769. Finally, for the class of diseases which is numerically most frequent among spontaneously-arising diseases, namely, the irregularly-inherited ones, it is difficult to make the kind of estimates (in terms of impaired life, life loss, etc.,) which Carter has made for other classes. The figures for those given in columns 3–7 of Table 50 are no more than crude guesses and may be associated with considerable errors. This limitation doubtless applies also to estimates of detriment associated with radiation-induced irregularly-inherited diseases.

770. In spite of these problems and difficulties, the Committee considers it worthwhile to attempt some estimates of detriment for radiation-induced genetic diseases, if only to illustrate a possible method and to gain some rough idea of the impact of these relative to that for spontaneously-arising ones. Such estimates are given in Table 55. It is worth reiterating that the numerical values are only approximate and must be viewed in the light of the number of reservations mentioned earlier.

771. It may be noted that the numerical figures given in column 2 of Table 55 (induced cases per 10^6 births) are those from Table 44, but the dominant and X-linked categories are shown separately. Furthermore, following Childs [C68], the first generation incidence for dominant and X-linked diseases is assumed to be 14% and 25%, respectively, of the equilibrium incidence. For chromosomal and irregularly inherited diseases, the figures given in column 2 are the same as those given in Table 44. For impaired life and life loss, the figures used are the same as those given in Table 50, except that for chromosomal diseases, the figures given in Table 49 for autosomal structural aneuploidy are employed.

772. The general conclusions to be drawn from Table 55 can be stated as follows: if a population is exposed to low dose rate, low-LET irradiation at a rate of 1 Gy per generation, the expected increment in genetic disease is of the order of about 2000 cases per 10^6 births in the first generation; this frequency is about one-seventh of that at equilibrium. These diseases are likely to cause about 50 000 years of impaired life per 10^6 births and an equal amount of life loss per 10^6 births in the first generation. At equilibrium, the figures are about 6 to 7 times higher. A comparison of these figures with the magnitude of detriment associated with spontaneously-arising genetic diseases (Table 50) will show that the former are relatively small for the stated radiation conditions. The Committee wishes to stress again that these figures (Tables 50 and 55) are crude, but may be useful in the comparison of detriment associated with spontaneously-arising and radiation-induced cancers.

E. SUMMARY AND CONCLUSIONS

773. In its 1977 report, the Committee made use of both the "direct" and "doubling dose" methods to obtain quantitative estimates of genetic radiation hazards in humans. The main conclusions were the following.

774. Using the direct method, the Committee estimated that following low-LET, low dose rate irradiation of males, there will be about 20 cases of affected progeny per million births per 10^{-2} Gy who will suffer from the effects of induced mutations having dominant effects. The data on the induction of dominant skeletal mutations in mice were used to make this estimate. For structural aberrations of chromosomes—predominantly reciprocal translocations—the risk was estimated to lie between 2 and 10 per million livebirths per 10^{-2} Gy under similar radiation conditions. The cytogenetic data on radiation-induction of reciprocal translocations in marmoset and human males were used for this purpose.

775. The risk for irradiation of human females, both from the induction of mutations having dominant effects and from the induction of reciprocal translocations was considered low, but no quantitative estimates were given.

776. The risk from the induction of sex-chromosome losses in either sex was also considered low, for the radiation conditions applicable to humans.

777. The risk estimate arrived at using the doubling dose method was that, under conditions of continuous radiation exposure to low-LET, low dose rate irradiation at a rate of 10^{-2} Gy/generation, the additional number of cases of genetic disease will be about 63 per million births in the first generation and about three times this frequency at equilibrium (over and above the 105 200 per million births occurring spontaneously). The doubling dose assumed was 1 Gy.

778. Since the publication of the 1977 report, new data have become available. Among these are those which confirm and further document the Committee's earlier conclusions; those that help to shed light on the validity of the assumptions and tentative conclusions (arrived at on the basis of limited data) or controversial view-points; those that are relevant in a qualitative sense, but which as yet cannot be used in quantitative risk assessments; and those that are of relevance for quantitative risk assessments. These have been briefly reviewed in this chapter. The new data pertain to the induction of dominant cataract mutations in mice and to the induction of reciprocal translocations in the rhesus monkey. Use was made of these data (in addition to those that were used in the UNSCEAR 1977 report) in quantitative hazard evaluations.

779. New publications on quantitative estimation of genetic hazards in humans (those of individual authors and of scientific bodies) have appeared since the UNSCEAR 1977 report. Brief summaries of the main conclusions reached in these are given, in addition to some detailed discussions on the similarities and differences between the conclusions reached by the UNSCEAR in 1977, an ICRP Task Group and the BEIR Committee in its 1980 report. It is pointed out that the conclusions reached by all three scientific bodies are similar and where differences exist, they stem from the different assumptions used (the basic data for all three are the same).

780. The Committee's current estimates of genetic hazards have also been made using the direct and doubling dose methods. With the former method, the risk from the induction of mutations having dominant effects in the progeny has now been estimated to lie in the range of 1000 – 2000 cases of affected individuals per million born per Gy of low-LET, low dose rate

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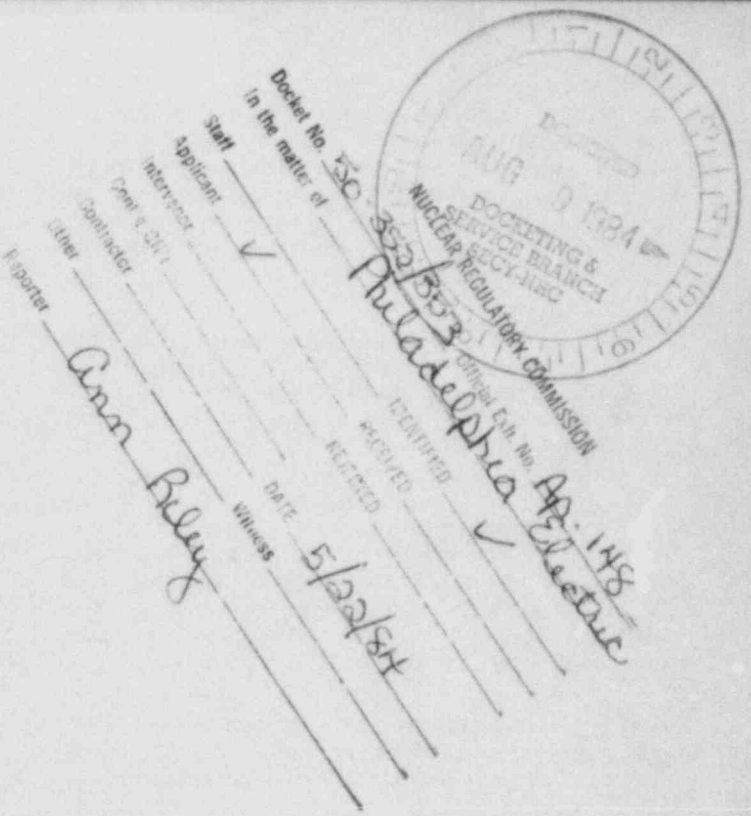
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irradiation of males. For the irradiation of females, the rough estimate of risk under similar conditions is 0–900 cases per million births. The lower limit of this estimate assumes that the mutational sensitivity of the human immature oocytes will be similar to that of mouse immature oocytes whereas the upper estimate assumes that the human oocyte will respond in a manner similar to that of maturing mouse oocytes under conditions of chronic low-LET irradiation.

781. The risk from the induction of reciprocal translocations has now been estimated to lie in the region of about 30 to 1000 cases of affected individuals per million births per Gy of low-LET, low dose rate irradiation of males; for irradiation of females, the very indirectly estimated risks are lower (range of 0–300 cases of affected individuals per 10^6 births).

782. As in the 1977 report, the Committee has used a doubling dose of 1 Gy to estimate risks using the doubling dose method (the argument that the doubling dose is likely to be higher than 1 Gy was considered, but it was decided to keep the figure of 1 Gy for this Annex until more data on this aspect accumulates). The quantitative estimates of risk arrived at in this Annex are slightly different from those arrived at in the 1977 report. It is now estimated that under conditions of continuous irradiation at a rate of one Gy per generation (low-LET, low dose rate), the expected total increment in the frequency of genetic diseases is about 2000 cases per million births in the first generation (instead an estimated 6300 cases per million) and about 15 000 cases of affected individuals per million births at equilibrium (instead of 18 000 cases per million). The reasoning for this change has been: recent calculations indicate that for dominant and X-linked diseases, the first generation increment is 15% of that at equilibrium (thus lowering the number of cases from 2000 per million to 1000 per million); the conclusion of the Committee (arrived at on the basis of all available evidence) that the assumption of a doubling dose of 1 Gy for all chromosomal disorders (most of which are numerical anomalies of chromosomes) rests on particularly uncertain grounds; the Committee's current assessments relate only to the structural component of chromosomal disorders; the risk from the induction of numerical anomalies is considered to be very small.

783. In this Annex, the Committee has reviewed data that bear on severity or detriment associated with genetic diseases and has also made a first attempt to give some crude estimates of genetic detriment based on a number of assumptions, for spontaneously-arising and radiation-induced genetic diseases. Under the assumption that the average life expectancy at birth is 70 years (and thus, for a million liveborn, 70 10^6 years), it has been estimated that overall, spontaneously-arising genetic diseases cause about 2 300 000 years of impaired life per million livebirths and about 3 000 000 years of life loss per million livebirths. For a population exposed to low-LET low dose rate irradiation at a rate of one Gy per generation, the additional cases of genetic disease induced, would cause about 50 000 years of impaired life per million livebirths and an approximately equal amount of life loss per million livebirths in the first generation following the radiation exposure. At equilibrium, the comparable figures are, 340 000 years of impaired life per million livebirths and about 286 000 years of life loss per million livebirths. The Committee wishes to reiterate that these estimates are very crude ones, but are illustrative of at least one method to estimate genetic detriment.

VIII. SUGGESTIONS FOR FUTURE RESEARCH

784. In this Annex, the progress that has been made in mammalian and human genetics, cytogenetics, somatic cell genetics and in other areas pertinent to the evaluation of genetic radiation hazards in man has been reviewed, and revised estimates of genetic risks have been presented. The Committee feels that, in order to increase our precision in risk assessment, more research effort along the following lines will be useful (the order in which these are listed do not reflect the order of importance).

(a) Human studies

Continuation of surveys on hereditary diseases in human populations and correlation of clinical data and chromosomal defects; studies on the contribution of mutations to irregularly-inherited disorders; continuation of studies on genetic disorders such as ataxia telangiectasia in which the cells derived from patients suffering from the disorders show enhanced sensitivity to damage induced by radiation and by other mutagens, using all possible approaches and comparisons.

(b) Studies with mammals and other higher eukaryotes

Continuation of studies on the nature of radiation-induced dominant and recessive mutations at defined gene loci; studies on the induction of mutations in germ cells and somatic cells at low doses and low dose rates; studies on factors modifying radiation-induced genetic damage and on mutational assay systems in somatic cells; studies on the possible influence of genetic background on the induced frequency of dominant mutations in higher eukaryotes.

(c) Studies at the chromosomal level

Studies on the induction of reciprocal translocations (including primates and human testis material where possible) using cytogenetic techniques, especially at low dose rates and low doses of radiation; studies on the induction of structural aberrations in mammalian oocytes; studies on factors influencing the induction and recovery of chromosome aberrations in germ cells and somatic cells in suitable mammalian systems.

(d) Biochemical studies using suitable prokaryotic and eukaryotic systems

On: the relationships between DNA damage, its repair and the origin of mutations and chromosome aberrations; mechanisms of constitutive and induced DNA repair by physical and chemical agents and their relevance for mutagenesis; mechanisms of regulation of DNA repair and of genetic recombination (possible role of hormones and growth factors) and their role in differentiation and carcinogenesis; DNA repair during gametogenesis; relationship of DNA lesions to changes in DNA sequences.

(e) Research on biological dosimeters to monitor radiation exposures

New approaches on the use of chromosomes as biological dosimeters; development of biochemical and immunological techniques for monitoring changes in DNA sequences and their application to assess cumulative doses arising from exposure to physical and chemical agents.

earlier assumptions and risk estimates remain essentially valid. These estimates have been compared with spontaneously-arising hereditary defects which affect, with different grades of severity, roughly 10% of all liveborn children. Physical agents such as ionizing radiation, as well as some noxious chemicals, may interact with the genetic material of the germinal cells in the testes or in the ovary by altering the genes, the elementary units of heredity (thus causing gene mutations), or with the structure or number of chromosomes on which the genes are carried (thus causing chromosomal aberrations). Changes in the genetic material may be associated with a variety of hereditary defects, some of which have severe clinical consequences.

44. Using gene mutations and chromosomal aberrations as end-points of experimental observations, data on dose-effect relationships have been compared in a variety of organisms. These comparisons have strengthened the assumption that one may expect a proportionality between the rates of spontaneous and of induced mutations of particular genes. This basic assumption has been applied in the indirect method of risk estimation.

45. Using the indirect method, the Committee estimated in 1977 that when a population is continuously exposed to low doses of low-LET radiation at a rate of 0.01 Gy per generation (1 generation = 30 years), 63 new cases of hereditary diseases per million first generation progeny would be expected. A substantial part of the hereditary diseases included in this estimate is related to those arising from numerical anomalies of chromosomes. However, data on experimental animals and man point to the possibility that the estimate for diseases falling under the category of chromosomal diseases may be lower than previously estimated. In view of this, the Committee has now estimated that when a population is exposed under the conditions specified above, the increment in genetic diseases is likely to be of the order of 20 (instead of 63) cases per million births in the first generation and about 150 (instead of 185) cases per million births at equilibrium (or about 2000 and 15 000 cases in the first generation and at equilibrium, respectively, when the exposure is at a rate of 1 Gy per generation).

46. As in the 1977 report, an estimate of risk for hereditary disorders has also been made using the direct method. The estimated values using these two different methods (i.e., indirect and direct methods) are in reasonable agreement.

47. The risk from the induction of a particular type of chromosomal effect of radiation (reciprocal translocations) has been re-evaluated on the basis of results from studies in marmosets, rhesus monkeys and man. However, the health consequences to the individuals carrying such translocations cannot be reliably assessed at present.

48. Further advances have been made in our knowledge of the dose-response relationships and other aspects of some of the more important types of genetic changes which can be induced by radiation in experimental mammals. Extensive use of experimental data for genetic risk assessment is still considered essential in the absence of significant results with respect to hereditary effects after human exposures. Suggestions have also been formulated for more detailed analyses of genetic effects with respect to detriment.

2. Somatic effects

49. One of the conclusions of the present report is that at low doses and dose rates the induction of non-neoplastic effects is not observed. This conclusion holds true for both whole-body and specific organ irradiation. At comparable doses and dose rates cancer induction may be the only somatic consequence of irradiation in animals and man.

50. In its 1977 report the Committee discussed factors which make any accurate assessment of risk of cancer induction in man very difficult. In spite of such difficulties, the Committee provided at that time an analysis of the human data and of the risk estimates to be derived therefrom, to be used as a necessary starting point for decisions of practical value, particularly as scientific criteria for radiation protection policies.

51. In view of the limited amount of new epidemiological evidence, there would have been no merit in repeating the same analysis in a short time interval. The Committee undertook instead to review whatever information might be of interest, in experimental animals and in man, in the light of some basic models of tumour induction. The scope was to assess the possible errors that might affect the estimates if one or another model of radiation action applied. Such a study might be regarded as an indirect way of estimating risk ranges at the low doses and dose rates where direct evidence is not available.

52. The Committee decided, however, to postpone the publication of a document based on this study when it became known that revisions had been proposed to the dosimetric estimates for the survivors of the atomic bombs at Hiroshima and Nagasaki on which some of the Committee's analyses had been based. Not only the total doses received by the exposed populations, but also the relative contributions of the neutron and gamma-ray components in the presently used T65D (Tentative 1965 Dose) were called into question. The effect of the proposed revisions is to reduce the neutron dose component at both cities and to increase the gamma component at Hiroshima substantially, while reducing the gamma component at Nagasaki slightly. In addition, many more factors must be examined and taken into account before reliable revised estimates of individual organ doses can be determined for the survivors. This matter is technically complex, and it appears unlikely that the proposed revisions can be thoroughly investigated and agreed upon within a short time.

53. The Committee awaits with interest the results of further studies in this field, as they would form one of the bases on which radiation risk estimates in man must be founded. In the meantime the Committee wishes to emphasize that it does not expect a significant impact of these revisions on the risk estimates contained in the 1977 report of the Committee, namely, that the risk of fatal cancer induction for x and gamma rays is of the order of $2\ 10^{-5}$ for an effective dose equivalent corresponding to one year of natural background, as an average for both sexes and all ages. This is so for two reasons. First, while it is impossible yet to say exactly what influence the revisions, if accepted, will have on the risk estimates, it is unlikely that this influence will exceed a factor of 2. Indeed, improved agreement between data from Hiroshima and Nagasaki may tend ultimately to strengthen confidence in the estimates. Secondly, the information derived from the survivors of