis	149	0.11	0.05
	Control	668	—	—
200	Dictyate	279	0.11	0.14
200	Late prophase I	309	0.38	0.36
200	Metaphase I	185	0.74	0.75
200	Anaphase I	193	0.69	0.68
200	Metaphase II	274	0.57	0.55
200	Pronucleus stage before or during DNA synthesis	130	0.15	0.21

A—total rate of induction (see footnote [a] to table VIII).
B—induced post-implantation deaths (see footnote [b] to table VIII).

TABLE XI. TRANSLOCATIONS IN SPERMATOGONIA OF MICE

Experiment	*Exposure (R)*	*Rate of delivery (R/min)*	F_1 *Males*	*Per cent semi-sterile*	F_1 *Females*	*Per cent semi-sterile*	*Total* F_1	*Per cent semi-sterile*	*Checked cyto-logically*	*References*
1	0		427	0.2	109	0	536	0.2	Yes	
	600 + 600	217	427	3.5 (1.7–5)[a]	104	6.7	531	4.1 (2.4–5.8)		198, 223
2	0		216	0.0					Yes	
	1,200	0.017	214	0.9						194
3	0		?	?					Yes	
	700	?	1,010	0.5 (0.02–1.6)						224
4	0		80	0.0	25	0.0			No	
	550	69	80	0.0	25	0.0				196
5	1,092	Acute	110	2.7 (0.6–8.7)					No	225
6	0						1,037	0.0	Partly	226
	350	Acute					452	2.2 (1.1–4.0)	Partly	
	700	Acute					444	3.2 (1.4–4.8)	Partly	
	1,000	Acute					238	2.5 (0.9–5.4)	Partly	
7	0		112	0.0						197
	275	75	112	0.0						
	55 × 5[b]	75	112	0.9					No	

[a] 95 per cent confidence limits.
[b] 5 R per day for fifty-five consecutive days.

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

Source	Total exposure (R)	Rate of delivery (R/min)	Number of offspring tested	Number of mutations observed	Mutations per locus per gamete × 10^5	Reference
			SPERMATOGONIA			
X ray	300	80–90	65,548 (40,408)[e]	40 (25)	8.7 (8.8)	237
X ray	600	80–90	119,326	111	13.3	237
X ray	1,000	80–90	31,815	23	10.3	394
X ray	600	60–70	10,761	11	14.6	395
Co^{60} x ray	600	24	44,352	33	10.6	396
X ray	600	9	40,326 (28,339)[e]	23 (14)	8.1 (7.1)	237
Cs^{137}	600	0.8	28,059 (27,840)[e]	10 (10)	5.1 (5.1)	237
Cs^{137}	300	0.009	58,457	10	2.4	237
Cs^{137}	516	0.009	26,325	5	2.7	237
Cs^{137}	861	0.009	24,281	12	7.1	237
Co^{60}	603	0.007–0.009	10,763	2	2.7	395
Co^{60}	609	0.005	58,795	16	3.9	288
Co^{60} and radium	37.5	0.0011–0.0078	63,322	6	1.4	247
Cs^{137}	86	0.001	59,810 (56,993)[e]	6 (6)	1.4 (1.5)	237
Cs^{137}	300	0.001	49,569[f]	15	4.3	237
Cs^{137}	600	0.001	31,652[f]	13	5.9	237
Fission neutrons[a]	307	0.002–0.003	41,875[f]	67	22.9	288
Fission neutrons	207	55–60	39,028[f]	8	2.9	287, 397
Fission neutrons	104	0.001	39,083[f]	27	9.9	287, 397
Fission neutrons	101	0.13	19,506[f]	20	14.6	237
Fission neutrons	63	0.17	18,194[f]	13	10.2	237
Fission neutrons	59	0.79	17,041[f]	12	10.1	237
Fission neutrons	59	79	16,758[f]	10	8.5	237
CONTROL	—	—	531,500 (544,897)[e]	28 (32)	0.8 (0.8)	237
			OÖCYTES			
X ray	400	90	11,124 (12,853)[b, e]	15 (16)	19.3 (17.8)	237
Cs^{137}	400	0.8	20,827 (36,083)[e]	7 (13)	4.8 (5.2)	237
Co^{60}	600	0.05	10,117	1	1.4	401
Cs^{137}	400	0.009	37,049[f]	2	0.8	237
Cs^{137}	258	0.009	27,174	1	0.5	237
Co^{60}	450	0.004	11,225[f]	0	0	397
X ray	50	81	127,391[c, f]	10	1.1	268, 269
X ray	50	81	54,621[d, f]	0	0	268, 269
Fission neutrons	63	79	43,000[c, f]	37	12.2	284
Fission neutrons	63	79	40,092[d, f]	0	0	284
Fission neutrons	63	0.17	46,301[c, f]	22	6.8	284
Fission neutrons	63	0.17	80,391[d, f]	0	0	284
Fission neutrons	104	0.001	12,058[f]	1	1.2	397
CONTROL	—	—	98,828	1	0.14	396
CONTROL	—	—	13,402	0	0	397

[a] Neutron doses in rads (gamma component is included).
[b] Includes data from an old experiment, which was later excluded.
[c] Oöcytes sampled up to first seven weeks after irradiation.
[d] Oöcytes sampled more than seven weeks after irradiation.
[e] Revised from the 1962 report.[2]
[f] New data.[237]

TABLE XIII. SPECIFIC LOCUS MUTATIONS IN EXPERIMENTAL ANIMALS

Species	Number of loci tested	Exposure (R)	Rate of delivery (R/min)	Spontaneous mutation rates at individual loci per generation × 10^5 induced mutation rates per locus per gamete per R × 10^5			
				Spermatogonia	Oögonia	Oöcytes	References
Mouse	7	0		752		144	2
		400	90			48	
		600	60–90	22			
Mouse	6	0		0			238
		600	88	5			
Drosophila	8	0					398
		900	85	1.5			
Dahlbominus ..	4	0			599		267, 399
		1,000	1,000		9		
		0				552	400
		1,000[b]	100			30	
		1,000	100			45	
		1,000	100			65	
Bombyx	Pe-locus[a]	0		8,900	9.200		266
		1,000	60–100	65	28		
		1,000	60–100	23	12		
		1,000	60–100	28	18		
	Re-locus[a]	0		0	8,800		
		1,000	60–100	32	24		
		1,000	60–100	9	5		
		1,000	60–100	6	12		
Mormoniella ..	5	0				717	311
		1,136	854			14	

[a] Cells irradiated on the seventh, eighth or ninth day after hatching of the larvae.
[b] Progressively older stages of oöcyte development.

TABLE XIV. SEX-LINKED RECESSIVE LETHALS IN SPERMATOGONIA OF *Drosophila* LARVAE[257, 258]

Total exposure (R)	Rate of delivery (R/min)	Number of offspring tested	Mutation frequency per cent
		ACUTE RADIATION	
0	—	25,650	0.30 (0.24–0.37)[a]
56	25	21,538	0.40 (0.33–0.49)
109	25	21,154	0.42 (0.34–0.52)
163	25	20,860	0.43 (0.53–0.36)
0	—	8,405	0.26 (0.18–0.39)
307	25	8,330	0.26 (0.18–0.39)
		CHRONIC RADIATION	
0	—	25,738	0.31 (0.25–0.39)
144	0.30	9,583	0.50 (0.38–0.66)
267	0.55	8,310	0.66 (0.51–0.86)
300	0.60	5,705	0.75 —
400	0.83	5,793	0.40 (0.27–0.60)
542	1.13	7,641	0.38 (0.27–0.55)

[a] 95 per cent confidence limits.

TABLE XV. INDUCTION OF SEX-LINKED RECESSIVE LETHALS IN OÖGONIA OF *Drosophila melanogaster* BY "4,000" R

(*Modified from Muller* et al.[203])

Rate of delivery (R/min)	*Room of irradiation*	*A*	*B*
7,333	Hot	1.6 ± 0.2	1.67 ± 0.23[a]
7,333	Hot	1.7 ± 0.15	2.07 ± 0.16
7,333	Hot	2.0 ± 0.15	2.21 ± 0.17
2; 1	Hot	1.7 ± 0.17	1.44 ± 0.18
1.7; 1	Dilution	1.0 ± 0.09	1.23 ± 0.11
0.2	Hot	0.86 ± 0.11	0.68 ± 0.09
0.2	Hot	1.0 ± 0.15	0.9 ± 0.14
0.1-0.2	Dilution	1.08 ± 0.11	1.28 ± 0.13
0.1-0.2	Dilution	1.4 ± 0.11	1.5 ± 0.11
0.1; 0.05; 0.02	Dilution	1.25 ± 0.15	1.42 ± 0.17
0.05; 0.02	Dilution	1.5 ± 0.5	1.7 ± 0.6

A — Percentage observed minus spontaneous lethals.
B — Percentage after correcting for results of sperm irradiation in females.
[a] Spermatid instead of spermatozoan frequency was used for obtaining correction factor.

TABLE XVI. MUTATION FREQUENCY IN THE MOUSE FROM SINGLE AND FRACTIONATED IRRADIATION

Cell stage	*Total exposure (R)*	*Exposure in each fraction (R)*	*Interval between fractions*	*Number of offspring*	*Mean number of mutations per locus per roentgen[a] × 10⁸*	*References*
Spermatogonia	0	—	—	531,500	—	274
	300	—	—	65,548	26.6	274
	600	—	—	119,326	20.9	274
	1,000	—	—	44,649	8.5	274
	600	100 and 500	24 hours	24,811	39.1	274
	1,000	600 and 400	>15 weeks	4,904	28.4	274
	1,000	500	2 hours	14,879	10.8	253
	1,000	500	24 hours	11,164	49.2	274
	1,000	200	24 hours	8,588	25.9	253
	1,000	200	1 week	10,968	18.8	274
Oöcytes	200	—	—	37,297	40.2	274
	400	—	—	12,853	44.5	274
	400	200	24 hours	6,086	52.8	274

[a] Mutation rate in oöcytes is not adjusted for the control value. Spontaneous mutation rate in females is not accurately known.

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back to first page