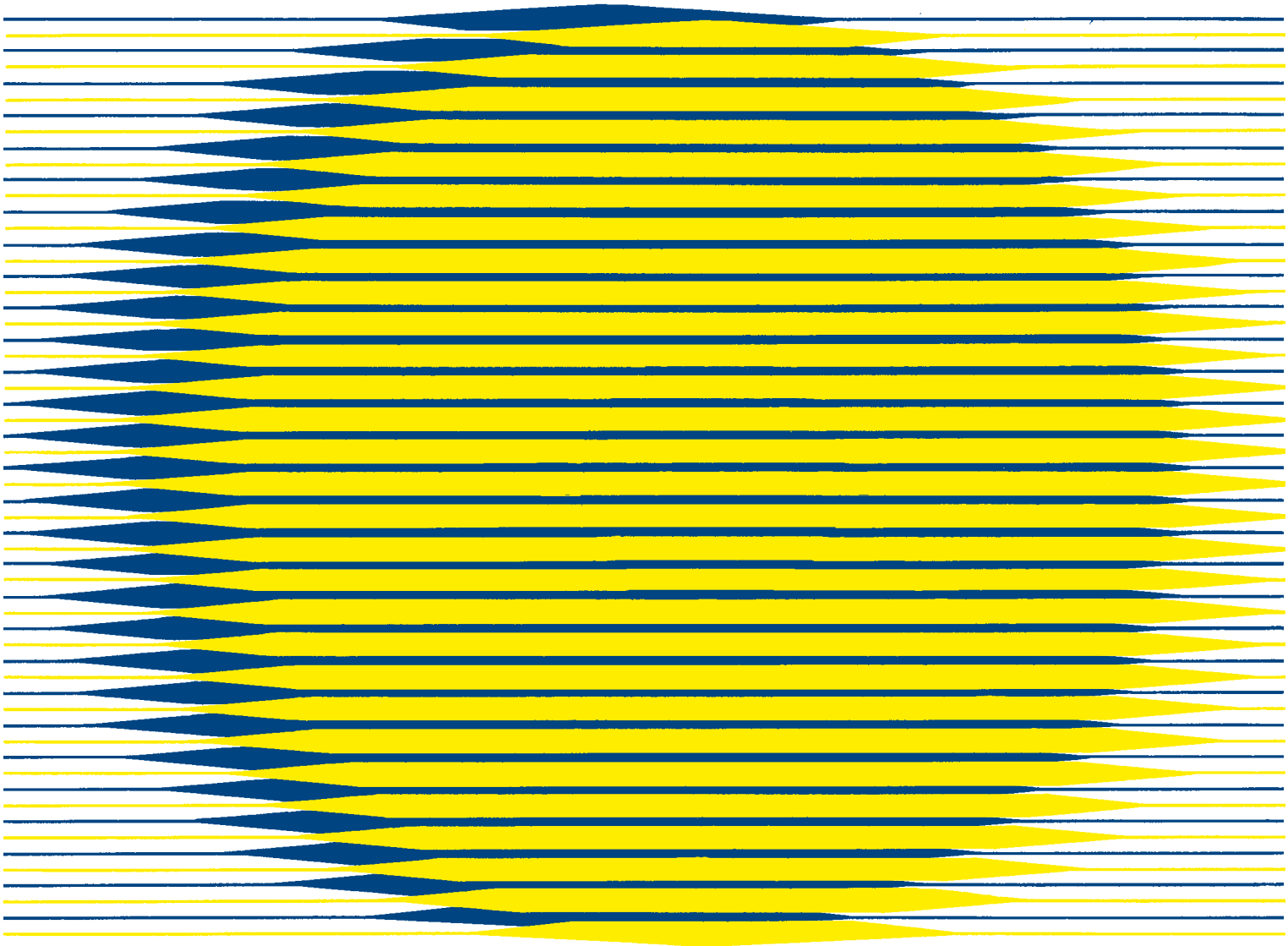
HEREDITARY EFFECTS OF RADIATION

United Nations Scientific Committee on the Effects of Atomic Radiation
UNSCEAR 2001 Report to the General Assembly,
with Scientific Annex



UNITED NATIONS

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UNSCEAR 2001 Report to the General Assembly, with Scientific Annex

UNITED NATIONS
New York, 2001

NOTE

The report of the Committee without its scientific annex appears as Official Records of the General Assembly, Fifty-sixth Session, Supplement No. 46 (A/56/46).

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CONTENTS

Report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly

1. During the past few years, the United Nations Scientific Committee on the Effects of Atomic Radiation[1] has undertaken broad reviews of the sources and effects of ionizing radiation. Estimates of the carcinogenic risk from exposures to ionizing radiation were presented in the UNSCEAR 2000 Report[2]. In its 2001 Report, the Committee has completed a comprehensive review of the risks to offspring (hereditary risks) following parental exposure to radiation. For the first time, the review included an evaluation of those diseases which have both hereditary and environmental components, the so-called multifactorial diseases. The major finding is that the total hereditary risk is 0.3–0.5 per cent per gray to the first generation following radiation. This is less than one tenth of the risk of fatal carcinogenesis following irradiation presented in the UNSCEAR 2000 Report.

2. The present report and its scientific annex were prepared between the forty-fourth and fiftieth sessions of the Committee. The following members of the Committee served as Chairman, Vice-Chairman and Rapporteur, respectively, at those sessions: forty-fourth and forty-fifth sessions: L. Pinillos-Ashton (Peru), A. Kaul (Germany) and G. Bengtsson (Sweden); forty-sixth and forty-seventh sessions: A. Kaul (Germany), L.-E. Holm (Sweden) and J. Lipsztein (Brazil); forty-eighth and forty-ninth sessions: L.-E. Holm (Sweden), J. Lipsztein (Brazil) and Y. Sasaki (Japan); and fiftieth session: J. Lipsztein (Brazil), Y. Sasaki (Japan) and R. Chatterjee (Canada). The names of members of national delegations who attended the forty-fourth to fiftieth sessions of the Committee as members of national delegations are listed in the appendix to the present report.

3. In approving the present report, the Committee applied its scientific judgement to the material it reviewed and took care to maintain an independent and neutral position in reaching its conclusions. Following established practice, only the main text of the report is submitted to the General Assembly.

4. The Committee wishes to acknowledge the assistance of the consultant, K. Sankaranarayanan, in the preparation of the scientific annex and the advice of the international experts, S. Abrahamson, J.F. Crow, C. Deniston, U.H. Elhing, V.A. McKusick, W.R. Lee, M.F. Lyon, K.G. Lüning, W.J. Schull and R.C. Woodruff, whose independent review was sought by the Committee in its deliberations.

5. The sessions of the Committee held during the period under review were attended by observers from the World Health Organization, the International Atomic Energy Agency, the International Commission on Radiological Protection and the International Commission on Radiation Units and Measurements. The Committee wishes to acknowledge their contributions to the discussions.

6. Radiation exposure has never been demonstrated to cause hereditary effects in human populations. The absence of observable effects in children of survivors of the atomic bombings in Japan, one of the largest study populations, indicates that moderate acute radiation exposures of even a relatively large human population must have little impact. However, experimental studies in plants and animals have clearly demonstrated that radiation can induce hereditary effects. Humans are unlikely to be an exception in that regard.

7. The Committee has concluded that a sounder basis now exists for estimating the hereditary risks of radiation exposure. Advances in molecular genetics are contributing to improved understanding of the structural and functional changes in genes that underlie hereditary diseases. Gains have also been made in evaluating the risk of multifactorial diseases such as coronary heart disease, diabetes and essential hypertension. Those diseases affect a large proportion of the population, occur throughout life, have varying severity and are affected by both genetic and environmental factors.

8. The Committee uses the doubling-dose method, which is based on equilibrium theory, for hereditary risk estimation. The doubling dose is the amount of radiation required to produce the same number of mutations as occur spontaneously in one generation of the population. The reciprocal of the doubling dose is the relative mutation risk per unit dose. A high doubling dose implies a low relative mutation risk, and vice versa. The risk due to radiation is quantified as the number of additional cases of genetic disease, over and above the baseline incidence, expected for a given radiation exposure. In the present report, the doubling dose has been estimated using spontaneous mutation rates of human genes and radiation-induced mutation rates of mouse genes, because there are no data on radiation-induced mutations in humans. The Committee now estimates the doubling dose to be of the order of one gray for low-dose, sparsely ionizing radiation. This is essentially the same as in earlier reports of the Committee, but supported by more data.

9. For a population exposed to radiation in one generation only, the risks to the progeny of the first post-radiation generation are estimated to be 3,000 to 4,700 cases per gray per one million progeny; this constitutes 0.4 to 0.6 per cent of the baseline frequency of those disorders in the human population.

10. At its fiftieth session, held in Vienna from 23 to 27 April 2001, the Committee decided on its new programme of work. The Committee will gather new data on radiation exposures from natural, man-made and occupational sources; extend its evaluation of medical exposures, especially in relation to new diagnostic procedures that can result in high doses; perform a comprehensive assessment of radon in homes and workplaces; and examine the effects of radiation on the environment as part of a study on radioecology. The Committee also plans to use the cellular and molecular concepts of its 2000 report to address radiation effects at the level of tissues and organs; examine the potential consequences for development of cancer risk from radiation of newly identified cellular responses to radiation; continue to perform epidemiological evaluation of cancer and additionally of diseases other than cancer that may be increased by radiation; and continue its studies on the radiological health effects from the Chernobyl accident. Those studies are expected to be completed and published in 2005.

Notes

1 The United Nations Scientific Committee on the Effects of Atomic Radiation was established by the General Assembly at its tenth session, in 1955. Its terms of reference are set out in resolution 913 (X) of 3 December 1955. The Committee was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt, France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics, United Kingdom of Great Britain and Northern Ireland and United States of America. The membership of the Committee was subsequently enlarged by the Assembly in its resolution 3154 C (XXVIII) of 14 December 1973 to include the Federal Republic of Germany, Indonesia, Peru, Poland and the Sudan. By its resolution 41/62 B of 3 December 1986, the Assembly increased the membership of the Committee to a maximum of 21 members and invited China to become a member.

2 For the previous substantive reports of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly, see *Official Records of the General Assembly, Thirteenth Session, Supplement No. 17* (A/3838); ibid., *Seventeenth Session, Supplement No. 16* (A/5216); ibid., *Nineteenth Session, Supplement No. 14* (A/5814); ibid., *Twenty-first Session, Supplement No. 14* (A/6314 and Corr.1); ibid., *Twenty-fourth Session, Supplement No. 13* (A/7613 and Corr.1); ibid., *Twenty-seventh Session, Supplement No. 25* (A/8725 and Corr.1); ibid., *Thirty-second Session, Supplement No. 40* (A/32/40); ibid., *Thirty-seventh Session, Supplement No. 45* (A/37/45); ibid., *Forty-first Session, Supplement No. 16* (A/41/16); ibid., *Forty-third Session, Supplement No. 45* (A/43/45), ibid., *Forty-eighth Session, Supplement No. 46* (A/48/46); ibid., *Forty-ninth Session, Supplement No. 46* (A/49/46); ibid. *Fifty-first Session, Supplement No. 46* (A/51/46); and ibid., *Fifty-fifth Session, Supplement No. 46* (A/55/46 and Corr.1 Arabic only). These documents are referred to as the 1958, 1962, 1964, 1966, 1969, 1972, 1977, 1982, 1986, 1988, 1993, 1994, 1996 and 2000 reports, respectively. The 1972 report, with scientific annexes, was published as *Ionizing Radiation: Levels and Effects, Volume I: Levels* and *Volume II: Effects* (United Nations publication, Sales Nos. E.72.IX.17 and 18). The 1977 report, with scientific annexes, was published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales No. E.77.IX.1). The 1982 report, with scientific annexes, was published as *Ionizing Radiation: Sources and Biological Effects* (United Nations publication, Sales No. E.82.IX.8). The 1986 report, with scientific annexes, was published as *Genetic and Somatic Effects of Ionizing Radiation* (United Nations publication, Sales No. E.86.IX.9). The 1988 report, with scientific annexes, was published as *Sources, Effects and Risks of Ionizing Radiation* (United Nations publication, Sales No. E.88.IX.7). The 1993, 1994 and 1996 reports, with scientific annexes, were published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales Nos. E.94.IX.2, E.94.IX.11 and E.96.IX.3, respectively). The 2000 report, with scientific annexes, was published as *Sources and Effects of Ionizing Radiation, Volume I: Sources and Volume II: Effects* (United Nations publication, Sales Nos. E.00.IX.3 and 4).

Appendix I

Members of national delegations attending the forty-fourth to fiftieth sessions

Argentina	D. Beninson (Representative), E. D'Amato, D. Cancio, P. Gisone
Australia	P. A. Burns (Representative), K. H. Lokan (Representative), J. Loy, D. I. Macnab, S. Solomon
Belgium	J. R. Maisin (Representative), A. Debauche, R. Kirchmann, H. P. Leenhouts, J. Lembrechts, K. Sankaranarayanan, P. Smeesters, J. van Dam, H. Vanmarcke, A. Wambersie
Brazil	J. L. Lipsztein (Representative), D. R. Melo, A. T. Ramalho, E. R. Rochedo
Canada	R. M. Chatterjee (Representative), D. B. Chambers, R. J. Cornett, N. E. Gentner (Representative), R. V. Osborne (Representative), S. Vlahovich (Representative)
China	Z. Pan (Representative), N. Gu, F. He, Q. He, J. Ma, B. Mao, K. Li, P. Liu, Y. Song, X. Su, Z. Tao, K. Wei, B. Xiu, G. Yang, H. Yang, J. Yu, L. Zhang, Y. Zhao, J. Zhou, B. Zhu
Egypt	A. M. El-Naggar (Representative), F. Hammad (Representative), M. A. Gomaa
France	J. F. Lacronique (Representative), A. Aurengo, M. Bourguignon, A. Flüry-Hérard, J. Lallemand, C. Luccioni, R. Masse (Representative), J. Piéchowski, A. Rannou, M. Tirmarche
Germany	W. Burkart (Representative), U. Ehling, W. Jacobi, T. Jung, A. Kaul (Representative), A. Kellerer, J. Kiefer, G. Kirchner, W. Köhnlein, C. Reiners, F.E. Stieve, C. Streffer (Representative), W. Weiss
India	K. B. Sainis (Representative), P. C. Kesavan (Representative)
Indonesia	K. Wiharto (Representative), T. Suprihadi, S. Zahir (Representative)
Japan	Y. Sasaki (Representative), T. Asano, M. Doi, H. Iizuka, T. Isoyama, S. Kumazawa, S. Mizushita, K. Morita, Y. Muramatsu, N. Nakagawa, J. Onodera, K. Sato, T. Sato, Y. Taguchi, K. Tatsumi, M. Yoshizawa
Mexico	J. R. Ortiz-Magaña (Representative), E. Araico Salazar (Representative)
Peru	L. V. Pinillos-Ashton (Representative)
Poland	Z. Jaworowski (Representative), M. Waligórski, L. Dobrzynski
Russian Federation	L. A. Ilyin (Representative), R. M. Alexakhin, L. A. Buldakov, N. P. Garnyk, K. I. Gordeev, A. K. Guskowa, V.K. Ivanov, J. B. Kholina, I. S. Koshkin, I. I. Kryshev, I. I. Kulyeshov, B. K. Lobach, O. A. Pavlovski, T. S. Povetnikova, M. N. Savkin, V. A. Shevchenko
Slovakia	D. Viktory (Representative), I. Bučina, P. Gaál, V. Klener, E. Kunz
Sudan	K. E. H. Mohamed (Representative), O. I. Elamin (Representative)
Sweden	L. E. Holm (Representative), G. Bengtsson (Representative), U. Bäverstam, L. Moberg, W. Leitz, J. O. Snihs
United Kingdom of Great Britain and Northern Ireland	R.H. Clarke (Representative), H. J. Dunster, V. Beral, F. A. Fry, J. W. Stather
United States of America	F. A. Mettler (Representative), L. R. Anspaugh, J. D. Boice Jr., N. H. Harley, E. V. Holahan, C. B. Meinhold, R. J. Preston, P. B. Selby, W. K. Sinclair

Secretariat of the UNSCEAR

B.G. Bennett
N.E. Gentner

ANNEX

Hereditary effects of radiation

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INTRODUCTION

1. Estimation of the genetic risks of exposure to ionizing radiation has been a continuing endeavour of the Committee. In the previous assessment in the UNSCEAR 1993 Report [U4], the Committee considered advances in human and radiation genetics relevant to estimating the risks of hereditary effects of radiation exposures. Additionally, it directed attention to a subset of human Mendelian diseases for which cancer of one type or another is the principal phenotype and reviewed the sensitivity of individuals with such genetic diseases to radiation-induced cancers. The material contained in Annex G, "Hereditary effects of radiation", and Annex E, "Mechanisms of radiation oncogenesis", of the UNSCEAR 1993 Report broadly defines the scope of this Annex and its starting point.

2. Knowledge of the molecular aspects of naturally occurring human genetic diseases and the mechanisms of their origin has been growing rapidly, especially since the beginning of the Human Genome Project, in 1990. Much progress has been made in mapping and cloning the genes that when mutated result in Mendelian diseases. Promising methods are now being developed for the "genetic dissection" of multifactorial diseases as well [L1, W1]. These advances are relevant to radiation risk estimation for at least two reasons:

(a) the yardstick for expressing genetic risks is "inducible genetic disease", the implicit assumption being that such diseases will be similar to those that occur naturally as a result of spontaneous germ-cell mutations; and

(b) insights gained into the nature and mechanisms of the origin of naturally occurring genetic diseases and into genotype-phenotype relationships, used together with data from mammalian radiation mutagenesis studies, constitute a sounder basis for inferring which of these diseases are potentially inducible by radiation.

3. These advances are already allowing the conceptual framework for risk estimation to be restructured and the critical questions to be reformulated. In fact, the new information suggests that radiation is less likely to have adverse genetic effects than had hitherto been assumed and that it is possible to reconcile the empirical results from human studies of genetic risks of radiation with predictions of such risks from mouse data. The aims of this Annex are, therefore, to capture the essence of these advances and to examine how they might allow estimates of genetic risks of radiation exposures to be revised. In presenting this review, the general framework of naturally occurring genetic diseases and their classification into Mendelian (those due to mutations in single genes), chromosomal (those due to chromosomal abnormalities), and multifactorial (those due to complex interactions between genetic and environmental factors) is retained, as was used in the earlier assessments of the Committee. This is done primarily for convenience, although developments in human molecular biology are making the distinction between these different classes less sharp, and radiation-inducible adverse effects may not always be classifiable into these three subgroups.

I. THE HUMAN GENOME

A. GENE NUMBER AND SIZE

4. The total length of the human haploid genome is about 3 million kilobases ($3\ 10^6$ kb, or 3,000 Mb), distributed between 22 types of autosomes and two types of sex chromosome (the X and Y) that can easily be differentiated by chromosome banding techniques. The amount of DNA varies from chromosome to chromosome. The longest, chromosome 1, contains about 263 Mb and the shortest, chromosome 21, contains 50 Mb. In a 550-band metaphase chromosome preparation, an average band corresponds to about 6 Mb of DNA [M55]. The genes are not distributed uniformly along the length of DNA; the Giemsa light-staining bands in metaphase chromosomes contain more genes than do dark-staining bands [S1].

5. The most often quoted range of gene numbers in humans is 50,000 to 100,000 [U16]. Antequera and Bird [A1] used the number and distribution of CpG islands in genomic DNA as a measure for the number of genes. The CpG islands are clusters of cytosine-(C) and guanine-(G) rich sequences present at the 5' ends (i.e. left ends) of all housekeeping genes and of a large proportion of genes with a tissue-restricted pattern of expression. Thus, the presence of a CpG island denotes the 5' end of the associated gene [C1, L2]. Since the number of CpG islands in the human genome is approximately 45,000, and 56% of the genes so far sequenced contain CpG-islands, the estimate of total gene number is about 80,000. Extrapolation from sequencing of large chromosomal regions suggests that there are 60,000 to 70,000 genes [F1]. It is worth noting that in any given tissue, only a relatively small proportion of the genes are expressed. Current estimates, based on the draft human genome sequences generated by Celera Genomics [C81] and the Human Genome Project [I15] and published in 2001 suggest that the number of genes may be of the order of about 26,000 to 40,000.

6. There is a wide range of size differences, from about 2 kb to 2,000 kb, between human genes. The size distribution of the 253 genes for which information is catalogued in McKusick's compendium [M1] is as follows: 59 (23%) are less than 10 kb, 90 (36%) are between 10 and 25 kb, 51 (20%) are between 25 and 50 kb, 33 (13%) are between 50 and 100 kb, 17 (7%) are between 100 and 500 kb, and 3 (1%) are more than 500 kb. Table 1 presents some examples.

B. GENE ORGANIZATION AND FUNCTION

7. As with other eukaryotic genes, most human genes are made up of coding (exon) and non-coding intervening (intron) sequences. Each individual gene differs not only with respect to its DNA sequence but also with respect to its structure. A few human genes, e.g. histone genes, interferon genes, and mitochondrial genes, are devoid of introns, whereas some possess a considerable number of introns, with their lengths varying from a few base pairs to several kilobase. Less than 5% of the genome consists of protein-coding sequences (exons of genes), the remainder being made up of non-coding regions (such as the various types of repeat sequences present in introns and between genes), whose functions remain to be elucidated.

8. The first two bases of the 5' end of each intron are guanine (G) and thymine (T), and the last two bases (at the 3' end of intron) are invariably adenine (A) and guanine (G). In the sense strand, at the 5' end of the gene is the ATG codon, which is the transcriptional initiation site. Upstream from this are a number of non-coding sequences, referred to as promoters, and further upstream are a number of cis-acting regulatory elements of defined sequence (TATAAA and CCAAAT motifs, which play a role in constitutive gene expression, and enhancers, which respond to particular proteins in a tissue-specific manner by increasing transcription). At the 3' end of the gene, following the termination codon (e.g. TAA, TAG, and TGA), is a poly(A) tail.

9. The process by which genetic information in the DNA is transmitted to mRNA is called transcription. During this process, the entire unit of both introns and exons is transcribed into precursor mRNA. The region of precursor RNA transcribed from the introns is then excised and removed and does not form mRNA and therefore does not specify the primary structure of the gene product. The accuracy of the excision is determined, at least in part, by the virtually invariant GT and AG dinucleotides present at the 5' and 3' exon-intron junctions, respectively. The precursor RNA from the exons is spliced together to form the definitive mRNA, which specifies the primary structure of the gene product. The definitive mRNA is transported to the cytoplasm, where protein synthesis occurs (translation). These aspects are discussed in detail by Lewin [L2].

II. MENDELIAN DISEASES

10. A large number of phenotypes of Mendelian genetic disease have been recognized. McKusick's 1994 compendium [M1] has 6,678 entries: autosomal dominant, 4,458; autosomal recessive, 1,730; X-linked, 412; Y-linked, 19; and mitochondrial, 59. As of January 2000, the on-line version of the above compendium [M2] had 11,062 entries. Well over 6,980 genes have been assigned to specific chromosomes and most of them to specific sites on those chromosomes. For many of these genes, extensive information is available, including sequence organization, the nature and function of the gene product, and the diseases associated with mutations in them; for others, the information on the gene is indirect and limited to linkage of a Mendelizing phenotype to the particular chromosomal site [M2, S2].

11. Although well over 1,100 clinical diseases have been mapped to specific chromosomal regions (about 1,000 loci), data on mutational spectra (i.e. nature, type, and distribution of mutations along the gene) are available for fewer than one half of the above. These data are more extensive for some of the genes, including the cystic fibrosis gene (*CFTR*) with more than 500 independent mutations; the β-globin gene (*HBB*) with more than 400 mutations; and the *factor IX* gene (haemophilia B), α-globin genes (*HBA*), and the *LDLR* gene (familial hypercholesterolemia), each with more than 100 allelic variants. With many other genes, these numbers are much smaller. Some of the reasons for these differences are size and function of the gene; clinical relevance of mutations and the amount of effort expended; ease of detection; availability for analysis; and the specificity of the type of mutational event, i.e. whether it is restricted to specific gene regions [S2].

A. MOLECULAR NATURE OF MUTATIONS

12. Point mutations and deletions are without doubt the most frequently encountered gene lesions that underlie Mendelian diseases. Other genetic changes comprise a mixed assortment of insertions, duplications, inversions, and complex rearrangements. Point mutations include transitions (substitution of one purine for another purine [e.g. A to G or vice versa] or of one pyrimidine for another [e.g. C to T or vice versa]) and transversions (replacement of a purine by a pyrimidine [e.g. A to T or vice versa]). These may result in the replacement of one amino acid by another (missense mutations, which do not affect the remainder of the protein) or the substitution of a codon for an amino acid to a stop or terminating codon (TGA, TAA, or TAG), which leads to premature termination of translation (nonsense mutations). Frameshift mutations occur when one or more nucleotides are either inserted or deleted; since the genetic code is read in non-overlapping triplets, if the number of bases inserted or deleted is not a multiple of three base pairs, such insertions or deletions change the reading frame, and the entire amino acid sequence of the protein is altered beyond the site of mutation, causing loss of function of the protein.

13. Mutations have been found to occur not only in the coding sequences but also in regulatory regions, promoter regions, splice junctions, within introns, and in polyadenylation sites. They may interfere with any stage in the pathway of expression, from gene to protein product. It is noteworthy that splicing defects are not uncommon; point mutations causing a defect in mRNA splicing appear to represent some 15% of all point mutations in Mendelian diseases [C2]. Some of the consequences of splice site mutations are a reduction in the amount of mRNA generated, production of an aberrant mRNA, and non-recognition by the cellular machinery of an exon or exons following the lesion. The result of the last of the above possibilities is that the non-recognized exons are excluded from the mature RNA transcript, a process called “exon skipping”.

14. So far, about 300 Mendelian diseases have been analysed [S3, S4]. The recorded molecular changes can be classified into three broad groups: (a) point mutations; (b) length mutations, including small and large intragenic or multigenic DNA deletions, insertions, rearrangements, and duplications; some of the latter are fundamentally the same as microscopically detectable chromosomal aberrations (i.e. deletions, insertions, rearrangements, and duplications); and (c) those that arise as a result of non-traditional mechanisms such as expansion of trinucleotide repeat sequences in the coding or untranslated regions of genes.

15. Based on the types of the molecular change so far delineated, the Mendelian diseases can be grouped into four categories, namely, those that are predominantly due to (a) point mutations, (b) both point mutations and length mutations, (c) large intragenic length mutations and microdeletions (contiguous gene deletion syndromes), and (d) those that arise as a result of non-traditional mechanisms. The results of analysing 309 Mendelian diseases belonging to the first three categories above are summarized in Table 2. Those of the fourth category are discussed in a later Section.

16. Overall, 200 of 309 diseases (65%) are due to point mutations, 69 (22%) are due to both point mutations and length mutations, and 40 (13%) are associated with length mutations and microdeletion syndromes. If only the 164 autosomal dominant and X-linked diseases are considered, 89 (54%) are due to point mutations, 42 (26%) are due to both point mutations and length mutations, and 33 (20%) are due to length mutations and microdeletion syndromes. It is important to bear in mind that both the numbers and the relative proportions will change when more data are analysed.

B. MUTATIONAL SPECIFICITIES

17. Both the earlier [S5, S6] and the more recent [S3, S4] analyses of the distribution of point mutations along the different genes show that in a small proportion of these, the mutational sites appear to be distributed nearly uniformly

throughout the gene; this is particularly true of many autosomal recessive and X-linked diseases and some autosomal dominant diseases. In contrast, with a large proportion of genes that underlie most autosomal dominant diseases, the distribution of mutational sites is non-random, i.e. there are apparent preferences for one or a few exons or parts of the gene. Examples of both nearly uniform as well as non-random distribution of mutational sites in genes are given in Table 3.

18. While part of the non-random distribution mentioned above may stem from differences in ascertainment and the extent of knowledge of the number of sites at which mutations are recoverable, the current view is that this non-random distribution is a reflection of the sequence organization of the gene and its genomic context. For transition-type point mutations, data consistent with this view are available (reviewed in [C2]). In many genes there are stretches of methylated CpG sites, and it is in these that a substantial proportion of C to T and the corresponding G to A transitions in the complementary strand occur. This is because of the high propensity of 5-methylcytosine to undergo spontaneous deamination to thymine. Of the 880 base changes reported to cause human Mendelian diseases (as of 1992), 38% were found to involve CpG dinucleotide and 86.5% of these (32.8% of the total) were either C to T or G to A transitions [C2]. Since not all transitions occur at CpG sequences, there must be other explanations for their origin.

19. For transversion-type point mutations, no such hotspots are known. Data from *in vitro* and prokaryotic systems [K1, K2, L3] show that transversions occur as a result of DNA polymerase infidelity, the bypass of apurinic sites, and chemical modification. The important point is that for both transitions and transversions, the processes involved are known to be DNA-sequence-dependent, so it is hardly surprising that the distribution of point mutations is non-random. Further, it should be borne in mind that the near-uniform distribution of mutational sites recorded in some of the genes does not exclude specificities at the molecular level, e.g. the presence of CG dinucleotide repeats in genes and the occurrence of C to T and G to A transitions; it merely means that mutations at any one of these sites results in a scorable phenotype.

20. Analyses of the distribution of break points in length-mutation-associated diseases show the same phenomenon of non-randomness and seem to be dependent on the sequence of the gene and its context. All of the 219 short (20 bp or less) deletions in 63 different genes analysed by Cooper and Krawczak [C2] have direct repeats of 2 bp or more flanking or overlapping them. The mechanism proposed to explain the origin of these small deletions involves misalignment and slippage during DNA replication. For large deletions, sequence homologies and repetitive sequences such as Alu located within and between genes appear to play an important role. Examples of Mendelian disease that are believed to arise through these mechanisms were discussed by Cooper and Krawczak [C2] and Sankaranarayanan [S5, S6] and in the UNSCEAR 1993 Report [U4].

C. GENOTYPE-PHENOTYPE RELATIONSHIPS

21. The concept that certain genetic diseases represent generalized single-gene-determined defects ("one mutation, one disease") is a simple one, especially when viewed from the perspective of the 1990s. It was heuristically powerful, because it predicted the practicability of identifying a unitary "cause" for each of these diseases; this prediction has been amply fulfilled, as evidenced by advances in the knowledge of the biochemical (and now molecular) basis of Mendelian diseases during the past few decades, notwithstanding the observations that mutant genes do not always express the mutant phenotype in all individuals carrying them (variable penetrance) or affect them to the same degree (variable expressivity).

22. At the same time, these advances underscore the fact that even in simple Mendelian diseases, when looked at closely, the relationship between the genotype and phenotype (or clinical manifestation) is not always invariant; there are now many examples of (a) mutations in the same gene causing different phenotypes, and (b) mutations in different genes resulting in the same or nearly the same phenotypes. In current terminology, the former situation is referred to as allelic heterogeneity and the latter, as locus- or non-allelic heterogeneity (or genetic heterogeneity). Furthermore, instances of identical mutations (thus, no allelic heterogeneity) causing large differences in clinical severity have also been reported.

23. In addition to the above, as discussed in the UNSCEAR 1993 Report [U4], phenomena such as mosaicism, genomic imprinting, and allelic expansion also introduce complexities into genotype-phenotype relationships. These complexities, however, do not detract from the fact that the genetic factors that influence these relationships in a given disease can often be studied individually and even quantified, thereby increasing the accuracy of prognoses (reviewed in [H1, W3]).

1. Mutations in the same gene causing different clinical phenotypes

24. In their survey of allelic variants in 767 genes, Schinzel et al. [S7] found that in 658 genes the variants were associated with one clinical disease, in 71 with two, in 30 with three, in 5 with four, in 1 with five, in 1 with six, and in 1 with seven diseases. Thus, out of 767 genes, 109 were found to be associated with more than one clinical disease. Some examples are given in Table 4, and a few of them are discussed below.

(a) Mutations in the *PMP22* gene

25. Of peripheral neuropathies, Charcot-Marie-Tooth disease type 1A (CMT1A) is the most frequent [B1, P1, S8]. In nearly 70% of the patients, a stable duplication of 1.5 Mb has been found in the CMT1A region of

chromosome 17p11.2. Within the CMT1A region, a gene coding for a peripheral myelin protein (PMP22) has been localized. However, in a number of cases without the duplication, point mutations have been identified in the *PMP22* gene, and most are dominant, although some recessive mutations have also been found [R1]. Clinically, the disease phenotype has been observed to vary, even among members of the same family, suggesting that additional factors influence the course of the disease [B1, P1]. Mutations in the *PMP22* gene have also been found in some patients with the hypertrophic demyelinating peripheral neuropathy known as Dejerine-Sottas disease.

26. In cases carrying the duplication mentioned above, *PMP22* is overexpressed, so a gene dosage effect is believed to be the cause of the disease. A deletion that is duplicated in the CMT1A region results in a condition referred to as hereditary neuropathy with liability for pressure palsies (HNPP) [B1, C3, P1, S8].

(b) Mutations in the *FGFR3* gene

27. Mutations of the fibroblast growth factor receptor *(FGFR)* genes cause diverse forms of skeletal disorders; these are discussed in the next Section. It will only be noted here that different point mutations in one of these genes, *FGFR3* on chromosome 4p16.3, have been found in achondroplasia (ACH), in hypochondroplasia (HCH), and in thanatophoric dysplasia (TD). Intriguingly, although individuals with a deletion of the short arm of chromosome 4 have one copy of *FGFR3* deleted (Wolf-Hirschhorn syndrome), they do not have any of the characteristics of ACH, HCH, or TD (no skeletal dysplasias).

(c) Mutations in the *CFTR* gene

28. In cystic fibrosis (CF), an autosomal recessive disease, the primary physiological defect is believed to be a reduced conductance of chloride ions in the epithelial tissues affected by the disease (hence the designation cystic fibrosis transmembrane conductance regulator, or *CFTR* gene). As a consequence, fluid secretion and salt absorption are impaired, and patients show, among other symptoms, chronic sinopulmonary disease, pancreatic insufficiency, and elevated sweat chloride levels.

29. The *CFTR* gene is distributed over 230 kb of genomic DNA on chromosome 7 and consists of 27 exons. The predicted protein is 1,480 amino acids long and comprises two transmembrane domains (containing 12 membrane-spanning regions), two ATP-binding domains or nucleotide-binding folds (NBF), and a highly polar domain (R) with many possible phosphorylation sites, believed to play a regulatory role [R3]. Over 500 mutations in this gene have been identified, the most common being ΔF508 in exon 10, a three-nucleotide deletion leading to the loss of phenylalanine at position 508 [K3, P3, T1].

30. In general terms, ΔF508 homozygotes seem to have a more severe disease than genetic compounds for the exocrine pancreatic and pulmonary functions. Severe mutations comprise all molecular types, in particular those that presumably block or impair synthesis of the CFTR protein, such as nonsense, frameshift, and splice-site mutations; most of these are located in the NBF domains. In contrast, most mutations that are mild are in the transmembrane domains and are predominantly missense, although some splice-site mutations have also been found.

31. In most CF patients, there is a good correlation between the different *CFTR* mutations and pancreatic insufficiency, but the correlations are not absolute. Other symptoms such as meconium ileus (a type of intestinal obstruction), which occur in some 10% of patients with pancreatic insufficiency, do not seem to be associated with specific genotypes. The severity of the pulmonary disease also varies independently of the respective mutations; thus, unrelated patients with the same genotype (e.g. homozygotes for the ΔF508 deletion) show a striking variation in lung function. Similar comments apply to sweat chloride concentrations. These and other differences point to the influence of other (genetic, environmental) factors not yet fully identified.

32. In about 97% of CF male patients, congenital bilateral absence of vas deferens (CBAVD), an obstructive azoospermia, has been observed. ΔF108 and Arg117His mutations are the most common mutations, and ΔF208/Arg117His is the most common genotype in isolated CBAVD; almost all other genetic compounds include one or the other.

2. Mutations in different genes causing similar phenotypes

33. Similar phenotypes can arise when, for instance, more than one gene is required for a common biochemical pathway or cellular structure. Further, mutations in members of a given gene family can give rise to a set of related pathologies. In their 1994 compilation, Schinzel et al. [S2] found that 26 diseases were associated with mutations in two different genes, 11 with mutations in three, 4 with mutations in four, 4 with mutations in five, 1 with mutations in six, 1 with mutations in seven, and 1 with mutations in ten different genes. Table 5 presents some examples, a few of which are discussed below.

(a) Osteogenesis imperfecta and Ehlers-Danlos syndrome type VII

34. Mutations in one of two structural genes for type I procollagen, namely *COL1A1* coding for proα1(I) and *COL1A2* coding for proα2(I), are responsible for more than 90% of the cases of osteogenesis imperfecta (four clinical types) and one type of Ehlers-Danlos syndrome, type VII (EDS-VII) (reviewed in [B2, D2, S10]). The main clinical feature that defines osteogenesis imperfecta I is bone fragility, whereas that of EDS-VII is severe multiple-joint hypermobility and ligamentous tears; congenital bilateral dislocation of the hip is the rule.

(b) Skeletal disorders associated with mutations in the *FGFR* genes

35. To date, seven skeletal disorder syndromes, namely, Apert syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, achondroplasia, thanatophoric dwarfism, and hypochondroplasia, have been found to be caused by mutations in three fibroblast growth factor receptor (*FGFR*) genes [B3, J1, M5, R4, R5, S11, S12, T2, W4]. All these syndromes show an autosomal dominant mode of transmission and share a number of craniofacial abnormalities that arise as a result of premature fusion of the flat bones of the skull, leading to an abnormal head shape. They are clinically distinguished largely on the basis of hand and foot abnormalities. There are at least two other craniosynostosis syndrome mutations that have been identified in genes on chromosome 7 (*GLI3*) [V1] and chromosome 5 (*MSX2* gene; the Boston type) [J2].

36. Each of the four *FGFR* genes described in humans encode receptor proteins that have an extracellular region with three immunoglobulin (Ig)-like domains, a transmembrane segment, and a split cytoplasmic tyrosine-kinase domain; they have amino acid identities of 55%–72% [J3] but differ in their ligand affinity and tissue distribution. The Ig-like II domain, the interloop region between Ig-like domains II and III, and the N-terminus of the Ig-III domain are implicated in ligand binding [G1, J3]. In addition, the C-terminal sequences of the Ig-like III domain appear to be important for ligand specificity.

37. Mutations in *FGFR* genes and the resultant phenotypes are shown in Table 6. Achondroplasia, the most common form of genetic dwarfism, has been shown to be due to mutations in the *FGFR3* gene: a G to A transition in codon 380 (glycine to arginine substitution) or G to C transversion in the same codon (also causing glycine to arginine substitution) in the transmembrane domain [B3, R4, S11]. Mutations in the tyrosine kinase domain of the same gene result in the phenotypically different and more severe thanatophoric dwarfism [T2] and also in hypochondroplasia [B4]. Individuals with Pfeiffer syndrome have mutations in either *FGFR1* (ligand-binding domain) or, more commonly, in the *FGFR2* genes (Ig-III domain). *FGFR2* gene mutations in the Ig-III domain are also responsible for Jackson-Weiss syndrome and Crouzon syndrome.

3. Identical mutations with different phenotypes

(a) β-S mutation in sickle-cell anaemia

38. Sickle-cell anaemia is a classic example of an autosomal recessive disease in which all patients are homozygous for the same β-globin (*HBB*) gene lesion (β-S mutation; GAG to GTG, resulting in the substitution of valine for glutamic acid at codon 6 of the β-globin gene). The disease shows wide variation in clinical severity (expressivity) in different patients, ranging from early childhood mortality to a virtually unrecognized condition. There is evidence that the clinical severity of this disease can be ameliorated by the effects of genetic variation either within the *HBB* gene regulatory regions, in far upstream regions controlling the expression of the linked G-γ (*HBG2*) and A-γ (*HBG1*) globin genes, or at the unlinked α-globin gene (or a combination of these) (see [C2, L1, W3]).

(b) Mutations in the *CFTR* gene

39. As discussed earlier, studies of individual mutations have shown that the *CFTR* cystic fibrosis phenotype is closely associated with pancreatic status and may influence chloride levels in sweat but is unrelated to the severity of lung disease. One patient homozygous for the ΔF508 was noted to have a sweat chloride level significantly lower than usually observed in these patients. DNA sequencing revealed a second alteration (resulting in an arginine 553 to glutamine change) in the first nucleotide binding fold domain in the *CFTR* gene. The authors suggested that this change might modify the effect of ΔF508 mutation [D3].

40. A second example, also in the *CFTR* gene, relates to the effect of a neutral amino acid polymorphism (phenylalanine 508 to cysteine) that was associated with the disease when combined with a second amino acid substitution (serine 1251 to asparagine) in the second nucleotide binding fold [K4]. A further example was provided by Kieswetter et al. [K5]; they showed that the phenotypic effects of one *CFTR* missense mutation (arginine 117 to histidine) varied depending on the length of the polypyrimidine tract in the splice acceptor site in intron 8.

4. Mutations in the same genes inherited as both dominant and recessive

41. There are now several examples of Mendelian diseases that are inherited as dominant in some families and recessive in others, although the same gene is mutated (see Table 14 in [M1]). Differences in the precise type and location of the mutations seem to be responsible for these differences in mode of inheritance. Two examples are discussed below.

42. Usually, β-thalassemias (haemoglobinopathies due to defects in β-globin chain synthesis) manifest a recessive pattern of inheritance and can arise as a result of a variety of molecular changes in the *HBB* gene (promoter sequence mutations, premature stop codons and frameshifts, splice junction mutations, and partial deletions of the gene). Heterozygotes are usually symptomless. However, an unusual dominant form of β-thalassemia also occurs and is often caused by heterozygous mutations in exon 3 of the *HBB* gene [K6]. A total of 16 different mutations (mostly but not exclusively in exon 3), causing the dominant form of the disease, were collated by Thien [T5], who classified them into three distinct groups:

(a) highly unstable β-globin chain variants caused by either base substitution or the deletion of intact codons;
(b) truncated β-globin chain variants caused by premature termination of translation; and
(c) elongated β-globin chain variants with an altered carboxyl terminal resulting from a frameshift mutation.

43. A comparison of these three variants has suggested mechanisms to explain why exon 3 mutations are some-times associated with a particularly severe phenotype [C2, T5]. Nonsense mutations occurring in the 5' half of the *HBB* gene (exons 1 and 2) do not give rise to a detectable β-globin product (owing to mRNA and/or protein instability), resulting in a typical heterozygous β-thalassemia phenotype due to a simple reduction in β-globin synthesis. Most unstable β-globin variants result in unbalanced globin synthesis; less unstable ones could still transiently form tetramers with α-chains, resulting in severe anaemia. β-globin chains truncated by exon 3 nonsense mutations may often be synthesized, but such chains are unlikely to be capable of forming viable tetramers, although they might still retain the ability to bind haem. Elongated β-chain variants, on the other hand, would possess an abnormal carboxy terminal end, causing instability and the subsequent aggregation and precipitation of an abnormal globin molecule. Thus, production of an abnormal β-chain may often be clinically more severe than the abolition of β-chain synthesis, a situation similar to collagen gene mutations, discussed earlier.

44. Christiano et al. [C5] found that a patient homozygous for a T to A transversion (resulting in a methionine to lysine change) in the 49-bp exon (in a highly conserved region of the C-terminus of type VII collagen) manifested a severe form of epidermolysis bullosa dystropica, a skin blistering disease; both parents of the patient were heterozygous for the same mutation but unaffected. However, a mutation in the *COL7A1* gene (G to A transition at the glycine residue 2040 in exon 73; glycine to serine), showed dominant inheritance [C6] (see McKusick [M1] for other examples of these types of effect).

5. Mosaicism, genomic imprinting, and uniparental disomy

45. Discussed in detail in the UNSCEAR 1993 Report [U4] were mosaicism, genomic imprinting, uniparental disomy, and allelic expansion (dynamic mutations), which are some other mechanisms/ phenomena that affect genotype-phenotype relationships. The following paragraphs focus on uniparental disomy, for which some new data have been published and mention only briefly the basic concepts of mosaicism and genomic imprinting. Allelic expansion, although it could be considered in this subsection, is deferred to the next in view of the extensive amount of information.

46. Mosaicism refers to the presence of normal cells and those carrying a mutation in the same individual; this can happen in somatic cells or in the germ-line or in both. If mosaicism for a dominant disease-causing mutation is present in the germ-line of an individual, the individual may not manifest the phenotype of the mutation but risks transmitting the mutation to his or her offspring. Germ-line mosaicism has been observed in a number of Mendelian diseases, such as Duchenne muscular dystrophy, Apert syndrome, and osteogenesis imperfecta type II [M1].

47. Genomic imprinting refers to a phenomenon in which an allele at a given locus is inactivated, depending on whether it is inherited from the father or mother (parent-of-origin effects); this implies a differential expression of genetic information depending on whether it is inherited from the father or the mother (see [B7, C2, H4, M1] for recent reviews). The best-characterized examples of genomic imprinting are Prader-Willi syndrome and Angelman syndrome. Both were mapped to the same chromosomal region, 15q11–q13, by the observation of *de novo* deletions in sporadic cases. The clinical features of the syndromes are quite distinct. Prader-Willi syndrome includes developmental delay and hypotonia in infancy but is particularly characterized by hyperphagia (bulimia), leading to gross obesity later in life. Angelman syndrome is characterized by ataxia, seizures, and severe mental retardation, with a particularly pronounced lack of speech.

48. Molecular studies using polymorphic markers from the 15q11–q13 region confirmed the similarity of the two deletions but revealed that the deletions in Prader-Willi syndrome arose on the chromosome inherited from the father, whereas deletions in Angelman syndrome arose on the chromosome inherited from the mother. This suggests that this genomic region is not functionally equivalent in both sexes and that the expression of genes in this region therefore depends on the parental origin, i.e. they are imprinted. The Angelman syndrome has been subsequently found to be a single-gene disorder, resulting from mutations in the *UBE3A* gene [K16, M22].

49. Uniparental disomy refers to a phenomenon in which an individual with a normal chromosome complement has both members of a chromosome pair (or chromosomal segments) inherited from a single parent (in contrast to the normal situation in which one member of each pair of chromosomes is paternal and the other maternal). The term "heterodisomy" is used when both chromosomes from one parent are present, and "homoisodisomy" is used when two copies of the same parental chromosome (arising through duplication) are present.

50. Uniparental disomy can create a situation in which a child with a well-known recessive disease is found to have only one heterozygous parent. When non-paternity or new mutations in the germ cells of the other parent can be excluded, it is possible to demonstrate, using DNA markers, that both the mutant chromosomes are derived from the heterozygous parent. This was first demonstrated in the case of cystic fibrosis, in which homozygosity for a mutation in the *CFTR* gene of the patient was found to have arisen as a result of uniparental disomy [S14, V3].

51. Uniparental disomy can result in a clinical disease not only by rendering the individual homozygous for a recessive mutation inherited from only one parent but also by uncovering the effects of gene imprinting [H4, R6]. In fact, the well-known examples of uniparental disomy, Prader Willi syndrome, Angelman syndrome, and Beck-with-Wiedemann syndrome (an overgrowth disorder due to paternal disomy for chromosome 11), have come to light because they involve regions of the human genome containing imprinted genes [M1]. Some further instances of uniparental disomy in humans, regardless of whether associated with an abnormal phenotype or not, are summarized in Table 7. The subject has been recently reviewed [M15].

6. Allelic expansion (dynamic mutations)

52. It has long been known that the human genome contains many nucleotide sequences that occur repeatedly. These repeat sequences vary in complexity from complete genes (such as the ribosomal *RNA* genes; >400 genes) down to simple sequences of one or a few base pairs. Among the repeats of simple sequences are the simple tandem repeats, which involve mono-, di-, tri-, tetra-, and pentanucleotide repeating units. Many simple tandem repeats are polymorphic (i.e. variable from individual to individual) in copy number in human populations. They therefore provide a rich source of linkage markers that have been (and are being) widely exploited in studies of the human genome. However, it was with the discovery, in 1991, of an expanded CGG repeat as the mutation causing fragile-X mental retardation [O1, Y1] that trinucleotide repeat expansions were recognized as an important and novel mutational mechanism in human genetic disease (see [B8, R7, S15] for recent reviews).

53. Thus far, at least 14 Mendelian diseases have been shown to be associated with trinucleotide repeat expansions. These include fragile-X syndromes A and B, spinal and bulbar muscular atrophy, Huntington disease, Machado-Joseph disease, Dentatorubral-pallidoluysian atrophy, spino-cerebellar ataxia types 1, 2, 6, and 7, myotonic dystrophy, Friedreich ataxia, oculopharyngeal muscular dystrophy, and synpolydactyly. The types of repeat and their location are given in Table 8. As noted in the footnote to this Table, a form of progressive myoclonal epilepsy has been found to be due to the expansion of a dodecamer repeat (i.e. 12 nucleotide repeat expansion) located upstream of the 5' transcription start site (untranslated region) of the *CSTB* (cystatin B) gene [L12, L20]. Of these, the fragile-X mental retardation syndrome, Huntington disease, and myotonic dystrophy are considered below because of their relatively moderate to high prevalences (and, accordingly, greater societal relevance).

(a) Fragile-X syndrome

54. The fragile-X syndrome of X-linked mental retardation has a prevalence that could be as high as 1 per 1,000 males (range: 0.3–1 per 1,000) and 0.6 per 1,000 females (range: 0.2–0.6 per 1,000) [W5]. The CGG repeats are located in the 5' untranslated region of exon 1 of the gene [K7, V4, Y2]. The risk of transmitting the disease phenotype is correlated with the size of the CGG repeat. The number of these repeats in the normal X chromosome is between 6 and 53, with 29 repeats the most frequent. Within this normal range, the alleles are stably inherited. At a length of more than approximately 50 copies, the allele sizes can increase, in a number of steps, through a clinically innocuous premutation phase with a repeat size of up to about 230 copies. The premutation is unstable, and the copy number increases to the full mutation range (>230 up to 1,000 copies). In a full mutation, the CpG residues in the repeat itself and in an adjacent CpG island (which is part of the promoter region of *FRAXA* gene) are methylated [O1], and this shuts down transcription of the gene [P6], generating the disease phenotype.

55. The chance of such large expansions depends on copy number in the premutation phase: if the repeat number is small (50–70 copies), the risk is low; if the repeat number is high (>90), the risk is almost 100%, i.e. the carriers of high-copy-number premutations are more likely to have affected children [F2, Y1]. Since this expansion occurs when the repeat array is transmitted from one generation to the next, the disease shows what is referred to as "anticipation", i.e. an increase in disease severity and/or a decrease in the age at onset as the disease passes through generations. Because of these unique features (transition from normal copy number to premutation to full mutation involving more than one step), the term "dynamic mutation" is used for this type of mutational mechanism (reviewed in [F3, S15]).

56. Males have been observed to transmit only the premutations, and these do not usually change much in size. Hence all daughters of male carriers of premutations have a premutation of about the same size as that of their father, but they never have the full mutations and, consequently, lack features of the fragile-X syndrome. Sherman delineated this paradox, which bears her name: that the mothers and daughters of males with premutations have very different risks of having children with fragile-X syndrome [S17, S18]. It is now known that these two groups of women are at different stages of progression of the dynamic mutation. The mothers of males with premutations have, on average, smaller premutations than the daughters of these males. The premutation usually increases in size when transmitted from the mothers to their sons but then goes relatively unchanged to the daughters of these males. Because the risk of pre-mutation changing to a full mutation on transmission by a female is a function of its size, the paradox can now be explained.

(b) Huntington disease

57. Huntington disease is a progressive neurodegenerative disease characterized by a diverse set of symptoms, including personality changes, progressive chorea, and dementia. It is inherited as an autosomal dominant and

affects about 1 in 10,000 individuals in most populations of European origin [H7]. The onset of symptoms generally occurs within the fourth or fifth decade but can vary from very early childhood to the late 70s. About 6% of cases have onset before age 21 years, and the disease progression is more severe. The CAG repeats are located in the first exon of the Huntington disease gene at amino acid residue 18 [H8]; both increases and decreases in length of CAG repeats upon maternal and paternal transmission have been found, but these are generally less than five repeat units. With paternal transmission, however, there is a higher percentage of increases, some of which are quite large. The majority of expansions in the large size range (>55) are paternally transmitted, including all juvenile patients with childhood onset [A3, B11, G3, H8, N3, S21].

58. It is now known that huntingtin, the gene product of the *HD* gene, is crucial for normal development and that translation and expression of mutant huntingtin result in neuronal death. Huntingtin is specifically cleaved during apoptosis by a key cysteine protease, apopain, known to play a pivotal role in apoptotic cell death. The rate of cleavage is strongly enhanced by longer polyglutamine tracts, suggesting that inappropriate apoptosis may underlie Huntington disease. These proteins have now been identified and shown to interact with huntingtin, two of these interactions being influenced by CAG length (reviewed in [N4]).

(c) Myotonic dystrophy

59. Myotonic dystrophy, like Huntington disease, is an autosomal dominant disease and is the most common form of adult muscular dystrophy, with an incidence of about 1 in 8,000 in most populations [H10]. In the Saguenay region of the province of Quebec, Canada, the prevalence is about 1 in 500 [D6, M8]. The disease is characterized by progressive muscle weakness and sustained muscle contraction, often with a wide range of accompanying symptoms (cataracts, cardiac conduction defects, mental retardation, testicular atrophy, etc.). The age at onset and severity of the disease show extreme variation, both within and between families, and can be broadly classified into three clinical groups: minimally affected (late onset), classical (early adult onset), and severe congenital (onset at birth; inherited almost solely from the mother) (reviewed in [W6]).

60. The disease is due to CTG repeat expansions located in the 3' untranslated region of a gene whose sequence predicts the protein product to be a member of the protein kinase family [B12, F4, M9]. Amplification of the repeat is frequently observed after genetic transmission, but extreme amplifications are not transmitted through the male line. This explains anticipation and the occurrence of the severe congenital form in the offspring of affected women. Inter-generational repeat size reductions occur predominantly with paternal transmission [L7, M9, M10, T7, W6, W7]. Worth noting is the finding that in myotonic dystrophy, the expansions of the CTG repeat can be very large and similar to those recorded in the *FRAXA* gene.

61. The mechanism of the disease has been hypothesized as follows: since the repeats are present in a very gene-rich region of the genome, the amplified repeats disrupt gene transcription, mRNA processing, or gene translation, resulting in abnormal levels or functionally altered forms of the protein product DMPK. The results published so far are contradictory, showing both increases and decreases in DMPK expression at the level of transcription. These results and those from animal model experiments suggest that other genes may be involved in the disease (reviewed in [H12]).

7. Summary

62. The examples discussed above document the fact that even for Mendelian diseases, the relationships between genotype and phenotype are not necessarily simple or straightforward. They show that

(a) different mutations of the same gene can have quite different clinical phenotypes (allelic heterogeneity);
(b) the same mutation in a given gene can result in different clinical phenotypes;
(c) mutations in different genes can have similar clinical phenotypes (non-allelic heterogeneity);
(d) mutations in the same gene can be inherited as dominant or recessive; and
(e) the non-traditional mechanisms of disease, e.g. mosaicism, genomic imprinting, uniparental disomy, and trinucleotide repeat expansions, introduce a new dimension of complexity in genotype-phenotype relationships.

63. In retrospect, the existence of allelic or non-allelic heterogeneities is not entirely unexpected, for at least two reasons. First, no gene exists in isolation, and no gene (or gene product) is completely insulated from genetic influences from its immediate sequence environment or from other gene loci. Likewise, as McKusick [M1] states "... in defining a given phenotype, the terms dominant and recessive are of diminishing significance the closer one comes to primary gene action". The difference, relative to earlier periods in human genetics, is that advances in human molecular biology are now permitting insights into these complex relationships between mutation and disease.

64. Secondly, the designations used so far for most genetic (including Mendelian) diseases are clinical or biochemical descriptors, based on the readily observable clinical or biochemical phenotypes. Considering the fact that a wide variety of molecular changes can occur in a gene but yet result in a restricted number of clinical or biochemical phenotypes, as well as the fact that the phenotypes of mutations in structurally and functionally related genes may overlap, it is not entirely surprising that a given clinical disease is caused by mutations in more than one gene. Thus, hyperlipoproteinaemia, for instance, is not really a genetic designation but a biochemical descriptor that refers to the presence of elevated levels of cholesterol-

and/or triglyceride-carrying proteins called lipoproteins in the blood; there are various genetic types of hyperlipoproteinaemia, depending on which of the several genes in the lipoprotein metabolic pathway is affected by mutation.

65. The problems presented by these heterogeneities in genetics and clinical medicine are obvious: molecular heterogeneity poses a clinical dilemma and clinical heterogeneity, a molecular dilemma. Both present a formidable challenge in genetic risk estimation. Further, as discussed in Section III.D, what have been traditionally regarded as multifactorial diseases are now beginning to yield to molecular techniques; these heterogeneous clinical entities are now beginning to be split up into genetically homogeneous constituent groups as the genes involved are identified. Stated differently, the boundaries between Mendelian and multifactorial diseases are slowly disappearing. These developments suggest that the strategies for genetic risk estimation require fine tuning.

66. The Committee takes note of these impending developments in the field and realizes that in future risk assessments it may become possible to focus on specific, clinically relevant genetic diseases, based on a knowledge of the underlying genes, their organization, their genomic context, and the extent to which induced mutations may be potentially recoverable in live births. The rates of induced mutations, however, have to be extrapolated from mouse data. This issue is discussed later.

D. BASELINE FREQUENCIES OF MENDELIAN DISEASES

67. The estimates of baseline frequencies of Mendelian diseases used until 1993 were based on the work of Carter [C67, C68] in the mid-1970s. The estimates were: autosomal dominant, 95 cases per 10^4 live births; autosomal recessive, 25 per 10^4; and X-linked, 5 per 10^4 (together, 125 per 10^4 live births). The advances that have occurred since then permit the revision of the above estimates to 150 per 10^4 for autosomal dominants, 75 per 10^4 for autosomal recessives and 15 per 10^4 for X-linked diseases (together 240 per 10^4) [S105] (Table 9).

68. Tables 10–12 provide details of the various diseases and their respective incidences on which the revisions shown in Table 9 are based. Included in Tables 10–12 are the earlier estimates of Carter [C67] and the additional ones (designated by footnote). If only population prevalence data are available, they are given in a separate column. The Mendelian Inheritance in Man (MIM) numbers for the different entries are from McKusick's compendium [M2]. The numbers of genes already known or mapped are given to provide an idea of what is now known about the genetic basis of these diseases. The original references to Carter's compilation are given in his 1977 paper [C67] and are not repeated here.

1. Autosomal dominant diseases

69. For autosomal dominant diseases (Table 10), the total "unadjusted" estimate for all the diseases included is of the order of about 92–96 cases per 10^4. Of the several additional (i.e. subsequent to Carter's compilation) diseases included in Table 11, two (hypercholesterolemia due to familial defective *ApoB-100* [FDB] and familial breast cancer due to *BRCA1* and *BRCA2* mutations) contribute substantially (10–15 per 10^4 and 10 per 10^4, respectively; together, 20–25 per 10^4) to the unadjusted total. FDB is due to rare mutations in the *ApoB* gene that affect the binding of LDL to the LDL receptor [I11] and is thus different from the well known classical form of familial hypercholesterolemia that is due to mutations in the LDL receptor (*LDLR*) gene [G17].

70. Many other new entries (neurofibromatosis type 2, Treacher Collins syndrome, craniosynostosis, holoprosencephaly, van der Woude syndrome, von Hippel Lindau syndrome, Williams syndrome, Velocardial syndrome, Hirschprung disease, Li-Fraumeni syndrome) contribute far less to the birth frequency estimates. For some disease entities such as antithrombin deficiency, familial hypertrophic cardiomyopathy, hereditary haemorrhagic telangiectasia, and dominant forms of adult onset deafness, only prevalence estimates are available and have not been included in the unadjusted total birth frequency.

2. Autosomal recessive diseases

71. For autosomal recessive diseases, the total "unadjusted" estimate is 50.8 cases per 10^4 (Table 11). The one significant addition to the list of these diseases is haemochromatosis, a disorder of iron metabolism in which increased absorption of iron causes iron overload; the excess iron is deposited in a variety of organs, leading to their failure and resulting in serious illnesses such as cirrhosis, hepatomas, diabetes, cardiomyopathy, arthritis, and hypogonadotrophic hypogonadism. Although it can be fatal if undetected [B68], life expectancy is normal if iron is removed by venesection in the precirrhotic stage of the disease [N22]. Patients often do not present until middle age. Until recently, haemochromatosis was considered a rare disease, but it is now clear that among individuals of north European descent about 1 in 300 (range: 1 in 400 to 1 in 200) are homozygotes [E19, L51, W29]. At least one candidate gene for haemochromatosis has been cloned, and mutations have been identified [F15].

3. X-linked diseases

72. The unadjusted total estimates for X-linked recessive diseases is 17.65 cases per 10^4 male births or 8.8 cases per 10^4 of all, i.e. both male and female births (Table 12). The significant addition is fragile-X mental retardation with an estimated live birth frequency of 5 per 10^4 male births [F3]. The entity that Carter designated as "X-linked non-specific mental retardation" and his estimate of 1 per 10^4 for this

have been retained in view of the fact that McKusick [M2] notes that at least 10 other X-linked genes associated with mental retardation have been mapped.

4. Revision of the total birth frequency estimates

73. The unadjusted total estimates for each of the three classes of Mendelian diseases have been adjusted upwards to obtain the revised estimates as follows: autosomal dominant, from 92–96 per 10^4 live births to 150 per 10^4; autosomal recessive, from 50.8 per 10^4 to 75 per 10^4 and X-linked, from 8.8 per 10^4 to 15 per 10^4. Together, the revised total frequency of 240 per 10^4 live births (Table 9) is about twice that estimated by Carter [C67].

74. The reasons for the upward adjustments were the following: (a) for some entries in Tables 10–12, only prevalence estimates are available and have not been included in the unadjusted totals, and no estimates are presented for breast/ovarian cancers associated with genes other than *BRCA1*; (b) the estimates in the above tables do not include all the inherited forms of mental retardation, abnormalities of motor and physical development, visual and auditory abnormalities, and behavioural disorders, to mention only a few; (c) at present, advances in the Human Genome Project are rapidly contributing to knowledge of a vast number of Mendelian diseases, although frequency estimates for individual diseases are still not available; and (d) as mentioned in paragraph 10, as of January 2000, the on-line Mendelian Inheritance in Man [M2] already lists over 11,000 entries (roughly two thirds with locus assignments to one or the other autosome or the X-chromosome); these numbers are only bound to increase in the coming years. Considering all the above and the fact that only about 10% of the human genome has been sequenced so far [G21], as well as the estimated number of genes (about 80,000; see Chapter I), the revisions mentioned in the preceding paragraph seem justified. The Committee will use these figures in risk assessment.

5. Population/ethnic differences

75. The estimates given in Tables 10, 11 and 12 represent a synthesis of information from studies on western European or western-European-derived populations in the mid-1950s to mid-1970s and as such provide some insights into the load of Mendelian diseases in these populations. However, marked differences between different populations or ethnic groups, especially in the frequencies of autosomal recessives, have long been known, and more such instances are being discovered.

76. In considering these differences (and similarities), it should be remembered that, in general, autosomal dominant diseases that are severely selected against (e.g. achondroplasia) will occur at similar frequencies in most populations and that most are due to new mutations. However, those dominant diseases for which there is little or no selection either because the abnormality is trivial or it manifests after reproduction has been completed (minimal or no selection), the incidence and prevalence may be quite different in different populations depending on factors such as population size, history, and breeding structure; most of these diseases (e.g. Huntington disease and familial hypercholesterolemia) are not due to new mutations. The above statements are generally true for X-linked recessive diseases as well. In the case of autosomal recessive diseases, however, selection pressures are much less efficient, because most of the mutant genes are carried by asymptomatic heterozygotes. For this reason and again depending on population size, history, and breeding structure, autosomal recessive diseases can appear at high frequencies in some isolated populations.

77. With the advent of molecular biology, it became possible to discern the unique pattern of DNA variation around the mutant genes and to use this to characterize the origin of the mutation and explain how enrichment for specific mutations in specific populations might have occurred. These high frequencies and enrichment for specific mutations are believed to have resulted from some type of bottle-neck in their history, revealing the consequences of "founder effects", "genetic drift", and inbreeding in their respective gene pools. The populations most extensively studied in this regard include the Ashkenazi Jews, the Finnish, the French-Canadians, and the Afrikaners of South Africa, descended from Dutch settlers; further, data are now becoming available for Arab populations from the Middle East. Illustrative examples are given in Tables 13 and 14.

78. The principal message of all these findings for radiation genetic risk estimation is that Carter's [C67] original lists and the revised lists (Tables 10–12) and the estimated frequencies provide reasonable insights into the burden of Mendelian diseases in western European and western-European-derived populations but do not reflect either the profile or the aggregate burden of such diseases in any specific population. It can therefore be argued that they may not constitute an entirely reliable baseline when other populations are considered, especially when these frequencies are used in the risk equation. For example, for the sake of argument, if one assumes that the rate of radiation-induced mutations in specific disease-causing genes is the same in different populations, the relative increase in risk, as estimated by the doubling-dose method, is expected to be different when the baseline frequencies are different. Consequently, there is the need for caution in extrapolating the radiation risk of Mendelian diseases from one population to another.

79. Two additional factors not discussed thus far also need to be borne in mind: (a) the spectrum and frequency of genetic diseases in different parts of the world can change as a result of increased mobility and population admixtures, and (b) at least in most industrialized nations of the world, the increasing availability of genetic screening, genetic

counselling, and prenatal diagnosis (and emphasis on early detection and primary prevention) may reduce the frequencies of certain diseases in the long run, although the magnitude of the reduction is hard to fathom at present.

6. Summary

80. Advances in human genetics during the last two decades now permit an upward revision of the estimates of birth frequencies of genetic diseases to about 150 per 10^4 live births for autosomal dominants, 75 per 10^4 live births for autosomal recessives, and 15 per 10^4 live births for X-linked diseases (together, 240 per 10^4 live births). The main contributors to the revised estimates are the following disease entities: autosomal dominant: familial breast and ovarian cancers due to mutations in the *BRCA1* gene (10 per 10^4) and hypercholesterolemia due to mutations in the *ApoB* gene (familial defective ApoB-100; 10–15 per 10^4); autosomal recessives: haemochromatosis (30 per 10^4); and X-linked: fragile-X syndrome (2.5 per 10^4).These estimates are based predominantly on data from studies of western European and western-European-derived populations.

81. In several population isolates or ethnic groups, some of these diseases, especially the autosomal recessives, are more common and/or show an enrichment for specific mutations due to "founder effects" and/or genetic drift, combined with high levels of inbreeding. This is demonstrated in studies of the Ashkenazi Jewish and Finnish populations. Differences between populations in the baseline frequencies of Mendelian diseases suggest the need for caution in extrapolating radiation risks between populations.

E. SPONTANEOUS MUTATION RATES

1. The concept of equilibrium between mutation and selection

82. Although new mutations arise spontaneously in every generation, the frequencies of the diseases in the population are believed to remain stable from one generation to the next. Population genetic theory dictates that in large, random-mating populations, this stability is a reflection of the existence of a balance between the rates of origin of spontaneous mutations and the rates of their elimination through selection (the equilibrium theory). For example, in the case of autosomal dominant and X-linked diseases with onset in childhood, if the individuals with the mutations die early or are so severely handicapped as to preclude reproduction (selection coefficient = 1), the birth frequencies and prevalences are determined mainly by mutation rate, and most cases with the disease will be new mutants (e.g. Apert syndrome and achondroplasia). If, however, disease onset occurs after the age at which reproduction has already occurred and the selection coefficient is less than 1 (e.g. familial hypercholesterolemia), the mutant genes will persist in the population for varying periods of time, and the affected individuals in the population represent pre-existing and new cases due to spontaneous mutations. For these diseases, the birth frequencies and prevalences can vary depending on the size of the population, history, and breeding structure, as discussed in the preceding Section.

83. For autosomal recessive diseases, the estimation of mutation rates is complicated [C69, M57, V20]. It is enough to note here that (a) the phenotypic incidence of these diseases is not directly proportional to mutation rate, since when a recessive mutation first arises, it is present in a heterozygote; (b) estimates of mutation rates for recessive mutations depend on the assumption that at some time in the past an equilibrium was reached between spontaneous mutations and their loss through selection, although a reduction in inbreeding in recent generations in most populations makes the assumption of current equilibria somewhat questionable; (c) in calculating mutation rates for autosomal recessive mutations, one should take into account the elimination of mutant alleles through their effects in heterozygotes, through consanguinity, and through the mutant gene's "meeting" a pre-existing mutant allele by chance; and (d) instances are known where the stability of the frequencies of recessive diseases (e.g. sickle-cell anaemia and cystic fibrosis) is believed to reflect a selective advantage for the recessive mutation in a heterozygous condition vis-à-vis the normal homozygote and the mutant homozygote. These diseases (that is to say, the mutant genes) are maintained in the population by selection alone [A24].

2. Spontaneous mutation rates for autosomal dominant and X-linked diseases

84. Methods for estimating the mutation rates of autosomal dominant and recessive and X-linked mutations and their difficulties and potential biases are discussed by Morton [M57], Crow and Kimura [C70], Childs [C39], Crow and Denniston [C69], and Vogel and Motulsky [V20]. The most important bias in mutation rate studies arises from the fact that genes that mutate frequently are more likely to be studied than those that mutate rarely, and obviously, those that have not been observed to mutate cannot be studied. This bias can enormously inflate estimates of a representative mutation rate, if there is one [C69, V20].

85. Table 15, taken from the classic reviews of Vogel and Rathenburg [V21] and Vogel and Motulsky [V20], presents some estimates of mutation rates for human genes, most of them based on population studies. As can be noted, the mutation rates are between 10^{-4} and 10^{-6} per gamete per generation and are heterogeneous. Of the autosomal dominants, neurofibromatosis has the highest mutation rate, about $1\ 10^{-4}$, and polycystic kidney disease the next highest, $5.5–12\ 10^{-5}$. These are followed by polyposis coli ($1.3\ 10^{-5}$), achondroplasia ($\sim 1\ 10^{-5}$), myotonic dystrophy ($0.8–1\ 10^{-5}$), and others with lower mutation rates. For the

X-linked recessives listed in Table 15, the median value is in the range 10–30 10^{-6} [C69].

86. Stevenson and Kerr [S106] made the first and so far the only serious attempt to obtain less biased estimates for X-linked diseases. Their data, based on 875,000 newborns, are summarized in Table 16, which includes 49 well-established diseases, excluding those whose frequencies are not dependent on a mutation-selection equilibrium (colour blindness, Xg blood groups, G6PD variants). The diseases that are estimated to have high mutation rates include Duchenne muscular dystrophy (50–70 10^{-6}), haemophilia A (20–40 10^{-6}), non-specific, severe mental retardation (10–20 10^{-6}; presently, this probably corresponds to fragile-X mental retardation), and haemophilia B (5–10 10^{-6}). For 24 conditions, the estimated rates are below 1 10^{-7}. Noting that the distribution of rates set out in Table 16 are "defective of the real total situation at the lower end", Stevenson and Kerr [S106] went on to say, "It is difficult to avoid the conclusion that the mean mutation rate to visibles on the X chromosome in man is not more than 10^{-6}, and in the absence of contrary information, there is no reason to suppose that such a level is not also representative of rates of occurrence of such mutations over the whole genome". The estimates in Table 16 have a median value of about 0.1 10^{-6}, which is two orders of magnitude lower than that for the sex-linked diseases included in Table 15 [C69].

87. The causes of the large differences in mutation rates between genes are not fully understood. Mutation rates estimated from phenotypes can be high if there is genetic heterogeneity (mutations in different genes resulting in similar clinical phenotypes), and several examples were given in Table 5, but this is certainly not the only explanation. In general, the mutation rate of a given gene is a function of the size and organization of the gene, the mechanisms involved, and the number of mutational sites. For example, the two genes with the highest mutation rate, namely those that underlie neurofibromatosis 1 and Duchenne/Becker muscular dystrophies, are also among the largest genes known (genomic sizes of ~300 kb and 2,400 kb, respectively), but again, size alone may not be the only explanation.

3. Sex differences in mutation rates and paternal age effects

88. The estimates of mutation rates presented in Table 15 do not distinguish between mutations in males and females; for autosomal genes, they represent the unweighted averages and for X-linked ones, the weighted averages. Since most spontaneous mutations arise as a consequence of errors introduced during DNA replication, one would *a priori* expect that the male germ line should have a higher mutation rate than the female germ line as a result of continual post-pubertal mitotic processes in the male. Further, the likelihood of germinal mutations should increase in older males (paternal age effect). By and large, these expectations have been fulfilled, and the data that bear on these issues have been reviewed [C71, C72, V20].

89. Vogel and Motulsky [V20] estimated that in the female the number of cell divisions from zygote to the mature egg (N_f) is about 24. In the male, there are about 30 cell divisions from zygote until the age of puberty (taken to be 15 years), ~ 23 per year thereafter and 6 for proliferation and meiosis. Thus the number of cell divisions prior to sperm production (N_m) in a 20-year-old male can be estimated to be $30 + (5 \times 23) + 6 \approx 151$, increasing to 381 at age 30, 611 at age 40 and 841 at age 50 [C4]. It is clear that the N_m/N_f ratio varies with the age of the male, being about 6 when the male is 20 years of age, increasing to 16 at age 30 years, to 25 at age 40 years and 35 at age 50 years. Assuming that the number of spontaneous mutations in the male is proportional to the number of cell divisions, Crow [C71, C72, C4] estimated that, in the age range from 17 to 52 years, fathers of children with *de novo* dominant mutations (Apert syndrome, achondroplasia, myositis ossificans, Marfan syndrome etc.) were *expected* to be older by 2.7 years on average, relative to those of unaffected children. The *observed* difference in paternal age, however, was about 6 years indicating a faster-than-linear increase in mutation rate with paternal age. The graphs in the paper of Crow [C72] suggest that even a quadratic relationship between mutation rate and paternal age is insufficient and that a cubic relationship fits better, although the accuracy of the data does not merit detailed curve-fitting [C4]. The subject has been recently reviewed by Crow [C13].

90. In addition to the diseases mentioned above, strong paternal age effects have also been found for basal-cell nevus syndrome, cleidocranial dysplasia, Crouzon syndrome, fibrodysplasia ossificans, oculodentodigital syndrome, Pfeiffer syndrome, progeria, and Waardenburg syndrome [R43]. Further, the demonstration in molecular studies that all *de novo* cases of multiple endocrine neoplasia types A (10 cases) and B (25 cases) and Apert syndrome (57 cases), a total of 92 cases, are paternal in origin lends support to the view that the mutation rate in males is higher than in females [C73, M58, S107]. Additional information that bears on the above but coming from studies of molecular evolution (male-driven molecular evolution) is provided in the papers of Drost and Lee [D32] and Crow [C72] and references cited therein.

91. There are exceptions to the above pattern, however. Two conspicuous ones are Duchenne muscular dystrophy (DMD) and neurofibromatosis 1 (NF1) neither of which shows a significant sex difference or a striking paternal (or in the case of X-linked muscular dystrophy, grandpaternal) age effect demonstrable for multiple exostoses, bilateral retinoblastoma, neurofibromatosis 1, Sotos syndrome, and Treacher Collins syndrome. For mutations in the factor IX gene (haemophilia B), a recent population-based study in the United Kingdom showed that the mutation rate in males is about 9-fold higher than in females [G7], but grandpaternal age effect was not studied. The work of Sommer and Ketterling [S108], however, provides some evidence for a maternal age effect, but the data are limited.

92. The explanation for sex differences and paternal age effect for mutations seems to lie in the nature of mutations. Grimm et al. [G8] reported on 198 mutations to DMD in which the parental origin could be determined. Of these 114 were deletions, 8 were duplications and 76 were not detectable by deletion screening and were presumably point mutations. The great majority of the latter were paternal, as expected, but more than half of the duplications and deletions were maternal. Although the maternal/paternal ratio is not significantly different from 1:1, the data at face value suggest that the rate of deletions may be higher in females. In any case, this difference between the sexes is not as striking as that recorded for base pair substitution mutations. The data for NF1 [L21] are similar: of the 11 point mutations, 9 were paternal and of the 21 deletions, 16 were maternal. The presence of both point mutations and deletions explain the weak paternal age dependence of spontaneous mutations that cause NF1.

4. Relevance of sex differences in spontaneous mutation rates and paternal age effects in humans

93. The reasons for discussing sex differences in spontaneous mutation rates and paternal age effects in humans are intimately related to the use of the doubling-dose method of risk estimation. Briefly, the use of this method requires an estimate of what is termed "the doubling dose" (DD), which is one of the quantities in the risk equation (risk per unit dose = P × 1/DD × MC). In this equation, P is the baseline frequency of the disease class, DD is the doubling dose and MC is the mutation component (a quantity that specifies the relative increase in disease frequency per unit relative increase in mutation rate; see Chapter IV). The doubling dose is the amount of radiation required to produce as many mutations as those that occur spontaneously. It is calculated as a ratio of the average rates of spontaneous and induced mutations in a set of defined gene loci. The reciprocal of the doubling dose (i.e. 1/DD) is the relative mutation risk per unit dose.

94. It would have been ideal to base doubling-dose estimates on human spontaneous and induced rates of mutations; however, this avenue was not open to risk estimators because of the lack of human data on radiation-induced germ cell mutations, and the situation has not changed in all these years. A less ideal approach was chosen in the 1972 BEIR Report [C47], namely, the use of human data on spontaneous mutation rates and mouse data on induced rates. This approach had the advantage that the only specific assumption needed was that the average rate of induced mutations in human germ cells was the same as that in mouse germ cells. This assumption was (and remains) defensible on the grounds of generally similar gene organization, 70%–90% homology in DNA sequence of genes and substantial conservation of synteny (i.e. a group of genes on a single chromosome in one species is observed to be similarly linked in another species) for many, although not all, chromosomal regions between humans and mice.

95. A much less ideal approach was to base the doubling dose on mouse data on rates of both spontaneous and induced mutations, predominantly those pertaining to recessive mutations at the seven extensively studied loci. This was the approach that gained currency in the UNSCEAR Reports from 1977 onwards [U4, U5, U6, U7, U8] and in the 1980 and 1990 BEIR Reports [C48, C49]. While it had the advantage that the same genes could be used for determining the spontaneous and induced rates of mutations, it implied the assumption of similarity of spontaneous mutation rates of human and mouse genes (i.e. the doubling dose could be extrapolated from mouse to humans). This assumption can no longer be considered correct in the light of sex differences and paternal age effects for spontaneous mutations in humans (discussed in the preceding Section) and data on the number of cell divisions in the mouse (discussed below).

96. In the mouse female, the number of cell divisions (N_f) from zygote to the mature egg is of the order of about 24 [D32], which is the same as that in the human female (see paragraph 89). In the male mouse, the number of cell divisions from zygote to sperm (N_m) is of the order of about 62 at age 9 months, assuming a 9-month generation [C74, D32]. The N_m/N_f ratio is thus 2.5 (i.e. 62/24), which is much lower than in the human male (see paragraph 89). The inference, therefore, is that the spontaneous mutation rates in mice are unlikely to be very different between the two sexes (in contrast to the situation in humans). Worth pointing out here is the fact that in most mouse experiments, the parental animals were used at a rather uniform age and the question of paternal age effects had not been specifically addressed.

97. The enormous difference in lifespan between humans and mice, the fact that the published estimates of spontaneous mutation rates in humans are unweighted averages of the rates in the two sexes (and therefore automatically incorporate the sex differences and paternal age effects) and the fact that it is the average rate that is relevant in the context of the doubling-dose calculation strongly suggest that extrapolation from short-lived mice to humans is unlikely to provide a reliable average spontaneous rate in a heterogeneous human population of all ages.

98. It is a curious fact that although sex differences in and paternal age effects for human spontaneous mutation rates had been known for a long time and were certainly well established by the mid-1970s, neither UNSCEAR nor the BEIR Committees considered these important enough to merit consideration in the context of the doubling-dose calculations. The Committee now feels that the arguments advanced in this and the preceding Sections are compelling enough to go back to the earlier approach used by the BEIR Committee in its 1972 Report [C47], namely, to base the doubling-dose estimate on human data on spontaneous mutation rates and mouse data on induced mutation rates. A further argument supporting the need for such a conceptual change comes from the uncertainties that have been recently uncovered in the calculation of spontaneous mutation rates in mice. This aspect is discussed in Chapter VI.

5. Summary

99. The population-genetic theory of equilibrium between mutation and selection (that is used to explain the stability of the incidence of genetic diseases in the population) was briefly reviewed in this Section, and published estimates of spontaneous mutation rates in humans that cause autosomal dominant and X-linked diseases were considered; these estimates vary over a wide range and the underlying causes are not fully understood. Additionally, the basis for the pronounced sex differences in mutation rates, the supporting evidence, and their relevance for doubling-dose calculations were addressed.

100. Estimates of the number of cell divisions between the zygote and the mature germ cell in humans predict that (a) the spontaneous mutation rates in the two sexes will differ (being higher or much higher in males, depending on age, than in females), and (b) in the male, the mutation rate will increase with the age of the father. Both these predictions have been amply fulfilled, and in addition there now is, as well, supporting evidence from molecular studies. In the mouse, the situation is different: no major sex differences in mutation rates are expected, and the question of paternal age effects on spontaneous mutations has not been specifically studied.

101. In the calculation of doubling doses, the spontaneous mutation rate constitutes the numerator (the denominator being the rate of induced mutations). The spontaneous mutation rate estimates used thus far in this calculation come from mouse studies. Since the spontaneous mutation rates in humans and mice are unlikely to be similar, the use of a doubling dose based on data on spontaneous rates in mice is conceptually flawed. The Committee now feels that the use of human data on spontaneous mutation rates (and mouse data on induced mutation rates) for doubling-dose calculation is the prudent way forward.

III. MULTIFACTORIAL DISEASES

102. The term "multifactorial" is a very general designation assigned to a disease known to have a genetic component but that cannot be described in a simple Mendelian fashion. Such diseases are interpreted as resulting from a large number of causes, both genetic and environmental, although the potential role of environmental factors has been delineated for only a few of these diseases (e.g. excess caloric intake rich in saturated fat is an environmental risk factor for coronary heart disease (CHD); environmental allergens are risk factors for asthma). The common congenital abnormalities (e.g. neural tube defects and cleft lip with or without cleft palate) and many common diseases of adult onset (e.g. coronary heart disease, diabetes mellitus, and essential hypertension) are examples of multifactorial diseases; most cancers also are multifactorial. Because of their high prevalence, they contribute very substantially to morbidity and mortality in human populations.

103. As mentioned above, the majority of multifactorial diseases do not fit Mendelian expectations in terms of transmission characteristics, i.e. they are not single-gene defects, but they occur at higher frequencies among relatives of affected individuals than in the general population. However, the risk to relatives varies from one multifactorial disease to another and from family to family. These features are not entirely surprising, because each of these clinical diseases is, in reality, a group of distinct diseases with different aetiologies, both genetic (multiple modes of inheritance) and non-genetic.

104. For most of these diseases, knowledge of the genes involved, their numbers, the types of mutational alterations, and the nature of environmental factors is woefully incomplete. At one extreme are the congenital abnormalities, for which there is virtually no information. At the other is coronary heart disease for which there is an overwhelming amount of information at the epidemiological, biochemical, genetic, and molecular genetic levels; however, the gene-gene and gene-environmental interactions are very complex and not understood. The situation is in between these two extremes for diseases such as essential hypertension and diabetes mellitus, for which at least a few of the genes have been identified.

105. In the UNSCEAR 1986 and 1993 Reports [U4, U6], the Committee reviewed some epidemiological aspects of multifactorial diseases. The currently known attributes and advances in the genetic dissection of these diseases that are pertinent in the context of risk estimation are discussed in this Chapter under two broad headings, congenital abnormalities and common multifactorial diseases.

A. CONGENITAL ABNORMALITIES

106. Congenital abnormalities are gross or microscopic structural defects present at birth whether detected at that time or not. The adjective "congenital" signifies only their presence at birth and has no aetiological connotation. Congenital abnormalities are the end results of dysmorphogenesis and can occur as isolated or multiple entities. Isolated congenital abnormalities are structural defects that can each be traced back to one localized error in morphogenesis; multiple congenital abnormalities are the

result of two or more different morphogenetic errors during development of the same individual [C33, C34, O5]. It should be emphasized here that all congenital abnormalities, including the least severe forms, are all-or-none traits, i.e. they are not metric traits, and at their least severe end do not shade into normality [O5].

1. Overall prevalences

107. A vast body of data on the prevalences of congenital abnormalities in different parts of the world has been published in the literature (e.g. [B36, C33, C34, C36, C37, C38, M36, S64]). The estimates vary over a wide range, from about 1% in live births to a high of about 8.5% in total births (i.e. still and live births), depending, among other things, on the definition, classification, and diagnostic criteria, entities included, method of ascertainment, duration of follow-up of liveborn children, and sample sizes.

108. In Table 17, the estimates of live birth prevalences of congenital abnormalities in Hungary [C37] are compared with those in the Canadian province of British Columbia [B36]. The comparison shows that under conditions of good ascertainment, the overall prevalences are similar and are of the order of 6%–7% (2%–3% if only major congenital abnormalities, i.e. lethal and severe ones, are considered).

2. Aetiological heterogeneity

109. A small proportion of many of the congenital abnormalities show Mendelian transmission, e.g. cleft lip with or without cleft palate found as part of autosomal dominant conditions (Van der Woude syndrome and of the ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome). A number of congenital cardiovascular malformations are found in association with different chromosomal abnormalities [S65] as well as with fetal alcohol syndrome [H35].

110. The British Columbia [B36] and Hungarian estimates [C37] of the relative proportions of congenital abnormalities due to single-gene mutations, chromosomal anomalies, and environmental (including maternal) factors are summarized in Table 18. Of the total prevalence of congenital abnormalities of 5.3% in British Columbia, one half are judged to be attributable to non-genetic causes (e.g. prenatal infections, known teratogen or birth trauma) and unknown causes; of the remaining one half, the vast majority (86.8%) are multifactorial. The Mendelian, chromosomal, and "genetics unknown" categories account for, respectively, 4.1%, 6.9%, and 2.1% of congenital abnormalities with a genetic basis. The estimates for Hungary are in good agreement with the Canadian estimates, showing similar relative proportions of Mendelian, chromosomal, and multifactorial categories (among those with genetic aetiologies); however, the "non-genetic and unknown" category is much smaller (about 20% compared with 50% in British Columbia).

3. Isolated congenital abnormalities

(a) Epidemiological features

111. As mentioned in paragraph 106, isolated congenital abnormalities are structural defects each of which can be traced back to one localized error in morphogenesis. The Hungarian prevalences of well studied isolated congenital abnormalities and some of their epidemiological features are presented in Table 19. As can be noted, the sex ratio departs from unity in most congenital abnormalities; there are racial/ethnic, regional, or seasonal differences in the birth prevalences of some congenital abnormalities; and the concordance rates in monozygotic twins are higher (from about 15% for undescended testicles to about 80% for congenital dislocation of the hip in Hungary) than those in dizygotic twins (0%–14%), but not 100%. For cardiovascular malformations in general, both the Hungarian [C33] and literature data [C36, N12] suggest that the concordance between monozygotic twins is of the order of 15%–20%. For dizygotic twins the rates are much lower.

(b) Recurrence risks

112. Data on the prevalences of isolated congenital abnormalities in relatives of index patients are given in Table 20. The findings are three: (a) the frequency of affected first-degree relatives of a proband is many times (5- to 50-fold) that of the general population; (b) there is a sharp decrease in the proportion affected as one passes from first- to second- to third-degree relatives; and (c) the relative increase in risk (i.e. relative to the birth prevalence in the population) is more marked with low birth frequency. For instance, in the case of congenital dislocation of the hip (birth prevalence of 2.8%), the risk to sibs is 13.8%, which is higher by a factor of 5; for cleft lip with or without cleft palate, with a lower birth frequency of 0.10%, the risk to sibs is 4.8%, which represents an increase by a factor of 48.

113. When the index case is of the more rarely affected sex, the proportion of affected relatives is generally higher (Table 21). For example, in Hungary, congenital hypertrophic pyloric stenosis has a birth prevalence of 0.07% in females and 0.22% in males. The risk to brothers of affected females is about 20%, which is much higher than the value of about 4% for the brothers of affected males [C33]. These estimates are comparable to those for the United Kingdom reported by Carter [C36] for brothers and sisters of male and female subjects, as well as for their sons and daughters.

114. However, for cleft lip with or without cleft palate, which has a higher prevalence in males (0.13%) than in females (0.08%), the risk to brothers of an affected male is about 11% whereas that to brothers of an affected female is only about 1% [C33]. For ventricular septal defect, for which sex difference in birth frequency in the population is small, the risk to sibs of affected females is higher by a factor of 1.5–2 relative to that of sibs of affected males. In the data from various studies summarized by Nora et al. [N12], this tendency (i.e. higher risk to offspring of

females) is seen not only for ventricular septal defect but for other cardiovascular malformations as well.

(c) Chromosome deletion map

115. Recently, Brewer et al. [B46] constructed a chromosome map of autosomal deletions associated with 47 different congenital abnormalities using detailed clinical and cytogenetic information on 1,753 patients with non-mosaic single contiguous autosomal deletions. The 1,753 deletions involved 258 of 289 (89%) possible autosomal bands (in a standard 400-band preparation). In the 47 malformations chosen for study, 283 malformation-associated bands were identified (a ratio of 1:6), indicating that there are indeed a large number of genes controlling developmental processes and that these are distributed in many different chromosomes. This distribution, however, was non-random: deletions involving 1q, 4p, 13, and 18p were significantly over-represented, while those involving 5p and 15 were under-represented. Further, there were chromosomal regions/chromosomes (8q, 12p, 16p, and 20q) that showed no significant associations with malformations, and only 1 of 1,753 reported deletions was in chromosome 19. As the authors noted, the deletion map may obviate the need for whole genome scans as a first approach to the identification of genes involved in developmental processes.

4. Summary

116. Congenital abnormalities arise as a result of developmental errors; the term “congenital” merely signifies their presence at birth and does not have an aetiological connotation. The estimates of their prevalence at birth varies from study to study, but in those in which ascertainment is good, the estimate of birth prevalence is of the order of about 6%.

117. The sex ratios depart from unity for most congenital abnormalities. The concordance rates in monozygotic twins are higher than in dizygotic twins but never approach 100%. The frequencies of congenital abnormalities are higher in relatives of affected individuals than in the general population. The recurrence risks in families vary with the congenital abnormality and the degree of biological relationship, being higher in first-degree than in second- and third-degree relatives.

118. The various attributes of congenital abnormalities are not readily explained on the basis of simple Mendelian patterns of inheritance; both genetic and shared familial environmental factors are postulated to play important roles in their aetiology.

119. The recently published deletion map of congenital abnormalities, showing that these abnormalities are associated with deletions in specific chromosomes/chromosomal regions, represents an important step forward in the identification of the genetic basis of congenital abnormalities.

B. MODELS OF INHERITANCE

120. The basic problem with conditions such as the congenital abnormalities discussed above and chronic diseases (to be discussed later) that are not simply inherited in a Mendelian fashion becomes one of assessing the relative importance of hereditary and environmental factors in their causation. Conceptualized this way, it is a problem of quantitative genetics, the theoretical basis for which was first established by Fisher [F21]. In that paper, Fisher showed that for a characteristic showing quantitative variation due to numerous Mendelizing genetic factors and non-genetic factors each having a very small effect, the central limit theorem can be applied to yield a normal (Gaussian) distribution of phenotypic values from which the components of variation due to genetic and non-genetic causal factors may be estimated and correlation between relatives derived.

1. The multifactorial threshold model

(a) Assumptions and predictions

121. Falconer [F22] introduced the concept of disease "liability" to overcome the difficulty of the all-or-none character of a disease (as in the case of congenital abnormalities), so that a graded scale of the degree of affectedness or of normality could be envisaged. On this premise, one would expect that all individuals above a certain value (the “threshold”) would exhibit the disease and all below it would not. The general concept of thresholds and “threshold characters”, however, dates back to the early work of Wright et al. (e.g. [W24, W36]) on otocephaly (head abnormalities) in guinea pigs. For the quantitative development of the idea of thresholds, it was necessary to assume that the distribution of liability in a population is Gaussian. With these concepts, it became possible to extend the usual methods of quantitative genetics developed for threshold characters to situations where the data in the form of incidences refer to an all-or-none classification. (Note that the term threshold does not have the same meaning here as in the context of non-stochastic effects of radiation.)

122. Details of the multifactorial threshold model (MTM) have been extensively discussed (e.g. [C33, C36, F22, F23, F24, S66, S67, S68, V15]). The assumptions of the simple version of the model are (a) all environmental and genetic causes can be combined into a single continuous variable termed liability, which, as such, is immeasurable; (b) liability is determined by a combination of numerous genetic and environmental factors, acting additively without dominance or epistasis, with each contributing a small amount of liability and therefore normally distributed; and (c) the affected individuals are those for whom the liability exceeds a certain critical threshold value (Figure I).

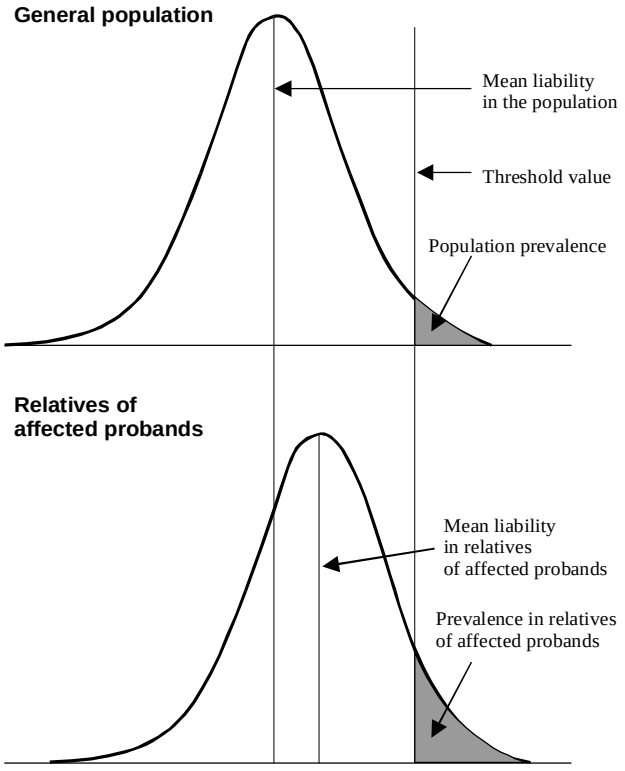

Figure I. Distribution of liability in the general population and in relating relatives according tp the multifactorial threshold model.

123. The multifactorial threshold model permits a number of predictions, among which are the following. First, the relative risk to relatives of an index case (compared with the general population) would be expected to be absolutely greater, but proportionately less, as the population frequency of the condition increases; this happens because when the population frequency is high, the genes for the condition are distributed throughout the population, so that the likelihood of exceeding the threshold is high; in a population in which the frequency in the population is low, only relatives have a significant risk. Inspection of Table 20 will reveal that, by and large, this prediction is fulfilled. Second, for conditions for which there are marked sex differences in prevalence, the multifactorial threshold model with the added assumption of different thresholds in the two sexes, would predict higher relative risks to the relatives of the less frequently affected sex. For example, congenital pyloric stenosis is more common in males than in females and the recurrence risk is higher for the children of a female proband than those of a male proband (Table 21). On the assumption that the threshold is farther from the mean in females than in males, it follows that the affected females would have to have more disease-predisposing alleles, on average, than would male patients. The relatives of the female patients would therefore receive more of these (being thus at correspondingly higher risk) than the relatives of male patients.

(b) The concept of correlation in liabilities between relatives

124. The multifactorial threshold model allows conversion of the information on the prevalence of a given multi-factorial trait in the population (p) and in the relatives of those affected (q) into an estimate of correlation in liability (r) between relatives, from which h^2 (heritability of liability; see later) can be estimated. To estimate correlation in liabilities between relatives, Falconer [F22] originally used the parameters of the normal curve and employed regression and selection methods on the assumption that the variance of liability was the same in the relatives as in the general population. However, as was pointed out by Edwards [E12] and Smith [S69], since the affected individuals (i.e. those exceeding the threshold) form a truncated group with a skewed distribution, the liability among the relatives of the affected individuals will not be normally distributed.

125. Smith [S69] used a different approach to the problem and advanced a slightly modified version of the multifactorial threshold model. Using a normally distributed liability and assuming that familial environment has no effect on liability or the phenotype, he showed that the correlation of liability (r) between relatives is a product of two quantities, $r = Rh^2$, where R denotes the coefficient of relationship between relatives (and is independent of the number of loci involved) and h^2 is the heritability of liability. The R values vary depending on the genetic relationship (1 for monozygotic twins; 0.5 for parent-offspring, dizygotic twins, and sibs; 0.25 for uncle-nephew; and 0.125 for first cousins).

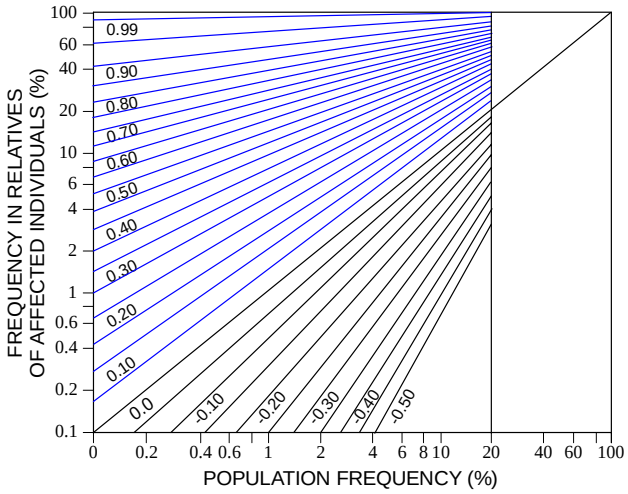

Figure II. Correlation in liability between relatives, given in the population frequency and the frequency in relatives of affected individuals [D17].

126. Smith's [S69] nomogram (Figure II) depicts the relationships between the three quantities r, p, and q. When p and q are known, r can be read directly from the nomogram. Thus, for cleft lip with or without cleft palate, assuming a birth frequency of 0.1% and proportions of affected monozygotic twins, first-, second-, and third-degree relatives of 40%, 4%, 0.7%, and 0.25% respectively,

the r values from Smith's nomogram are approximately 0.90, 0.45, 0.20, and 0.09. These may be compared with the theoretical correlations of 1.0, 0.5, 0.25, and 0.125, which would be expected if all the liability were due to additive polygenic inheritance.

(c) The concept of heritability of liability

127. Heritability is a common statistic in quantitative genetics for expressing the relative importance of transmissible genetic effects in the overall phenotypic variation [F34]. It is a ratio of variances and not of actual phenotypic values. Since the estimate depends on the magnitude of all the components of variance (see below), a change in any one of these will affect it. Further, the same trait in different populations may have different heritabilities. It should also be borne in mind that heritability estimates say nothing about the number of genes or about how they work.

128. Since the phenotype owes its origin to genetic and environmental factors, the total phenotypic variance is usually partitioned into two components, genetic and environmental. If the total variance is denoted by V_P, genotypic variance by V_G, and environmental variance by V_E, then, assuming that the genotypic and environmental values are independent of each other (i.e. they are not correlated), $V_P = V_G + V_E$.

129. The ratio V_G/V_P provides a measure of the relative importance of the genotype as a determinant of the phenotypic value. This ratio is called the broad sense heritability, or degree of genetic determination, and is symbolized by h_B^2.

130. The genotypic variance, V_G, can be subdivided into an additive component, V_A, and a component attributed to deviations from additivity. Additive genetic variance is the component that is attributable to the average effect of genes considered singly, as transmitted in the gametes. The ratio V_A/V_P expresses the extent to which the phenotypes exhibited by parents are transmitted to the offspring, and it determines the magnitude of correlation between relatives. This quantity is termed heritability in the narrow sense and is denoted by h_N^2. Examples of h^2 estimates for the Hungarian data on congenital abnormalities (based on correlations between sibs) are given in Table 22.

131. The non-additive genetic variance is due to the additional effects of these genes when combined in diploid genotypes and arises from dominance, V_D, interaction (epistasis), V_I, between genes at different loci, and assortative mating, V_{AM}. Note that in the absence of these sources of genetic variance, $h_N^2 = h_B^2$.

2. Other models and concepts

132. The multifactorial threshold model remains useful for understanding familial aggregations and excess risks within families. However, it does not address questions of specific genetic causes and mechanisms of disease susceptibilities. Further, although the model assumes a large number of contributing factors, each with small effect, it provides a reasonable approximation for traits with fewer contributing factors, and for this reason it is not a good analytical tool for discriminating between different modes of inheritance. The fact that the multifactorial threshold model is not discriminatory has engendered attempts to fit the familial aggregations observed with putative multifactorial traits to Mendelian models (with appropriate choice of assumptions regarding penetrance, epistasis, and dominance) or to combinations of major locus and polygenic models [E13, K31, K32, L29, M37]. These are mentioned here merely to indicate that models other than the classic multifactorial threshold model exist, and their current value lies in the fact that they are helpful in the search for the underlying genes. As discussed in Section IV.D, the Committee has used a modified version of the multifactorial threshold model to predict the responsiveness of multifactorial diseases to an increase in mutation rate.

3. Summary

133. Congenital abnormalities and other multifactorial diseases do not follow simple Mendelian rules of inheritance but run in families. The models that have been proposed to explain their transmission patterns and that have been used to predict recurrence risks in families rely on principles of genetics developed for quantitative traits, with suitable extensions to make them applicable to all-or-none traits.

134. The multifactorial threshold model of disease liability is commonly used for predicting recurrence risks in families and risk to relatives from data on the population prevalence of the disease. The model assumes that numerous genetic and environmental factors contribute to what is referred to as liability to develop a disease; these factors act additively without dominance or epistasis, each contributing a small amount of liability. Because these factors are assumed to be numerous, the distribution of liability in the population is normal (Gaussian). Affected individuals are those whose liability exceeds a certain threshold value.

135. The multifactorial threshold model, which makes use of the properties of the normal curve, enables a number of predictions, such as the relative risk to relatives of an index case, recurrence risks in families, and the sex differences in prevalences. It also enables the conversion of information on the prevalence of a multifactorial trait in the population and in relatives of affected individuals into estimates of correlation in liability, from which a useful statistic called heritability of liability can be estimated. Heritability of liability, which is a ratio of genetic variance to the total phenotypic variance, provides a measure of the relative contribution of transmissible genetic effects to the total phenotypic variation, which has both genetic and environmental components.

136. The multifactorial threshold model is descriptive and does not address questions on specific genetic causes or the

mechanisms of disease susceptibilities. Modified versions of the multifactorial threshold model as well as single-locus models, using additional assumptions, have been proposed to explain the inheritance patterns of multifactorial conditions.

137. The conclusions on models (of the type discussed above) reached by Edwards [E12] in 1969 remain as appropriate now as then. As he stated, "... the many-factor model, where the factors are so numerous and individually so feeble, that the central limit theorem can be applied to yield the smooth and tractable luxury of the normal curve, and the single-factor model, in which the influence of one factor is so great that all others can be regarded as trivial, are the extreme interpretations between which reality must lie ...". The multifactorial threshold model nonetheless provides a useful conceptual framework in the field of multifactorial inheritance.

C. COMMON MULTIFACTORIAL DISEASES

1. General concepts

138. Common adult diseases (e.g. diabetes, coronary heart disease, essential hypertension), like the congenital abnormalities discussed in the preceding Sections, do not fit Mendelian patterns of transmission. The genetic basis of a common disease is the presence of a genetically susceptible individual who may or may not develop the disease, depending on the presence or absence of other risk factors, which may be genetic and/or environmental (such as other genes, diet, physical activity, and environmental exposures) [K34]. Thus, for these diseases, the more appropriate concepts are "genetic susceptibility" and "risk factors". While there are subgroups of common diseases associated with single mutant genes (e.g. mutations in the *LDLR* receptor gene causing an autosomal dominant form of familial hypercholesterolemia), for most common diseases, susceptibility is genetically heterogeneous (i.e. different genetic mechanisms lead to the same clinical endpoint) and is therefore more complex. Furthermore, not all genetically susceptible individuals will develop the disease, and non-genetic, environmentally produced phenocopies sometimes occur.

139. Some diseases require the simultaneous presence of mutations in multiple genes (oligo- or polygenic). These may be classified as discrete traits, measured by a specific outcome (e.g. development of type I diabetes mellitus or death from myocardial infarction), or quantitative traits, measured by a continuous variable (e.g. diastolic blood pressure, fasting glucose concentrations, or immunoglobulin E [IgE]), whose levels may be set by the combined action of individual quantitative trait loci. Discrete traits may represent a threshold effect (produced whenever an underlying quantitative variable, influenced by multiple genes, exceeds a critical threshold), or an effect requiring the simultaneous and joint action of each of several mutations [F22, F23].

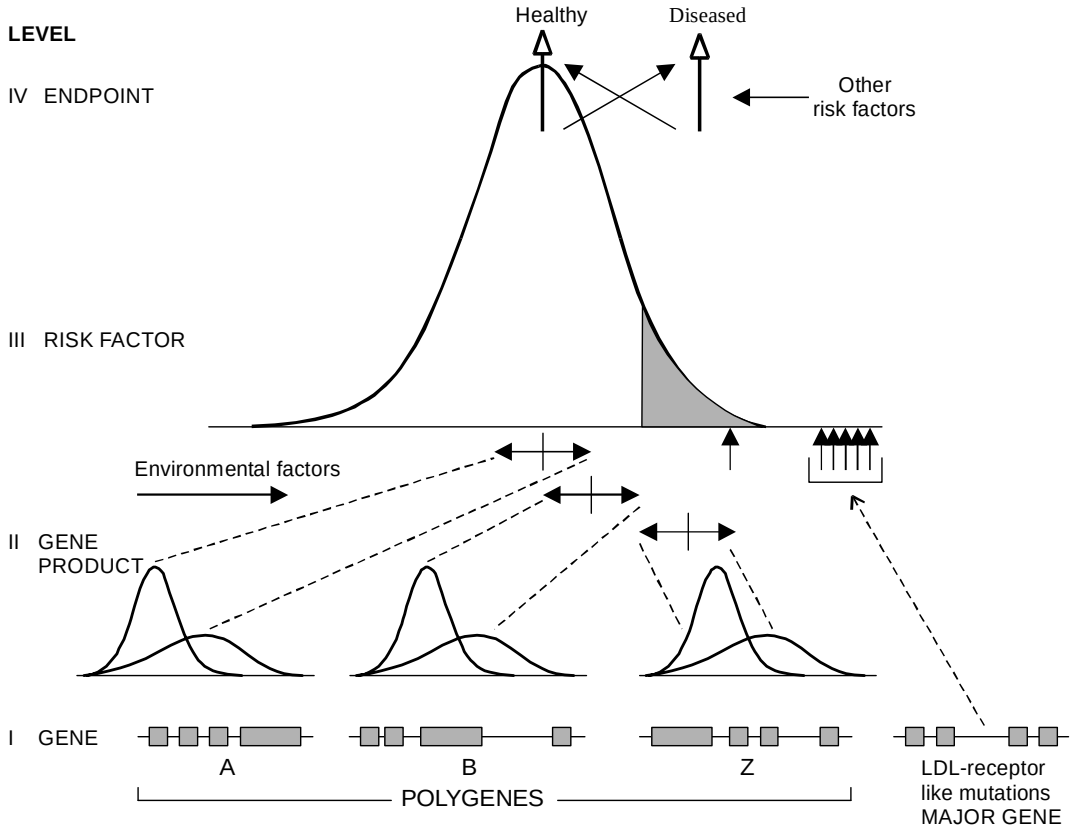

Figure III. A general model illustrating the role of polygenes, major genes- and environmental factors in the aetiology of a chronic multifactorial disease [S70].

140. The general principles that have emerged from studies on coronary heart disease provide a convenient conceptual setting to examine the relationships between gene mutations and diseases. Figure III, from the paper of Sing and Moll [S70], provides a visual summary. Note that four levels are distinguished linking mutations in genes (level I), which through their products (level II) and environmental effects contribute to quantitative variability of a biological risk factor trait (level III) and thus ultimately to disease outcome (level IV). At level I, two classes of genes are distinguished: "polygenes", whose mutant alleles individually have small to moderate effects on the risk factor trait (indicated in Figure III as A, B, Z), and "major genes", whose mutant alleles have strong effects (indicated by *LDLR* mutations).

141. Because polygenic mutations are common, they contribute to the bulk of variation of the risk factor trait in the population at large. In contrast, mutations in major genes are associated with discrete phenotypic categories, each with a discrete risk of developing disease, and are much less subject to environmental effects (e.g. *LDLR* mutations resulting in the autosomal dominant form of familial hypercholesterolemia). Such single-gene mutations contributing to chronic diseases are rare. Although such mutations may have a devastating effect on the individual who carries them, they make only a minor contribution to the variability of the quantitative risk factor trait in the population at large and thus account for only a small proportion of the chronic disease.

142. It is thus obvious that, unlike in the case of Mendelian diseases, the use of genetic information to predict susceptibility to the common chronic diseases presents several unique problems. For example, having a genetic defect is not equivalent to having the disease. Further, no single gene defect will be expected to be causal in all or even in a majority of cases. The genetic "dissection" of common multifactorial diseases therefore represents a great challenge for medical genetics. In what follows, the general attributes of common multifactorial diseases are first considered. These attributes are then illustrated with three selected examples (diabetes mellitus, essential hypertension, and coronary heart disease) to provide a look at the complexities and how these differ between the diseases. The subject has been recently reviewed [S98].

2. Overall prevalences and epidemiological features

143. A broad overview of the epidemiological features of some common multifactorial diseases in Hungary and in other parts of the world is presented in Table 23 [C35]. In Hungary, the overall population prevalence of these diseases is of the order of about 65%, including all age groups; the estimates for individual diseases were computed taking into account the age structure of the Hungarian population and are, therefore, age-standardized. For instance, if the prevalence figure pertains to the adult population (above age 14 years), this figure was reduced by 21%, since the 0–14 age group represents 21% of the total Hungarian population. In arriving at these figures, sex differences have been ignored. The prevalence estimates given in parentheses are those from the study of Unoka [U17], in which all inhabitants over the age of 14 years in one administrative unit in Hungary (n = 3,707) were screened for the various diseases. This sample represented 96% of the entire population of that administrative unit.

144. The ranges of estimates for other parts of the world are from data published in the literature; these are not age-standardized, since such information was not always available. As can be seen, the total Hungarian prevalence of 65% is in good agreement with that (i.e. the total of the median estimates for the individual estimates) for other countries. Not obvious from Table 23 is the fact that some individuals may (and do) have more than one disease, since there was no easy way to exclude counting the same individual more than once. The complete population survey of Unoka [U17] is instructive in this regard. Among the 3,707 individuals studied, 618 (17%) did not have any of the diseases for which the screening was made; the remaining 3,089 individuals had a total of 10,097 diseases. The overall population average was thus 2.7 diseases per individual (10,097/3,089).

145. Apart from a few diseases (or disease sub-entities) such as insulin-dependent diabetes mellitus and epilepsy, most of the diseases included in Table 23 have mean onset ages in middle life. With the exception of asthma, for which the age distribution is bimodal (i.e. having two peaks, one in early life and another in middle or late life), for most others the age distribution is normal, i.e. a low prevalence in young age groups, a high prevalence in middle age groups, and a falling off at later ages. There are no striking sex differences in prevalence for some (e.g. diabetes mellitus, epilepsy, and essential hypertension), whereas for others there is either male or female preponderance. Finally, the estimates of heritability of liability, h^2, encompass a wide range, from 0.30 to 0.90.

3. Diabetes mellitus

146. Diabetes mellitus is a genetically heterogeneous group of disorders that share the common feature of elevated blood sugar. Collectively it is one of the most common chronic diseases, afflicting up to 5%–10% of individuals in Western countries. On the basis of several sources of data, Rotter et al. [R19] concluded that over 8 million people in the United States (3%) have diabetes. Diabetics have a variety of clinical features, ranging from an asymptomatic state to acute diabetic ketoacidosis and chronic microvascular (nephropathy, retinopathy) and macrovascular (atherosclerosis) complications.

147. Two main types (Type 1, or insulin-dependent diabetes mellitus [IDDM], and type 2, non-insulin-dependent diabetes mellitus [NIDDM]) and a number of secondary types are distinguished [H36, N14]. Additionally, over 60 Mendelian

syndromes and some mitochondrial mutations have been described that are associated with glucose intolerance and in some cases, clinical diabetes mellitus; roughly one third of the Mendelian syndromes are associated with IDDM or glucose intolerance and the remainder with NIDDM or insulin resistance [B40, O8, R19]. All these contribute to the genetic heterogeneity of diabetes mellitus.

148. It has been estimated that 35%–45% of long-term diabetics will develop clinical nephropathy, which is known to occur in all forms of diabetes (e.g. [V16]). Hypertension is another independent risk factor for nephropathy; it is twice as prevalent in diabetic as in non-diabetic subjects (e.g. [E7, N13]). Diabetic retinopathy is a complication of diabetes (e.g. [R22]). Clinical diabetes has long been known to be an independent risk factor for macrovascular disease, and the latter accounts for at least 50% of all deaths of diabetics (e.g. [J8, L33]).

(a) Insulin-dependent diabetes mellitus

149. IDDM is a chronic autoimmune disease characterized by low or absent circulating insulin levels as a result, at the final stage, of the complete destruction of the insulin-secreting cells (the β cells in the pancreas), pancreatic islet cell antibodies, and episodes of ketoacidosis. The patient presents with signs of insulin deficiency, although the pathological process leading to this may predate clinical presentation by 10–15 years. When the disease is fully developed, the patients require exogenous insulin for survival.

150. ***Epidemiology.*** In the United States, it is estimated that about 5%–10% of all diabetics are of type 1 (i.e. about 12–14 per 100,000 in children 0–16 years of age). The worldwide incidence is accurately known only for about 2% of the world population: the estimated incidences range from a low of less than 1 per 100,000 children in Japan to more than 25 per 100,000 in Scandinavia; the figure for Finland is especially high, about 35 per 100,000. Most incidence estimates fall in the range 6–15 per 100,000 [K35, K36, R19].

151. ***Risk factors.*** The main defined risk factor for IDDM is genetic susceptibility. However, as discussed below, the observations that the concordance in monozygotic twins is less than 50% suggest that environmental factors may be important. Because of the potentially long natural history of IDDM, the roles of specific environmental factors remain difficult to delineate. These may function as initiating factors (i.e. they begin or continue the aetiologic processes that eventually terminate in IDDM) or precipitating factors (i.e. they convert preclinical diabetes into overt clinical disease). It is clear, however, that these factors must act on genetically susceptible individuals.

152. ***Family and twin studies.*** Most patients who develop IDDM have no family history of the disease, and only 10%–15% of them know of an affected relative. The risk of developing IDDM, however, is clearly increased in families where a family member is affected. On the basis of a number of such studies, Rotter et al. [R19] estimated that the empirical recurrence risk to the sibling of an IDDM patient is of the order of 5%–10% and the risk to offspring is about 2%–5%. Further, the risk to offspring of fathers with the disease (4%–6%) is about twice that to offspring of mothers with the disease (2%–3%).

153. In a population-based study of young twins in Denmark (n = 20,888), Kyvik et al. [K37] found that the crude concordance rate for IDDM was 53% for monozygotic twins and 11% for dizygotic twins. When adjusted for age at onset of diabetes and age at last observation among unaffected twin partners, the cumulative risk from birth to age 35 years was estimated to be 70% and 13% for mono- and dizygotic twins, respectively. The overall conclusion from these and other studies not reviewed here is that not everyone with a genetic predisposition to IDDM develops the disease.

154. ***Genetics.*** Among Caucasian patients, the strong and consistent association of IDDM (but not NIDDM) with leukocyte human antigen (HLA) has long been known and remains an active area of research (reviewed in [S71]). The HLA class II region contains at least three genetic loci, namely, *HLA-DR*, *HLA-DQ*, and *HLA-DP*. They are highly polymorphic (i.e. many alleles are known) (reviewed in [H36 R19]). IDDM is associated with the *HLA-DRB*, *-DQA*, and *-DQB* alleles. The relative risk for IDDM in individuals who have both *DR3* and *DR4* is greater than those homozygous for either *DR3* or *DR4*. Analysis of *DR* and *DQ* in a population-based study using several statistical methods identified *DR4* as having a lesser risk than *DQ8*, and *DR3* as having a higher risk than *DQ2* [K39]. In Caucasians, *DQ8* is the most prevalent haplotype, detected in 74% of Swedish patients, followed by *DQ2* in 52% [S71]. The *DR2* haplotype is strongly negatively associated with IDDM [R21].

155. An association between IDDM and a polymorphic region in the 5' flanking region of the insulin gene (*INS*) on chromosome 11p15.5 has been known for some time (e.g. [B42]). However, several studies, while establishing that the *INS* gene region (19 kb) contains an important genetic susceptibility locus, failed to demonstrate linkage of these alleles to IDDM in families (e.g. [B43, J9]). This is partly because the putative disease-associated allele is present at a high frequency in the general population.

156. Lucassen et al. [L32] made a detailed sequence comparison of the predominant haplotypes in the *INS* gene region in a population of French Caucasian IDDM patients and controls and narrowed the region of susceptibility to a 4.1-kb segment of DNA spanning the *INS* gene and associated 5' VNTR region (VNTR: Variable Number of Tandem Repeats). They were able to show that 10 polymorphisms within this region are in strong linkage disequilibrium with each other and extend across the *INS* gene and the VNTR situated 365 bp 5' to it. The putative locus in this region was designated *IDDM2*, and it has been

suggested that it might account for about 10% of the familial clustering. The "mutation" has now been mapped within the VNTR itself [B44, K40].

157. Finally, a genome-wide search for IDDM-susceptibility genes [D15, M38, T21] and other studies [H36] have shown that, in addition to *IDDM1*, which accounts for a large proportion of familial clustering, and *IDDM2*, there are at least 10 other loci on nine chromosomes. Further, it appears that *IDDM1* and *IDDM2* function epistatically (multiplicatively), whereas *IDDM1* and *IDDM4* may act independently, although this may depend on the geographical origins of the families studied [M38].

158. ***Summary.*** IDDM is a group of heterogeneous diseases probably resulting from exposure to some environmental agent(s) of individuals with a genetically determined susceptibility. The disease is the result of the destruction of insulin-producing β cells of the pancreas, principally by immunologically mediated (autoimmune) mechanisms. The main defined risk factor is genetic susceptibility, and apart from *IDDM1* (linked to the *HLA* complex) and *IDDM2* (in the insulin gene region), at least 10 other genes are involved, mutations in which cause susceptibility to IDDM. Some of these genes may act independently, while others act epistatically.

(b) Non-insulin-dependent diabetes mellitus

159. NIDDM is characterized by a relative disparity between endogenous insulin production and insulin requirements, leading to an elevated blood glucose. In contrast to IDDM, there is always some endogenous insulin production, and many NIDDM patients have normal or even elevated blood insulin levels. Hyperinsulinemia and insulin resistance are characteristic of NIDDM patients [R19]. NIDDM occurs usually, but not exclusively, in persons over the age of 40 years. Approximately 60% of the patients are obese. It is the more common form of diabetes mellitus in Caucasian populations.

160. ***Epidemiology.*** It is estimated that between 500,000 and 600,000 persons in the United States become diabetic each year. While the overall incidence of NIDDM in the United States is estimated to be around 32 per 100,000 for ages of 20 years or more, the actual incidence is difficult to determine, owing to the mild onset of the disease in some individuals and the estimated high proportion of undiagnosed cases [R19]. In terms of prevalence, it is thought that 4%–5% of the population in the United States aged 20–74 years have NIDDM and an additional 4%–11% have impaired glucose tolerance [H36]. In the United Kingdom, at least 3% of the middle-aged and elderly population have NIDDM [P26]. The rates are higher among the very elderly. The lowest prevalence rates (<2% of adults) are recorded among Inuits, Alaskan Athabascan natives, Japanese, Chinese, and Indonesians and the highest known prevalences are among the Pimas, other native American groups, and Pacific Islanders (as high as 60%) [K35, R19].

161. ***Family and twin studies.*** Family and twin studies have long suggested a strong familial component for susceptibility to NIDDM. From published data, Rotter et al. [R19] estimated that the empirical recurrence risk for first-degree relatives of NIDDM is of the order of 10%–15% for clinical NIDDM and 20%–30% for impaired glucose tolerance. This increased risk appears to be only for NIDDM and not for IDDM. For most cases of maturity onset diabetes of the young (MODY), i.e. those in whom it is an autosomal dominant disease, the risk to siblings and offspring is 50%.

162. Studies of twins demonstrate high concordance rates (55%–100%) for NIDDM in monozygotic twins [B41, P27], although lower rates (such as 40%) have also been recorded [K38]. In any case, these rates are higher than those for IDDM. However, studies of migrants and of populations from developing countries indicate that the environmental and lifestyle changes that accompany westernization promotes NIDDM in those who are genetically susceptible [R19]. The current view is that NIDDM, like IDDM, is also genetically heterogeneous.

163. ***Genetics.*** In most population groups, NIDDM shows no association with HLA antigens [B45, R19]. MODY, a rare subtype of NIDDM, is an autosomal dominant form and has early onset (before age 25 years), although family members may be diagnosed at older ages [B44, F25, V17]. MODY has been found to occur in about 13% of Caucasian NIDDM families studied in France [F26].

164. In a small subgroup of NIDDM presenting with hyperglycemia, hyperinsulinemia, and yet a normal responsiveness to exogenous insulin, autosomal dominant point mutations in the insulin gene (*INS*) have been found (reviewed in [M1]). Important to note here is that in a population of NIDDM patients screened for mutant insulin, fewer than 0.5% were found to have such mutations [S72]. Likewise, known gene defects in the insulin receptor gene (*INSR* on chromosome 19p13.3) are rare and associated with rare syndromes of severe insulin resistance [M1].

165. Mutations in the *GCK1* gene appear to be the most common in MODY in France and are present in 56% of the families [F11, V17] (see also [S74]). There is some evidence that the *GCK1* region may also be important in more common forms of NIDDM. There is a simple tandem-repeat polymorphism roughly 10 kb 3' to *GCK1*. In African-Americans, in whom the prevalence of NIDDM is relatively high, Chiu et al. [C42] found a statistically significant association between NIDDM and one of the PCR-defined alleles, suggesting the involvement of *GCK* region in "ordinary" NIDDM in a proportion of the cases. However, no mutations in the coding region of the gene were found [C43]. In three other populations, Mauritian Creoles, southern Indians, and elderly Finnish men, *GCK* was positively associated with NIDDM [C42, C44, M39, M40]. In some other population groups, however, there was no such association [H36]. Finally, Hanis et al. [H17] reported the results of a genome-wide search for NIDDM genes in 408 Mexican-Americans from Starr County, Texas. The

important finding was that one of the 490 molecular markers, D2S125 on chromosome 2 (band 2q37), showed significant evidence of linkage to NIDDM.

166. ***Summary.*** NIDDM is a very common disease whose main determinant in Western countries is genetic susceptibility. Compared with insulin-dependent diabetes mellitus, the concordance rates in monozygotic twins and risks to first relatives (of those afflicted) are higher. With the exception of the subtype of diabetes with earlier onset, most cases have onset in middle or late life. The known geographical variations in the prevalence and studies of migrant populations suggest that environmental factors might also be important.

167. The number of genes in which mutations cause susceptibility to NIDDM is not yet known. No major gene has yet been identified, although several candidate genes are currently being investigated. Rare forms such as MODY are due to dominant genes, and still rarer forms with abnormal insulin production are due to mutations in the insulin gene itself.

4. Essential hypertension

168. Hypertension is a pathological elevation of blood pressure level. An individual is diagnosed as having high blood pressure when repeated measurements show systolic blood pressure is higher than 140 mm Hg or diastolic blood pressure is higher than 90 mm Hg. Blood pressure is a continuously distributed trait with no intrinsic break at the upper end of the scale. In the recently revised system recommended by the Joint National Committee for Detection, Evaluation and Treatment of High Blood Pressure in the United States [J10], optimal blood pressure is defined as a systolic level <120 mm Hg and a diastolic level <80 mm Hg; the classification scheme is shown in Table 24. Among the four stages of hypertension, stage 1 is the most common (80%) and stage 4 is the least common [W23].

169. The clinical importance of hypertension stems from the fact that it is an important risk factor in the development of cardiovascular and renal diseases, specifically stroke, atherosclerosis, coronary heart disease, congestive heart failure, and renal failure [A13, B50, C54, K45, W25]. The cut-off points for identifying hypertension are arbitrary and chosen for their operational suitability in clinical practice (i.e. to define the level of blood pressure at which risks for cardiovascular and renal diseases become worrisome and to facilitate therapeutic decision-making and preventive efforts) and do not reflect a clear biological distinction between hypertension and normotension.

170. ***Epidemiology.*** Estimates of the prevalence of essential hypertension in the population vary considerably, depending on the cut-off points chosen and the methods of measurement, and they are influenced by population characteristics such as age, gender, race, and socioeconomic status [E15, M43]. Surveys of industrialized societies show that the prevalence in the general population is of the order of 10%–25% (see Table 10–2 in Burke and Motulsky [B50]). In the 1988–1991 National Health and Nutritional Examination survey, which used the criteria in Table 24, the prevalence in the general population of the United States varied from 4% in those aged 18–29 years to 65% in those older than 79 years [B51, W23]. The overall pattern of age-related increases in blood pressure has been found in a number of population studies in industrialized countries [E15, W23].

171. It is instructive to note that essential hypertension is practically non-existent in several populations or population groups from a variety of national backgrounds, including Malaysians, Polynesians, Australian aborigines, Central and South American natives, and Inuits [C52, E15, M43, P28]. In these populations, there is as well no normal rise in blood pressure with age, as is seen industrialized populations. Ethnic differences in blood pressure have been extensively studied in African-Americans and whites of northern European origin; in the former group, elevated blood pressure is evident in all age groups and across the range of blood pressure values; these data have been reviewed [B50, K47, M45].

172. ***Risk factors.*** Both genetic and environmental factors play important roles in the development of essential hypertension and its sequelae (e.g. [B50, M44, W26]). Among the environmental factors are common life-style-related factors such as high body weight and central obesity (which itself has genetic determinants), sodium intake that greatly exceeds physiological needs, excessive consumption of alcohol, insufficient physical activity, and stress. Further, abnormalities of glucose, insulin, and lipoprotein metabolism are common among patients with essential hypertension. It has been hypothesized that these metabolic abnormalities may play a role both in the pathogenesis and complications of essential hypertension in many patients [R24].

173. ***Family and twin studies.*** Family studies in various populations document familial aggregation of blood pressure at all levels of blood pressure and across all age groups; both genetic and environmental factors contribute to this familial aggregation [B50, C51, C54, S77]. Most frequently, these studies have estimated blood pressure correlations for individuals paired according to their biological relatedness. While the magnitude of these correlations (r) varies from study to study, in general the closer the biological relationship, the higher the correlation (see Table 10–4 in Burke and Motulsky [B50]). Some representative values of correlation coefficients determined in family studies of hypertension are shown in Table 25. Note that the correlations are slightly higher for systolic blood pressure than for diastolic blood pressure. The wide range in correlations recorded in the different studies may in part stem from genetic heterogeneity as well as the many environmental factors that affect blood pressure (e.g. [A14, L39, M47, P29]).

174. ***Genetics.*** At present, four rare Mendelian syndromes associated with essential hypertension are known: glucocorticosteroid-remediable aldosteronism (GRA), Liddle syndrome (or pseudo-aldosteronism), pseudoaldosteronism type II (Gordon syndrome), and the syndrome of apparent mineralocorticosteroid excess (AME). Glucocorticosteroid-remediable aldosteronism is an autosomal dominant disorder that has been shown to be due to a chimeric gene duplication resulting from unequal crossing-over between aldosterone synthase gene and steroid 11β-hydroxylase gene [L36, L37]. Only 51 cases have been reported worldwide. Liddle syndrome is also autosomal dominant and is due to mutations in the β or γ subunit of the gene encoding the epithelial sodium channel (*SCNN2, SCNN3*) [S76]; only 50–60 cases have been reported worldwide. Apparent mineralocorticosteroid excess is autosomal recessive and is due to mutations in the renal isozyme of 11β-hydroxysteroid dehydrogenase gene; only about 25 cases have been reported worldwide [M48]. The genetic basis of Gordon syndrome is not known.

175. A number of genes whose biological function makes them logical candidates or markers for blood pressure homeostasis have been studied in recent years (reviewed in [H41, L35, T22]). Among these are loci coding for the renin-angiotensin system, RAS, involving the *REN, ACE, AGT,* and *AT1* loci (this system plays a vital role in kidney function and renal homeostasis, and hence in blood pressure regulation, and is also a target system for antihypertensive agents), sodium-hydrogen exchanger isoform 1, kallikrein, estrogen receptor, and the *SAH* gene (rat hypertension-associated homolog).

176. ***The ACE locus.*** The evidence from studies in Caucasians on the possible influence of variants at the *ACE* (angiotensin-converting enzyme) locus on blood pressure has been either negative or equivocal [S78, T22], in contrast to the situation recorded in rats [H42, J11, O9]. Likewise, an insertion/deletion (I/D) polymorphism in intron 16 of the *ACE* gene was found to be associated with different levels of circulating ACE; those with the D/D genotype had twice the level of ACE as the I/I genotype, whereas those with I/D genotypes had intermediate levels [T23], but these differences did not correlate with blood pressure levels [J12]. However, in a cohort of 52 hypertensive and 37 normotensive African-Americans, the frequency of the ACE deletion allele was found to be higher in hypertensives than in normotensives [D22]. Additionally, the stratification of hypertensives in different age groups by Morris et al. [M46] revealed a marked and selective decrease in the frequency of the *ACE* D/D genotypes with age.

177. There is some evidence that certain *ACE* locus genotypes may increase the risk of myocardial infarction [C50, L40]. In a study of a group of 316 unrelated patients with NIDDM (132 of whom had a myocardial infarction or significant coronary stenosis), the D allele was found to be a strong risk factor for coronary heart disease [R25].

178. ***The AGT locus.*** In contrast to the studies mentioned above, the evidence on the role of variants at the *AGT* locus (which encodes the renin substrate angiotensinogen) in essential hypertension is more substantial. In two large cohorts (Paris and Salt Lake City) of Caucasian hypertensive sib pairs (involving a total of 379 sib pairs), Jeunemaitre et al. [J13] obtained evidence of linkage between a GT dinucleotide polymorphism in the 3' flanking region of the *AGT* gene and essential hypertension. This observation prompted the search for molecular variants in the *AGT* gene that might be causal in the pathogenesis of essential hypertension. Two such variants, Thr174→Met and Met235→Thr, were found to be significantly more frequent in all hypertensive cases than in normotensive controls. The frequencies were Thr174→Met: controls 9%, all index cases 14%, and more severe index cases 17%; and Met235→Thr: controls 36%, all index cases 47%, and more severe index cases 51% (see also [C53, F31, H40]).

179. ***The AT1 locus.*** In a case-control study of 206 white hypertensives and 298 normotensives, Bonnardeaux et al. [B57] identified five polymorphisms in the *AT1* gene sequence, two in the coding region, and three in the 3' untranslated region. Only the allele frequency of the A1166→C nucleotide variant was found to be increased in hypertensive patients (36% vs. 28%).

180. ***Hypertension and risk of stroke and coronary heart disease (CHD).*** Stroke is a heterogeneous disorder that encompasses cerebral infarction (ischaemic stroke being the most common type), intracerebral haemorrhage, and subarachnoid haemorrhage. Epidemiological studies have repeatedly documented the thesis that essential hypertension is an important and independent risk factor for stroke and coronary heart disease [B55, D21, M44, P30]. In the multiple risk factor intervention trial (MRFIT), in which 350,977 men were screened and given a six-year follow-up, the main risk factor for mortality was stroke; about 40% of strokes could be attributed to systolic blood pressure of more than 140 mm Hg [I10, R26].

181. MacMahon et al. [M42] summarized data from nine prospective observational studies involving 418,343 adults aged 25–70 years. None of these individuals had a history of coronary heart disease or stroke when the study began. They were followed for an average of about 10 years. The difference between the highest (105 mm Hg) and lowest (76 mm Hg) stratum of diastolic blood pressure was only 30 mm Hg. However, even within this narrow range, the risk of stroke was more than 10 times higher and that of coronary heart disease nearly five times higher for those in the highest (compared with the lowest) stratum of mean overall diastolic blood pressure during follow-up. These data suggest that a 5–6 mm Hg lower level of diastolic blood pressure is associated with a 20%–25% lower risk of coronary heart disease.

182. The risk of mortality from coronary heart disease increases as systolic blood pressure increases. In the MRFIT, which involved 347,978 men, the risk of mortality

from coronary heart disease clearly increased with progressively higher levels of systolic blood pressure; compared with those in the lowest stratum of systolic blood pressure (>110 mm Hg), individuals in the highest stratum (≥180 mm Hg) had a 5.65-fold higher risk [S79]. Further, less than a quarter of the cohort had hypertension (n = 82,347), but this group accounted for more than two thirds of the excess risk of coronary heart disease mortality related to excess systolic blood pressure. Additionally, the risk of high blood pressure was substantially increased by the presence of other risk factors; for example, in the MRFIT, there was a big difference in risk between those who were smokers and others in the upper quintiles for both blood pressure and serum cholesterol.

183. ***Hypertension and the risk of congestive heart failure and end-stage renal disease.*** In a 34-year follow-up of the Framingham Heart Study Cohort, Kannel and Belanger [K46] found that the risk of congestive heart failure was 2–4 times higher for those in the highest than for those in the lowest quintile of blood pressure at entry into the study. Similarly, for an average of 15.3 years follow-up of 361,639 individuals screened in the MRFIT study, after adjusting for other concomitant variables (age, race, cigarette smoking, serum cholesterol concentration, treatment for diabetes, previous myocardial infarctions, and income), the estimated risk of end-stage renal disease rose with an increase in systolic blood pressure.

184. ***Summary.*** Essential hypertension is a common multifactorial disease affecting some 10%–25% of the population of industrialized countries. Its clinical relevance stems from the fact that it is one of the major risk factors for cardiovascular and renal diseases, especially stroke, coronary heart disease, and end-stage renal disease. The role of genetic factors in essential hypertension is made clear by family studies in which correlations in blood pressure levels have been studied. The coefficients of correlations are in the range of 0.12–0.37 for sib-sib and parent-child relationships, rising to about 0.55–0.72 for monozygotic twins. The variations in the range and magnitude of these correlations, however, suggest that environmental factors must play an important role, varying from individual to individual and population to population.

185. As in the case of NIDDM, no important genes controlling blood pressure have been identified, and at present it is difficult to estimate the number of genes involved. However, during the past five years or so, linkage and association studies have shown that there are at least three gene loci (*AGT, AT1,* and *ACE*) at which polymorphism contributes to essential hypertension; however, the relative proportion of hypertensives in the population that each of these accounts for remains to be determined. Additionally, the molecular basis of three rare Mendelian disorders associated with hypertension, namely those involved in glucocorticosteroid-remediable aldosteronism, Liddle syndrome, and apparent mineralocorticosteroid excess have been delineated.

5. Coronary heart disease

186. Cardiovascular diseases occupy the number one position in the morbidity and mortality statistics in most industrialized countries of the world. Among these, coronary heart disease constitutes the predominant group, accounting for roughly one half of all cardiovascular deaths. The terms coronary heart disease, ischaemic heart disease, and coronary artery disease are more or less synonymous; they all result from atherosclerosis, the obstruction of blood flow through the arterial network, when the vessels that nourish the heart muscle are affected by the formation of fibrous tissue called atheromatous plaque. Clinical symptoms of atherosclerosis do not usually occur until over half of the lumen becomes obstructed (occluded) by the plaque, typically in the fifth and sixth decades of life. Among the clinical manifestations of coronary heart disease are congestive heart failure, conduction defect, arrhythmia, angina pectoris, and myocardial infarction.

187. ***Epidemiology: mortality profiles.*** The death rates from coronary heart disease and their trends in time vary widely in different parts of the world (e.g. [H47, W21]). Until the 1960s, the trend in mortality from coronary heart disease was generally upward in industrialized countries and was more pronounced for men than for women. During the 1960s and 1970s, a peak was reached, followed by a downward trend in many countries, although in some countries such as Poland and Hungary increases have been registered during the last decade.

188. In the United States, more than 300 deaths per 100,000 were observed in the mid-1960s. Since that time, the mortality has been declining at 2%–3% per year, with a lessened rate of decline in recent years. In the late 1980s, about 27% of deaths were due to coronary heart disease, and it is still the principal cause of death. Finland has the highest mortality rate from coronary heart disease and Japan the lowest. The death rates from coronary heart disease in 1977 ranged from 878 per 100,000 for Finnish men aged 35–74 years to 103 per 100,000 for Japanese men [S79]. The reported figures in general are higher in countries consuming a Western diet and lower in countries where the consumption of fat and cholesterol is low [M50, S85].

189. The importance of environmental factors is also indicated by studies of migrants. When individuals from Japan migrated to Hawaii, their coronary heart disease mortality rate doubled, and when they emigrated to the United States mainland, it tripled [R35]. Similar changes were noted for Irish immigrants in Boston compared with those who stayed in Ireland [K52]. Among the various immigrants, the rates became nearly similar to those in their adopted countries within 10–20 years.

190. ***Risk factors.*** Current evidence documents the premise that positive family history, high low- density lipoprotein (LDL), and low high-density lipoprotein (HDL) cholesterol levels (separately as well as jointly), high ApoB levels (the main protein fraction of the LDL particle), high

Lp(a) (lipoprotein(a)) levels, high levels of plasma fibrinogen concentration, hypertension, diabetes, high dietary fat intake, obesity, increased levels of homocysteine (all these themselves have genetic determinants), lack of exercise, stress, and smoking are important risk factors (e.g. [B59, D25, H37, H50, K49, K51, N15, R28, S82, U15]).

191. ***Family and twin studies.*** Familial aggregation of coronary heart disease has long been known (reviewed in [B58, M53]). First-degree relatives of affected patients have about a 2–6-fold higher risk of the disease than matched controls. The familial aggregation increases with decreasing age of the affected patients. While women have a lower frequency of coronary heart disease than men, the first-degree relatives of index women run a higher risk than those of affected index males.

192. Twin studies (reviewed in [B58]) have demonstrated that the concordance rates for monozygotic twins are higher than those for dizygotic ones. The estimates for monozygotic (MZ) and dizygotic (DZ) twins in Denmark were 39% and 29% for males and 44% and 14% for females. The corresponding figures for twin pairs in Sweden were 48% and 28%. In a study in Norway, the concordance rates for angina pectoris and/or myocardial infarction were 0.65 for monozygotic and 0.25 for dizygotic twin pairs; if only twins with premature coronary heart disease appearing before the age of 60 years were included, these figures were 0.83 and 0.22, respectively. Some representative data on odds ratios from family and twin studies are summarized in Table 26.

193. ***Total cholesterol levels.*** It is now well known that, first of all, variation in cholesterol concentrations in a population is determined by both genetic and environmental factors and that the mean and the normal range of total plasma cholesterol levels vary in different populations. Secondly, as the total concentrations increase throughout the range observed in the population at large, there is a marked increase in the risk of developing coronary heart disease, i.e. the majority of coronary heart disease occurs in individuals with cholesterol levels that are distributed near the mean of the population, the coronary heart disease risk being graded and continuous without a threshold; only a small fraction of the disease burden is associated with elevated cholesterol levels that are discretely separate from the so-called normal range of variability. Figure IV illustrates these points.

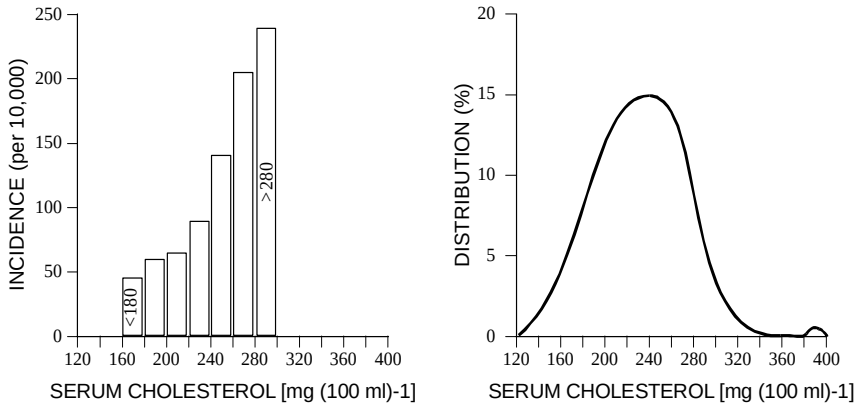

Figure IV. The relationship between the distribution of total serum cholesterol and incidence of coronary heart disease.
The data are from the Framingham Massachussetts survey for males of 30-39 years of age. Incidence is for 10 years of follow-up.

194. ***Cholesterol, plasma lipids, and lipoproteins.*** Very early studies of the atherosclerotic plaque, which were shown to be deposits of cholesteryl esters, focussed attention on the metabolism of plasma lipids. The main plasma lipids are cholesteryl esters and triglycerides. The plasma lipids are transported as complexes with other lipids and proteins called lipoproteins. The lipoproteins are spherical particles with a coat consisting principally of phospholipids and proteins called apolipoproteins and a core that contains varying proportions of triglycerides and cholesteryl esters.

195. The main classes of apolipoproteins of particular interest for the aetiology of coronary heart disease are chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), LDL, and HDL. These designations are based on their buoyant density and ultracentrifugation profiles (reviewed in [B62, B64]). Some of their properties and the associated apolipoproteins are summarized in Table 27. Not shown in this Table is the class of lipoproteins designated as Lp(a), which was originally discovered by Berg [B60]. Subsequent work using quantitative immunochemical methods showed that the Lp(a) concentration is a quantitative genetic marker whose concentration can vary greatly between individuals (from near zero to over 1,000 mg dl^{-1}) [S83]. The Lp(a) particle has a lipid composition that is nearly identical to LDL, and like LDL, it contains a single copy of apolipoprotein B-100. However, unlike LDL, it also contains a glycoprotein called apo(a). Lp(a) is highly homologous to plasminogen, and the latter is a member of a protein superfamily composed of regulatory proteases of the fibrinolytic and blood coagulation systems [E16, M51].

196. ***Genetics of lipoprotein and other lipid-related genes.*** Lipoprotein levels are determined by genes that code for proteins that regulate lipoprotein synthesis, interconversions, and catabolism (e.g. [B62, B64]). These include the apolipoproteins A1, A2, A4, B, C1, C2, C3, D, E, and apo(a); the lipoprotein- processing proteins lipoprotein lipase, hepatic triglyceride lipase, lecithin cholesteryl acyltransferase, and cholesteryl ester transfer protein; and the lipoprotein receptors LDL receptor, chylomicron remnant receptor, and scavenger receptor. Most of these genes have been isolated, sequenced, and mapped in the human genome.

197. Mutations in the genes mentioned above may cause disturbances in one or more of the pathways in lipoprotein metabolism, resulting in hyper- or, less commonly, hypolipoproteinaemia. Some of these disorders lead to premature atherosclerosis. Such conditions fall into two main groups, those due to rare single-gene mutations having large effects (major gene effects) and those due to mutations in several different genes, each having small to moderate effects (polymorphisms).

198. ***Major gene effects.*** The classic example of major gene effects in hyperlipidaemia is familial hypercholesterolaemia (FH). This is an autosomal dominant trait with a population frequency in heterozygotes of 1 in 500. The pioneering studies of Goldstein and Brown [G17], Goldstein et al. [G18], and Brown and Goldstein [B65] established that the basic defect concerns the LDL receptors. FH heterozygotes have levels of circulating LDL that are twice normal, and these people begin to have myocardial infarctions as young as age 30 years. The level of circulating LDL in homozygotes is 6–10 times higher than the normal level. Although mutations in such genes are important for those individuals who carry them, they have less importance for the population at large.

199. The second example is hyperlipidaemia due to familial defective ApoB-100, which is also an autosomal dominant trait. This is caused by a mutation leading to a defect in the ligand, interfering with the binding of apoB to LDL receptor. The mutation is (CGG to CAG; arginine to glutamine) at codon 3500 of the *apoB* gene. Affected patients are heterozygotes, and unlike in FH due to *LDLR* mutations, no homozygotes have yet been reported. Studies among United States and European whites suggest a frequency of around 1 in 500 to 1 in 700, similar to that of FH [I11, S84].

200. ***Polymorphisms.*** The group known as polymorphisms includes conditions due to many genes that are polymorphic in the population and for which the alleles have moderate effects. The contribution of such polymorphic loci to total genetic variation is large, and interaction between these and environmental factors is probably the commonest cause of hyperlipidaemia in the population. Of these, the impact of polymorphism at the *apoE* locus on cholesterol levels has been the subject of extensive studies (reviewed by Davignon et al. [D23]).

201. ***ApoE.*** ApoE is a key protein in the modulation of the metabolism of the highly atherogenic apoB-containing lipoproteins. The *ApoE* gene is polymorphic: three common alleles designated ε4, ε3, and ε2 determine six genotypes: three homozygous (ε4/ε4, ε3/ε3, and ε2/ε2) and three heterozygous (ε4/ε3, ε3/ε2, and ε4/ε2). The corresponding plasma phenotypes are inherited in a co-dominant fashion and are designated as E4/4, E3/3, E2/2, E4/3, E3/2, and E4/2.

202. The relative frequencies of the *ApoE* alleles and their impact on apoE, as well as on total cholesterol, HDL cholesterol, triglyceride, and apoB levels, have been studied in a number of populations (see Table 1 in Davignon et al. [D23] and the references cited therein). The findings from the above and other studies of particular importance in the present context are as follows: (a) ε2/ε2 genotypes had the lowest average levels of total cholesterol, while individuals with the ε4/ε4 genotypes had the highest average levels; (b) the rank of genotype means was ε2/ε2 <ε3/ε2 <ε3/ε3 <ε4/ε4 in every study; and (c) on average, a single ε4 allele raises the total cholesterol level by about 7 mg $(100\ ml)^{-1}$, whereas the ε2 allele lowers it by about 14 mg $(100\ ml)^{-1}$ (Table 28).

203. The average effects on plasma cholesterol level for any given individual can be roughly predicted from the *ApoE* genotype and can be considerable. Thus in the Nancy (France) series, the average cholesterol level for the ε2/ε2 homozygotes was 199 mg $(100\ ml)^{-1}$ and that for the ε4/ε4 genotypes was 240 mg $(100\ ml)^{-1}$. The highest ε4 allele frequency (0.226) is observed in Finland, where the highest cholesterol levels and coronary heart disease mortality have been observed. Thus, a small but definite proportion (6%–14%) of the variability in total cholesterol levels can be ascribed to ApoE polymorphism. In principle, therefore, *ApoE*-related differences in cholesterol levels could be translated into significant variation in coronary heart disease frequencies, although in some populations, the ApoE genotypes did not perfectly correlate with coronary heart disease rates (see Davignon et al. [D23] and Motulsky and Brunzell [M53] for details and references).

204. ***ApoE polymorphism and Alzheimer's disease.*** The *ApoE* polymorphism discussed above has also been shown to be an important risk factor for late onset familial cases of Alzheimer's disease (FAD). The important finding was that the ε4 heterozygotes had a threefold increase in risk of developing FAD, and the ε4 homozygotes had an eightfold increase in risk of developing the disease (to a near certainty) by the age of 75 years [C58, C59, S86, S87]. The association of the ε4 allele with FAD has been confirmed in family studies, clinical case series, and population-based series. At least in some studies, there is evidence that the ε2 allele may be associated with a decrease in the risk of developing the disease and with a later onset age [H45].

205. ***ApoB.*** Since apoB is the principal constituent of LDL cholesterol, there are strong correlations between levels of total cholesterol, LDL cholesterol, and apoB [A15]. The rare mutation in the *apoB* gene underlying familial

defective apoB-100 has already been mentioned. Population association studies have uncovered a few generally confirmed associations of DNA variants at the *apoB* locus with apoB levels. For example, an RFLP at the 3' end of the *apoB* gene is detectable using the restriction enzyme *XbaI*. The allele lacking the *Xba* site (i.e. the X-allele) was found to be associated with reduced levels of total cholesterol, LDL, apoB, and possibly triglycerides. Paradoxically, the same allele has been reported to be more common in survivors of myocardial infarction and patients with coronary heart disease [B25, B23]. Bohn and Berg [B23] concluded that the (X− X−) genotype confers increased risk of myocardial infarction but is probably not mediated through lipids and apolipoproteins and is unrelated to the effects of polymorphisms on lipid levels.

206. ***ApoA1-C3-A4.*** Low HDL level is a strong risk factor for coronary heart disease. Because the product of the *ApoA1* gene plays an important role in HDL formation and function, a number of studies have addressed the question of genetic mechanisms. Several epidemiological studies have reported that the levels of both HDL cholesterol and apoA1 are inversely related to the incidence and severity of coronary heart disease and can independently predict the risk of the disease [L42, R29]. Various environmental factors have been identified that affect plasma HDL levels, including steroid hormones, alcohol intake, stress, infection, amount of exercise, body mass index, some drug therapy (such as β-blockers), and smoking. Despite this large contribution of environmental factors, the heritability of HDL cholesterol and apoA1 is in the range of 0.43 to 0.66 [H46]. A strong genetic effect on levels of HDL cholesterol and apoA1 has been demonstrated in twin and family studies [A11, H44]. Recent evidence points to the possibility that genetic variation in hepatic lipase activity may be an important determinant of plasma HDL cholesterol levels [G16].

207. The three genes *ApoA1, C3,* and *A4* are clustered in the long arm of chromosome 11 and span about 4 kb. More than 10 common restriction enzyme polymorphisms along the length of this part of the genome have been detected within this cluster, occurring within introns, exons, intergenic, and flanking sequences. Many studies have found associations between some of these polymorphisms and variations in levels of lipids and lipoproteins in healthy individuals and patients [C56, H48, H49]. In several studies, the association was also seen in patients with coronary heart disease. Overall, these data support the existence of a mutant gene in the *apoA1-C3-A4* cluster that lowers HDL levels, elevates triglyceride levels, and predisposes to coronary heart disease.

208. Summarizing the results of different studies, Davignon et al. [D23] concluded that approximately 60% of the phenotypic variation of the total cholesterol concentrations is genetic and the remainder environmental and that as much as one half of genetic variation is contributed by three of the many proteins involved in lipid metabolism (apoE, apoA4, and apoB). This lends credence to the view that for cholesterol variability in the population at large, the polygenic variance may be attributed to fewer loci with moderate effects than is generally assumed by the classic biometrical models, which include a very large number of loci, each with small additive effects.

209. ***Apo(a).*** The observations that the plasma levels of Lp(a) vary widely among individuals and the possibility that Lp(a) may be an important (perhaps an independent) risk factor for coronary heart disease were mentioned earlier. In reviewing many studies, Berg [B47] concluded that all carefully conducted retrospective and prospective studies confirm that high Lp(a) levels constitute an independent risk factor for coronary heart disease and an additional risk factor for coronary heart disease patients with familial hypercholesterolemia. High Lp(a) levels have been implicated in the aetiology of cerebrovascular disease.

210. The discovery that Lp(a) is highly homologous to plasminogen (from which the enzyme plasmin, which dissolves fibrin blood clots, is released by tissue plasminogen activator) and the identification of the *apo(a)* locus that determines plasma Lp(a) levels [M51] provided the conceptual link between plasma lipids and atherogenesis on the one hand and thrombogenesis on the other. There is a high degree of allelic heterogeneity at the *apo(a)* locus, with more than 20 common alleles having been identified [K48, L41]; each allele determines a specific number of multiple tandem repeats of a unique coding sequence known as Kringle 4 (a unique pretzel-like structure reminiscent of a Danish cake called Kringle). The size of the *apo(a)* gene correlates with the size of the Lp(a) repeat: the smaller the size of the Lp(a) protein, the higher the Lp(a) levels.

211. ***Genetic risk factors other than hyperlipidaemia.*** In addition to hyperlipidaemia, a classic risk factor for coronary heart disease, the role of other potential risk factors, such as the blood coagulation and fibrinolytic systems homocysteine and paraoxanase, in the pathogenesis of coronary heart disease has been addressed. [C57, D12, E17, G6, H3, H49, M21, M52, R27, S29]. The authors of the European Concerted Action Project [G6] concluded that increased plasma total homocysteine confers an independent risk of vascular disease similar to that of smoking or hyperlipidaemia. Likewise, commenting on the role of paraoxanase polymorphism, Heinecke and Lusis [H3] noted that this polymorphism should now be added to the short list of other genes for which there is significant evidence of a contribution to coronary heart disease.

212. ***Summary.*** Coronary heart disease is a common multifactorial disease and one of the major contributors to mortality in most industrialized countries. Coronary heart disease mortality has significantly declined in the United States and several other countries during the last 20 years. The disease is caused by atherosclerotic obstruction of the coronary arteries.

213. Family and twin studies show that genetic factors play an important role in coronary heart disease. A positive family history for premature coronary heart disease (occurring before age 60 years) is a strong risk factor by itself. Many genetic and environmental factors act in combination to determine interindividual variability in risk factor traits for coronary heart disease. Evidence from epidemiological studies, clinical correlations, genetic hyperlipidaemias, etc. indicates that lipids play a key role in the pathogenesis of coronary heart disease. In every population, plasma cholesterol has been implicated as a risk factor for coronary heart disease. Specifically, high levels of LDL cholesterol and low levels of HDL cholesterol are strong risk factors.

214. About 60% of the variability of the plasma cholesterol is genetic in origin. While a few major genes have been identified with rare alleles having large effects on this trait (e.g. *LDLR*, familial defective *apoB-100*), variability in cholesterol levels among individuals in most families is influenced by allelic variation in many genes (polygenic variation) as well as environmental exposures. Therefore, in most families coronary heart disease does not segregate with allelic variation at a single gene.

215. A proportion of the polygenic variation can be accounted for by two alleles of the *apoE* locus that increase (ε4) and decrease (ε2) cholesterol levels. The apoE polymorphism is also relevant in the context of late-onset familial Alzheimer's disease. HDL levels are genetically influenced and are related to *apoA1* and hepatic lipase gene functions. Polymorphism at the *apoA1-C3* region is often associated with hypertriglyceridaemia.

216. The *apo(a)* gene, which codes for Lp(a), is highly polymorphic, each allele determining a specific number of multiple tandem repeats of a unique coding sequence known as Kringle 4. The size of the gene correlates with the size of the Lp(a) protein: the smaller the size of the Lp(a) protein, the higher the Lp(a) levels. Higher Lp(a) levels constitute an independent risk factor for coronary heart disease.

217. Some genetic risk factors other than hyperlipidaemia are hyperhomocysteinaemia and polymorphisms in genes that code for paraoxanase and in those that seem related to elevated plasma fibrinogen levels. The precise nature and intensity of these associations and the biochemical mechanisms involved remain to be fully elucidated.

D. MECHANISMS OF MAINTENANCE OF MULTIFACTORIAL TRAITS IN THE POPULATION

218. As discussed in Section B of this Chapter, the multifactorial threshold model is descriptive and not mechanistic, i.e. it is not designed to address the question of the impact of an increase in mutation rate on disease frequency in the population. The prediction of the effects of an increase in mutation rate on disease frequency, however, requires knowledge of the possible mechanisms of maintenance of multifactorial diseases in the population. While no specific theories or models have been developed for this purpose, a wealth of literature exists on mathematical population genetic models dealing with mechanisms of maintenance of polygenic variability in populations (e.g. [C61, C62, K53, K54, L13, L43, L44, T27, T28, T29]; reviewed in [S62]).

219. The main concept in these studies (as in the case of mutations involving single genes) is the existence of a steady-state or equilibrium in the population between mutation and some form of selection. For example, Lande [L13, L43, L44] showed that large amounts of genetic variation in polygenic traits can be maintained in the population even when there is strong stabilizing selection (i.e. selection for an intermediate optimum). Turelli [T27, T28, T29], however, argued that unless selection is very weak or the per locus mutation rates are extremely high (i.e. $>10^{-4}$), the equilibrium variance is considerably lower than that estimated by Lande, and therefore much of the additive polygenic variance observed in natural populations cannot be explained by mutation-selection balance. In approximations that apply for lower mutation rates per locus, Turelli [T27] in comparing his results with those of Lande, noted that: (a) his results do not refute Lande's conclusion (i.e. considerable additive genetic variance may be maintained by mutation-stabilizing selection balance in the population), and (b) the validity of Lande's conclusion can only be determined with additional data on selection intensities and on mutation rates in metric traits.

220. Stabilizing selection, however, is by no means the only type of selection that has been envisaged in these models. For example, "directional selection" (broadly defined as selection for an extreme expression of a given character) and one form of this, "truncation selection" (selection beyond a certain cut-off point, called the truncation point, which is equivalent to the threshold in the multifactorial threshold model discussed earlier) are other concepts that have been used. Truncation selection is known to be the most efficient form of directional selection, because in this form, selection induces the maximum change in gene frequency for a given effect of the gene on the trait. Kimura and Crow [K54] and Crow and Kimura [C62] quantified efficiencies of truncation selection in terms of the average effects of alleles on the phenotypic trait and showed that truncation selection may indeed reduce the mutational load despite high rates of mutations. However, as they themselves noted [C62], the truncation selection model may be too simplistic even for threshold traits, because the existence of intermediate optima and antagonistic effects among components of fitness cannot be ruled out.

221. By its very nature, the dynamics of mutation-selection balance studied in these models are very complex and not readily applicable to human situations. Several factors

contribute to this complexity. First, most models are fully specified by several parameters, each of which has its own sensitivity regarding model predictions. Second, selection is specified in such models by mathematical functions that do not take into account the attained age of the individual; in contrast, for most multifactorial diseases discussed earlier, fitness is age-dependent. Third, generations are treated as discrete in these models, while at one time, a human population consists of individuals of three or more overlapping generations. Fourth, as in most population genetic models, parameters such as effective population size, selection intensities etc. are assumed to be constant over generations. As a consequence, these models when applied for risk estimation purposes, are at best approximations to the real situation.

222. In conclusion, although several different models with different degrees of complexity have been proposed to explain the maintenance of multifactorial traits in the population, not all of them can be used for risk estimation. Therefore, some judgement needs to be made on which of the concepts/models discussed can be used, taking into account current knowledge of the genetics of multifactorial diseases. Within the framework of an ICRP Task Group [I2], it was considered feasible to develop first, a theoretical approach by incorporating mutation and selection into the multifactorial threshold model and to use this modified model to examine the responsiveness of multifactorial diseases to an increase in mutation rate through computer simulations. It is to be noted that the concepts of mutation and selection are already built into the doubling-dose method of risk estimation for Mendelian diseases, although the application of the method for multifactorial diseases has not thus far been rigorously examined. The rationale and pertinent details of the model that was developed are discussed in the next Chapter.

IV. THE MUTATION COMPONENT FOR GENETIC DISEASES

A. BACKGROUND

223. In genetic risk estimation, the aim is to predict the effects of a small dose of radiation (which causes an increase in the mutation rate) in terms of its impact on disease incidence in the population. As may be recalled (paragraph 93), one of the methods used for this purpose is called the “doubling-dose” method. The doubling dose is the amount of radiation required to produce as many mutations as those occurring spontaneously in a generation. It is estimated as the ratio of the average spontaneous mutation rate of a given set of genes relative to the average rate of induction of mutations by radiation in the same set of genes:

$$DD = \frac{\text{Average spontaneous rate}}{\text{Average rate of induction}} \qquad (1)$$

224. The reciprocal of the doubling dose, 1/DD, is the relative mutation risk per unit dose. Since the risk due to radiation is conventionally expressed as the expected number of cases of genetic disease (over and above the baseline incidence) for autosomal dominant diseases (for which the disease frequency is approximately proportional to the mutation rate), the risk is estimated as a product of two quantities, the baseline incidence, P, and the relative mutation risk, 1/DD:

$$\text{Risk per unit dose} = P \times [1/DD] \qquad (2)$$

225. The population genetic theory that underlies equation (2) is the equilibrium theory (see paragraph 82): the stability of the disease incidence is assumed to be a consequence of the balance between two opposing forces, namely, spontaneous mutations, which occur in every generation, and natural selection, which eliminates them. In other words, P in equation (2) represents the equilibrium incidence. If the mutation rate is increased as a result of radiation, say in every generation, the prediction is that the population will attain a new balance (over a number of generations) between mutation and selection. For autosomal dominant diseases, if there is an x% increase in the mutation rate, it will be reflected as an x% increase in disease at the new equilibrium. The important point is that multiplying P by 1/DD gives the expected total increase in disease frequency at the new equilibrium. Traditionally, estimates of risk for the first, second, or any subsequent generation have been obtained by back-calculating from that at the new equilibrium. If the population is exposed to radiation in one generation only, there will be a transient increase in the mutation frequency in the first generation after irradiation, followed by a progressive decline to the old equilibrium.

226. The response of X-linked recessive disease to changes in mutation rate is approximately similar to that of autosomal dominant diseases, discussed above, while that for autosomal recessive diseases is a little more involved, since a recessive mutation does not immediately lead to a recessive disease. For multifactorial diseases such as congenital abnormalities and chronic degenerative diseases, the situation is more complex since there is no simple relationship between mutation and disease.

227. In order to assess the responsiveness of genetic diseases in general and of multifactorial diseases in particular to induced mutations, in its 1972 Report [C47], the BEIR Committee introduced the concept of what is referred to as the mutation component (MC). In that report,

the mutation component of a genetic disease was defined as the "proportion of its incidence that is directly proportional to mutation rate". It was suggested that for multifactorial diseases as a whole, the mutation component could be as low as 5% or as high as 50%. Later, in the 1980 BEIR Report [C48] and in publications of Crow and Denniston [C63, C69] and Denniston [D14], the concept was elaborated and mathematical formulations for estimating mutation component were presented. When mutation component is incorporated in the risk equation, the equation becomes:

$$\text{Risk per unit dose} = P \times [1/DD] \times MC \qquad (3)$$

228. Although the mutation component concept was originally developed to address the problem of multifactorial diseases, it is equally applicable to Mendelian diseases. In fact, as discussed below and by Chakraborty et al. [C66], in estimating the expected increase in the frequency of autosomal dominant diseases at the new equilibrium (under conditions of radiation exposure in every generation) and using this to back-calculate risks to the first (or any post-radiation) generation of interest, the reports of UNSCEAR and BEIR have implicitly used the mutation component concept, although they did not specify how this was actually done. This is one reason why the mutation component concept was not fully understood in the past and was equated to the genetic component of a disease, which it is not. In this Chapter the concept is discussed first from the standpoint of Mendelian diseases and then extended to multifactorial diseases.

B. DEFINITION OF MUTATION COMPONENT

229. The mutation component can be derived from quantities related by the following formulation:

$$\Delta P/P = [\Delta m/m] \times [\Delta P/P]/[\Delta m/m] \qquad (4)$$

where P is the disease incidence before an increase in mutation rate and ΔP is its change due to a Δm change in the mutation rate, m. In this equation $\Delta P/P$ is the relative change in disease incidence and $\Delta m/m$ is the relative change in mutation rate. The formal definition of mutation component becomes

$$MC = [\Delta P/P]/[\Delta m/m] \qquad (5)$$

Thus, mutation component is the relative change in disease incidence per unit relative change in mutation rate.

230. Despite the slight differences in the notations used, equation (4) is the same as the familiar risk equation used for risk estimation with the doubling-dose method, namely:

$$\text{Risk per unit dose} = P \times [1/DD] \times MC$$
$$\text{or}$$
$$\text{Risk per unit dose} \div P = [1/DD] \times MC \qquad (6)$$

Note that risk per unit dose $\div$ P = $\Delta P/P$ in equation (4). Since DD = $m/\Delta m$ (i.e. spontaneous rate/rate of induction), $1/DD = \Delta m/m$. Therefore, if m increases to m(1 + k), the disease frequency increases from P to P(1 + k MC), showing that the concept of mutation component is relevant only in the context of a change in mutation rate.

231. As mentioned above, the mutation component measures the responsiveness of the disease under consideration to a unit relative change in mutation rate. Traditionally, such responses are measured over a large number of generations. The population is assumed to be in mutation-selection equilibrium when the increase in mutation rate occurs. The impact of such a change depends on whether it occurs in a "burst" (i.e. in one generation only) or in every generation (permanent change). Under the first scenario, the impact measured by ΔP relative to the old equilibrium value P will be maximally manifest in the first generation following the mutation rate increase and progressively diminishing in subsequent generations, when the population returns to the old equilibrium. When this occurs, mutation component becomes zero.

232. In contrast, when the change caused by Δm of any given magnitude persists for all subsequent generations, that is, m is now permanently changed to $(m + \Delta m)$, the population approaches a new equilibrium value of 1. In both situations (a one-time-only or a permanent increase in mutation rate), the quantity ΔP depends on the number of generations following the change.

C. MUTATION COMPONENT FOR AUTOSOMAL DOMINANT DISEASES

1. Mutation component in the absence of sporadics

233. The procedures for estimating mutation component for autosomal dominant diseases, as well as for autosomal recessive and X-linked diseases, and the necessary mathematical equations are discussed in detail by Chakraborty et al. [C66] and in the ICRP Task Group Report [I2]. Some Mendelian diseases, such as Apert syndrome and Crouzon syndrome, are entirely due to germinal mutations, whereas others, such as retinoblastoma and breast cancers, include a proportion of cases due to somatic mutations (i.e. not due to germinal mutations; these are called here "sporadics"). The discussion in this Section pertains to those that do not have sporadics.

(a) The population before irradiation

234. Consider a hypothetical autosomal dominant mutation in a population under Hardy-Weinberg equilibrium (Hardy-Weinberg equilibrium refers to the concept that both gene frequencies and genotype frequencies will remain constant from generation to generation in an infinitely large interbreeding population in which the mating is at random

and there is no differential selection, migration, or mutation). For a single-locus, two-allele situation, if p is the mutant gene frequency and q the frequency of the non-mutant (i.e. the wild-type), and p + q = 1, the genotypic frequencies are

$$p^2 + 2pq + q^2 \quad (7)$$

in which p^2 is the frequency of mutant homozygotes, 2pq that of heterozygotes, and q^2 that of normals.

235. Assume that the spontaneous mutation rate $m = 1\ 10^{-5}$ and the selection coefficient s = 0.5. For an autosomal dominant mutation, the equilibrium frequency of the mutant gene is given by

$$p \approx m/s \approx 2\ 10^{-5} \quad (8)$$

At low mutant gene frequencies, the disease frequency, P, is approximately $2p = 4\ 10^{-5}$, because only heterozygotes [2pq in equation (7)] contribute to disease frequency.

(b) A one-time or a permanent increase in mutation rate

236. Assume that as a result of radiation exposure, the mutation rate becomes twice that of the spontaneous rate and that this increase occurs either in only one generation or permanently (i.e. generation after generation). For a one-time increase in mutation rate ("burst", indicated by the subscript b in MC_b below), the dynamics of change in mutation component with time, t, at any generation is given by the equation

$$MC_b(t) = s(1 - s)^{t-1} \quad (9)$$

and for a permanent increase in mutation rate (indicated by the subscript p), by

$$MC_p(t) = 1 - (1 - s)^t \quad (10)$$

237. Equations (9) and (10) show an interesting property of the effects of the two scenarios of mutation rate changes: a one-time or a permanent increase in mutation rate has the same impact in the first generation following the increase, namely, $MC_b = MC_p = s$. With no irradiation in subsequent generations (scenario 1), the mutation component gradually decays to zero at a rate of (1 – s) per generation. With a permanent increase in mutation rate, mutation component continues to increase in subsequent generations to attain a value of 1 at the new equilibrium.

238. The pattern of changes following a one-time or permanent doubling of the mutation rate is depicted in Figure V and numerically illustrated in Table 29. The left panel in Figure V shows the change in population frequency of a hypothetical autosomal dominant disease with time (in generations) when radiation exposure causes the mutation rate to increase from $1\ 10^{-5}$ to $2\ 10^{-5}$ (i.e. doubling) either in one generation ("burst", shown by the broken line) or permanently (solid line). The initial disease frequency, P, before the mutation rate increase is assumed to be $4\ 10^{-5}$ (see paragraph 235) and the selection coefficient s = 0.5. The right panel of Figure V shows the changes in mutation component for the same conditions.

239. As Figure V and Table 29 show, for a single-generation doubling of the mutation rate, the disease frequency shows a transitory increase in the first generation and is followed by a progressive decline towards the old equilibrium value in subsequent generations. The pattern is similar for changes in mutation component: a transitory increase in the first generation followed by a progressive decline to zero in subsequent generations. With the selection coefficients used, a permanent doubling of the mutation rate leads to a doubling of the disease frequency by the fourth or fifth generation, by which time the mutation component becomes nearly 1.

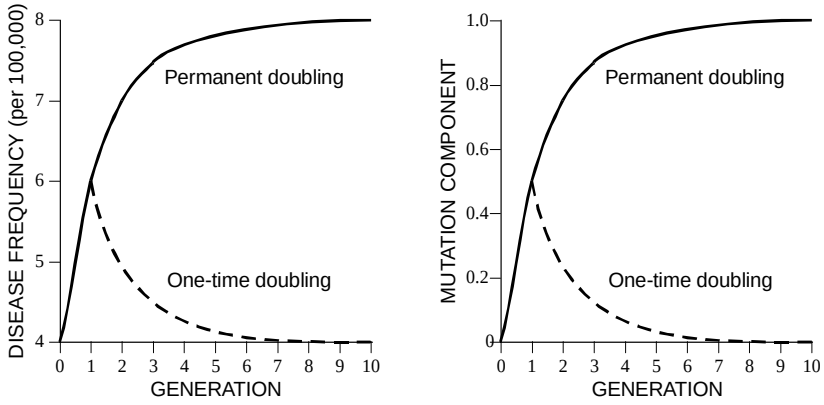

Figure V. Patterns of change in disease frequency and mutation component following a one-third or permanent doubling of the mutation rate.
The initial mutation rte is assumed to be $1\ 10^{-5}$ and the selection coefficient is 0.5

240. It is now easy to see that although the earlier UNSCEAR and BEIR Reports did not provide explicit expressions for estimating mutation component for autosomal dominant diseases, their use of equation (2) for estimating the total risk (under conditions of radiation exposure in every generation) implied the concept that the

equilibrium MC = 1, which is another way of saying that under the above conditions, the equilibrium frequencies of these diseases are directly proportional to mutation rate. Likewise, their estimates of risk in the first generation implied that MC = s in that generation. Now, with the availability of explicit algebraic formulations to estimate mutation component, a direct evaluation of the impact of an increase in mutation rate in any post-radiation generation of interest has become possible, obviating the need to back-calculate from the estimate at the new equilibrium.

2. Mutation component in the presence of sporadics

241. In the preceding Section it was assumed that genetic disease is entirely due to germinal mutation. However, there are instances where this assumption may not hold (e.g. about 40% of retinoblastoma cases are due to germinal mutations and the remainder are sporadic). For such diseases, the disease frequency at equilibrium can be assumed to take the form $P = A + Bm$. With A (sporadic component) and B (germinal component) as constants, only the second term will cause the trait frequency to increase with an increase in mutation rate. Assume that the dose dependence of the mutation is linear, namely, that $m = \alpha + \beta D$. Substituting this form of m in the equation for P above, one obtains

$$P = A + B\alpha + \beta BD \qquad (11)$$

so that $\Delta P/P = \beta BD/(A + B\alpha)$ and $\Delta m/m = \beta D/\alpha$. Consequently,

$$MC = B\alpha/(A + B\alpha) \qquad (12)$$

Thus, depending on the value of B/A, the mutation component of a disease in the presence of sporadics will be smaller than 1, i.e. the larger the fraction of sporadics, the smaller the B/A ratio and mutation component.

242. Three messages are implicit in equation (12): (a) when A = 0 and B = 1, as they are for most Mendelian diseases, MC = 1 at equilibrium; (b) as long as there is a sporadic (or non-genetic) component A, the mutation component at equilibrium will be less than 1, with the logic being easily extended to early generations; and (c) mutation component and the genetic component of the disease are not the same entities. Mutation component quantifies the mutation-responsiveness of the genetic component when there is a change in mutation rate and has meaning only when there is such a change.

D. MUTATION COMPONENT FOR X-LINKED AND AUTOSOMAL RECESSIVEDISEASES

243. The estimation of mutation components for X-linked and autosomal recessives is more involved than that for autosomal dominants. Since this is discussed in detail by Chakraborty et al. [C66], only the principal conclusions are summarized below.

244. For a one-time increase in mutation rate, the first generation mutation component is equal to the selection coefficient (and therefore similar to that for autosomal dominants) but adjusted to take into account the fact that only one third of the X chromosomes are in males. For autosomal recessives, the first generation mutation component is substantially smaller (than that for autosomal dominants) and is close to zero. In subsequent generations, mutation component gradually decays to zero.

245. With a permanent increase in mutation rate, for both kinds of diseases the mutation component progressively increases to reach a value of 1 at equilibrium, but the rates of approach to equilibrium are different for X-linked and autosomal recessive diseases and are dictated by selection and time (in generations) following radiation exposure. A comparison of the effects of increases in mutation rate on mutation component for autosomal dominant, X-linked, and autosomal recessives shows that the effects are more pronounced for autosomal dominants, followed by X-linked, and are far less pronounced for autosomal recessive diseases.

E. MUTATION COMPONENT FOR MULTIFACTORIAL DISEASES

1. Rationale for the development of a finite-locus threshold model

246. As discussed in Section III.B, the standard multifactorial threshold model of disease liability remains useful for understanding familial aggregations and excess risks within families and makes good predictions even when there is uncertainty about the underlying mechanisms. However, it is essentially a descriptive model and cannot be used to understand the mechanisms that underlie the stable incidence of multifactorial diseases in the population or the impact of an increase in mutation rate on disease incidence. Likewise, the population genetic models on the maintenance of polygenic variability in populations (Section III.D), also cannot be directly used to determine the impact of mutation rate increases on the incidence of multifactorial diseases.

247. In considering the various options for risk estimation for multifactorial diseases, the Committee feels that a useful first approach is to utilize and combine concepts of both the multifactorial threshold model and the mechanistic population genetic models. This approach was also taken by the ICRP Task Group [I2]. The devised hybrid model, referred to henceforth as the finite-locus threshold model (FLTM), assumes a finite number of loci, uses a redefined concept of threshold, and incorporates mutation and selection as two additional parameters. As discussed below, in this form, the model permits estimating the mutation component, MC, which is one of the quantities of interest for estimating the risk of multifactorial diseases.

248. The choice of the FLTM rather than the standard multifactorial threshold model is dictated by the following considerations. First, it is now evident that the standard model which assumes an essentially infinite number of loci, cannot be sustained at present. The biometrical and molecular studies of diseases such as coronary heart disease or essential hypertension lend credence to the view that the number of loci underlying these diseases is probably small, each with moderate effects; genes with large effects at the population level seem to be infrequent.

249. Secondly, in the absence of precise knowledge of the genetic basis of most multifactorial diseases, the FLTM provides a useful starting point, because with such a model, the meaning of parameters reflecting mutation rates and selection coefficients can be quantitatively assessed in terms of those for single-gene effects; further, even if the number of loci is large, the predominant contribution to the variance is still from those genes with large effects at the population level (i.e. the kind of polymorphic loci discussed in the Sections on chronic diseases), and these loci may be only a few in number.

250. Thirdly, the concept of thresholds is implicit in clinical medicine. For example, dietary therapies are recommended for individuals whose cholesterol concentrations (a risk factor for coronary heart disease) are 5.2–6.5 mM l^{-1}, more stringent dietary recommendations and some drug therapy for those with concentrations of 6.5–7.8 mM l^{-1}, and aggressive individualized therapies for concentrations exceeding 7.8 mM l^{-1} (and LDL cholesterol exceeding 4.9 mM l^{-1}). A similar situation is true for essential hypertension.

2. The model and its predictions

251. The details of the FLTM and its predictions are discussed in the ICRP Task Group Report [I2] and by Denniston et al. [D17]. In general terms, the model assumes that the liability underlying the trait, which is made up of genetic and environmental factors, is a continuous variable and that the environmental contribution has a normal (Gaussian) distribution. It differs from the standard multifactorial threshold model in that the genetic contribution to liability is assumed to be discrete (i.e. it comes from a finite number of loci), and mutation and selection are incorporated as two additional parameters, which are two opposing forces responsible for the stable incidence of the trait in the population.

252. The mathematical formulations of the model do not permit expressing the effects of an increase in mutation rate on mutation component in the form of a single equation. However, the model's predictions can be iteratively evaluated from the computer programme that was developed for this purpose. The programme is run using a particular set of parameter values (mutation rate, selection coefficients, threshold, etc.) until the population reaches equilibrium between mutation and selection; once this occurs, the mutation rate is changed once or permanently. The computer run is resumed with the new mutation rate (with the other parameters remaining the same), and the changes in mutation component and its relationship to heritability (h_B^2) following the mutation rate increase are then examined in desired generations following the mutation rate and at the new equilibrium. The estimates of h_B^2 are not inputs but outputs of the computer programme, obtained by using different combinations of s (selection coefficient), s_e (environmental standard deviation), and T (threshold).

(a) Effects on mutation component of a permanent increase in mutation rate

253. Figure VI shows, for a five-locus model, the relationships between the heritability of liability (x axis) and mutation component (y axis) at equilibrium following a permanent 15% increase in mutation rate (from 10^{-6} $locus^{-1}$ $generation^{-1}$ to 1.15 10^{-6} $locus^{-1}$ $generation^{-1}$). The selection coefficients, s, assumed in these calculations are 0.2 and 0.8. Other assumptions include the following: (a) the loci are unlinked (free recombination); (b) the starting gametic frequencies are equal ($1/2^n$); (c) the mutation rate for all loci is the same; (d) there is no epistasis or dominance at the liability level; and (e) there are no sporadics.

254. The different data points in Figure VI come from different computer runs using different combinations of parameter values (threshold, selection coefficient, and environmental standard deviation). The figure shows that for h_B^2 values higher than about 0.1, mutation component is above 0.8 at equilibrium; for h_B^2 values higher than 0.4, mutation component is essentially 1. In other words, for diseases with heritability values in the range from 0.4 to 0.8, a 15% increase in mutation rate, will result in a 15% increase in disease frequency at equilibrium.

255. The predicted effects in the early generations (i.e. generation 1, 5 and 10) following a mutation rate increase identical to that assumed in Figure VI are summarized in Figure VII. From the difference in the y axis scale between Figures VI and VII it is clear that the mutation component in the early generations is very small, being often much less than 2% for the specified conditions of the model.

256. Figure VIII compares the mutation component values at equilibrium and in generation 10, following a permanent increase in mutation rate. The shaded areas in the figure are the ones of interest in risk estimation. The calculations reinforce the main qualitative result, i.e. for a 15% permanent increase in mutation rate, the mutation component at equilibrium is close to 1, whereas even in generation 10, the corresponding mutation components are very small indeed.

(b) Effects on mutation component of a one-time increase in mutation rate

257. The numerical algorithm used for the above calculations was also used to examine the consequences of a one-time increase in mutation rate, i.e. the mutation rate

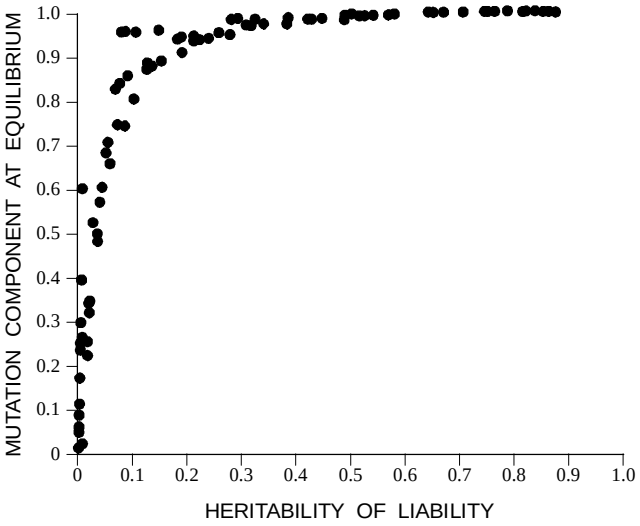

Figure VI. Relationship between mutation component and heritability of liability at equilibrium.

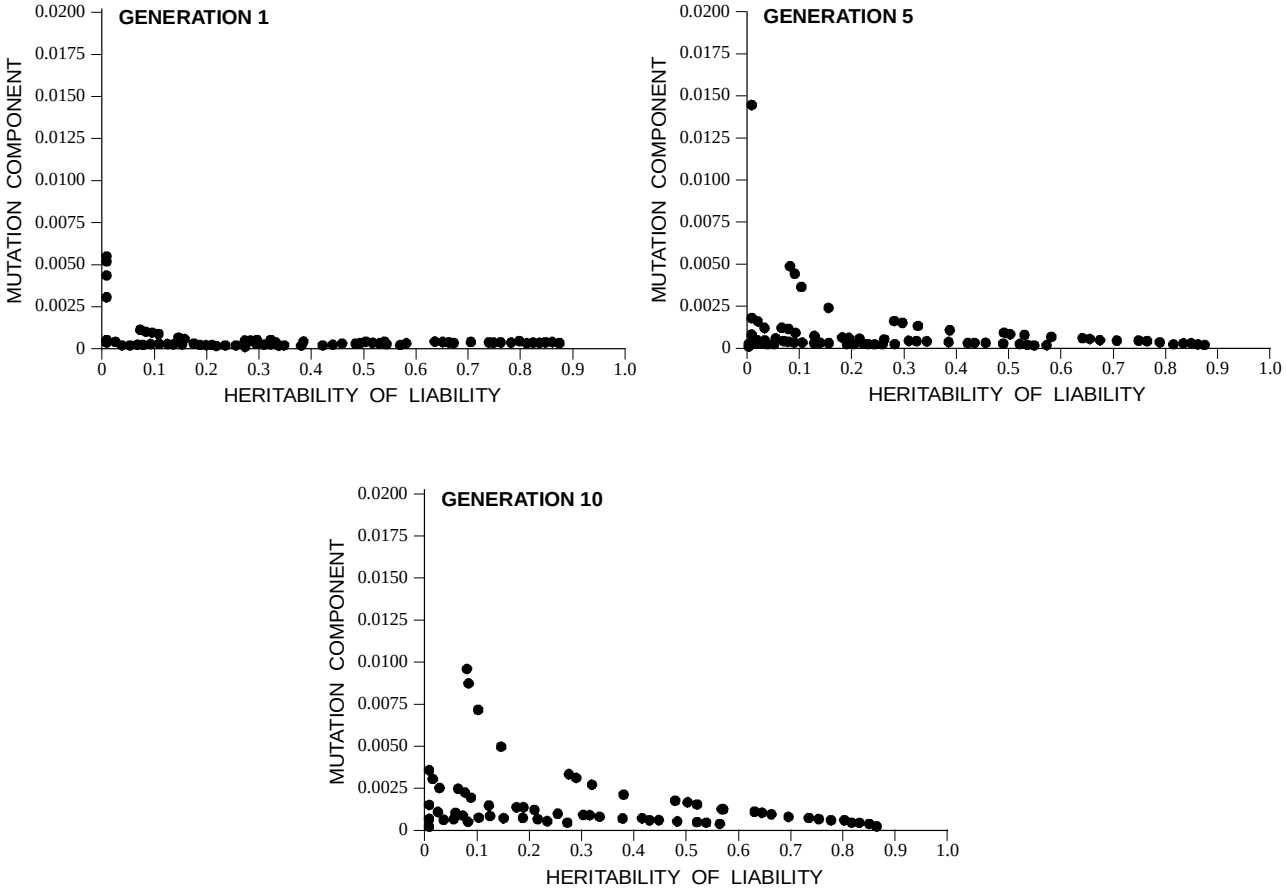

Figure VII. Relationship between mutation component and heritability of liability in early generations.

was increased once by 15% and then brought back to the original value for all subsequent generations. As expected, the first- generation mutation component is the same as that shown in Figure VIII, and this is followed by a gradual decline back to zero in subsequent generations (data not shown). Given the relatively small mutation component in the first generation, details of these computations are of little consequence.

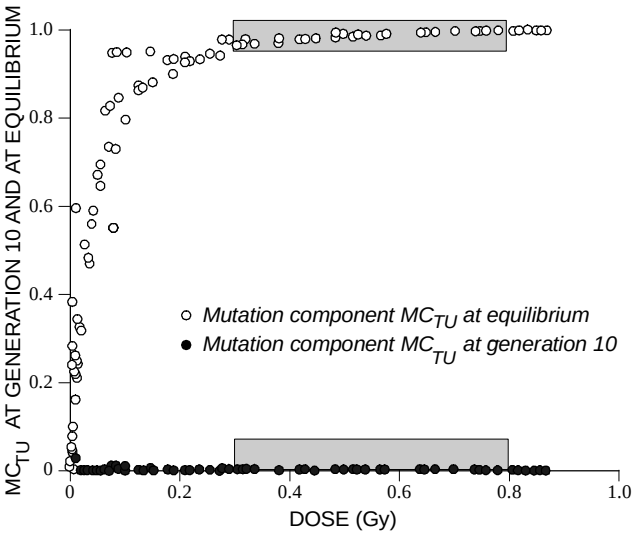

Figure VIII. Relationship between heritability and mutation component at equilibrium and at generation ten under conditions of a permanent increase in mutation rate [D17].
The shaded areas are those of interest in risk estimation.

(c) Effects of gene interactions and sporadics

258. The effects of interactions between genes on quantitative phenotypes at risk of complex diseases are varied and do not readily lend themselves to modelling. However, when some assumptions on these interactions were incorporated into the model, it was found that the results were qualitatively the same as those obtained under conditions of no gene interactions, i.e. the mutation component remains basically unaltered and in early generations is below 2% even for large values of h_B^2. The results of calculations using n (the number of loci) = 3, 4, or 6 are almost identical (data not shown).

259. As expected, the presence of sporadics (individuals who are affected by the disease for reasons unrelated to the genotype) was found to lower the magnitude of mutation component both at equilibrium and in the early generations. The factor by which the numerical results are changed can be estimated to be $[1-(a/P_T)]$, where a/P_T represents the proportion of sporadic cases among the total number of affected individuals.

(d) Validity of the assumed numbers of loci and selection coefficients

260. The theoretical formulations of King [K33] for mutation load are applicable to the FLTM discussed in this Chapter. For the directional mutation-selection balance assumed, unless the heritability is very low, the relationship between incidence of disease, the number of loci underlying the disease, and the mutation rate per locus is summarized by the expression

$$P \leq 2n\mu/s \qquad (13)$$

where P is the frequency of individuals above the threshold, n is the number of loci, μ is the mutation rate per locus, and s is the selection against those above the threshold.

261. The results of numerical calculations given in Table 30 provide some notion of the numbers of loci predicted by the model over a range of s values. It is obvious that the model can explain the current incidences of multifactorial diseases only when the mutation rates are very high (much above 10^{-6} to 10^{-5} per locus, generally assumed for human mutations) or when the selection coefficients are much smaller than the ones used in Table 30, or some combination of the above two factors. For example, for a congenital abnormality to have an incidence of the order of 10^{-3} (0.001), if one assumes a mutation rate of the order of 10^{-5}, for s = 1, 0.5, and 0.1, the numbers of loci predicted by equation (10) are: 50, 25, and 5, respectively. Therefore, when selection is very strong (for example, s = 1), a larger number of loci are needed than when selection is weak.

262. There is no *a priori* reason to assume that the mutation rates of genes underlying the multifactorial diseases are much higher than those in Mendelian diseases. If this view is correct, the selection coefficients need to be much smaller than the ones in Table 30. Progress in the clinical management of congenital abnormalities over the last few decades provides evidence for a reduction of selective pressures on previously deleterious traits, so that s values have become much smaller [C60]. The fact that most chronic multifactorial diseases have their onset in adult life, after the individuals have had children, is consistent with the inference that selection coefficients for them are also very small. The overall conclusion, therefore, is that the FLTM discussed here allows a reasonable assessment of the impact of induced mutations on the frequencies of multifactorial diseases.

(e) Robustness of predictions of the model

263. The model predicts that with a permanent increase in the mutation rate (of the magnitude of interest for risk estimation), the mutation component in the early generations is generally very much less than 2% for a broad range of heritability values above 30% (see Figure VIII). This conclusion holds for so many combinations of parameter values (truncation points, selection coefficients, number of loci, environmental variances, background mutation rates, increases in mutation rates, levels of interaction between genes, etc.) that it can be considered relatively robust, and the predictions of the model are valid within the framework of the assumptions used. On biological grounds, however, one of the assumptions of the model, namely that the mutation rate is increased for all the genes underlying a given multifactorial disease, can be contested, since this is unlikely to occur at low radiation doses. This means that the effective mutation component is likely to be far less than 2%. This point is taken up again in Chapter VIII.

(f) Application for specific multifactorial diseases

264. In evaluating the impact of an increase in mutation rate on mutation component, specific assumptions have been made about the dynamics of disease incidence before the change in mutation rate, the range of the liability scale on which selection operates, and how environmental factors act, in addition to allelic effects of the loci underlying a quantitative trait. Besides, the combination of parameter values used to examine model predictions were selected for convenience of computation (ease of convergence to equilibrium, manageable numbers of gametes, and the like). Thus, many of the assumptions and parameter values may not necessarily correspond to any of the specific multifactorial diseases discussed earlier.

265. In principle, it would be interesting to examine the impact of induced mutations on the responsiveness of each of the multifactorial diseases of concern. There has, however, been no attempt to fit the model to empirical data because such model-fitting involves (a) the estimation (reconstruction) of mutation rates and selection coefficients that should have operated in the past to result in the present-day equilibrium incidences assumed for the various multifactorial diseases and (b) the use of these estimates as a starting point to examine the consequences of an increase in mutation rate with different selection coefficients. In the light of the results obtained, the Committee, as also the Task Group, feels that such efforts would be unlikely to add any more precision to the conclusions reached and therefore did not undertake them.

F. SUMMARY

266. The concept of mutation component was first introduced in the 1972 BEIR Report [C47] as a means of assessing the responsiveness of the different classes of genetic diseases to an increase in mutation rate, and for this reason it is important within the framework of genetic risk estimation. The concept was subsequently elaborated, and the results obtained from a recent study of the problem by the ICRP Task Group are presented. Mathematical expressions are given to estimate the mutation component for autosomal dominant diseases (for which the relationship between mutation and disease is straightforward) under conditions of a permanent or a one-time increase in mutation rate and for any post-radiation generation of interest. The following points are emphasized: (a) the mutation component concept is valid only in the context of a change in mutation rate; (b) mutation component enables quantifying the responsiveness of the genetic component of the disease; and (c) mutation component is not the same as the genetic component of the disease.

267. A finite-locus threshold model was presented and its properties and application to estimate mutation component for multifactorial diseases discussed; this model incorporates the concepts of liability and threshold from the standard multifactorial threshold model and of mutation and selection from quantitative population genetic models that have been proposed to explain the dynamics of polygenic variability in populations on an evolutionary time scale.

268. While mutation component is in principle a function of mutation rates, selection, threshold value, environmental variance, recombination, and the magnitude of increase in the mutation rate, its value at the new equilibrium as well as in early generations following a mutation rate increase can be roughly predicted from the currently available information on heritability of multifactorial diseases. For a permanent small increase in mutation rate, over a broad range of heritability values (about 30%–80%) that are of interest in risk estimation, the mutation component in the first few generations following the mutation rate increase is less than 2%, often much less. Stated differently, multifactorial diseases are predicted to be far less responsive to induced mutations than Mendelian diseases, so the expected increases in disease frequencies are very small.

269. In response to the question whether estimates of the number of genes and the spontaneous mutation rates underlying multifactorial diseases and selection coefficients used in studying the properties and predictions of the model are realistic, it is concluded that the model is indeed compatible with current understanding of the numbers of genes underlying these diseases, their mutation rates, and the selection coefficients in present-day human populations.

V. CANCER PREDISPOSITION, RADIOSENSITIVITY, AND THE RISK OF RADIATION-INDUCED CANCERS

270. It has long been known that among Mendelian diseases, there is a subset in which a cancer of one type or another is the sole or frequent phenotypic manifestation of the mutant gene (e.g. [M16]). Individuals carrying such mutant genes are said to be cancer-predisposed, cancer-prone, or cancer-susceptible. Mulvihill's 1999 compilation [M23] shows that 635 (6.2%) entries in McKusick's 1998 compendium [M17] represent genes and/or disorders that predispose to or are associated with neoplasia.

271. In 1968, Cleaver [C16] discovered that in patients with xeroderma pigmentosum (XP), an autosomal recessive

disorder characterized by predisposition to skin cancer, defective DNA repair is the biochemical cause for cellular UV-hypersensitivity, which in turn leads to solar-radiation-induced skin cancers. Around the same time, Gotoff et al. [G5], Morgan et al. [M18], and Feigin et al. [F9] found that patients with ataxia-telangiectasia (A-T), another autosomal recessive disorder with immune system defects and predisposition to a number of malignancies, reacted catastrophically to conventional x-ray therapy. These discoveries set the stage for and catalyzed studies of the relationships between possible enhanced cellular radiosensitivity, the nature of biochemical defects, and cancer predisposition in Mendelian diseases known to be associated with cancer [L10, L11] (reviewed in [M19]).

272. Thus far, about 20 Mendelian disorders have been studied in relation to ionizing radiation exposure. The initial expectations engendered by the XP paradigm have not, however, been fulfilled; while fibroblasts and/or lymphocytes from patients with most of these diseases appeared to manifest increased sensitivity to ionizing radiation (primarily to cell-killing effects), in most instances the magnitude of the enhancement in sensitivity was small and not always reproducible. Only in cells derived from patients with A-T and Nijmegen breakage syndrome is there unequivocal evidence for a high sensitivity to ionizing radiation [A10, C25, F12, T13]. Until recently, for most of these disorders no clear links could be forged between gene defects, biochemical sequelae, and cancers.

273. These two themes, cancer predisposition and the potentially increased sensitivity of such predisposed individuals to ionizing-radiation-induced cancers, are now coming into sharper focus in both basic cancer biology and radiation carcinogenesis. There are at least three reasons for this:

(a) the discoveries that mutations underlying some of these disorders are in tumour-suppressor genes and/or in genes involved in the maintenance of genomic stability, cell-cycle control, and DNA repair have imparted a new dimension to thinking about cancer predisposition;
(b) a view that has been gaining currency in recent years is that in addition to the rare mutant genes that confer a high cancer risk, there may be a much larger group that confers a lesser degree of risk without obvious familial clustering [E3, E4, P11, P12]. The inference here is that such inherited predisposition may contribute significantly more to the cancer load in the population than has hitherto been assumed; and
(c) there is some evidence that cancer-predisposed individuals may also be more sensitive to ionizing-radiation-induced cancers. Should this turn out to be true, the risk of radiation-induced cancers in a population in which these radiosensitive subgroups exist may be higher than in a population that does not have these subgroups.

274. In this Chapter, some essential information on genetic predisposition to cancer and the sensitivity of cancer-prone individuals to ionizing-radiation-induced cancers is considered to provide a basis for assessing the possible increases in risk of radiation-induced cancers. Since the focus is on the relationship between cancer predisposition and the sensitivity of the predisposed individuals to ionizing-radiation-induced cancers, diseases such as xeroderma pigmentosum, Fanconi anaemia, and Bloom's syndrome, which are not relevant in the present context, are mentioned but not discussed; instead, they are considered in Annex F, "DNA repair and mutagenesis", of the UNSCEAR 2000 Report [U1]. In what follows, the terms "cancer-predisposing genes" and "familial cancer genes" are used interchangeably. The subject has recently been reviewed [C17, C18, F33, S32] and was also considered by the ICRP Task Group [I1].

A. FAMILIAL CANCER GENES

275. While most cancers are sporadic (attributable to somatic mutations), some of them (the proportion varies according to cancer type) occur in individuals who are at a higher risk than the remainder of the population because of an inherited predisposition due to specific germ-line mutations in various inherited cancer genes. Collectively, these mutations are believed to account for about 1% of cancer patients [F33].

276. So far, about 30 familial cancer genes have been cloned and for several more the chromosomal localizations are already known. Table 31 summarizes information on the cloned genes, their location, the established or inferred normal functions, and the associated cancers. As can be noted, these include tumour-suppressor genes (most of the entries), three proto-oncogenes (the *RET*, *MET*, and *CDK4*) and DNA repair genes (those responsible for A-T, Bloom's syndrome, xeroderma pigmentosum, and Fanconi anaemia).

277. It is important to note the distinction between proto-oncogenes and tumour-suppressor genes: proto-oncogenes are those genes in which variant alleles with gain-of-function (activating) mutations cause cancer, whereas tumour suppressors are genes in which both alleles with loss-of-function (inactivating) mutations cause cancer [F33]. Most of the inherited cancer syndromes show a dominant pattern of inheritance and result from inactivating mutations in tumour-suppressor genes rather than from activating mutations in proto-oncogenes. Consistent with Knudson's two-hit hypothesis [K21] (see paragraph 281), the germ-line tumour-suppressor gene defect is recessive at the somatic cell level, and the corresponding normal allele is inactivated by somatic mutations during cancer development. In contrast to mutant tumour-suppressor genes, activated proto-oncogenes act dominantly, and somatic mutation in the other allele is not necessary for cancer development. Nevertheless, whether the germ-line mutation is in a tumour-suppressor gene or in a proto-oncogene, additional somatic mutations are needed for cancer development.

278. The familial cancer genes shown in Table 31 pertain to only a small subset of the "cancer genes" thus far known. The cancer genes include, among others, the cellular oncogenes [A7, B17, B18, B19, B20] and transforming genes identified through cloning of rearrangement break points in myeloid and T-lymphoid cancers (reviewed in [E5, M56, R13, R14]). In what follows, some selected examples of familial cancer genes, as well as the postulated functions and mechanisms of cancer predisposition, are discussed, with emphasis on recent data.

1. The *RB1* gene and retinoblastoma

279. Retinoblastoma is a childhood eye tumour occurring in both familial and sporadic forms. A high proportion (40%) of children with retinoblastoma carry a germ-line mutation in one allele of the *RB1* gene; 85% of these children develop multifocal tumours affecting both eyes (bilateral tumours). The mutation predisposes them to retinoblastoma in infancy and is transmitted as an autosomal dominant. The tumours that they develop, however, have both alleles mutated. The other 60% of children with retinoblastoma have unifocal tumours and have only a 15% chance of a germ-line *RB1* mutation, although in their eye tumours both alleles are mutated [C19, H18, V8].

280. Apart from retinoblastoma and osteosarcomas associated with germ-line mutations at the *RB1* locus, *RB1* inactivation is also observed in retinoblastomas and sarcomas of purely somatic mutational origin and in several other, more common tumours (e.g. most small-cell lung carcinomas and some non-small-cell lung, bladder, and breast carcinomas) in which the gene inactivation is also presumed to derive exclusively from somatic events [H18, S37, W15].

281. On the basis of statistical analysis of clinical data, Knudson [K21] proposed, in 1971, the now classic two-hit model for the genesis of retinoblastoma; he inferred that in those individuals carrying a predisposing mutation, a single additional event (which was later proved to be at the homologous normal locus) is sufficient for tumorigenesis. In familial cases, individuals who inherit one normal and one mutant allele, the loss or inactivation of the normal allele (loss of heterozygosity or reduction to homozygosity) occurs somatically through chromosome loss, deletion, mitotic recombination, or gene conversion. The prediction that in sporadic (non-familial) cases the events inactivating both alleles should occur somatically, i.e. that the tumours should show a loss of function of both alleles, was indeed found to be true [C20, D11]. Further, the model appears to fit the data for mutations in genes involved in neurofibromatosis (*NF1* and *NF2*) and in the von-Hippel-Lindau (VHL) and Li-Fraumeni syndromes (see [E4, K17] and the references cited therein). Knudson's model thus provided a basis for (a) explaining why the *RB1* mutation is dominant in pedigrees but recessive at the cellular level; (b) conceptualizing the recessive mode of action of dominantly inherited tumour-suppressor genes in general; and (c) establishing the use of loss of heterozygosity as a hallmark in the search for other tumour-suppressor genes. For some other dominant cancer syndromes, however, the situation appears to be more complex; these are considered below in Section V.A.6.

2. The *p53* gene and Li-Fraumeni syndrome

282. Acquired (i.e. somatic) mutations in the *p53* gene are the most frequently encountered events in human malignancy, being present in about 50% of some cancers (e.g. cancers of the colon, lung, oesophagus, breast, liver, brain, and reticuloendothelial and haemopoietic tissues; reviewed in [H19, L15, V9]). Testicular tumours, neuroblastomas, and thyroid tumours are among the known exceptions in which few *p53* mutations have so far been detected [K22, P15, V10].

283. Germ-line mutations of the *p53* gene result in the Li-Fraumeni syndrome (LFS), which is a rare autosomal dominant cancer syndrome. It is characterized by the occurrence of sarcomas and multiple primary cancers in affected family members [B22, M24, M25, M26, S39]. Other cancers do occur, and of these, early-onset breast cancer is most frequently encountered. Although acquired alterations of the *p53* gene or its encoded protein are frequently identified in sporadic breast cancers, the frequency of germ-line *p53* mutations in breast cancer patients outside of families with the classical Li-Fraumeni syndrome is not known. Most of the reported germ-line mutations are missense, although occasional nonsense mutations (base pair deletions or insertions) have also been described (reviewed in [M24, M25]). There is a report on the occurrence of a 2.53 kb germ-line deletion in a Li-Fraumeni syndrome patient [P14].

3. *BRCA1* and *BRCA2* genes and breast and ovarian cancers

284. Breast cancer is an extremely common malignancy, affecting approximately 1 in 10 women during their lifetime, with more than 180,000 women having been diagnosed in the United States in 1993. Ovarian cancer is the second most common female gynaecologic malignancy, with about 22,000 new cases in the United States in 1993 [M20]. Most cases of both these cancers are sporadic. While germ-line mutations in several genes confer some susceptibility to breast cancer (e.g. *p53*, the androgen receptor gene [for male breast cancer] and the *ATM* gene), they account for only a minority of breast cancer cases. The initial linkage analysis [C21, C22, S40, W14] and subsequent cloning [M12, T12] of two genes, *BRCA1* and *BRCA2*, established the important contribution of mutations in these two genes to familial breast and ovarian cancers and gave a boost to studies in this area.

285. Early on in these studies, it was assumed (based on observations of loss of heterozygosity for markers in the 17q12–q21 region in the case of *BRCA1* and 13q12–13

region in the case of *BRCA2)* that these genes would be tumour suppressors and that mutations in them would play a role in both inherited and sporadic breast and ovarian cancers (reviewed in [B24, C27]. Analyses of tumours of patients with *BRCA1* germ-line mutations indeed showed loss of the wild-type allele [C10, F6]. This was also true of *BRCA2* [C27]. However, so far, few clearly disease-causing somatic mutations in *BRCA1* or *BRCA2* have been found in sporadic cancers, suggesting that mutations in these genes may not be critical for the development of the majority of breast and ovarian cancers [C27, F5, S48].

286. A worldwide effort is now underway to clarify the genetics of breast and ovarian cancers, and the published work already permits a number of conclusions (Table 32; reviewed in [S93]). First, it is clear that the proportion of high-risk families with breast and ovarian cancer attributable to *BRCA1* mutations varies widely in different populations. *BRCA1* mutations are by far the most common in the Russian Federation, occurring in 79% of the breast/ovarian cancer families in which the mutation-carrying families have one or two common alleles [G19]. The proportion of familial breast and ovarian cancers associated with *BRCA1* is next highest in Israel, occurring in 47% of high-risk families [L45], and Italy (29% of families). Finally between 20% and 25% of high-risk families in France, Great Britain, Hungary, and Scandinavia have *BRCA1* mutations, and in each region, *BRCA1* mutations are substantially more common than *BRCA2* mutations [A16, G10, G11, G19, J17, R39, S94]. In Iceland, however, *BRCA2* mutations are more frequent. Further, one specific mutation (999del5) explains virtually all inherited breast and ovarian cancers in Icelandic families [T30]. Inherited *BRCA1* mutations explain less than 20% of high-risk (i.e. early onset) families in Belgium, Germany, Japan, the Netherlands, and Norway [A16, H29, H43, I5, J18, P32].

287. In most populations, *BRCA1* and *BRCA2* mutations together explain 6%–10% of breast and ovarian cancer unselected for family history; in Israel, the proportion is somewhat higher (15%) [S93]. In about 30% of high-risk families, no *BRCA1* or *BRCA2* mutations have been detected. In families with male breast cancer, *BRCA2* mutations are more common than *BRCA1* mutations. The combined data from the United States studies suggest that *BRCA2* is responsible for 19% of familial male breast cancer but a considerably lower fraction of male breast cancer in the general population. Finally, in Ashkenazi Jews, two ancestral mutations, *BRCA1* 185delAG and *BRCA2* 617delT, each appear in the general population at about 1% frequency [A17].

288. For non-Jewish Caucasian women in the United Kingdom, on the basis of two population-based databases on cancer mortality in first-degree relatives of breast and ovarian cancer patients, Ford et al. [F14] and Peto et al. [P16] estimated that the *BRCA1* gene frequency is 0.0006 (95% CI: 0.0002–0.01). As stated above, the gene frequency of 0.0006 implies that about 1 in 833 women carries a mutation, and even at the upper confidence limit of 0.01, the carrier frequency would be 1 in 500 (note that to derive carrier frequency from mutant gene frequency, the following expression is used: carrier frequency of an autosomal dominant mutant genes = 2pq, where p is the mutant gene frequency and q = 1-p, the non-mutant gene frequency; see Section V.C). The calculations of Ford et al. [F14] show that the proportion of breast cancer cases in the general population due to *BRCA1* is 7.5% between ages 20 and 29 years, falling to 5.1% between 30 and 39 years, 2.2% between ages 40 and 49 years, and 1.1% between ages 50 and 70 years. In their paper, Ford et al. noted that an important unresolved issue is the genetic basis of familial breast cancer that is not explained by *BRCA1* or *BRCA2*. They estimated that the combined gene frequency of other highly penetrant genes, including *BRCA2*, might be of the order of 0.0003, (implying that about 1 in 1,600 women carries the mutation). On the basis of the prevalence estimate of 1 in 833 in non-Jewish women [F14] and 1 in 107 for the 185delAG mutation in Jewish women [S49] and the age-dependent penetrance curves for the observed risk of breast cancer in *BRCA1* families, Collins [C24] estimated that for women with breast cancer, 7.5% of non-Jewish women and 38% of Jewish women under age 30 years would be expected to have germ-line *BRCA1* mutations.

289. A number of studies have examined whether there are correlations between the position of the mutation in the *BRCA1* gene and the risk of breast or ovarian cancer (reviewed in [S48]). Truncating *BRCA1* mutations in families with a high proportion of ovarian cancers tended to be located in the 5' two thirds of the gene, while families with predominantly or exclusively breast cancer tended to have mutations in the 3' third of the gene [G10, H26]. Similarly, with BRCA2, it was found that truncating mutations in families with the highest risk of ovarian cancer relative to breast cancer were clustered in a region of approximately 3.3 kb in exon 11. Other published data on *BRCA2*-linked families support this finding [G11].

4. Hereditary colorectal cancers

290. At least 50% of the populations of Western countries develop a colorectal tumour by the age of 70, and in about 1 in 10 of these individuals progression to malignancy ensues [K41]. Epidemiological studies have suggested that at least 15% of colorectal cancers occur in dominantly inherited patterns [C65, H30]. The two best-defined familial forms are familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC). In the last six years, the genetic bases for both these syndromes have been discovered, providing new insights into their nature.

(a) Familial adenomatous polyposis (FAP)

291. FAP is an autosomal dominantly inherited disease that affects about 1 in 7,000 individuals [K41]. Patients with FAP typically develop hundreds to thousands of colorectal tumours (called adenomas or adenomatous polyps) during their second to third decade of life. Although these tumours

are not individually life-threatening, their large numbers virtually guarantee that some will progress to invasive lesions (cancers or carcinomas). Additionally, FAP patients often develop extracolonic manifestations, including retinal lesions, osteomas, desmoids of the skin, and brain tumours.

292. Patients with germ-line mutations of the *APC* gene do not necessarily develop colorectal cancer; they are simply at a much a greater risk of doing so than the general population. For tumours to form, additional genetic alterations are required. Thus, although FAP patients each develop numerous colorectal tumours, only about 1 in 10^6 colorectal epithelial stem cells gives rise to such a tumour. Studies in humans with FAP, as well as in mice with analogous mutations of the murine homolog of *APC* (*Apc*), have suggested that the rate-limiting step in tumour initiation is a somatic mutation of the wild-type *APC* allele inherited from the unaffected parent [I4, L46, L47].

293. The relationship between phenotype and genotype is complex, and FAP patients do not develop uniform clinical features despite the fact that all have mutations of the same gene and most of these mutations result in C-terminally truncated proteins. For example, retinal lesions (congenital hypertrophy of the retinal pigment epithelium, or CHRPE) are associated with truncating mutations between codons 463 and 1387 [O10]. Truncating mutations between codons 1403 and 1578 are associated with increased extracolonic manifestations such as desmoids and mandibular lesions, but patients with such mutations lack CHRPE [D28]. On the other hand, patients with identical mutations can develop dissimilar clinical features: some patients develop Gardner syndrome (mandibular osteomas and desmoid tumours) while others do not [N21].

(b) Hereditary non-polyposis colon cancer (HNPCC)

294. HNPCC is one of the most common cancer predisposition syndromes and accounts for 2%–4% of all colorectal cancers in Western countries [L48]. Sporadic cancers with microsatellite instability (see below) account for another 14% of all colorectal cancers [K41]. Assuming that HNPCC contributes only around 2% of colon cancer and using a lifetime cumulative colon cancer rate of 3% for a population in the United States [P18], a provisional estimate can be made of about 1 in 2,000 individuals carrying the genetic determinants for HNPCC. Affected individuals develop tumours of the colon, endometrium, ovary, and other organs, often before 50 years of age.

295. The search for the genes involved was catalyzed by the finding of instability of microsatellite DNA and other short repeat sequences and the accumulation of a large number of mutations scattered over the whole genome in HNPCC cells [A9, P19, T15]. Since this looked like the typical hallmark of a mutator gene at work, it did not take long before a link was forged between the HNPCC phenotype and that of mutS and MSH2 mutants in *E. coli* and *S. cervisiae*, all of which are deficient in DNA mismatch repair correction. So far, four genes involved in HNPCC have been cloned [B17, F17, L17, L18, N11, P13], and both germ-line and somatic mutations in one or the other of the above genes of HNPCC patients have been identified [F28, H27, L19, M28, V18] and their involvement in DNA mismatch repair demonstrated [P20, P21, R15] (reviewed in [E14, L48]).

5. Ataxia-telangiectasia

296. Ataxia-telangiectasia is a multisystem disorder. Its clinical attributes include immune deficiency and a high incidence of neoplasia, especially leukaemia and lymphoma. The clinical, cellular, and genetic features of A-T and the response of A-T cells to ionizing radiation have been extensively reviewed [B27, H28, J7, S52, T16, T17, T18]. The overall incidence of A-T observed in the United States is about 1 in 300,000, with the highest observed incidence within the United States being in Michigan (1 in 90,000) [S53]. For the United Kingdom, the observed incidence is 1 in 100,000 [P22]. On the basis of pedigree analysis, in which the gene frequency is estimated from the proportion of affected close relatives of homozygous probands, Swift et al. [S53] estimated the most likely gene frequency to be 0.007 on the assumption that A-T is a single homogeneous genetic syndrome. This would correspond to a heterozygote frequency of 1.4%. The A-T gene has been cloned (designated as *ATM*) [B28, S54, S55] and was found to be mutated in all A-T patients, despite the fact that cellular complementation analyses had suggested the existence of at least six complementation groups.

297. Early retrospective as well as prospective studies have reported that A-T heterozygotes are at a higher risk for several cancers, especially female breast cancer [S56, S57]. The estimated relative risk for female breast cancer was 6.8 in the retrospective [S56] and 5.1 in the prospective [S57] study. From these analyses, Swift et al. [S57] estimated that perhaps as many as 9% of all breast cancer cases in the United States occur in A-T heterozygotes with a propensity for early onset. In 1994, Easton [E8] addressed the question of breast and other cancers in A-T heterozygotes and the contribution of A-T mutations to familial breast cancer. Published data on the birth prevalences of A-T and cancers in A-T heterozygotes, including an updating of cancer mortality in the 1988 study in the United Kingdom [P22], were used in the analysis. The main findings were that (a) the contribution of A-T mutations to familial breast cancers is about 8% for those below 40 years and about 2% for those between 40 and 59 years, and since only a small proportion of breast cancers is familial, the contribution of A-T mutations to familial breast cancer is therefore very small, and (b) there is no consistent evidence for increased risk of any other cancer in A-T heterozygotes.

298. Three papers published in 1996–1997 presented apparently discrepant results on the risk of breast cancer in A-T female heterozygotes. In two of these [F29, V11], there was no evidence for the involvement of mutations in

the *A-T* gene. In contrast, the work of Athma et al. [A12] showed that A-T heterozygotes may be at an increased risk of breast cancer. The authors followed the identified *ATM* mutation through the families of those with clinically recognized A-T; analysis of the markers flanking the *A-T* gene allowed the authors to identify precisely which female relatives with breast cancer carry an *ATM* mutation. On the basis of the genetic relationship between each relative and the proband, the *a priori* probability that these should share the *ATM* mutation was calculated. This led to an estimated relative risk of 3.8 (95% CI: 1.7–8.4) compared with non-carriers.

299. The potential reasons for the apparent discrepancy between the findings of Athma et al. [A12] and of Fitz Gerald et al. [F29] were discussed by Bishop and Hopper [B49]. They noted that (a) in the work of FitzGerald et al., the conclusions are based on finding four A-T heterozygotes in a total of 603 women, giving a confidence interval ranging from no increase in risk to a sevenfold increase in risk, and are, accordingly, not incompatible with the results of Athma et al. [A12]); (b) because the confidence interval in the Athma et al. study does not include 1.0, it does show significant evidence of an increase in risk; and (c) when relying on such small number of mutation carriers as the FitzGerald study does or on such a small number of breast cancers as in the Athma et al. study, chance is a big factor and the precision of the estimate suffers (for more details, see Annex F, "DNA repair and mutagenesis", of the UNSCEAR 2000 Report [U1]).

6. Functions of familial cancer genes and mechanisms of cancer predisposition

300. As noted in Table 31, the proteins encoded by inherited cancer genes are implicated in a diverse array of cellular processes, including proliferation, differentiation, apoptosis, and maintenance of genomic integrity. These proteins appear to function as transmembrane receptors (MET, PTH, and RET), cytoplasmic regulatory or structural proteins (NF1, NF2, APC, and PTEN), transcription factors (p53, WT1, RB1, and VHL), cell-cycle factors (CDK4 and p16), or DNA damage repair pathway proteins (MSH2, MLH1, PMS2, A-TM, BRCA1, BRCA2, FACC, FACA, XPA, XPB, XPD, and BLM). In several cancer syndromes for which genetic heterogeneity has been found, such as HNPCC, inherited melanoma, and breast cancer, all of the implicated genes appear to function in a conserved pathway. For instance, inactivation of *MSH2, MLH1*, and *PMS2* in patients with HNPCC alters the fidelity of DNA mismatch recognition and repair. Mutations in *p16* and *CDK4* in individuals with inherited predisposition to melanoma presumably alter cell-cycle control, including phosphorylation of p105-RB and entry into the DNA synthesis (S) phase of the cell cycle.

301. Recent studies of the BRCA1 and BRCA2 proteins suggest that both interact directly or indirectly with homologues of the yeast Rad51 protein, which functions in the repair of double-strand breaks in the DNA [S96, S97]. In addition to showing that BRCA2 binds to Rad51, Sharan et al. [S97] reported that *Brca2*-knockout mice show early embryonic lethality and hypersensitivity to ionizing radiation, similar to that observed in *Rad51*-knockout mice [T14]. *Brca1*-knockout mice also show embryonic lethality [H31]. BRCA1 and Rad51 proteins also show striking co-localization along synaptenemal complexes (junctions between meiotic chromosomes, necessary for homologous recombination) [S96].

302. The findings that both *Brca2*- and *Rad51*-knockout mice show hypersensitivity to ionizing radiation in embryonic and trophoblast cells and the known role of *Rad51* in DNA double-strand break repair lend credence to the view that disruption of this *BRCA/Rad51* pathway might lead to genetic instability. Although the nature of this putative instability is not clear, studies of *Rad51* provide a clue: mouse cells that are deficient for *Rad51* show frequent abnormal mitoses with a markedly reduced chromosome number, suggesting that alterations of this pathway might lead to gross chromosomal changes [L50]. There are now data that show that *BRCA2* gene product functionally interacts with the p53 tumour suppressor and the Rad51 proteins, suggesting that *BRCA2* participates in maintaining genomic integrity [M11].

303. Kinzler and Vogelstein [K26, K41] provided a stimulating conceptual framework for envisioning cancer predisposition by dividing the underlying genes into two groups, gatekeepers and caretakers, and showing how the two have different attributes, although inherited mutations in either group of genes predispose a person to neoplasia. The principal lines of their reasoning and conclusions are the following. Gatekeepers are genes that directly regulate the growth of tumours by inhibiting growth or promoting death. Each cell type has only one (or a few) gatekeepers, and inactivation of a given gatekeeper leads to a very specific distribution of cancer. For example, inherited mutations of the *RB1, VHL, NF1,* and *APC* genes lead to tumours of the retina, kidney, Schwann cells, and colon, respectively. Inactivation of these genes is rate-limiting for the initiation of a tumour, and both the maternal and paternal copies must be altered for tumour development. Cancer-predisposed individuals inherit one copy of the mutant gatekeeper gene, and so they need only one additional (somatic) mutation to initiate neoplasia. Sporadic tumours arise in those who do not have a germ-line mutation when both copies of the relevant gatekeeper gene become mutated somatically. Because the probability of acquiring a single somatic mutation is far greater than that of acquiring two such mutations, individuals with a hereditary mutation of a gatekeeper gene are at a much greater risk ($>10^3$) of developing tumours than the general population. This is the essence of Knudson's hypothesis [K21], discussed earlier in this Chapter.

304. In contrast, inactivation of a caretaker gene does not promote tumour initiation directly. Rather, neoplasia occur indirectly; inactivation leads to genetic instabilities, which

result in increased mutation of all genes, including gatekeepers. Once such a tumour is initiated by inactivation of a gatekeeper gene, it may progress rapidly, owing to an accelerated rate of mutation in other genes that directly control cell proliferation or death.

305. In dominantly inherited cancer predisposition syndromes of the caretaker type, the individual inherits a single mutant caretaker gene, and three subsequent somatic mutations are usually required to initiate cancer: mutation of the normal caretaker allele inherited from the unaffected parent, followed by mutation of both alleles of a gatekeeper gene. Because three mutations are needed, the risk of cancer in affected families is generally only 5- to 50-fold greater than in the general population and much less than the risk in families with inherited defects in a gatekeeper gene [K26]. Further, mutations in caretaker genes would not be expected to lead to sporadic cancer very often, as four mutations would be required (two caretaker alleles plus two gatekeeper alleles).

306. Known caretaker genes include the nucleotide-excision-repair genes (in XP and HNPCC). To this list can be added *BRCA1* and *BRCA2*. Consistent with the reasoning mentioned above, mutations in *BRCA1* or *BRCA2* are rarely found in sporadic cancers. The data of Scully et al. [S96] and of Sharan et al. [S97] relating *BRCA1* and *BRCA2* to *Rad51* provide a biochemical explanation that supports the hypothesis. In the case of A-T, the predicted gene product is a protein with considerable homology to a family of signal transduction molecules encoded by a gene family known as the phosphatidylinositol-3-kinases involved in cell-cycle control and response to DNA damage (reviewed in [J7]). This family of transducing proteins is novel in that it responds to DNA damage signals originating in the cell nucleus rather than the cell membrane and transmits these signals downstream to enzyme pathways associated with the maintenance of genomic stability and cell viability, including protection against ionizing radiation.

7. Summary

307. The material discussed in this Section documents the existence of a subset of genes in the human genome at which germinal mutations predispose the carriers to cancers. These familial cancer genes include the tumour-suppressor genes, DNA replication/repair genes, and at least three proto-oncogenes. Mutations in most of these genes have high penetrance, i.e. they are certain to cause cancer. About 30 of these genes have been cloned.

308. It has been postulated that in addition to these mutant genes, there may be a much larger group of genes in which mutations cause a lower degree of cancer predisposition and which are therefore difficult to detect. More data are needed on both the numbers of such cancer-predisposing genes and the extent of cancer predisposition to reliably assess the contribution of germinal mutations to the background load of cancers in the population.

309. The transmission patterns of tumour-suppressor genes are Mendelian dominant, although at the cellular level they are recessive, i.e. cancers arise when both copies of the gene are mutated. While for some cancers caused by tumour-suppressor gene mutations (e.g. *RB1, NF1, NF2,* and *VHL*) the loss-of- heterozygosity model (the two-hit model) proposed by Knudson is adequate to explain the resultant cancers; for most adult cancers that result from the accumulation of additional mutations in other genes, the two-hit model does not fully describe the genetic changes that occur.

310. Germinal mutations in the *p53* gene cause a rare cancer syndrome, the Li-Fraumeni syndrome. However, the relevance of *p53* gene mutations in the context of human cancers goes far beyond the Li-Fraumeni syndrome; *p53* mutations are present in at least 50% of some human cancers.

311. As a result of efforts around the world, considerable progress has been made in studies of the genetics of breast and ovarian cancers. Germinal mutations in the *BRCA1* and *BRCA2* genes account for between 6% and 10% of breast and ovarian cancers unselected for family history. In Israel, this proportion is higher, about 15%. The proportion of high-risk families with breast or ovarian cancer varies widely between different populations (the range is from about 10% in Japan to 79% in Russia for *BRCA1*-linked families and 9%–64% for *BRCA2*-linked families). In virtually all populations, *BRCA1* mutations are much more common than *BRCA2* mutations. In Iceland, however, *BRCA2* mutations are more common, and one specific mutation explains virtually all inherited breast and ovarian cancers in Icelandic families. In families with male breast cancer, *BRCA2* mutations are more common than *BRCA1* mutations.

312. The best defined forms of familial colorectal cancers are familial adenomatous polyposis and hereditary non-polyposis colon cancer. During the past few years, the genetic bases of these forms have been delineated. For HNPCC, at least four genes in which mutations predispose to hereditary non-polyposis colon cancer are now known.

313. Ataxia-telangiectasia, an autosomal recessive, multisystem disorder that was originally thought on the basis of cellular complementation tests to be due to mutations in at least six genes, is now known to be due to mutations in one gene. A-T patients (i.e. homozygotes for the *ATM* mutations) are afflicted by a variety of neoplasms, especially leukaemia and lymphoma. A-T heterozygotes also develop breast cancers, but the proportion of familial breast cancers attributable to *ATM* mutations appears small. The question of an increase in the risk of breast cancers in A-T heterozygotes is not settled.

314. Evidence from cellular and biochemical studies supports the view that the familial cancer genes are involved in the maintenance of genomic integrity (DNA

repair, replication, cell-cycle control, and apoptosis) in a system of interconnected and coordinated network pathways. Mutations in these genes are therefore expected to liberate the cells from the constraints imposed by these genes, causing uncoordinated growth characteristic of cancer. The mechanisms appear to be different, depending on whether the inactivation is in a gatekeeper gene (one that directly regulates the growth of tumours by inhibiting growth or promoting cell death, e.g. the tumour-suppressor genes such as *RB1, VHL,* and *APC* genes) or in a caretaker gene (inactivation of this type of gene does not directly promote tumour initiation but results in genetic instabilities and increased mutations in many genes, including gatekeeper genes, e.g. *XP* genes and mismatch repair genes).

B. RADIATION SENSITIVITY OF CANCER-PREDISPOSED INDIVIDUALS

315. As discussed above, one effect of spontaneous mutations in genes intimately involved in the maintenance of genomic integrity is the liberation of cells from normal cellular constraints, resulting in the uncontrolled proliferation characteristic of cancer; such mutations also impart genomic instability. Essentially the same lines of reasoning can be extended to radiosensitivity by postulating that heterozygosity for inherited germ-line mutations in these genes may render the genome more sensitive/ vulnerable to radiation-induced cancers by exacerbating the already existing derangement of the cell-cycle machinery and may drive the cells towards overt cancer. Cancer-predisposed individuals may therefore be at a higher risk for radiation-induced cancers. The human and animal data that bear on this point are discussed in the following paragraphs (see also [I1, S32]).

1. Human epidemiological and molecular studies

316. Human epidemiological data on the risk of radiation-induced cancers in cancer-predisposed individuals or on radiation-induced mutations in cancer-predisposing genes are limited at present. However, the resurgence of interest in this question and on-going studies (retrospective examination of cancer data from this perspective and prospective inquiries, including molecular analysis of mutations in cancers in human populations exposed to radiation) are likely to provide useful information.

317. Data that provide some evidence for the enhanced sensitivity of cancer-predisposed individuals to radiation-induced cancers and for a reduction in tumour latencies are summarized in Table 33. Note that not all the material presented in this table pertains to cancers, and a sizeable proportion of the studies did not report significant differences; the estimated relative risks have wide confidence limits. The evidence presented is therefore suggestive but by no means compelling. It does, however, allow identifying situations that may merit further study.

318. In 1991, Swift et al. [S57] (Table 33, item 1) reported that the blood relatives of A-T patients (female A-T heterozygotes) have about five times the breast cancer risk of the general population, that 20% of heterozygotes have been exposed to diagnostic or occupational exposures of $\leq$10 mGy, and that those exposed have about six times the breast cancer risk of the non-exposed remainder. These data have been criticized on a variety of grounds [B33, H32, K29, L27] (see also Annex F, "DNA repair and mutagenesis", of the UNSCEAR 2000 Report [U1]). The estimates provided by Swift et al. [S57] imply relative risks for the non-exposed and exposed heterozygotes of 2.6 and 15.6 times, respectively, the risk of the general population. The ratio of excess relative risks in the two groups, 1.6 to 14.1, is 8.8, which seems very unlikely considering that the contribution of mutations in the *A-T* gene to familial breast cancers is quite small.

319. The high relative risk for early-onset breast cancers in survivors of the atomic bombings [L28, T26] is consistent with the notion that a putative breast-cancer-predisposing gene mutation may underlie the sensitivity of the genome to radiation-induced cancers. As Land et al. [L28] noted, it was possible to detect this because for those women exposed before age 20 years and diagnosed before age 35 years, the rates for both baseline and radiation-related breast cancer are normally low.

320. The apparent increase in the risk of radiation-induced breast cancer in the contralateral breast of women who received radiotherapy before the age of 45 years [B34] likewise suggests that mutations at a putative gene may affect the sensitivity of the breast to radiation-induced cancers.

321. A susceptibility gene or genes for Hodgkin's disease have not yet been identified, and an increased risk of breast cancer in radiotherapeutically treated Hodgkin's disease survivors is not well established. The study of Hancock et al. [H33], however, suggested high breast cancer risks, again for those irradiated when young. Because of this, this study has been included in Table 33. The retinoblastoma studies [D13, E11, R18, S30] indicate that irradiated "genetic" cases have a higher risk of second neoplasms than non-irradiated ones. This finding is highly suggestive of the possibility that individuals predisposed to retinoblastoma due to inherited *RB1* mutation are at a higher risk for radiation-induced second tumours. Further, the possible reduction in latency periods for second primary cancers [S30] in irradiated retinoblastoma cases is consistent with expectations discussed earlier.

322. An increase in nevoid basal-cell carcinoma syndrome in radiotherapeutically treated medulloblastoma cases [S30, S31] has been noted. These data, like data from some of the retinoblastoma studies, also suggest a reduction in latency period in the irradiated individuals. The evidence in survivors of the atomic bombings [S61] for a high excess relative risk of stomach cancer mortality for those who were exposed at less than 10 years of age may also suggest the existence of a cancer-predisposing radiosensitive gene mutation for this type of cancer.

2. Mouse models

323. In the past decade, advances in molecular and cell biology, gene targeting, and embryonic stem-cell technologies have led to the creation of mouse models that have germ-line mutations of various tumour-suppressor genes. These models permit systematic analyses of their functions within the mammalian organism and are potentially important models for familial cancer syndromes in humans. They have demonstrated the importance of the function of these genes in embryonic development and tumorigenesis and have also revealed that not all these models emulate their corresponding human syndromes [J4]. The subject has been recently reviewed [V19]. Table 34 summarizes the 10 mouse models currently available and their attributes. Only a limited number of radiation studies have been carried out, however.

(a) Studies with mice heterozygous for a *p53* mutation or lacking the *p53* gene

324. In experiments involving 4 Gy whole-body gamma irradiation of 7–12-week-old mice that were wild-type or heterozygotes for a *p53* mutation, Kemp et al. [K25] found that (a) none of the irradiated wild-type mice developed tumours; (b) unirradiated heterozygous mice developed lymphomas and sarcomas at a median age of more than 70 weeks, whereas irradiated heterozygotes developed tumours (also lymphomas and sarcomas, but with fewer osteosarcomas and more lymphomas) at a median age of about 40 weeks; and (c) 20 of 23 (96%) of the tumours from irradiated heterozygotes showed loss of the wild-type *p53* allele (detected through Southern analysis), suggesting that the *p53* gene itself may be a target for radiation-induced loss of the wild-type allele. No firm conclusions can as yet be drawn, however, because the sample sizes were small and the period of observation was not long enough, especially for irradiated wild-type mice.

325. In untreated control heterozygotes, 5 of 7 tumours (71%) showed loss of the wild-type allele. In other published studies with untreated *p53* heterozygotes cited by the authors, the frequencies of loss of the wild-type allele in tumours were also lower than in the radiation experiment mentioned above [18 of 33 tumours (55%), 5 of 9 tumours (56%), and 9 of 12 tumours (75%)].

326. Another important finding in the study of Kemp et al. is that in *p53* heterozygotes, 14 of 17 (82%) radiation-induced tumours showed duplication of the mutant allele, whereas this was true of only 1 in 5 in spontaneous tumours. The authors suggested that mitotic recombination, non-disjunction with reduplication, or gene conversion could explain the results in the majority of radiation-induced tumours; in spontaneous tumours, the pattern of loss of heterozygosity with no duplication was consistent with deletion of the wild-type allele.

327. In the same study, but involving seven-week-old *p53* null mice and 4 Gy of irradiation, Kemp et al. [K25] noted that there was no decrease in tumour latency, presumably because of the already very rapid rate of spontaneous tumour development in these mice. However, with six-day-old mice irradiated with 4 Gy and two-day-old mice with 1 Gy, there was a decrease in tumour latency from a median of 21 weeks of age in controls to 14–15 weeks of age in the null mice. Additionally, in *p53* null mice, multiple tumours (23 tumours in 14 mice) were observed in the 4 Gy group but in only 1 mouse in the 1 Gy group.

328. In follow-up studies, Bouffler et al. [B48] compared the cytogenetic response of wild-type, *p53* heterozygous, and *p53* null mice by analysing stable structural and numerical chromosomal aberrations in bone marrow cell populations sampled 29–30 days after 3 Gy irradiation. Additionally, chromatid damage repair, sister chromatid exchanges (SCEs), and mitotic delay were studied in spleen cells *in vitro*. The important findings were the following: (a) in *p53* heterozygous and *p53* null mice, the spontaneous frequencies of stable structural and numerical aberrations were about 20-fold higher than in the wild-type; (b) there was no excessive induction of stable structural chromosomal aberrations *in vivo*, and *in vitro* studies provided no evidence of a significant effect of p53 deficiency with respect to chromatid damage repair or SCE induction after irradiation; and (c) in contrast, *p53*-deficient genotypes were 10- to 15-fold more sensitive to the induction of numerical chromosomal changes (chromosome gains >> losses) and in the *in vitro* studies, there was a profound defect in the operation of post-radiation mitotic delay in spleen cells from *p53*-deficient mice, implying a failure of a G_2/M cell-cycle checkpoint for repair. The authors concluded that this checkpoint failure might underlie increased hyperploidy, which subsequently provided the drive for the increased tumorigenic radiosensitivity of *p53*-deficient mice.

(b) Studies with *Brca2* mutation in mice

329. In the work of Sharan et al. [S97], blastocysts were isolated at day 3.5 from crosses of *Brca2*/+ females mated to *Brca2*/+ males and exposed to 4 Gy from acute gamma-radiation and then cultured for seven days. Survival and outgrowth of the inner cell mass and trophoblast cell numbers were compared in homozygous mutant, heterozygotes, and normal embryos. In the unirradiated series, the values for the above were the same for the mutant and control embryos; in the irradiated series, the inner cell mass outgrowth was marginally reduced in wild-type and heterozygous embryos and totally ablated in the homozygotes. Additionally, whereas gamma radiation reduced the number of trophoblast cells in wild-type and heterozygous embryos slightly, in homozygous embryos this effect was more pronounced (reduction to about one half of that seen in the cells derived from the wild-type and heterozygous embryos). These findings, which are similar to those obtained with *Rad51* mouse mutants, have been interpreted to mean that the cell proliferation defect of homozygotes is probably secondary to a response to a defect in DNA repair.

3. The rat model for the human tuberous sclerosis-2

330. Hereditary renal carcinoma in the rat, an autosomal dominant cancer, was originally described by Eker and Mossige [E18]. At the histological level, these carcinomas develop through multiple stages from early pre-neoplastic lesions, which begin to appear at 2–3 months of age, to adenomas in virtually all heterozygotes by the age of one year. Homozygotes die in the fetal stage. Kobayashi et al. [K27] and Hino et al. [H15] found that the Eker mutation was in fact a germ-line insertion of an approximately 5 kb DNA fragment in the tuberous sclerosis *(Tsc2)* gene located on rat chromosome 10p. Although the overall phenotypic manifestations in human tuberous sclerosis patients differ from that of *Tsc2* mutation in rats in many respects, they share a strong predisposition to renal cancers.

331. Hino et al. [H16] irradiated male and female rats carrying the Eker mutation with gamma-ray doses of 3, 6, and 9 Gy to the renal region. The animals were killed at 10–11 months, and the incidence of kidney tumours was assessed in serial sections. It was found that in both sexes, the mean number of tumours per animal, calculated according to a linear regression analysis, increased with dose. In males, for example, it was 59 at 9 Gy vs. 4.4 in controls; in females, it was 30 vs. 2.8, which is some 11 to 13-fold higher. Taking into account the limitations of this study (the heterozygous and normal animals could not be identified before irradiation and the irradiated animals were therefore made up of equal numbers of +/+ and +/– animals; the mutant homozygotes (–/–) die *in utero*; and the radiation effects seen were in the heterozygotes and normal animals), the ICRP Task Group [I1] made a preliminary estimate that the tumorigenic radiosensitivity of the +/– animals may be 170 times that of +/+ animals. It cautioned that since +/– animals develop these tumours at an earlier age than +/+ animals, the above estimate may overestimate the true tumorigenic radiosensitivity.

4. Summary

332. The modest amount of human epidemiological data that are available are consistent with the possibility that heterozygotes for mutations in familial cancer genes may exhibit enhanced tumorigenic radiosensitivity, although no firm conclusions can as yet be drawn about the magnitude of such an effect. The earlier claims for a higher risk of radiation-induced breast cancers in women heterozygous for the *ATM* mutation no longer appear tenable.

333. Mice heterozygous for the *p53* mutations are susceptible to radiation-induced tumours, and these tumours develop with shorter latency periods. The limited data currently available from these studies suggest that the *p53* gene itself may be a target for radiation-induced mutations. New data on *Brca2* mutations in mice suggest that cells derived from homozygotes are very sensitive to radiation-induced cell-killing effects.

334. Data from the Eker rat model for mutations in the human tuberous sclerosis gene (TSC2) show that heterozygotes may be more sensitive than the wild type for the induction of renal tumours.

C. COMPUTATIONAL MODELLING TO ESTIMATE RADIATION RISK IN A HETEROGENEOUS POPULATION

335. The material discussed in the preceding Sections of this Chapter substantiates the premise that individuals with a genetic predisposition to cancer as a result of germinal mutations exist in human populations and that they may also be sensitive to cancers induced by radiation. It is possible, using principles of population genetics, to estimate the amount by which the radiation risks in such a heterogeneous population will be increased compared to a population that does not contain such subgroups.

336. The basic characteristic of gene frequency in large populations is its stability over time in the absence of differences in viability or fertility among the genotypes at the locus under consideration. In the further absence of assortative mating, i.e. the tendency of like to mate with like, migration, mutation, and geographical subdivision of the population, genotypic frequencies also remain constant from generation to generation. This is reflected, in the case of genetic diseases, as stable prevalences of genetic diseases in the population. These properties are summarized in the Hardy-Weinberg equilibrium concept, which is one of the fundamental concepts in population genetics when large random-mating populations are considered.

1. Numerical illustration for an irradiated population

337. A Mendelian one-locus, two-allele dominant model of cancer predisposition and radiosensitivity can be illustrated by the following numerical example. Consider a single autosomal locus at which there are two alleles, the normal or wild-type allele, a, and the dominant cancer-predisposing mutant allele, A, in a population under Hardy-Weinberg equilibrium. The individuals in the population will have one of the following three genotypes: AA, Aa, or aa. If the frequency of the mutant allele, A, is 0.01, then the frequency of the non-mutant allele, a, is 0.99 and the distribution of genotypes in a population of 10,000 is 1(AA), 198(Aa), and 9,801(aa).

338. ***Situation 1.*** Assume that none of the genotypes is cancer-predisposed and that the background cancer risk is 0.001 for all genotypes. In 10,000 individuals, one would therefore expect 10 cancers, most of them in aa individuals.

339. ***Situation 2.*** Assume now that the population receives radiation at a dose that confers a risk of 0.01. The number of cancers due to radiation exposure will be 100. Most of the induced cancers will again occur in aa individuals because of their high frequency. So, the total number of cancers in this population is 100 + 10 = 110.

340. ***Situation 3.*** Assume that the A allele confers cancer susceptibility and that AA and Aa individuals are cancer-predisposed ("susceptibles") and to the same extent and that aa individuals are not ("non-susceptibles"). Assume further that the background cancer risk for aa individuals is 0.001 (as in situation 1) and that the risk for AA and Aa individuals is 0.1, i.e. the last two genotypes have a 100-fold higher "normal" cancer risk than aa individuals. In this situation, the distribution of the expected number of cancers will be as follows: for AA: $1 \times 0.1 = 0.1$; for Aa: $198 \times 0.1 = 19.8$; for aa: $9{,}801 \times 0.001 = 9.8$. The total is about 30. Note that a large proportion of the cancers (~20/30) occur in the susceptible individuals.

341. ***Situation 4.*** Assume that the above population is irradiated and that the dose is such that it confers a risk of 0.01 to aa but that AA and Aa individuals respond with a risk of 0.5 (50-fold higher). The expected number of radiation-induced cancers will be as follows: for AA, $1 \times 0.5 = 0.5$; for Aa, $198 \times 0.5 = 99$; for aa, $9{,}801 \times 0.01 = 98$. The total is about 198. The total number of cancers is $198 + 30 = 228$ in 10,000 individuals.

342. It is clear that in a homogeneous population (no cancer-predisposing genotypes present), the total number of cancers is 110, i.e. 10 background and 100 induced. In a heterogeneous population, with 199/10,000, or roughly 2%, of individuals cancer-prone (100x) and more radiosensitive (50x) and assuming that all these cancers are due to mutations at this locus, the radiation cancer risk in this population is greater by a factor of about 2 (i.e. 228/110) than in a homogeneous population.

343. For the sake of illustration, no account was taken in the above example of the fact that in most cancers (e.g. breast and colorectal cancers) the proportion attributable to allelic variation at a single locus is small or of the fact that several concomitant variables such as age and radiation dose influence the risk. Models taking into account the above factors and a number of others (e.g. different mutant gene frequencies, strengths of predisposition, radiosensitivity differentials, proportions of cancers attributable to mutant genes at given loci) have been published [C26, C40, C41]. While the derivations of expressions for the different epidemiological measures of risk need not be of concern here, some of the important assumptions of the model, the general strategies, and main conclusions are relevant and are discussed below.

2. Results of computational modelling

344. ***Assumptions.*** The model developed by Chakraborty and Sankaranarayanan [C40] and Chakraborty et al. [C41] is a one-locus, two-allele autosomal dominant model of cancer predisposition and radiosensitivity. The model in the latter paper is an improved version and is considered below. Its principal assumptions are the following:

(a) the dominant allele A confers cancer predisposition and a is the normal allele;
(b) the predisposed genotypes, i.e. the homozygotes (AA) and heterozygotes (Aa), also have enhanced sensitivity to radiation-induced cancers compared with the non-predisposed genotype (aa);
(c) only a proportion of cancers (π) of a given type are due to the locus under study;
(d) the genotype frequencies conform to Hardy-Weinberg expectations; and
(e) differential radiosensitivity is mediated through the same predisposing locus.

345. Penetrance (i.e. the fraction of mutation carriers who manifest a specific phenotype associated with that mutation) is represented by the parameter θ. When θ has the value 1, there is complete penetrance, meaning all individuals having the mutant gene manifest the phenotype; when it is less than 1, the mutant gene is incompletely penetrant.

346. To incorporate dose dependence of radiosensitivity differentials in the model, it is assumed that in the non-predisposed individuals (aa), a radiation dose D increases cancer risk by a factor $(1 + \beta D)$ in comparison with the background risk (R_0). In the predisposed genotypes (the AA homozygotes and a portion of the Aa heterozygotes), the same dose of radiation increases the cancer risk by a factor $(1 + \beta D R_i)$.

347. Mathematical expressions were derived incorporating all the above to provide estimates of total risk, $R_T(D)$, in the irradiated population at dose D; relative risk, RR(D), i.e. the risk of cancer in cancer-predisposed radiosensitive genotypes compared with the risk in non-predisposed genotypes; attributable fraction, AF(D), i.e. the fraction of cancers attributable to the predisposed genotypes; and the fraction due to radiosensitivity differentials alone, $\alpha(D)$.

348. ***Choice of parameter values to study model predictions.*** The parameter values chosen come from data on breast cancers discussed in Chapter V of this Annex and from data on breast cancers in the survivors of the atomic bombings [T20]. They are as follows:

(a) mutant gene frequency, p, in non-Jewish Caucasian women = 0.0006 [F14, P16];
(b) proportion of breast cancers, π, attributable to *BRCA1* mutations = 1.7% for those diagnosed before age 70 years and 7.5% for those diagnosed before age 30 years;
(c) mutant gene frequency, p, Ashkenazi Jewish women = 0.0047 [S49];
(d) proportion of breast cancers, π, due to *BRCA1* mutations diagnosed before age 30 years in Ashkenazi Jewish women = 0.38 [C24];
(e) penetrance, $\theta = 0.50$, 0.75, and 1.00;
(f) slope of the dose-effect curve, $\beta = 2.0\ Gy^{-1}$ [T26];
(g) range of predisposition strength, R_p (arbitrary) = 10 to 1,000;
(h) range of radiosensitivity differentials for the predisposed genotypes, R_i (arbitrary) = 10 to 100; and
(i) radiation doses (arbitrary) = 0.5, 1.0, and 2.0 Gy.

349. ***Results.*** The results obtained for the different combinations of parameter values for breast cancer are illustrated in Table 35. Note that RR quantifies the risk of radiation-induced cancer in a population in the presence of predisposition and radiosensitivity differentials relative to that risk in the absence of both these factors. The results shown in the first two parts of Table 35 may be deemed applicable to radiation-induced breast cancers in non-Jewish Caucasian women ($p = 0.0006$ and $\pi = 1.7\%$ for women under 70 years of age and 7.5% for those under 30 years of age).

350. As can be seen from Table 35, RR values are detectably different from 1 only when R_i and R_p are both very high (e.g. at $R_i = 100$ and $R_p = 1{,}000$, for 100% penetrance RR becomes 2.64 at 2.0 Gy). Similarly, the proportion of excess cancers in the irradiated population that is due to predisposition and radiosensitivity, also called the attributable fraction (AF), is also low unless both R_i and R_p are high. However, most of these excess cancers are contributed by the radiosensitivity differential alone (i.e. α is quite high even when RR is close to 1 and AF is close to zero). With an increase in π, all risk measures become more pronounced for the same levels of R_i and R_p.

351. Other general observations that can be made from the first two parts of Table 35 are the following: (a) an increase in penetrance, θ, causes an increase in RR and AF; (b) at all levels of θ and combinations of R_i and R_p values, the RR and AF increase with radiation dose, but the dose dependence of RR, AF, and α diminishes at higher doses; (c) incomplete penetrance dilutes the effect; and (d) incomplete penetrance and dose dependence of radiosensitivity differential do not change the main conclusion, namely that RR, AF, and α increase with an increase in mutant gene frequency and/or an increase in the proportion, π, of cancers due to the predisposing allele.

352. The third part of Table 35, which may be applicable to radiation-induced breast cancers in Ashkenazi Jewish women for cancers before age 30 years, shows that when both p and π are high, the risks become appreciably higher at lower values of R_i and R_p. Even in such high-risk situations a larger value of R_p (rather than a larger one of R_i) contributes to the elevation of risk in a more pronounced manner.

3. Summary

353. Genetic predisposition to cancer and enhanced radiosensitivity of the susceptible genomes have an impact on radiation cancer risks.

354. A Mendelian one-locus, two-allele model of cancer predisposition and radiosensitivity is discussed and used to assess the impact of cancer predisposition and radiosensitivity differentials on cancer risks in an irradiated population. The model predictions are illustrated using breast cancers in non-Jewish Caucasian and Ashkenazi Jewish women as examples and ranges of possible values for the strength of predisposition and radiosensitivity differentials.

355. Comparisons of radiation cancer risks are made between a heterogeneous population, i.e. one that consists of cancer-predisposed and non-predisposed individuals and where the predisposed individuals are assumed to be more sensitive to radiation-induced cancers, and a homogeneous population, i.e. one in which there are no cancer-predisposed subgroups and all individuals are equally sensitive to radiation-induced cancers. It is shown that after radiation exposure the ratio of risks between the above two populations, the relative risks, increases with increasing dose, but the dose dependence of the relative risks diminishes at higher doses.

356. Likewise, the attributable risk, which is the proportion of cancers due to both increased cancer susceptibility and increased radiosensitivity, and the proportion of attributable risk due to radiosensitivity differentials alone increase with an increase in dose, and the dose dependence of each measurement also diminishes at higher doses. However, when the proportion of cancers due to the susceptible genotypes is small (<10%), as is likely to be the case for breast cancers in non-Ashkenazi women, the increase in the relative risk and attributable risk are marked only when there are very large increases in cancer susceptibility (>1,000-fold) and radiosensitivity (>100-fold) in the susceptible group.

357. When the proportion of cancers due to the susceptible genotypes is appreciable ($\geq$10%), as may be the case for breast cancer in Ashkenazi Jewish women, there may be large increases in the relative risk and attributable risk for relatively modest increases in cancer susceptibility (>10-fold) and radiosensitivity (>100-fold) in the susceptible subgroup. For any given combination of strength of predisposition and radiosensitivity differential, incomplete penetrance dilutes the effect.

VI. OTHER RELEVANT STUDIES

A. HUMAN STUDIES

1. Genetic disease in offspring of long-term survivors of childhood and adolescent cancer

358. The work of Byrne et al. [B69] addressed the question of genetic risks to the offspring of survivors of childhood and adolescent cancer. Genetic disease was defined as a syndrome of malformations known to have an associated cytogenetic abnormality (regardless of whether karyotypes were available), a single-gene (i.e. Mendelian) disorder, or any one of the 15 common simple birth defects. The data and analysis pertain to 2,198 offspring of 1,092 cancer survivors and 4,544 offspring of 2,032 control parents; of the cancer survivors, 72.8% received non-mutagenic therapy and the remainder received therapy that could be classified as mutagenic. The authors noted that the dosages of radiation and chemotherapeutic agents were not quantified because of the complexities involved, but they can be assumed to have been high.

359. The list of Mendelian diseases included achondroplasia, acrocephalosyndactyly, aniridia, Apert syndrome, myotonic dystrophy, Gardner syndrome, Marfan syndrome, multiple polyposis, neurofibromatosis, osteogenesis imperfecta, polycystic kidney disease, retinoblastoma, and Steinert syndrome. The two main findings were the following: (a) when types of genetic disease, as defined above, were examined individually or together, the rates of these defects in offspring of survivors and of controls were not significantly different (3.4% vs. 3.1%), and (b) there was no association of the risk of sporadic genetic disease in children with the treatment status of the parents (a condition was considered sporadic if in the opinion of two reviewing physicians, no relative had the same or a related genetic disease). An earlier report of this study [B21] showed that radiation therapy below the diaphragm depressed fertility in both sexes and that chemotherapy with alkylating agents was associated with decreased fertility in male survivors. Byrne et al. [B69] noted that, "… although this may represent genetic damage, infertility is a complicated outcome with many causes … [and] a genetic aetiology for infertility has not been studied".

2. Reproductive outcome in women irradiated during infancy for skin haemangiomas

360. Källen et al. [K30] conducted a detailed analysis of the possible impact of early gonadal irradiation with beta particles, gamma rays, and x rays by examining 19,494 infants born to 10,237 women who had been irradiated at the age of 18 months or less for skin haemangiomas in Sweden. The ovarian dose distribution of the mothers and the numbers of children in the different maternal dose groups were as follows: <0.01 Gy (14.7% of women, 4,949 children); 0.01–0.05 Gy (43.7%, 8,522 children); 0.06–0.1 Gy (13.3%, 2,586 children); 0.11–0.2 Gy (10.3%, 2,014 children); 0.21–0.5 Gy (6.7%, 1,301 children); >0.5 Gy (0.6%, 122 children). The mean ovarian dose was 0.06 Gy and the maximum, 8.55 Gy.

361. The main findings were the following:

(a) women with ovarian doses of more than 0.01 Gy had fewer infants than women who received less than 0.01 Gy (14,545 children vs. 15,401 expected);
(b) there was a small excess of perinatal deaths (stillbirths plus early neonatal deaths) in the >0.01 Gy groups, but this was not related to dose;
(c) overall, there was a small excess in the rate of congenital malformations (about 8%), but again, this was unrelated to dose and was presumably the result of variable recording practices. Only for neural tube defects was there a statistically significant increasing rate with maternal ovarian dose and for cleft lip with or without cleft palate, although at levels significantly below expectation; both findings may represent chance results of multiple statistical testing;
(d) the frequencies of infants with low birth weight (<2,500 g) and of infants born pre-term (<37 weeks of gestation) were lower than expected compared with those calculated from all births in Sweden; the authors interpreted these findings as a reasonable consequence of the longer educational durations and the fact that these women smoked less; and
(e) there was no increase in the rate of infants with Down's syndrome or in childhood malignancies.

3. Possible genetic effects of radiation exposures resulting from the Chernobyl accident or from living in the vicinity of a nuclear power plant

(a) Down's syndrome and congenital abnormalities

362. In the UNSCEAR 1993 Report [U4], it was mentioned that the results of Czeizel et al. [C23] had showed no increase in the prevalence of selected sentinel anomalies (predominantly autosomal dominant and X-linked diseases of childhood onset and Down's syndrome) in Hungary after the Chernobyl accident. Sperling et al. [S35], however, reported that in West Berlin, nine months after the Chernobyl accident (i.e. in January 1987), there was a significant increase in Down's syndrome; a cluster of 12 cases was found compared with two or three expected. (Note that the term cluster is used here in an epidemiological sense and not in the sense used in genetics to describe mutations originating from a single

progenitor cell.) After excluding factors that might have explained the increase, including maternal age distribution, only exposure to radiation after the Chernobyl accident remained. In six of the seven cases that could be cytogenetically studied, the extra chromosome was found to be of maternal origin. The occurrence of the above cases coincided with the time of highest radiation exposure (when the conceptions should have occurred), particularly inhalation of ^{131}I, prompting the authors to suggest that exposure to ionizing radiation, especially ^{131}I, might be the causal factor. This interpretation is open to doubt, however, in view of the very low radiation doses.

363. In another study carried out in Germany, Burkart et al. [B26] recorded an increase in Down's syndrome births (10 observed vs. 4.4 expected) in northern Bavaria in December 1986, close in time to the occurrence of the Down's syndrome cluster in West Berlin. Further analysis revealed that the increase in northern Bavaria was due mainly to four diagnoses made in the urban areas of Nuremberg, Fuerth, and Erlangen. Chernobyl radiation exposure could be excluded as the cause, because the areas had received very little contamination and because the peak occurred in December 1986, one month before the occurrence of the Down's syndrome cluster in West Berlin.

364. In commenting on the Berlin cluster, Burkart et al. [B26] noted that (a) biological considerations argue against Chernobyl fallout as a plausible cause of the Berlin cluster; (b) the Chernobyl exposure cannot have been a common causal factor in northern Bavaria and West Berlin, since the higher rates in the former area can be traced to a time period shortly before fallout took place; and (c) in the absence of further clues, the close temporal relationship of the Berlin and the Bavarian clusters should be carefully analysed to generate hypotheses on a common factor influencing the incidence of Down's syndrome.

365. De Wals et al. [D26] reported on the results of a survey on the incidence of chromosomal syndromes (including Down's syndrome) in Europe registered in 19 birth defects registries from January 1986 to March 1987. The study population comprised 764 chromosomal syndrome cases, of which 621 were Down's syndrome cases in 482,193 total births. No evidence for any clustering was found in any of the registries for the period January to March 1987. Analysis of the frequency rates by month of conception also did not indicate any increase after May 1986.

366. Little [L30] provided a comprehensive review of studies undertaken in the wake of the Chernobyl accident with particular reference to those on congenital abnormalities and other adverse reproductive outcomes. The main points that emerge are the following: (a) an increased frequency of Down's syndrome in West Berlin in January 1987 and increases in the frequency of neural tube defects in several small hospital-based series in Turkey are not confirmed in larger and more representative series in Europe; (b) no clear changes are apparent in the birth prevalence of congenital anomalies in Belarus or the Ukraine (the republics with the highest exposures), although the data are difficult to interpret because the methods of acquisition were not described and were not reported in full; (c) the conclusion that there is no consistent evidence on congenital anomalies applies to other measured outcomes of pregnancy as well (miscarriages, perinatal mortality and low birth weight, sex ratio shifts, and multiple births); (d) there is evidence of indirect effects: an increase in induced abortions due to anxieties created, which is substantial enough to show up as a reduction in the total number of births; (e) no data are available on the reproductive outcomes of women pregnant at the time of the accident who were evacuated from the 30-km zone of contamination, of workers on site at the time of the accident, or of recovery operation workers; and (f) no data are available from several of the countries closest to the Chernobyl area (see also [B5, G9]).

367. Siffel et al. [S34] studied the occurrence of sentinel anomalies (also including congenital abnormalities and Down's syndrome) in children (n = 26,893) born within a 20-km radius of the Paks nuclear power plant in Hungary. Comparisons of the frequencies of sentinel anomalies, congenital abnormalities, unidentified multiple congenital abnormalities, and Down's syndrome before and after the operation of the power plant revealed no significant differences. It was concluded that the slightly elevated radiation background (0.2–0.4 μSv a^{-1}) attributable to the operation of the power plant did not affect germinal and somatic mutation rates. Izhevsky et al. [I9], carried out a retrospective study on the pregnancy outcomes and pre-reproductive mortality of children of workers of the Mayak nuclear power plant. The workers were occupationally exposed to gamma radiation during 1948–1954, and data on doses and medical documents of the families were available. The authors found indications for a possible increase in pre-reproductive mortality of the children of exposed mothers.

(b) Mutations in human minisatellite loci

368. ***Background.*** As discussed in paragraph 52, a significant fraction of the eukaryotic (including the human) genome is composed of repetitive-sequence DNA. Much of this DNA has been grouped into various families based on sequence, organization, and size [S92]. In some of these families, variations in sequence and/or in the number of repeat units occur within and between species. One class of the repetitive DNA elements, simple tandem repeats, is characterized by a motif of short oligonucleotide core sequences reiterated in tandem arrays. These elements have been variously called minisatellites [J15], midisatellites [N17], and microsatellites [L34]. This repetitive DNA has been found to occur at many highly polymorphic (hypervariable) loci dispersed throughout the genome. The exceptionally high levels of polymorphic variation at these loci are due to variation in the number of tandem repeat cores. Family studies have demonstrated that simple tandem repeat loci are inherited in a co-dominant Mendelian fashion [K42] (see Jeffreys et al. [J5] for a recent review.)

369. The diversity of alleles at both human and mouse minisatellite loci is a result of mutation rates that are orders of magnitude higher than those of most protein-coding genes (e.g. [J5, J16, K42, K43, S63]). The principal advantage of these high mutation rates is that significant changes can be detected with smaller sample sizes. There is evidence to suggest that in somatic cells, the new length alleles may arise by mitotic recombination or unequal sister chromatid exchange; replication slippage does not appear to be a dominant process [J5, W22]. Analysis of minisatellite mutations in sperm suggests that they may arise by gene-conversion-like events, the reasonable candidate stage being meiosis [J5]. Worth noting here is that minisatellite variations very rarely have phenotypic effects (e.g. trinucleotide repeat expansions; see Table 8).

370. ***Radiation-induced minisatellite mutations.*** Dubrova et al. [D19] studied germ-line minisatellite mutations among children born between February and September 1994 to parents who were continuously resident in heavily polluted areas of the Mogilev region of Belarus after the Chernobyl accident. Blood samples were collected from 79 families (father, mother, and child) for DNA analysis. The control sample consisted of 105 non-irradiated Caucasian families from the United Kingdom, sex-matched to the offspring of the exposed group. DNA fingerprints were produced from all families by using the multi-locus minisatellite probe 33.15 and two hypervariable single-locus probes, MS1 and MS31. Additionally, most families were profiled with the minisatellite probes MS32 and CEB1. For the Mogilev families, the level of ^{137}Cs surface contamination was used as a dose measure, i.e. families were divided according to the median ^{137}Cs contamination levels into those inhabiting less contaminated areas (<250 kBq m^{-2}) and more contaminated areas (>250 kBq m^{-2}).

371. The important findings are that (a) the frequency of minisatellite mutations is about twice as high in the children of the exposed families as in controls, and (b) the mutation frequencies show a correlation with the level of caesium contamination as demarcated above. The authors suggested that these findings are consistent with radiation induction of germ-line mutations but also noted that other non-radioactive contaminants from Chernobyl, such as heavy metals, could be responsible for the observed, apparently dose-dependent increase in the mutation rate.

372. In a subsequent extension of the above study, Dubrova et al. [D29] recruited 48 additional families from the affected region and used five additional minisatellite probes, including the multi-locus probe 33.6 and four hypervariable single-locus probes. These additional data confirmed the twofold higher mutation rate in children of exposed parents than in those of non-exposed. The spectra of mutations seen in the unexposed and exposed groups were indistinguishable, suggesting that the increased mutation frequency observed over multiple loci arise indirectly by some mechanism that enhances spontaneous minisatellite mutations. Obviously, further work is needed to clarify the structural basis of radiation-induced minisatellite mutations.

373. It has been argued [N19] that the use of control families from the United Kingdom introduces a significant confounding factor as well as possible ethnic/genetic differences from the population of Belarus. Secondly, the families in the United Kingdom may have experienced different patterns of environmental exposure to potentially mutagenic industrial and agricultural chemicals that might have contributed germ-line variation. Thirdly, it is not clear from the surface contamination maps of the region why control families receiving insignificant radiation doses were not obtained or why a second set of controls of children conceived prior to the accident could not be identified. Fourth, the trend in mutation frequency with likely dose received is also dependent on the division of families into just two groups on the basis of radiocaesium contamination; an analysis of trends based on individual assessment of contamination would be more revealing. Finally, from the data presented, it would seem that the germ-line doses in the whole region remain sufficiently uncertain to question the true significance of a less than twofold difference in mutation frequency between the two groups.

374. In a pilot feasibility study carried out on the children of survivors of the atomic bombings in Japan, Kodaira et al. [K44] (see also Neel [N18] for a commentary) screened 64 children from 50 exposed families and 60 from 50 control families for mutations at six minisatellite loci using the following probes: Pc-1, λTM-18, ChdTC-15, pλg3, λMS-1, and CEB-1. The cell lines chosen for this study were from the most heavily exposed parents, whose average parental combined gonadal equivalent dose was 1.9 Sv. A total of 28 mutations were found, but these were at the pλg3, λMS-1, and CEB-1 loci (there were no mutations at the other three loci). Twenty-two of these were in controls (of 1,098 alleles tested, i.e. 2%), six in the children derived from the irradiated gametes (among 390 alleles, i.e. 1.5%). Thus, there was no significant difference in mutation frequencies. Since they used different loci from Dubrova et al., the authors suggested that the use of the DNA fingerprint probes 33.16 and 33.15 may be worthwhile in studies of the children of survivors of the atomic bombings. However, the subsequent preliminary results of Kodaira and Satoh [K50] and Satoh and Kodaira [S44] using the above two probes showed no significant difference in mutation frequencies between the children of the exposed parents and the control children.

4. Summary

375. Two studies of the genetic effects of radiation in humans have recently been published. One of them involved the offspring of survivors of cancer who had received chemo- and/or radiotherapy treatments and the other involved females who had been exposed to radiation (from beta particles, gamma rays, and x rays) during infancy for the treatment of haemangiomas. Neither of these found significant effects attributable to parental exposure to chemical agents and/or radiation.

376. The results of studies of minisatellite mutations in the children of those exposed in areas contaminated by the Chernobyl accident and in the children of those exposed to the atomic bombings in Japan are not consistent: in children from Chernobyl areas, the mutation frequencies were increased, while in the Japanese children, there were no such increases. It should be noted that the control children for the Chernobyl study were from the United Kingdom.

377. The search for genetic effects associated with Chernobyl exposures in Belarus or Ukraine, which had the highest contamination, and in a number of European countries provide no unambiguous evidence for an increase in the frequencies of one or more of the following: Down's syndrome, congenital anomalies, miscarriages, perinatal mortality, etc.

B. ANIMAL STUDIES

1. Radiation-induced minisatellite mutations in mouse germ cells

378. In work that preceded the Chernobyl investigation, Dubrova et al. [D18] conducted a pilot study to determine the inducibility of minisatellite mutations in mouse germ cells by radiation. Hybrid (F_1) male mice (101/HY × C3H/SnY) were given acute gamma-ray exposures of 0.5 or 1 Gy and mated to unirradiated females. The progeny derived from stem-cell spermatogonia at the time of irradiation and the parents were used for detecting new (i.e. not present in either parent) mutations in their DNA fingerprints. Two multi-locus minisatellite probes, 33.6 and 33.15 [J15], were used. The results showed that the frequencies of mutations in the progeny derived from irradiated males were higher than in the controls (ratios to controls 1.9 and 1.6 for mice irradiated at 0.5 and 1 Gy, respectively).

379. Dubrova et al. [D18] stressed three points: (a) in this study, evidence for radiation induction of minisatellite mutations was obtained in a total of 232 offspring from 26 control and irradiated families at radiation doses and sample sizes substantially lower than those used in conventional genetic studies with specific-locus mutations in mice; (b) if induced mutations can be verified both for the mouse pedigrees and for the offspring of well characterized control and irradiated human populations, then minisatellite mutations may be of use in monitoring germ-line mutations in humans; and (c) the probable selective neutrality of minisatellite mutants should ensure that mutants will not be lost prenatally.

380. In a subsequent investigation, Dubrova et al. [D4] studied the x-ray induction of mutations at the mouse minisatellite loci in premeiotic and post-meiotic stages of spermatogenesis. Two experiments were designed: in one, the frequency of mutations was measured in three groups of offspring conceived 3, 6, and 10 weeks after paternal acute x-irradiation with 1 Gy to sample, respectively, irradiated spermatids (3 weeks) and spermatogonia (6 and 10 weeks). In the second experiment, mutation frequencies were determined after irradiation (0.5 and 1 Gy) of premeiotic stages in males. By using two multi-locus and two single-locus probes, 30 different minisatellite bands were scored per animal. The results showed a linear dose-effect relationship for mutations in spermatogonial cells, but there was no evidence for induced mutations in spermatids.

381. Dubrova et al. [D4, D5] suggested that these findings support the interpretation that they advanced earlier [D19], namely, the minisatellite loci themselves are not direct targets for radiation-induced mutations; if they were, then the observed rate would require an unrealistically high number of induced DNA double-strand breaks or other damage in the genome. If the inference is correct that induced minisatellite mutations are non-targeted events, this would mean that damage elsewhere in the genome or in other "sensor molecules" might be relevant. The authors also noted that similar mutation rates in the spermatogonial cells sampled 6 and 10 weeks post-irradiation can be interpreted to mean that the mutations result from damage accumulated in germ cells prior to meiosis but do not necessarily indicate that the mutational events themselves occur premeiotically rather than later, for example, in meiosis. Since, however, meiotic stages were not included in the study, no firm conclusions can be drawn.

382. In similar experiments, Sadamoto et al. [S36] and Fan et al. [F32] investigated ^{60}Co gamma- radiation-induced germ-line mutations at a hypervariable minisatellite mouse locus (ms6hm). Male C3H/HeN mice were acutely exposed to 3 Gy from ^{60}Co and mated to C57BL/6N females. The matings were made at 1–7, 15–21, and 71–77 days post-irradiation to sample progeny from irradiated spermatozoa, spermatids, and stem-cell spermatogonia. DNA from parents and the progeny was analysed in Southern blots to screen for new mutations. The locus-specific Pc-1 probe was used. The data showed that the frequencies of mutations in the progeny in the irradiated group were higher than in the controls, and this was true of all the germ-cell stages (in contrast to the work of Dubrova et al., which showed that no minisatellite mutations were induced in spermatids). However, as in the study of Dubrova et al., significant increases could be detected with relatively small sample sizes.

2. Genetic effects in mice exposed in the Chernobyl accident

383. Shevchenko et al. [S73] and Pomerantseva et al. [P17] studied adverse genetic effects in mice caught in 1986 and 1987 within a 30-km radius of the Chernobyl reactor (four different sites with different levels of gamma radiation background and with estimated doses from <0.01 Gy to 1.5 Gy). The frequencies of cytogenetically ascertained reciprocal translocations were found to be consistent with previous findings of the effects of dose and dose rate on translocations. Of 122 male mice, 2 (from the maximally

contaminated region) were sterile and for the rest, there was a period of temporary sterility. Nonetheless, in these males, the frequencies of abnormal sperm were in the range 2%–5%, with no radiation-dose-dependent effects. In matings of these males with laboratory females, post-implantation mortality rates were nearly the same for sites II, III, and IV, i.e. they did not depend on the degree of radioactive contamination. However, in matings of males from site I within the first two weeks of capture, there was a significant increase in post-implantation mortality. This was an expected result when one considers the fact that post-meiotic germ-cell stages were sampled in these matings.

384. Other data reported in the paper of Shevchenko et al. [S73] pertain to parallel experiments in which laboratory mice were exposed to elevated background radiation in the Chernobyl region for 22–25 days, resulting in absorbed gonadal doses of 0.1, 0.3, and 2.5 Gy (gamma rays) in one set of experiments and 3.4 Gy (gamma rays) and 2.7 Gy (beta rays) in the other (in the first, only males were exposed, while in the latter, both males and females as well as pregnant females were exposed). In the first series of experiments, the most significant effects were injuries to testes that caused irreversible sterility at high doses. In the second, when the exposed males were mated to unexposed females in the laboratory, the overall embryonic mortality (i.e. pre- and post-implantation mortality) during the first weeks was four to six times as high. In the case of exposed females mated to unexposed males three months after the termination of the exposures, there were no significant differences compared with controls. However, of 74 males exposed as embryos, 4 (5.4%) showed significant increases in post-implantation mortality in the range 40%–63%; cytogenetic analysis revealed that males were heterozygous for reciprocal translocations.

3. Cytogenetic nature of radiation-induced germ-line mutations in the mouse

385. Genetic and cytogenetic analyses of mutations recovered in large-scale mutation work with the mouse 7-locus specific-locus method have provided evidence for the induction of large deletions and other forms of gross chromosome imbalance by radiation and/or chemical mutagens [D20, R16, S42]. Among these loci are the dilute (*d*) and short ear (*se*) loci on chromosome 9, the albino (*c*) and pink-eye (*p*) loci on chromosome 7, and the brown (*b*) locus on chromosome 4 (e.g. [R12, S42]). The largest of these spanned 4–9 cM (8 to about 16 Mb) and are cytologically visible.

386. Some dominant mutations at loci such as the steel (*Sl*) on chromosome 10 and the splotch locus (*Sp*) on chromosome 1 were associated with runting, reduced viability, and either pre- or post-implantation loss of homozygotes. Cytogenetic analysis revealed visible deletions at the respective loci that removed between 2% and 30% of the chromosomes ([C45] and references cited therein). Prompted by these findings, Cattanach et al. [C46] undertook a systematic cytogenetic analysis of these and other mutants recovered in the course of their specific-locus experiments (6 Gy from acute x-irradiation) and/or chemical mutagen treatments of stem-cell spermatogonia as well as of animals that showed only the growth retardation (runting) phenotype.

387. The principal findings were the following: (a) animals with radiation-induced mutations at the most radiosensitive locus, the *s* (piebald spotting), were growth-retarded to different degrees and also showed other phenotypic abnormalities, such as head shaking or waltzing behaviour; all of the 21 analysed by Cattanach et al. proved to be large deletions, variably comprising from 2.5% to 30% of the distal region of chromosome 14 spanning the *s* locus; (b) *Sl* mutations were also frequently recovered in radiation experiments; all of the eight analysed were deletions comprising up to 10% of chromosome 10 spanning the locus; and (c) mutations at the other known loci (*W*, *Ph*, and *T*) were also associated with deletions, but relative to *Sl*, they were smaller.

388. In addition to deletions associated with known gene phenotypes, cytogenetically visible deletions without specific mutant genotypes were found to be distributed throughout the genome. Besides growth retardation, these animals showed associated head abnormalities, dark coats etc., often with limited levels of white spotting. Several of these effects may be secondary to runting, as they are common to a number of different deletions involving different chromosomes.

389. Even in the group of deletions identified mainly on the basis of known gene phenotypes, it was clear that the distribution across the genome was non-random. Thus, no deletions have been found so far in four chromosomes (11, 12, 15, and 19), only rarely are they found in others (chromosomes 2, 6, 7, and 9) and multiple examples in some others (chromosomes 1, 3, and 8). Multiple deletions were most evident in chromosome 1, where 12 independent deletions were found; other examples of multiple deletions were found in chromosomes 3 and 8.

390. This non-random distribution does not seem to be associated with a refractoriness of some chromosomes to radiation-induced breakage, as there is no hint of a correlation with the distribution of translocation breakpoints. It would thus seem that the non-random distribution of the recovered deletions is a reflection of the non-random distribution of haplo-sufficient and haplo-insufficient genes in the genome (the terms refer to the situation where loss of one copy of the gene is compatible [haplo-sufficient] or not compatible [haplo-insufficient] with viability).

391. In addition to deletions, 24 duplications (including two insertions) were also found in growth-retarded animals. The distribution of the deletions was non-random; multiple examples were found in chromosomes 7, 9, 14, and 16, and in chromosome 9, duplication of up to 10% of the chromosome was compatible with viability. The recovery

of multiple examples of chromosome 9 duplications contrasts with the rarity of deletions in this chromosome. Six inversions and 24 translocations were also detected by chance but were not associated with growth retardation.

392. It is difficult to estimate the incidence of the various types of chromosomal change because of the subjectivity in the recognition of the associated phenotypes and, in the case of duplications, the modifications to the screening process employed throughout the studies. Also, the cytogenetic identification of the changes is governed both by the resolution of the light microscope and the quality of the G-bands; losses or gains of <2% will probably be undetected.

393. Notwithstanding these limitations, some crude estimates are possible. From about 30,000 young screened from four specific-locus experiments in which males had been exposed to spermatogonial irradiation (6 Gy), 394 were selected for screening by phenotype. Of the 360 screened so far, 33 (9.2%) proved to carry large deletions and 15 (4.2%) carried duplications. If the percentage of deletions in the remaining 34 progeny is the same as in the 360 screened, based on the total number of 30,000 progeny, the overall rate of deletions can be estimated to be about $12\ 10^{-4}$. If the *s* locus mutations are included, this rises to about $18\ 10^{-4}$, and if all untested and tested *Sl* mutations are included, to about $20\ 10^{-4}$. The frequency of duplications, however, is much lower, reflecting the late introduction in the study of screening for growth retardation without other phenotypic effects, which proved effective for detecting this category of damage.

394. Twenty-seven of the 360 animals carrying translocations unassociated with phenotypic effects were incidentally found in these tests (7.5%), providing an independent measure of radiation effect with which to compare the deletion and duplication frequencies. A second measure is provided by the overall specific-locus mutation frequency; however, since virtually all the *s* locus mutations were large deletions, the specific-locus mutation frequency for the remaining six loci, excluding the *s* locus mutations, is $14.5\ 10^{-5}$ per locus per gamete.

4. Summary

395. Laboratory studies with mice have now provided evidence for radiation-induced minisatellite mutations in male germ cells. In one study, significant increases in the frequencies of these mutations could be detected in progeny descended from irradiated spermatogonia, spermatids and spermatozoa. In another study, focussed on spermatids and stem-cell spermatogonia alone, increases were detected in spermatogonia but not in spermatids.

396. In other work, mice caught in 1986 and 1987 within a 30-km radius of the Chernobyl reactor (i.e. after the accident; with estimated doses from <0.01 Gy to 1.5 Gy) were found to have higher frequencies of translocations induced in spermatogonia. Two of the 122 male mice caught in the maximally contaminated region were sterile, while others had a period of temporary sterility followed by resumption of fertility; the tests revealed that 2% to 5% of the sperm were abnormal.

397. Cytogenetic studies of the progeny of irradiated male mice that had known mutant phenotypes (recovered in the specific locus tests) and of those that had only the runting phenotype have shown that (a) a significant proportion of these animals carry large deletions and duplications that are compatible with survival of the heterozygotes even if they reduce viability and cause growth retardation and other developmental abnormalities; (b) the distribution of these structural changes is non-random across the genome; and (c) not all growth-retarded mutants carry detectable deletions. The studies suggest that smaller deletions below the range of cytogenetic detection will also occur and may be detected by molecular techniques.

C. MOSAIC MUTATIONS AND MUTATION CLUSTERS

1. General comments

398. As mentioned in paragraph 46, mosaicism, the occurrence of two or more genetically different cell lines derived from a single zygote, is an important cause of phenotypic modification resulting in variation in clinical expression of an inherited trait or disease. Mosaicism for a specific gene mutation may be confined to somatic cells or to the germ line or may be present in both, depending on the developmental stage at which the mutation occurs. Pure somatic mosaicism, where the mutant clone is not present in the germ line, is not relevant to inherited disease and will not be considered further.

399. Germ-line mosaicism (the occurrence of a *de novo* mutation in a germ-line cell or one of its precursors during early embryonic development), however, will result in a "mutant sector" in the gonad of an otherwise phenotypically normal individual, and such an individual will generate gametes carrying the mutation, which in turn may result in individuals carrying the same mutation in the following generation ("mutant clusters"). The occurrence of germ-line mosaicism provides an explanation for the inheritance patterns in cases where multiple affected children are born to clinically normal parents. For instance, some diseases that satisfy two of the requirements for autosomal recessive inheritance, namely, expression in the offspring of unaffected parents and recurrence within sibs, may actually be due to a dominant mutation that was present as a mosaic in the parental germ line. In organisms such as the Drosophila and the mouse, a sizeable proportion of spontaneous mutations is known to arise as mosaics in the germ line and can be readily inferred from the occurrence of clusters of identical mutations in the progeny of single-pair matings [F27, R40, S99, S100, S101, S102, W28].

2. Mosaic mutations in humans

400. In humans, mosaicism for constitutional and somatic chromosomal anomalies has long been known, but its occurrence among single-gene mutations leading to Mendelian diseases, although suspected from family studies, could be demonstrated only after investigators began to use molecular techniques. Thus, for instance, in Duchenne muscular dystrophy (DMD), "restriction fragment length polymorphism tracking" has been used to demonstrate that deletions of the *DMD* gene were transmitted to two or more offspring by mothers who themselves showed no evidence of the mutation in their somatic cells (e.g. [B67]). The available data for DMD suggest that the proportion of mosaics among the mothers of sporadic patients may be about 7% [G20]. Known examples of germ-line mosaicism include osteogenesis imperfecta type 2, neurofibromatosis 1, retinoblastoma, pseudoachondroplasia, Ehlers-Danlos syndrome, dominantly inherited ectrodactyly, tuberous sclerosis (autosomal dominant), haemophilia A, ornithine trans-carbamylase deficiency, and agammaglobulinemia (X-linked), and several more are being reported in the literature. The subject has been reviewed [C2, H20].

3. Mosaic mutations and clusters in mice and their relevance for risk estimation

401. In the mouse, data on spontaneous mosaic mutations come from studies on recessive visible specific-locus mutations that have recently been published [R9, R40]. The following general points are applicable to mosaic mutations and clusters of mutations detected in the mouse specific-locus work: (a) the wild-type animals used in mutation tests ("the treated generation", the authors' terminology for G_1 generation) are obtained by crossing two inbred laboratory strains (G_0 generation); (b) these (treated or control animals) are mated to the tester stock, which is homozygous for seven recessive visible markers; (c) mutations are scored in the progeny of the treated animals ("the scored generation", G_2 generation); (d) mosaic mutations at five coat colour loci (of the seven loci in the tester stock) are detectable by their mottled phenotypes (visible mosaics) of the progeny in the scored generation; confirmation of gonadal mosaicism requires breeding studies; (e) gonadal mosaics that arise in the G_0 generation will not be visible in the G_1 generation (called "masked mosaics", because the mosaic is covered by the wild-type allele from the other parent) but will give rise to clusters of mutations in the G_2 generation; and (f) in the work of Russell and Russell [R40], the mean of the observed (flat-topped) distribution with respect to the proportion of germ-line mosaicism for 50 visible mosaics is 50%. They suggest that a 50:50 mosaic could result from (a) a double-strand mutation at the two-cell stage, or (b) a single-strand mutation occurring in a parental germ cell any time after the last premeiotic mitosis and before the first post-meiotic mitosis in one of the parental genomes (in G_0 or G_1 generations), a stage that they refer to as the perigametic interval. The authors favour alternative (b).

402. The following flow chart summarizes the origin of mosaics and clusters and their detection in the mouse specific-locus experiments discussed above:

G_0		G_1		G_2
[grandparental generation]	→	[treated generation] (animals treated or kept as controls)	→	[scored generation] (progeny scored)
A mosaic mutation arises	→	remains "masked"	→	mutant cluster
		A mosaic mutation arises	→	"visible mosaic" (mottled animals)

403. Russell and Russell [R40] suggested that: (a) the most likely frequency of visible mosaics (in generation G_2) is $9.6\ 10^{-6}$ locus^{-1}; (b) the frequency of singletons (those mutants that do not occur in clusters and based on published data from Oak Ridge, Neuherberg, and Harwell) is $6.6\ 10^{-6}$ locus^{-1} (generation G_2); (c) the best estimate of the spontaneous mutation rate is derived from the G_2 generation, namely, including visible mosaics with singletons (and allowing for the fact that mosaics contribute only half as many new mutations to the next generation), i.e. $6.6 + (9.6 \times 0.5) = 11.4\ 10^{-6}$ locus^{-1}, which is 1.7×6.6, the singleton rate; (d) adding the female contribution of singletons ($1.6\ 10^{-6}$) [R41] and mosaics, assuming that the latter is the same in females, yields $17.8\ 10^{-6}$ (i.e. $11.4 + 1.6 + 4.8 = 17.8$), which is more than twice the singleton rate; and (e) a less reliable way of computing the total spontaneous rate is from mutations detectable in G_1 (rather than G_2) by adding masked mosaics (weighted by ½) to heterozygotes (also masked) appropriately weighted), which gives a rate that is 1.4 times the singleton rate.

404. The main message of the above paper, therefore, is that taking visible mosaics into account will approximately double the spontaneous rate of $6.6\ 10^{-6}$ locus^{-1}. It is clear that if the new estimate is to be used in the doubling-dose calculations, then the doubling dose will become twice the currently used value of 1 Gy (for low-LET, low-dose, or chronic exposures), which in turn means that the relative mutation risk per unit dose will be halved.

405. Selby [S101, S102] tabulated the data on clusters in the mouse specific-locus experiments carried out at Oak Ridge,

Harwell, and Neuherberg and showed that these are not uncommon. Note that for the occurrence of a cluster in the scored generation, the mutations must have existed as masked mosaics in the parental generation. Selby has argued that the method used by Russell and Russell (i.e. adding the rate of visible mosaics to the singleton rates) seriously underestimates the spontaneous rate per generation. He developed a computer programme to model specific locus experiments that incorporates the hypothesis originally advanced by Russell [R9, R36] for the origin of mosaics, namely the "first cleavage gonadal mosaic" hypothesis (FCGM). He used the programme to estimate the consequence of the FCGM hypothesis on the total mutation frequency. His results from computer simulation show that the combined spontaneous mutation frequency in both sexes is of the order of $39.6\ 10^{-5}$ mutations per gamete, or $5.66\ 10^{-5}$ per locus. The latter is about three times higher than $17.8\ 10^{-6}$, given in paragraph 403. He has further argued that, if the increase in mutation rate with paternal age known in humans is used to correct the mouse mutation rate, the spontaneous mutation rate will be even higher. The message therefore is that if the mouse spontaneous rates of mutations are to be used with the corrections suggested by Selby, the doubling dose will be much higher than the 1 Gy thus far used in risk estimation.

406. As discussed in Section II.E.3, when the Committee (in 1977) and BEIR (in 1980) began using the mouse-data-based doubling dose for risk estimation in humans, neither addressed the basic questions of (a) paternal age effects for spontaneous mutations in humans and their impact on spontaneous mutation rates, and (b) whether it is indeed appropriate to extrapolate spontaneous mutation rates from short-lived mice to a heterogeneous human population of all ages (especially since males at increasingly advanced ages are siring offspring). Evidently, the conceptual basis for using mouse spontaneous rates had been erroneous all these years, and the Committee now feels that it is important to rectify this error. Additionally, because of the new awareness of mosaics and clusters in the mouse, the spontaneous mutation rate in mice has become even more uncertain than had been thought.

407. Although the potential importance of mosaics and clusters is recognized, and it may eventually become possible to take them into account for estimating spontaneous mutation rates, the Committee believes that for the purpose of risk estimation at present, the prudent way forward is to revert to the use of data on human spontaneous and mouse induced rates for calculating doubling doses as was done in the 1972 BEIR Report [C47] for several reasons.

408. First, most of the available human data on germinal mosaics are in the form of case reports that do not permit reliable quantitative estimates of their contribution to the spontaneous mutation rate. The main relevance of germ-line mosaicism in humans stems from the fact that there may be a real risk for the recurrence of disease in subsequent offspring in what had been previously thought to represent a risk-free situation.

409. Second, if germ-line mosaics arise at a finite rate in every generation and result in clusters in the generation following their origin, these may affect not only the estimates of spontaneous mutation rates (as Selby's computer simulations show) but also the estimates of disease frequencies in the population. It is therefore incorrect to introduce corrections to spontaneous mutation rates and not to disease frequencies; corrections for the latter are not possible at present.

410. Third, whereas clusters are detected in the mouse because of large numbers of progeny from a single parent, human family sizes are generally too small to detect clusters. (In fact, it can be argued that clusters are far less relevant in humans because of small family sizes.) Even if clusters had occurred, they would have been automatically counted, since human geneticists include all mutants that arise anew in calculating spontaneous mutation rates. Judging from the numbers of mutants actually recorded in the various studies of spontaneous mutations and disease frequencies in humans, it seems very unlikely that there were mutant clusters causing "mutational explosions" in our species. Consequently, it is difficult to extrapolate from data on mosaics and clusters in mice to spontaneous mutation rates in humans.

411. Finally, placing heavy reliance on the spontaneous mutation rate estimated from a small number of genes in the mouse (and extrapolating from this to the human genome) ignores both the availability of spontaneous mutation rate estimates for a much larger number of human genes (discussed in Chapter II) and the fact that these estimates included paternal age effects (and clusters had they occurred). It should also be noted that when human spontaneous rates are used, one less assumption is needed.

4. Summary

412. The occurrence of mosaic mutations in humans, of mosaics and clusters in mice and the difficulties in using the data on the latter for the calculation of spontaneous mutation rates for the purpose of estimating the doubling doses are reviewed. Arguments are advanced to support the present conclusions of the Committee, namely, that: (a) the use of entirely mouse-data based doubling doses to estimate human genetic risks is conceptually incorrect; (b) it is not possible to extrapolate from mouse data on mosaics and clusters to human spontaneous rates at present; and (c) the prudent way forward is to use spontaneous mutation rates of human genes and rates of induced mutations in mouse genes to estimate doubling doses, as was first done in the 1972 BEIR Report.

VII. CONCEPTS, DATA AND ANALYSES USED FOR THE ESTIMATION OF GENETIC RISKS

413. As mentioned in the Introduction to this Annex, the years following the publication of the Committee's 1993 Report [U4] have witnessed a number of significant advances in human (especially molecular) genetics and experimental radiation genetics that are particularly relevant for the estimation of genetic risks of radiation. Among these advances are: (a) the revision of the estimates of incidence of Mendelian diseases in human populations (Chapter II); (b) the use of human data on spontaneous mutation rates and mouse data on induced mutation rates (instead of using mouse data for both these rates as had been done thus far) for calculating the doubling dose (Chapter II) [S22, S105]; (c) the development of methods, using the mutation component (MC) concept, for predicting the extent to which the frequencies of Mendelian [C66] and multifactorial [D17] diseases will increase as a result of radiation exposures (Chapter IV); (d) the delineation of the concept of disease-class specific potential recoverability correction factors to bridge the gap between radiation-induced mutations that have been recovered in the progeny of irradiated mice and the potential risk of inducible genetic diseases in humans [S16]; and (e) the introduction of the concept that multisystem developmental abnormalities are likely to be among the principal phenotypes of radiation-induced genetic damage in humans [S43]. Of these, items (d) and (e) incorporate advances in human molecular biology and in molecular studies of radiation-induced mutations in experimental systems.

414. The aim of this Chapter is to recapitulate the advances discussed in the earlier Chapters, review those that have not been considered, and present a synthesis of how they can be used to adapt the conceptual framework for the doubling-dose method of risk estimation, thus setting the stage for risk estimates discussed in Chapter VIII. The equation used until 1993 for estimating risks provides a convenient starting point to consider these advances:

$$\text{Risk per unit dose} = P \times 1/DD \times MC \qquad (14)$$

in which P is the incidence of the class of genetic disease considered, 1/DD is the reciprocal of the doubling dose, which is the relative mutation risk per unit dose, and MC is the mutation component, which provides a measure of the relative increase in disease frequency (relative to the baseline incidence) per unit relative increase in mutation rate (relative to the spontaneous rate).

A. FREQUENCIES OF GENETIC DISEASES IN HUMANS

415. Incidence estimates of genetic diseases constitute an integral part of the risk equation used with the doubling-dose method. The first comprehensive estimates of the frequency of genetic diseases in humans were presented by Stevenson in 1959 for the population of Northern Ireland [S103]. Since then, these estimates have been periodically reviewed and revised in the light of advances in knowledge in this area (e.g. [C67, C68, D30, S104, T25, U5]). The estimates used until 1993 (e.g. [N20, U4]) date back to the compilations of (a) Carter [C67, C68] for Mendelian diseases; (b) Czeizel and Sankaranarayanan [C37] for congenital abnormalities and (c) Czeizel et al. [C35] for common chronic diseases. Additionally, the results of several newborn surveys for chromosomal abnormalities (reviewed in [U7]) provided estimates of incidence for this class of diseases.

416. There are no compelling reasons at present to consider revising the estimates for chromosomal (40 per 10^4 live births) and multifactorial diseases (congenital abnormalities, 600 per 10^4 live births, and chronic multifactorial diseases, 6,500 per 10^4 in the population) used in the 1993 Report [U4]; however, as discussed in Chapter II, progress in human genetics during the last several years now permits an upward revision of the estimates for Mendelian diseases. The revised estimates are:150 per 10^4 for autosomal dominants, 75 per 10^4 for autosomal recessives, and 15 per 10^4 for X-linked diseases, together 240 per 10^4 (Table 9).

B. THE DOUBLING DOSE

417. The doubling dose is the amount of radiation required to produce as many mutations as those that occur spontaneously in a generation and is obtained as a ratio of spontaneous and induced rates of mutations in a set of defined gene loci. The value of the doubling dose used in risk estimation since the mid-1970s was 1 Gy (for low-LET, chronic/low dose radiation) and was based on mouse data on spontaneous and induced rates of mutations (predominantly at the 7 specific loci mutating to recessive visible mutations).

418. The two main reasons for reverting to the use of the concept in the BEIR 1972 Report [C47] namely, the use of human data on spontaneous mutation rates and mouse data on induced mutation rates for doubling-dose calculations (instead of using mouse data on both these rates) were discussed in Chapters II and VI. Briefly, the arguments are the following: (a) the pronounced sex differences in spontaneous mutation rates, the increase in the rate of spontaneous mutations with paternal age in humans, and the fact that the human lifespan is longer than that of the mouse considered together strongly suggest that extrapolating from the short-lived mice to humans is unlikely to provide a reliable average spontaneous rate in a heterogeneous human population of all ages, and (b) the recent analysis of mouse

data on mutations that arise as germinal mosaics (which result in clusters of identical mutations in the following generation) has introduced considerable uncertainty about the magnitude of the spontaneous mutation rate in this species; at present, there are no easy ways to extrapolate from mouse data on mosaics and clusters to the situation in humans.

419. In view of the above (and the lack of an alternative to the use of mouse data for induced mutation rates), the Committee considers that it is prudent now to base doubling-dose calculations on human spontaneous and mouse induced rates. The advantages in using human spontaneous mutation rates for the doubling-dose calculations are: (a) they pertain to human disease-causing genes; (b) the mutation rate estimates in humans, because they are averaged over both sexes, automatically include sex differences and paternal age effects; and (c) in estimating mutation rates, human geneticists count all mutants that arise anew irrespective of whether they are part of a cluster or not; consequently, should clusters of mutations occur, they are also taken into account.

1. The average rate of spontaneous mutations in humans

420. Since the purpose of calculating doubling doses is to use its reciprocal to estimate the risk of societally important Mendelian diseases (such as those included in P in the risk equation), it would seem that the choice of spontaneous rates needs to be guided by diseases that have high population incidences and/or genes that have high mutation rates. In practice, however, the situation is not that simple, as illustrated below. Consider the main contributors to disease incidence such as polycystic kidney disease (8 per 10^4), familial hypercholesterolemia (20 per 10^4), hypercholesterolemia due to familial defective apoB-100 (10–15 per 10^4), and *BRCA1*-associated breast and ovarian cancers (15 per 10^4) (Table 10). These are all adult-onset diseases and together account for roughly one third of the total estimated incidence of 150 per 10^4 of all autosomal dominant diseases. Of these four, autosomal dominant polycystic kidney disease has an estimated mutation rate of 87.5 10^{-6} [V20], but it is now known that this disease can be due to mutations in either of two autosomal genes, *PKD1* and *PKD2*. For the other three diseases, no new spontaneous mutations have been reported, and the preferred interpretation is that their high incidence is due not to high mutation rates but to small selection coefficients.

421. Examples of diseases that fall at the high end of the distribution of spontaneous mutation rates are neurofibromatosis (~70 10^{-6}; average from two studies; for this disease, at least two genes, *NF1* and *NF2*, are now known), spherocytosis (~22 10^{-6}), myotonic dystrophy (~18 10^{-6}; average from two studies), achondroplasia (~11 10^{-6}; average from four studies), and osteogenesis imperfecta (~10 10^{-6}; average from two studies; at least two genes are known to underlie this disease). Their estimated incidence in live births are, respectively, 4, 2, 2, 0.2, and 0.4 per 10^4, showing that there is no clear correspondence between high mutation rates and high incidences.

422. It can therefore be concluded that a reasonable procedure to obtain a representative average of spontaneous mutation rates of human genes is to (a) use all the available estimates for individual autosomal dominant diseases (for which estimates of selection coefficients are also available; see later) irrespective of whether these diseases have a high or low incidence or high or low mutation rates, and (b) also include the numbers of genes thus far known or estimated to underlie the various diseases [M2, S105] (see Chapter II and Table 10). Note that taking into account the numbers of genes represents an important departure from the earlier practice of basing mutation rate estimates on disease phenotypes alone (i.e. earlier, a one-to-one relationship between mutation and disease phenotype was assumed because the information that now exists on the numbers of genes was not available then for most of the diseases). The relevance of the estimates of selection coefficients stems from the fact (discussed in Chapter IV) that they enable the determination of mutation components for autosomal dominant diseases.

423. Table 37 taken from the paper of Sankaranarayanan and Chakraborty [S22], summarizes the data that have been used to obtain an estimate of the average spontaneous mutation rate of human genes. These 26 disease phenotypes encompass an estimated 135 genes. The average (unweighted) mutation rate obtained from these data is 2.95 ± 0.64 10^{-6} locus^{-1} generation^{-1}. This figure is well within the range 0.5 10^{-6} and 5 10^{-6} per locus used in the 1972 BEIR Report [C47].

424. It should be noted that the 26 diseases used in the above calculations are but a subset of dominant diseases (Table 10) used to provide the basis for the incidence estimate for autosomal dominant diseases. These “other” diseases were not included in the present analysis because of lack of information on mutation rates and selection coefficients. Further, X-linked genes have not been considered; instead, it has been assumed that the average spontaneous mutation rate calculated for autosomal dominants also will apply to the X-linked diseases. The justification for this assumption rests on the following lines of reasoning: (a) among Mendelian diseases, autosomal dominants constitute the most important group from the standpoint of genetic risks, and (b) while X-linked recessive diseases are also expected to respond directly to an increase in mutation rate, since their incidence is an order of magnitude lower than that of autosomal dominants (0.15% vs. 1.5%), the assumption of similar average spontaneous rates of mutations for autosomal dominants and X-linked recessives is unlikely to result in any significant underestimation of the total risk (in fact, it is because of this reason that these two classes of diseases are considered together in risk estimation).

2. The average rate of induced mutations in mice

425. For estimating the average induced rates of mutations in mice, the Committee has now made an important departure from its previous practice [U8] of basing it on data on recessive mutations induced at the 7 specific loci extensively studied and the 5 additional loci used by Lyon and Morris [L5], for which the data were (and remain) much less extensive. Instead, it examined all available data on induced mutations in defined genes in mice; these relate to recessive specific locus mutations at the 12 loci mentioned above (but including additional data), "bio-chemical mutations" (mutations in enzyme-coding genes that cause loss of enzyme activity [C12, P10]; data of Lewis and of Peters, cited in [N8]) and autosomal dominant mutations at four loci (*Sl*, *W*, *Sp*, and *T*) collected in the course of specific-locus experiments conducted at Harwell (together, 72 loci). The inclusion of data for the above autosomal dominant mutations in these calculations was dictated by the consideration that, although the underlying genes were not well defined at the time these experiments were conducted (but mutations were "frequently" observed and recorded and so the ascertainment is believed to be complete), not only their identity is known, but also the molecular nature of mutations in these genes.

426. All of the data considered are from studies involving stem-cell spermatogonia. The data from female mice have not been used, since, as discussed in the UNSCEAR 1988 Report [U5], there is uncertainty whether mouse immature oocytes would provide a good model for assessing the mutational radiosensitivity of human immature oocytes. The argument rests on (a) the strikingly higher sensitivity of mouse immature oocytes to radiation-induced killing (the majority are destroyed by 0.5 Gy [O6] in contrast to those of human and rhesus monkey immature oocytes, for which the dose required is at least 100 times higher [B6]), and (b) the insensitivity of mouse immature oocytes sampled 7 weeks after irradiation to radiation-induced mutations in contrast to mature and maturing oocytes [R37]. In view of the uncertainty of the mutational response of human immature oocytes, the Committee will use the conservative assumption that the rate estimated for males will also be applicable to females.

427. Tables 37 and 38 present summaries of the data considered for the estimation of induced mutation rates in mice. Details of data from individual experiments are discussed in Sankaranarayanan and Chakraborty [S22]. In these experiments, male mice were exposed to either single, acute high doses of x- or γ-irradiation or to high dose fractionated x-irradiation (usually two fractions separated by 24 hours). The rates for the latter were appropriately normalized to acute x-irradiation conditions to facilitate easy comparisons (see footnotes *d* of Table 37 and *b* and *c* of Table 38).

428. Table 37 shows that the average rate of induced mutations is highest for the original 7 specific loci $3.03\ 10^{-5}$ $locus^{-1}\ Gy^{-1}$. For the 6 loci used in the experiments of Lyon and Morris [L5], the rate is about one third of the above, being $0.78\ 10^{-5}$ $locus^{-1}\ Gy^{-1}$; one locus, the *a* is common to both sets of loci). For the various sets of biochemical loci at which null mutations have been scored, the estimates vary from $0.24\ 10^{-5}$ to $1.64\ 10^{-5}$ $locus^{-1}\ Gy^{-1}$. The average rate for dominant visibles is within the above range. The unweighted average of the induced mutation rates is $1.09\ 10^{-5}$ $locus^{-1}\ Gy^{-1}$. The use of this rate for doubling-dose calculations is somewhat problematic since (a) there is overlap of one or more loci in different data sets, (b) in some studies, all the loci involved could not be ascertained (see footnote *e* in Table 37), and (c) there is no simple way of taking into account the inter-locus variation and sampling variance of induced rates from the above average estimate of $1.09\ 10^{-5}$ $locus^{-1}\ Gy^{-1}$.

429. Therefore the following approach was used to derive the average induced rates of mutations. All data from individual experiments (detailed in [S22]) were first grouped by loci, so that an unweighted estimate of the locus-specific induced rates could be derived from the average of the estimates from all experiments involving each of the loci. Subsequently, the locus-specific rates were averaged across loci to arrive at the induced mutation rate. This procedure permitted the estimation of the standard error the estimated rate that incorporated sampling variability across loci as well as the variability of the rates in individual experiments. The algorithm of these computations is described in [S22]. In this approach, the unpublished data of Lewis (cited in [N8]) were excluded since details of the identity of all the loci and the loci at which mutations were recovered were not available. Although fewer data were used (the total number of loci became 34), this procedure was preferred because (a) no locus was double-counted while averaging over all loci; (b) the loci and the corresponding mutant phenotypes were clear; (c) the standard error of mean (which took into account both intra- and inter-locus variability) could be given. The locus-specific rates for the 34 loci used are given in Table 39. These data permit an overall average estimate of $1.08 \pm 0.30\ 10^{-5}$ $locus^{-1}\ Gy^{-1}$. With a dose-rate reduction factor of 3 traditionally used (the original basis for which was provided by the studies of Russell et al. [R38]), the rate for chronic low-LET radiation becomes $0.36 \pm 0.10\ 10^{-5}$ $locus^{-1}\ Gy^{-1}$.

3. The doubling-dose estimate

430. With the estimate of $2.95 \pm 0.64\ 10^{-6}$ $locus^{-1}$ $generation^{-1}$ for the rate of origin of spontaneous mutations in humans (paragraph 423) and of $0.36 \pm 0.10\ 10^{-5}$ $locus^{-1}$ Gy^{-1} for induced mutations in mice (paragraph 429), the doubling-dose estimate becomes 0.82 Gy, which is not very different from 1 Gy based on mouse data that has been used thus far.

431. Since the doubling dose is defined as a ratio of spontaneous and induced rates of mutations, with these rates estimated by m_s and m_i, respectively, the estimate of

the doubling dose, DD, is given by:

$$DD = m_s/m_i \quad (15)$$

for which the approximate sampling variance can be written as:

$$V(DD) = (DD)^2\left[\frac{\sigma^2 m_s}{m_s^2} + \frac{\sigma^2 m_i}{m_i^2} - \frac{2r_{si}\,\sigma m_s\,\sigma m_i}{m_s m_i}\right] \quad (16)$$

where $\sigma^2 m_s$ and $\sigma^2 m_i$ are the sampling variances of m_s and m_i, respectively, and r_{si} is the correlation between m_s and m_i across loci. In principle, to apply equation (15), the correlation of the estimated spontaneous and induced mutation rates should be based on the same set of loci. This not being the case in the present analysis, one can assume that r_{si} is equal to zero (i.e. the estimates of m_s and m_i are independent). With $m_s = 2.95\ 10^{-6}$, $\sigma_{ms} = 0.64\ 10^{-6}$, $m_i = 0.36\ 10^{-5}$ and $\sigma_{mi} = 0.10\ 10^{-5}$, the variance and the standard error of the doubling dose estimate are 0.0834 and 0.29, respectively. It should be noted that the standard error calculation for the doubling dose (which in turn is based on the estimated standard errors of the average spontaneous and induced rates of mutations) is valid for the small sample of genes included in the analysis and may not apply to all radiation-responsive genes in the genome. When more data become available on the spontaneous and induced rates, there may be a need to revise the average rates (and their standard errors), and the doubling dose (and its standard error). The currently revised doubling dose of 0.82 ± 0.29 Gy is not significantly different from 1 Gy that has been used thus far, but the conceptual basis of the former (and the database used for estimating the average spontaneous and induced rates of mutations) is now different. The Committee will use the round figure of 1 Gy for doubling dose for risk estimation in the next Chapter.

4. Summary

432. In this Section, the arguments presented in Chapters II and VI on the need to to revise the conceptual basis for the calculation of the doubling dose are recapitulated. Although in the past, the Committee had assumed that a doubling dose calculated on the basis of spontaneous and induced mutation rates of mouse genes could be used for estimating the risk of genetic disease in humans, this assumption is no longer considered valid. In this Annex, therefore, the Committee has adopted the use of human data on spontaneous mutation rates and mouse data on induced mutation rates for estimating the doubling dose, as was done in the 1972 BEIR Report.

433. Published data on spontaneous mutation rates in humans have been analysed taking into account the current knowledge of the numbers of genes (n = 135) underlying 26 autosomal dominant disease phenotypes. These data permit an estimate of the average spontaneous mutation rate of $2.95 \pm 0.64\ 10^{-6}$ per gene per generation.

434. The average rate of induced mutations in mice for calculating the doubling dose has been estimated on the basis of locus-specific rates for 34 loci taking into account both inter-locus and intra-locus variabilities of rates in the different experiments. The rate estimated in this way is $1.08 \pm 0.30\ 10^{-5}$ locus^{-1} Gy^{-1} for acute x-irradiation and $0.36 \pm 0.10\ 10^{-5}$ locus^{-1} Gy^{-1} for chronic irradiation.

435. The doubling dose based on the actual estimates of spontaneous and induced mutation rates (the latter for chronic irradiation) becomes 0.82 ± 0.29 Gy. The Committee will use the round figure of 1 Gy in risk estimation.

C. MUTATION COMPONENT

436. The third quantity in the risk equation, i.e. equation (1), is MC or the mutation component. As discussed in Chapter IV, the relationship between induced mutations and disease is one of the central problems in risk estimation. The relationship is straightforward for autosomal dominant and X-linked diseases, slightly complicated for autosomal recessives (since an induced recessive mutation does not result in disease in the immediate post-radiation generations) and much more complicated for multifactorial diseases. The use of the mutation component concept enables one to predict the impact of an increase in mutation rate on disease frequency for the different classes of genetic diseases. With the mathematical formulations now available, the mutation component can be evaluated in any post-radiation-exposure generation of interest following either a one-time or a permanent increase in the mutation rate (i.e. radiation exposure generation after generation).

437. For a one-time increase in mutation rate ("burst"; indicated by the subscript b in MC_b below) the dynamics of change in mutation component with time t (in generations) is given by the equation:

$$Mc_b(t) = s\,(1-s)^{t-1} \quad (17)$$

and for a permanent increase in mutation rate (indicated by the subscript p)

$$Mc_p(t) = 1-(1-s)^t \quad (18)$$

Equations (17) and (18) show that $MC_b = MC_p = s$ for the first post-radiation generation following either a one-time or a permanent increase in mutation rate. With no irradiation in subsequent generations, mutation component will gradually decay back to zero at a rate of (1−s) per generation. With a permanent increase in mutation rate, mutation component will continue to increase to attain a value of 1 at the new equilibrium.

438. On the basis of the analysis of published data summarized in Table 36, an estimate of the average selection coefficient s for autosomal dominant diseases has been derived. This is of the order of ~0.3, a value which defines the first generation mutation component. Although no X-linked diseases are considered in these computations, it can

be argued that the assumption of the same mutation component value for autosomal dominant plus X-linked diseases for risk computations will not underestimate the risk because (a) the net effect of selection for X-linked diseases is lower (s/3 for these as opposed to s for autosomal dominants) in the first generation, and (b) the baseline incidence of X-linked diseases is an order of magnitude lower than that of autosomal dominant diseases. The Committee will use the value of MC = 0.3 for computing the risk of autosomal dominant and X-linked diseases for the first post-radiation generation. It is nonetheless aware of the fact that selection intensities in present-day human populations is probably lower than the above estimate.

439. Autosomal recessive diseases do not merit any detailed consideration here, since their mutation component is close to zero in the first few generations. For multifactorial diseases, as discussed in Chapter IV, the estimate of mutation component, obtained using the finite-locus threshold model is not more than ~0.02 for the first several post-irradiation generations for a radiation scenario involving radiation exposure in every generation. The Committee, however, will use this value only for chronic diseases. For congenital abnormalities the mutation component cannot be reliably estimated for reasons explained in Section E of this Chapter.

D. THE CONCEPT OF POTENTIAL RECOVERABILITY CORRECTION FACTOR

440. The concept of potential recoverability correction factor (PRCF) is a new one in risk estimation and represents one of the logical outcomes of integrating advances in human molecular biology into the framework of genetic risk estimation [S16]. Since the Committee will use this for the first time in risk estimation to bridge the gap between the rates of induced mutations determined in mouse studies and the risk of inducible genetic diseases in human live births, the rationale underlying the concept and how the potential recoverability correction factors can be estimated for the different classes of genetic diseases are reviewed in this Section.

1. Background

441. As may be recalled from equation (14), the risk per unit dose is predicted to be a product of three quantities (i.e. P × 1/DD × MC). The disease entities included in the estimate of P are those considered to be societally relevant. In multiplying P by the other quantities, it is assumed that the genes (at which spontaneous mutations cause these diseases) will respond to induced mutations, that these induced mutations will be compatible with live births and that they would be "recoverable"in the offspring. This assumption gained support from studies in a variety of experimental systems demonstrating that, by and large, the phenotypes of radiation-induced mutations in the specific genes that were used were similar to those of spontaneous mutations. Despite this evidence, no radiation-induced germ-cell mutations, let alone genetic diseases attributable to induced mutations, have thus far been identified in human studies [B69, N20, O11].

442. Progress in human molecular biology and in radiation genetics during the past few years now permits an understanding of the causes for the above discrepancy between prediction and observation. More specifically, it is now evident that induced mutations in only a small proportion of the human genes of relevance may be compatible with live births. This is because spontaneous disease-causing mutations and radiation-induced mutations studied in experimental systems differ in a number of important ways. Since these have been discussed in detail [S4, S6, S43], only the salient points are considered below.

2. Differences between spontaneous and radiation-induced mutations

(a) Types of molecular changes

443. As discussed in Chapter II, the molecular alterations identified in Mendelian diseases include point mutations (base-pair changes) and small and large intragenic deletions, followed by insertions, duplications, inversions, complex rearrangements, and multigene deletions or microdeletion syndromes. In addition, at least 14 Mendelian diseases are known in which the predominant molecular change is the expansion of specific trinucleotide repeat sequences in the coding or untranslated regions of the gene (Table 8). However, although the types of changes (e.g. point mutations, small and large deletions, and complex rearrangements) induced by radiation in experimental systems are similar to those seen in disease-causing spontaneous mutations in humans, most radiation-induced mutations are DNA deletions; point mutations constitute a minority group. The deletions include not only the gene under study but often adjacent genomic regions as well, i.e. they are multi-locus deletions [R44, S38, S41, T3]. The extent of the deletions, however, varies with the genomic region in which the gene under study is located.

(b) Mechanisms

444. The different types of molecular alterations seen in Mendelian diseases have their origin in a variety of mechanisms, most of which are dependent on the DNA sequence organization of the genes and their genomic context (Chapter II). In contrast, radiation-induced deletions originate through random deposition of energy in the cell (i.e. one can assume that the initial probability of radiation inducing such changes may not be different between different genomic regions). However, their recoverability in live births seems more dependent on whether the loss of the gene/genomic region is compatible with viability in heterozygotes.

445. Genes are known to differ in their response to radiation-induced mutations. For example, data on recessive specific-locus mutations in mouse spermatogonia show that

even among the small number (n = 7) of genes studied, there is more than a 30-fold difference in their observed radiation mutabilities, with the *s* locus being the most mutable and the *a* locus the least mutable [R17, R20]. If one includes the loci studied by Lyon and Morris [L5], the range is even wider. Further, there are those such as the histocompatibility (*H*) genes in the mouse [K23, K28] or the ouabain resistance gene in mammalian somatic cells, at which no radiation-induced mutations have been recovered [A8, T4].

446. The observations that in mice most radiation-induced recessive mutations at specific loci, although initially identified through the phenotype of the marker gene under study, are often multi-locus deletions strongly support the view that differences in response between genes for induced mutations stem not only from the properties of the marker gene but also from the genomic region in which it is located. One would therefore expect that in some genes, radiation-induced mutations will be recovered at high frequencies because either they or the genomic region in which they are located can tolerate deletions and yet be compatible with viability of the heterozygotes (*in vivo* studies) or of the cell carrying the mutation (somatic cell studies). In other genes, however, induced mutations will be recovered at lower frequencies or not at all, because these genes or the genomic regions can tolerate only specific types of changes or no change at all. These considerations underscore the general concept that the structural and functional attributes of the genes and their genomic context are among the major determinants that permit, minimize, or exclude an induced genetic change (e.g. a deletion) being recovered in a liveborn offspring.

(c) Mutational changes and their effects on gene function

447. With Mendelian diseases, the effects of mutational changes can be classified according to whether the changes cause loss of normal gene function or gain of a new function. As is well known, normal gene function can be abolished by different types of point mutations, partial or total gene deletions, disruption of gene structure by translocations or inversions, etc. In most cases, loss-of-function mutations in enzyme-coding genes are recessive. This is so because for most of these genes, 50% of the product is sufficient for normal functioning.

448. Loss-of-function mutations in genes that code for structural or regulatory proteins result, however, in dominant phenotypes through haplo-insufficiency (i.e. a 50% reduction of the gene product in the heterozygote is insufficient for normal functioning but is compatible with viability) or through dominant negative effects (the mutant product not only loses its own function but also prevents the product of the normal allele from functioning in a heterozygous individual). Dominant negative effects are seen particularly with genes whose products function as dimers or multimers [B2, S10].

449. In contrast, a gain of function is likely when only specific changes in a gene cause a given disease phenotype. While gains of truly novel functions are unusual except in cancer, in inherited diseases, gain of function usually means that the mutant gene is expressed at the wrong time in development, in the wrong tissue, in response to the wrong signals, or at an inappropriately high level [S13]. The mutational spectrum of gain-of-function mutations would therefore be more restricted, and deletion or disruption of the gene would not produce the disease.

450. Radiation-induced mutations, on the other hand, because they are often multigenic deletions, cause loss of function through haplo-insufficiency. It is an interesting fact that most mutation systems used thus far to study radiation-induced mutations were designed to score for induced recessive mutations, although some were aimed at dominant mutations in (as yet) unknown genes. Attempts to recover radiation-induced mutations in genes in which the mutant phenotype is due to a dominant gain of function (e.g. mutations in histocompatibility genes in the mouse) or when a specific base-pair change is involved (e.g. electrophoretic mobility variants such as those used in genetic studies of the children of atomic bomb survivors) have been unsuccessful. Gene systems in which the mutant phenotype is due to loss of function arising via dominant negative effects have not been used in studies of radiation-induced mutations.

3. Radiation-induced mutations and their recoverability in radiation mutagenesis studies

451. In spite of the number of differences between spontaneous and radiation-induced mutations, the fact remains that radiation mutagenesis studies with a variety of experimental systems have been very successful. The possible reasons for this are now becoming evident: although the initial choice of marker genes for the study of induced mutations (in Drosophila, mice, etc.) was dictated more by practical considerations such as obtaining sufficient numbers of mutants and their easily recognizable mutant phenotypes than by their relevance to human genetic diseases, in retrospect, it is clear that the successful mutation test systems (such as the mouse specific-locus systems) have been those in which, by and large, the genes chosen for study and their genomic regions were not essential for survival of the heterozygotes, and most of the mutational events scored are of the recessive loss-of-function type involving the marker and several neighbouring genes. Consequently, induced mutations (predominantly multi-locus deletions) could be identified through the phenotype of the marker genes and recovered for further studies.

452. Considering the potentially large numbers of genes involved in the development of the vertebrate skeleton and of the lens of the eye and in which mutations can result in skeletal abnormalities and cataracts, respectively, the absolute numbers of mutations recovered in the skeletal and cataract mutation tests with mice (e.g. [E10, E21, F16, S109, S110]) are much lower than those in the recessive

specific-locus tests. Again, this is not unexpected, since the induced mutational events scored are predicted to be of the dominant loss-of-function through haplo-insufficiency type, and the recoverability of such mutations, especially the multi-locus deletions, must be associated with far more functional constraints than that of recessive loss-of-function mutations. Finally, the test systems that have been least successful (e.g. the H-loci in the mouse [K23, K28] or ouabain resistance in mammalian somatic cells [A8] are those in which the genes themselves are essential for survival and/or are located in gene-rich regions of the genome and for that reason cannot tolerate induced deletions.

453. The above concepts are illustrated in Table 40 in which the genes studied in experimental systems are ranked in descending order of recoverability of mutations induced in them. The genes at which induced mutations have been recovered belong to the first two categories. Although there are no empirical data for genes assigned to ranks 3–5 and 7–9, such genes have been included in Table 38 to provide a framework for inquiring which of the studied human genes may be judged to be potentially responsive to recoverable induced deletions, as discussed in the next Section.

4. Criteria for recoverability and the potential recoverability correction factor (PRCF) concept

454. Since at present, there is no alternative to the use of "recovered" mutations in the mouse for quantitative prediction of risks in humans, ways need to be found to bridge the gap between these and the possible risk of genetic diseases to liveborn progeny of irradiated parents. One way to do this is to define some tentative criteria for recoverability on the basis of "recovered" mutations in studies with experimental systems, apply these criteria to human genes of relevance on a gene-by-gene basis and assess which of these may be considered to be candidates for potentially recoverable radiation-induced mutations in live births. The operative words are "potentially recoverable" because (a) knowledge of the structural and functional genomics of the human genome is incomplete at present; (b) no radiation-induced germ cell mutations have been found thus far in humans to provide a frame of reference or to verify the validity of the assessments; and (c) at the present state of knowledge, the criteria cannot be considered anything more than tentative; they will certainly change with advances in knowledge.

(a) Criteria for recoverability

455. To keep the arguments simple, one starts with the assumption that a multigenic deletion is induced in a genomic region containing the gene of interest and the question asked is: given the structural and functional attributes of the gene and genomic region, can this deletion be considered potentially recoverable in a live birth? Among the attributes considered in applying these criteria are: gene size, location, normal function, known mutational mechanisms, the spectrum of naturally-occurring mutations, whether the genomic region of the gene is gene-rich and whether intragenic (including the whole gene) and multi-locus deletions are known.

456. In assessing gene-richness, the MIM gene map [M2] which presents the cytogenetic location of "disease" genes and other expressed genes in given cytogenetic bands, is used. While it is clear that the resolution of the cytogenetic map is coarse (an average band in a 550 band metaphase chromosome preparation contains about 6 Mb of DNA, an amount sufficient to accommodate many, even large-sized genes), there is no other alternative at present to judge gene-richness of different chromosomal regions. On further point relates to deletions. Although, as discussed in Chapter II, naturally occurring deletions do not occur randomly (and have specificities determined by DNA organization of the genomic region in which they occur), for the purpose of these assessments, it has been assumed that the recoverability of an induced deletion is governed more by whether a given genomic region can tolerate large changes and yet be compatible with viability than by structural organization *per se*. The criteria used for the assessments are the following:

(a) An induced deletion of a gene/genomic region is considered "unlikely to be recovered" when the phenotype of a given naturally occurring disease is due to (a) specific gain-of-function mutations or loss-of-function mutations through dominant negative effects or is the result of expansion of trinucleotide repeats; (b) loss-of-function mutations restricted to only a part of the gene; and (c) overexpression of the wild-type gene product (for example, with specific duplications). The assessment "unlikely to be recovered" also applies when the gene is located in a cytogenetic (sub)band in which at least a few additional genes are also located;

(b) The potential recoverability of an induced deletion is judged to be "uncertain" (a) when the gene is large, codes for an essential structural protein, the known genetic changes are missense and nonsense mutations (or small intragenic deletions or insertions) and when whole gene deletions are rare and (b) with structural protein coding genes in which naturally arising whole gene deletions are not rare, but the gene is located in a putative gene-rich region (not necessarily in the same cytogenetic band) and information on the other genes and/or their functions is insufficient.

(c) An induced deletion in a gene/genomic region is considered "potentially recoverable" when that gene is non-essential for viability of the heterozygotes and is also located in a genomic region that is also not essential for viability (e.g. when the gene is large and whole gene as well as multi-locus deletions are known to occur in that region). Additionally, if rearrangements (e.g. translocations or inversions) are known to occur with breakpoints in the gene/genomic region of interest and produce the disease phenotype, then "mutations" in that region are also assessed to be

potentially recoverable. The presumption is that such genes are similar to the mammalian genes used in experimental studies on induced mutations; categories 1 and 2 in Table 40.

(b) The concept of potential recoverability correction factor (PRCF) and revision of the risk equation

457. The criteria defined above provide a reasonable basis to classify the response of the genes of interest to recoverable induced deletions into three groups, namely, group 1, "unlikely to be recovered", group 2, "uncertain" and group 3, "potentially recoverable". It should be noted that the assignment to group 1 is less subjective and therefore more reliable than that to the other two groups. In general terms, if one analyses a total of N genes, and if n among them can be excluded as "unlikely to be recovered", the remainder (made up of the "uncertain" and "potentially recoverable" groups) together constitutes $(N - n)$ and the fraction $(N - n)/N$ provides a crude measure of genes at which induced mutations may be recovered. This fraction is called the unweighted potential recoverability correction factor (PRCF).

458. The potential recoverability correction factor as estimated above, however, does not take into account the differences in the incidence of the diseases that are assigned to the different groups. For example, if a disease with a high incidence belongs to group 1, societal concern about radiation effects will be far less than when it belongs to the other two groups. Consequently, some weighting for disease incidences is required.

459. If P is the total incidence of diseases due to mutations in N genes and p is the incidence of diseases due to mutations in $(N - n)$ genes classified in groups 2 and 3, then the weighted PRCF becomes $p(N - n)/(PN)$. The Committee suggests, however, the use of a range provided by the unweighted and weighted PRCFs to avoid the impression of undue precision. One would hope that advances in structural and functional genomics of the human (and mouse) genomes and in molecular studies of radiation-induced mutations in experimental systems might permit defining the magnitude of PRCFs with greater precision than is now possible.

460. It is obvious that when the potential recoverability of induced mutations is taken into account, the predicted risk will become smaller than when it is not. Stated differently, the rate of induced mutations in human disease-causing genes that are compatible with viability will be smaller than the estimated rate of such mutations in the mouse experiments that provide the basis for risk estimation. In principle, one can envisage three ways of incorporating the concept of potential recoverability of induced mutations within the framework of the risk equation, i.e. equation (13): (a) suitably increase the doubling dose (DD) such that 1/DD becomes a smaller fraction; (b) decrease the mutation components (MCs) for the different classes of genetic disease; (c) introduce disease-class-specific potential recoverability correction factors into the risk equation. Of these, the third alternative is preferable for two reasons: (a) the original definitions of doubling dose (i.e. a ratio of spontaneous and induced rates of mutations of a set of known genes based on empirical observations) and mutation component (a quantity that predicts the relative increase in disease incidence per unit relative change in mutation rate, but which does not take into account recoverability of induced mutations) can be retained without modifications and (b) with further advances in structural and functional genomics of the human genome and in the molecular analysis of radiation-induced mutations, there is the real prospect of defining potential recoverability correction factors with greater precision than is now possible. With the incorporation of potential recoverability correction factor, the revised risk equation becomes:

$$\text{Risk per unit dose} = P \times [1/DD] \times MC \times PRCF \quad (19)$$

461. It is worth stressing here that the starting assumption in the assessments is that the principal type of radiation-induced genetic change is a multi-locus deletion and that the genomic region containing the gene of interest has sustained such a deletion. Consequently, the potential recoverability correction factor as estimated above does not tell anything about the absolute radiation risk of a genetic disease; it only indicates which disease-causing mutations, if induced, may be potentially recoverable within the framework of the criteria used.

5. Potential recoverability correction factor for autosomal dominant and X-linked diseases

462. Tables 10 and 12 provide the basic information on estimates of incidence of autosomal dominant and X-linked diseases and on the genes that underlie these diseases. Since not all of them fulfill the requirements for inclusion (sufficient data on: incidence, chromosome map position of the genes, gene size, structure and function, genomic context), only a subset of diseases considered could be used for the present analysis. The diseases (genes) included in the different groups are given in Table 41. Full details of the assessments are discussed in [S16].

463. Inspection of Table 41 reveals that in group 1 are diseases which are due to (a) trinucleotide repeat expansions (e.g. Huntington disease, spinocerebellar ataxias, myotonic dystrophy); (b) specific point mutations causing gain of function (e.g. mutations in the *FGFR3* (achondroplasia), *FGFR2* (Apert syndrome) and *RHO* (retinitis pigmentosa); (c) a specific tandem duplication causing gain of function (i.e. overexpression of the wild-type gene product) (e.g. *PMP22*-gene associated Charcot-Marie Tooth (CMT) disease; and (d) a restricted array of point mutations (e.g. mutations in *ApoB-100* (in one form of autosomal dominant familial hypercholesterolemia) or point mutations, small specific intragenic deletions which

cause loss of function due to dominant negative mechanisms (e.g. *MYH6, MYH7, TNNI3* and others in familial hypertrophic cardiomyopathies) and *COL1A1, COL1A2 and COL1A3* in osteogenesis imperfecta types II to IV and *FBN1* in Marfan syndrome). Also included in this group are genes which are relatively small in size which are located in putative gene-rich regions (e.g. *VMD2* gene in Best macular dystrophy, *PBGD* gene in acute intermittent porphyria and *TP53* gene in Li-Fraumeni syndrome).

464. The group 2 is comprised of genes for which the genomic context information is insufficient (e.g. *VHL, BRCA2, EDNRB*) and/or those in which large intragenic and multilocus deletions are rare. Group 3 includes genes which are generally large and constitutional deletions, some extending beyond the confines of the genes (and translocations and inversions with the breakpoints in the gene causing the disease phenotype) are known in spite of the putative gene-rich nature of the region (e.g. *ANK1, EXT1, EXT2, RB1*).

465. For X-linked diseases, the assessment is based on whether the induced deletion will be compatible with viability in males and cause disease (since the loss of even the whole X chromosome is compatible with viability but results in 45,X females).

466. The summary of the analysis, presented in Table 42 shows that 42 of 59 genes involved in autosomal dominant diseases (71%) are judged to belong to group 1 ("unlikely to be recovered"group) and the remaining 17 (29%) to the other two groups, yielding an unweighted PRCF estimate of 0.29. The estimated incidence for the former group of 42 diseases is $46.45/10^4$ live births and that for the latter group of 17 diseases, $55.9/10^4$. Therefore, the weighted PRCF becomes 0.157 (i.e. [17 × 55.9]/ [59 × 102.35] = 0.157). If X-linked genes are included, the comparable estimates for unweighted and weighted PRCFs become, respectively 0.36 (i.e. 24/67) and 0.199. Since the overall estimated incidence of autosomal dominants is an order of magnitude higher than that for X-linked diseases (i.e. $150/10^4$ versus $15/10^4$; Table 9), the PRCF estimates for the former are more relevant in the context of risk estimation. The Committee therefore suggests the use of the PRCF range of 0.15 to 0.30 in the risk equation for estimating the risk of autosomal dominant and X-linked diseases.

6. Potential recoverability correction factor for autosomal recessive diseases

467. The recoverability of induced recessive mutations is also subject to constraints imposed by the structure, function and the genomic contexts of the underlying genes. However, since these mutations are first present in heterozygotes (and 50% of the gene products are generally sufficient for normal function), one can assume that even large deletions may be recoverable in heterozygotes (unless the deletion involves neighbouring essential structural genes, resulting in inviability of heterozygotes). Additionally, induced recessive mutations do not, at least in the first few generations, result in recessive diseases. As discussed in Chapter IV and in Section C of this Chapter, the mutation component for recessive diseases is close to zero in the first few generations. Consequently, there is no need to estimate potential recoverability correction factor for this class of diseases. Note, however, that ignoring potential recoverability is equivalent to assuming PRCF = 1, which theoretically will result in an overestimation of the risk, i.e. see equation (19). However, in reality, since mutation component is close to zero, the use of the above assumption has no consequence to the estimate of risk.

7. Potential recoverability correction factor for multifactorial diseases

(a) Chronic multifactorial diseases

468. The finite-locus-threshold model used to estimate the mutation component of multifactorial diseases (Chapter IV), assumes that (a) the genetic component of liability to disease is due to mutations in a finite number of genes; (b) the affected individuals are those whose genetic component of liability exceeds a certain threshold; and (c) radiation exposure causes a simultaneous increase in mutation rate in all the underlying genes, which in turn, causes the liability to exceed the threshold. Consequently, the requirement of potential recoverability also applies to all the induced mutations as well.

469. A crude approximation of total potential recoverability (for each multifactorial phenotype) is the x^{th} power of that for mutation at a single-locus, where x is the number of gene loci, assumed to be independent of each other, controlling a multifactorial disease. If, as discussed earlier, the potential recoverability correction factor for autosomal dominant and X-linked diseases is in the range of 0.15 to 0.3, for chronic multifactorial diseases, these figure becomes 0.15^x to 0.30^x. With the assumption of just 2 loci, the estimates become 0.02 to 0.09 and with more loci, will be even smaller. Intuitively, these conclusions are not unexpected when one considers that here one is estimating the probability of simultaneous recoverability of induced mutations in 2 or more independent genes, mutations at which underlie a multifactorial disease.

470. The Committee will use the range of 0.02–0.09 for risk estimation noting that this range (based on just 2 loci) is unlikely to underestimate the risk: this is because of the fact that at low doses of radiation of interest in risk estimation, even the initial probability of simultaneously inducing mutations in at least 2 genes underlying a chronic multifactorial disease must be very small.

(b) Congenital abnormalities

471. Although naturally occurring congenital abnormalities are classified as a subgroup of multifactorial diseases (Chapter III), it should be realized that the adjective "congenital" (meaning present at birth), has no aetiological connotation. As discussed in Section E of this Chapter, in

contrast to naturally occurring congenital abnormalities, radiation-induced ones are predicted to show, by and large, autosomal dominant patterns of inheritance, as has indeed been found to be the case in mouse radiation studies on skeletal abnormalities, cataracts, growth retardation, etc. (e.g. [C45, C46, E10, E21, E22, F16, K24, K18, K19, L52, S109, S110]). It is therefore possible to develop a composite estimate of the risk of these effects on the basis of mouse data, without recourse to the doubling-dose method, obviating the need to calculate potential recoverability correction factor for this class of diseases (see Section VII.E).

8. Summary

472. In this Section, a new concept, namely that of potential recoverability radiation-induced mutations in human live births is advanced and the procedure for estimating what are referred to as the potential recoverability correction factors (PRCFs) are discussed. It is suggested that the inclusion of disease-class specific potential recoverability correction factors in the risk equation permits one to bridge the gap between radiation-induced mutations recovered in mouse experiments and the potential risk of radiation-inducible genetic disease in humans.

473. On the basis of mutations recovered in mouse experiments, criteria for assessing the potential recoverability of induced mutations in human genes are developed and applied to human genes of interest from the disease point of view on a gene-by-gene basis. The attributes of human genes considered in applying these criteria are: gene size, location, normal function, known mutational mechanisms, the spectrum of naturally occurring mutations, whether the genomic region of the gene is gene-rich and whether intragenic (including whole gene) and multi-locus deletions are known.

474. The analysis permits the estimation of unweighted potential recoverability correction factors or PRCFs (i.e. the fraction of genes among the total studied that may be responsive to recoverable induced mutations) and weighted potential recoverability correction factors (i.e. weighted by the respective incidence of the diseases). The results show that the potential recoverability correction factors for autosomal dominant and X-linked diseases are of the order of 0.15 (weighted) to 0.30 (unweighted) and unlikely to be more than 0.02 (weighted) to 0.09 (unweighted) for chronic multifactorial diseases. The potential recoverability correction factor calculations are not made for autosomal recessive diseases, since for these diseases, one of the factors in the risk equation, namely, the mutation component is close to zero and the projected risks are already very small for the first few generations. For congenital abnormalities, the potential recoverability correction factor calculations are unnecessary, since the available empirical mouse data on developmental abnormalities can be used to obtain an approximate estimate of risk without recourse to the doubling-dose method.

475. With the revision of the risk equation by including potential recoverability correction factors, the risk per unit dose becomes a product of four quantities, i.e. risk per unit dose = P × 1 / DD × MC × PRCF. Since potential recoverability correction factor is a fraction, the estimate of risk obtained with the revised risk equation will be smaller.

E. MULTISYSTEM DEVELOPMENTAL ABNORMALITIES AS MANIFESTATIONS OF RADIATION-INDUCED GENETIC DAMAGE IN HUMANS

1. Background

476. The concept advanced in this Section, namely that radiation-induced genetic damage in humans is more likely to be manifest as multisystem developmental abnormalities rather than as single-gene diseases in the progeny of irradiated parents, is also new and used for the first time by the Committee. It does not necessarily contradict the view that there may be a finite but small risk of radiation-inducible Mendelian diseases when the potential recoverability correction factors discussed in Section D are taken into account. This concept represents another logical outcome of the integration of knowledge and insights from human molecular genetics into the framework of genetic risk estimation [S43]. The basis for this concept, the experimental data supporting it and the implications for risk estimation are discussed in the following paragraphs.

477. In the work of the UNSCEAR and BEIR Committees, naturally occurring genetic diseases have been (and still are) used as a convenient framework for risk estimation. The general logic remains easy to defend. If, in well conducted studies, significant increases could be demonstrated, this would be cause for concern; however, if, as it turned out, no increases could be seen, this would strengthen the premise for the conclusion that the genetic risks of radiation are likely to be small (as extrapolated from the specific genetic diseases considered). This, in turn, reassured geneticists and the public alike. However, the above inference provides only a partial answer to the broader question of the genetic risks of radiation exposures.

478. Consider the following: radiation does not “know” that genetic risk estimators are interested in mutations in certain genes, and it is unlikely to “respect” the fact that geneticists have classified these diseases as Mendelian, chromosomal, and multifactorial for convenience of study. What if the phenotype of damage induced in regions of the genome other than the genes under study goes undetected and is therefore not scored? It is clear that the problem becomes one of delineating the phenotypes of those changes that are compatible with viability and thus recoverable and that may not necessarily have the phenotypes of known, studied mutations.

479. For the sake of the present discussion, assume that a multigenic deletion has been induced in a certain region of

the genome in stem-cell spermatogonia or oocytes. To be recoverable in a live birth, the induced deletion must successfully pass through the screen of gametogenesis, fertilization, and embryonic development and result in a viable birth. Induced genetic changes, including deletions, that are incompatible with viability will not come to view in live births; they will add to the already high amount of spontaneously occurring genetic changes that is normally eliminated either as zygotic deaths, early embryonic losses, or spontaneous abortions.

480. A proportion of the induced damage, however, may be compatible with viability and could therefore be recoverable in the offspring if it is known what their phenotypes are likely to be, bearing in mind that the recoverable damage may be induced in regions of the genome for which there are, as yet, no "windows". Some insights into the potential phenotypes of such changes come, again, from human molecular biology, namely, from studies of naturally occurring microdeletions in the human genome.

2. Insights from studies of human microdeletion syndromes

481. The microdeletion syndromes, also termed contiguous gene deletion syndromes or segmental aneusomy syndromes, are conditions that result from deletions of multiple, often functionally unrelated yet physically contiguous loci that are compatible with viability in heterozygous condition; they are identified clinically through a characteristic association of unusual appearance and defective organ development. Mental retardation and growth retardation are often prominent features.

482. It is now known that some chromosomes, such as 19 and 22, are relatively gene-rich (the same is true of Xq22.3, Xq21.2, and Xp11.4–p11.3), whereas other chromosomes, such as 4, 13, and 18 (and the Y) are relatively gene-poor, and that the gene density is high in telomeric regions [M2]. The fact that except for trisomy 21, only trisomy 13 and 18 are compatible with viability speaks also to the relative scarcity of genes on these chromosomes. Considering the large variations in gene density in different chromosomes/ chromosomal regions, one would *a priori* expect that if viability-compatible microdeletions occur in gene-rich regions, they may have a clinically recognizable phenotype; if not, the diagnostic hallmarks may be fewer. For instance, in the Xq22.3 region, small and large deletions of one to six genes have been found [B9, S13], with the affected males showing superimposed features of contiguous loss of genes, depending on which have been deleted.

483. Many examples of autosomal microdeletions (detected cytogenetically and/or using molecular methods) are now known (Table 43). These examples show that their distribution across the genome is non-random. This is not unexpected in the light of differences in gene density in different chromosomes (and chromosomal regions) discussed above. The important point here is that despite their occurrence in different chromosomes, the common denominators of the phenotype of many of these deletions are mental deficiency, a specific pattern of dysmorphic features, serious malformations, and growth retardation [E9, E20, S13]. The non-random distribution of cytogenetically visible deletions across the genome is also supported by the recent analysis of Brewer et al. [B46], discussed in Chapter III.

3. Other naturally occurring chromosomal structural changes and associated disease phenotypes in humans

484. The fact that, in addition to deletions, a proportion of naturally occurring translocations, inversions etc. may be associated with clinical effects such as mental retardation and/or congenital abnormalities, spontaneous abortions, infertility etc., has long been known and continues to be reported in the literature (e.g. [F10, F13, J6, P2]). When studies were made on the location of the breakpoints of these chromosomal abnormalities, they were found to be non-randomly distributed in the different chromosomes (e.g. [C32]). Most of these studies were carried out using conventional chromosome banding techniques, and consequently, subtle chromosome rearrangements would escape detection.

485. Prompted by a number of case reports showing that subtle chromosome rearrangements at the ends of chromosomes (subtelomeric regions), which are beyond the resolution of coventional banding techniques, may constitute an important cause of developmental defects and mental retardation. In particular, Knight et al. [K11] used the FISH technique (fluorescent *in situ* hybridization), to study the integrity of chromosome ends of 284 children with unexplained moderate to severe mental retardation. The authors found that such subtle chromosome rearrangements (mostly translocations and unbalanced products derived from them) occurred with a frequency of 7.4% in the children with moderate to severe mental retardation and of 0.5% in the children with mild retardation. The abnormalities were familial in almost half of the cases. The reason for mentioning these observations on chromosomal abnormalities other than deletions is that radiation is capable of inducing such structural changes and a proportion of these can cause clinical effects of the types mentioned above.

4. Empirical mouse data on the phenotypic effects of radiation-induced genetic damage other than mutations in known genes

486. The general predictions that (a) multisystem developmental abnormalities (which include growth retardation) are likely to be among the principal phenotypes of deletions and other gross changes induced in different parts of the genome, and (b) by and large, these phenotypes will show autosomal dominant patterns of inheritance are supported by mouse data on radiation-induced skeletal abnormalities [E10, E21, S109, S110] and cataracts [E22, F16, K24], both of which can be considered as developmental malformations. The congenital

abnormalities were ascertained through *in utero* analysis of pregnant females [N1, N9, N10, N16, K18, K19, L52], and consequently, no transmission tests could be carried out. It is known, however, among the malformed fetuses about 30% to 50% are growth retarded [N1, N9, N10, N16, K18, K19], and a proportion of these survive to live birth and adulthood. [C45, C46, S33]. Searle and Beechey [S33] showed that the phenotype of growth retardation is transmissible as autosomal dominant albeit with variable penetrance. Further, as may be recalled from Section VI.B.3, the studies of Cattanach et al. [C45, C46] showed that radiation-induced multi-locus deletions, duplications and other gross changes constitute the genetic basis for a significant proportion of the growth-retarded animals recovered in their work.

487. It might seem that there is a conceptual contradiction between naturally occurring developmental abnormalities, which are interpreted as being multifactorial in origin (Chapter III), and radiation-induced ones in mice, which are predicted to show autosomal dominant pattern of inheritance (because the underlying events are multi-locus deletions or other gross changes in the genome) and that are documented here to the extent possible. However, when one views these differences in the light of the following, it is obvious that the contradiction is only an apparent and not a real one: (a) the existence of non-allelic heterogeneities (mutations in different genes resulting in similar phenotypes); (b) the existence of a very large number of genes involved in developmental processes and which are located in different chromosomes; (c) the primary reasons for treating naturally occurring developmental abnormalities as multifactorial are the absence of knowledge on the genetic factors involved, aetiological heterogeneity, and the role of environmental factors in the causation of several of these; and (d) the emerging concept that human developmental abnormalities may be treated as inborn errors in development or morphogenesis in obvious analogy with and as an extension of the classical concept of inborn errors of metabolism [E20]. Therefore, diverse dysmorphogenetic causes (including those "driven" by multi-locus deletions) can produce similar malformations.

488. It is possible to obtain a crude estimate of risk for developmental abnormalities using mouse data on skeletal abnormalities, cataracts, and congenital abnormalities diagnosed *in utero*, all involving irradiation of males [S111]. The rates of induced skeletal abnormalities in the work of Ehling [E10, E21] is about 11 10^{-4} gamete^{-1} Gy^{-1} (5 in 754 progeny after 6 Gy of acute x-irradiation) and about 15 10^{-4} gamete^{-1} Gy^{-1} (5 in 277 after fractionated x-irradiation with 1 + 5 Gy, separated by 24 hours; the actual rate is divided by 2 to take into account the enhancing effect of fractionated irradiation to normalize it to acute x-irradiation conditions). The comparable rate for the studies of Selby and Selby [S109] is about 12 10^{-4} gamete^{-1} Gy^{-1} (37 in 2,646 after fractionated irradiation as above; normalized to acute x-irradiation conditions). The average of the above three estimates is about 13 10^{-4} gamete^{-1} Gy^{-1}. In discussing these data, the Committee previously noted [U8] that only about 50% of the skeletal abnormalities observed in the mouse are likely to impose a serious handicap in humans. Consequently, the rate adjusted for severity of effect, becomes about 6.5 10^{-4} gamete^{-1} Gy^{-1}. For dominant cataracts, the rate is much lower, being about 0.33 10^{-4} gamete^{-1} Gy^{-1} (5 sets of experiments with acute irradiation doses from 1 to 6 Gy [F16].

489. Data on the induction of congenital abnormalities in mice have been published by various investigators [K18, K19, L52, N1, N9, N10, N16]. The following discussion is restricted to experiments in which males were irradiated and abnormal live fetuses (descended from irradiated stem cell spermatogonia) were scored *in utero*. In one of their two experiments, Kirk and Lyon [K18] found that the frequency of malformed fetuses in the controls was high (2.1%) as a consequence of which, no increases could be demonstrated at dose levels in the range of 1.08 to 5.04 Gy. In the second experiment [K19], however, the frequency in the controls was 0.7% and in the radiation groups, 2.2% (5 Gy) and 3.1% (5 + 5 Gy, 24 hours interval). The latter two frequencies were significantly higher than that in the controls.

490. In the work of Nomura [N10], involving four doses in the range from 0.36 Gy to 5.04 Gy, the data show that the frequencies increase linearly up to 2.16 Gy followed by a falling off at 5.04 Gy. In the light of the above, the Committee considers it justifiable to restrict its calculations to Nomura's data pertaining to doses up to 2.16 Gy. The data and the rate estimated from these (68 10^{-4} Gy^{-1}) are summarized in Table 44. It should be stressed that these abnormalities were scored *in utero*, and a significant proportion of them are lethal after birth. In a review of his studies over the years, Nomura [N10] made comparisons of the frequencies of abnormalities in live fetuses with those ascertained at one week after birth, taking into account those that could not have been seen in the fetuses (e.g. hypogenic testes, atresia hymenalis; see footnote to Table 1 in [N10]). From these, one can estimate that about 40% of the abnormalities are compatible with survival up to 1 week [S43]. This means that the rate applicable to human live births is about 40% of 68 10^{-4} or 27 10^{-4} gamete Gy^{-1}.

491. When the rates estimated for skeletal abnormalities, cataracts and congenital abnormalities are combined, (i.e. [6.5 + 0.3 + 27] 10^{-4}), the resultant figure is about 34 10^{-4} gamete^{-1} Gy^{-1}. The above rate is for acute x-irradiation. With an assumed dose-rate reduction factor of 3 for chronic radiation conditions, the rate applicable for humans becomes about 10 10^{-4} gamete^{-1} Gy^{-1}. Assuming further that this rate is also applicable to irradiation of females, the rate for radiation of both sexes becomes twice the above, i.e. 20 10^{-4} gamete^{-1} Gy^{-1} [S111]. The Committee will use this rate in risk estimation.

492. In extrapolating from mice to humans, the Committee is fully cognizant of the fact that rigorous comparisons of the abnormalities in the mouse and humans are fraught with considerable uncertainties, since the types of abnormalities one can detect as well as their effects on the individual are

different in the mouse and humans [N8, S19]. Nonetheless, in view of the fact that many of those observed in mice (albeit lethal in this species) are similar to those known in human live births, the Committee considers it useful to gain some notion, even if only a crude one, of the magnitude of risk of congenital abnormalities.

5. Summary

493. In this Section, the concept is advanced that multi-system developmental abnormalities are likely to be among the more important phenotypic manifestations of radiation-induced genetic damage in humans than mutations in single genes. The concept is based on what is known about the nature of radiation-induced mutations in experimental systems (i.e. predominantly multi-locus deletions) and the phenotypes of multi-locus deletions that occur in different chromosomal regions in humans (multisystem developmental abnormalities). The concept predicts that radiation-induced developmental abnormalities, by and large, will show autosomal dominant patterns of inheritance. This has been fulfilled: mouse experiments on radiation-induced skeletal malformations, cataracts, and growth retardation show that these phenotypes are transmitted as autosomal dominant. It is suggested that these data and those for congenital abnormalities ascertained *in utero* can be used to provide an approximate estimate of the risk of these developmental abnormalities without using the doubling-dose method.

494. The mouse data on skeletal abnormalities, cataracts, and congenital abnormalities diagnosed *in utero* considered together permit a crude estimate of risk of developmental abnormalities of about $10\ 10^{-4}\ Gy^{-1}$ for chronic irradiation of either sex and twice this value for irradiation of both sexes.

VIII. RISK ESTIMATES

495. In this Chapter, the concepts, data and analyses, discussed in the earlier Chapters and summarized in the preceding one, are used for predicting the risk of different classes of genetic diseases and the revised estimates are compared with those made by the Committee in the UNSCEAR 1993 Report [U4]. Additionally the principal message from the genetic studies carried out on survivors of the atomic bombings in Japan [N20], i.e. a lack of demonstrable adverse genetic effects of radiation, are considered in the light of the present risk estimates.

496. The risk of Mendelian and chronic multifactorial diseases is predicted with the doubling-dose method for which the revised equation is:

$$\text{Risk per unit dose} = P \times 1/DD \times MC \times PRCF \qquad (20)$$

where P is the baseline frequency of the disease class under consideration, 1/DD is the relative mutation risk per unit dose, MC is the disease-class-specific mutation component for the generation of interest, and PRCF is the potential recoverability correction factor.

497. For developmental abnormalities, which are predicted to be due to radiation-induced multi-locus deletions and other gross changes, however, the risk estimate is based on empirical mouse radiation data on skeletal abnormalities, cataracts, and congenital abnormalities diagnosed *in utero*, i.e. the doubling-dose method is not used. The direct method, which was used together with the doubling-dose method until recently, has now been abandoned, but as mentioned above, the data on skeletal abnormalities and cataracts used with the direct method (along with those on congenital abnormalities diagnosed *in utero*) now provide the basis for estimating the risk of developmental abnormalities as a whole. Additionally, it is no longer considered necessary to make separate estimates of the risk of chromosomal diseases, since these are already assumed to be included with developmental abnormalities.

498. The two radiation scenarios considered here are (a) radiation exposure in every generation and (b) radiation exposure in one generation only. Although the emphasis is on the risks to the first two post-radiation generations (for both scenarios), some speculations are made with respect to the increase in risk at equilibrium for the first scenario.

A. INPUT PARAMETER VALUES

1. Baseline frequencies

499. The baseline frequencies of diseases, P, used in this Annex are 16,500 per million live births for autosomal dominant and X-linked diseases, 7,500 per million live births for autosomal recessive diseases, 650,000 per million of the population for chronic multifactorial diseases, and 6,000 per million live births for congenital abnormalities (Table 9; Chapters II and VII).

2. Doubling dose

500. The doubling dose, calculated in this Annex using human spontaneous mutation rates and rates of induction of mutations in mouse genes, is 1.0 Gy for chronic, low-dose, low-LET radiation exposures and is assumed to apply to both sexes (Chapter VII).

3. Mutation component

501. As in the previous reports, autosomal dominant and X-linked diseases are considered together and are assumed

to have the same mutation component for the purpose of risk estimation. For the first post-radiation generation (following radiation exposure either in one generation or in every generation), MC = s = 0.3; for the second generation, mutation component is calculated using the equations 9 or 10 discussed in Chapter IV (paragraph 236) for autosomal dominant diseases. For autosomal recessive diseases, mutation component in the first few post-radiation generations is assumed to be zero (paragraph 244). For chronic multifactorial diseases, a value of 0.02 is used for the first as well as the second post-irradiation generation for both radiation scenarios (paragraphs 255 and 268).

502. Radiation-induced developmental abnormalities are now assumed to result from induced multi-locus deletions (predominantly) and hence predicted to show, by and large, autosomal dominant patterns of inheritance (Section VII.E). Since the empirical mouse data on induced developmental abnormalities can be used to obtain a provisional estimate of risk of this type of effects to the first generation progeny (i.e. without recourse to the doubling-dose method), an estimate of mutation component is not necessary. However, for the estimation of risk to the subsequent post-radiation generations (under conditions when the population sustains radiation exposure in one generation only or in every generation), knowledge of mutation component (which is dictated by the magnitude of the selection coefficient, *s*) is required (see equations (17) and (18)). Useful clues in this regard are provided by the mouse data of Nomura [N11] and of Lyon and Renshaw [L52] on congenital abnormalities and of Selby and Selby [S109, S110] on skeletal abnormalities. Tests of F_1 male progeny of irradiated [L2, N11] or chemically-treated mice [N11] (i.e. mating of the F_1 males to unirradiated females and intrauterine examination of pregnant females) showed that abnormalities indeed occurred in the later generations albeit with reduced penetrance and variable expressivity. Likewise, most animals with induced skeletal defects (and cataracts) lived to breed [S109, S110] although characterized by variable expressivity. These observations support the view that *s* is not equal to 1 although it is difficult to estimate its magnitude. The Committee will assume that, for all induced developmental defects considered overall, *s* may be in the range from 0.2 to 0.5 for the second post-radiation generation (meaning that between 20% and 50% of the abnormal progeny may transmit the damage to the second generation).

4. Potential recoverability correction factor

503. The potential recoverability correction factor values used are 0.15–0.30 for autosomal dominant and X-linked diseases (paragraph 466), and 0.02–0.09 for chronic multifactorial diseases (paragraph 470). For autosomal recessive diseases, potential recoverability correction factor is not necessary and hence not estimated (paragraph 467). Note that the range for potential recoverability correction factor reflects biological and not statistical uncertainties. For congenital abnormalities, no potential recoverability correction factor estimates are made.

B. RISK ESTIMATES

504. The calculation of risks is very straightforward once the estimates for the input parameters are known. However, to be very clear on the basis for the estimates, the procedures are presented explicitly in the paragraphs below.

1. Radiation exposure in every generation

(a) Autosomal dominant and X-linked diseases

505. ***Risk per Gy to the first generation progeny***

$$= 16{,}500\ 10^{-6} \times 1 \times 0.3 \times (0.15 \text{ to } 0.30)$$
$$\quad P \qquad 1/DD \quad MC \qquad PRCF$$

$$\approx 750\text{–}1500 \text{ cases per million}$$

Risk per Gy to the second generation progeny

$$= 16{,}500\ 10^{-6} \times 1 \times [1 - (1 - 0.3)^2] \times (0.15 \text{ to } 0.30)$$
$$\quad P \qquad 1/DD \qquad MC \qquad PRCF$$

$$\approx 1300\text{–}2500 \text{ cases per million}$$

(b) Autosomal recessive diseases

506. As stated in paragraph 501, since the mutation component for autosomal recessive diseases is close to zero in the first few post-radiation generations, the risk of recessive diseases in the second generation is also assumed to be zero.

(c) Chronic multifactorial diseases

507. ***Risk per Gy to the first generation progeny***

$$= 650{,}000\ 10^{-6} \times 1 \times 0.02 \times (0.02 \text{ to } 0.09)$$
$$\quad P \qquad 1/DD \quad MC \qquad PRCF$$

$$\approx 250\text{–}1200 \text{ cases per million}$$

Since the mutation component in the early generations is estimated to be about the same, i.e. 0.02, the estimate of risk to the second generation is the same as shown above, i.e. there will be no noticeable increase.

(d) Developmental abnormalities

508. As discussed in Chapter VII (paragraph 491), based on mouse data (on skeletal abnormalities, cataracts and congenital abnormalities scored *in utero*), the risk of developmental abnormalities to the first generation progeny can be estimated to be about 2,000 cases per million per Gy. The risk for the second generation is likely to be [(0.2 to 0.5) × 2,000] + 2,000 = 2,400 to 3,000 cases per million per Gy.

2. Radiation exposure in one generation only

(a) Autosomal dominant and X-linked diseases

509. ***Risk per Gy to the first generation progeny***

$$= 16{,}500\ 10^{-6} \times 1 \times 0.3 \times (0.15 \text{ to } 0.30)$$
$$\quad P \qquad 1/DD \quad MC \qquad PRCF$$

$$\approx 750\text{–}1500 \text{ cases per million}$$

Risk per Gy to the second generation progeny

$= 16{,}500\ 10^{-6} \times 1 \times (0.3 \times 0.7) \times (0.15 \text{ to } 0.30)$

P 1/DD MC PRCF

$\approx$ 500–1000 cases per million

(b) Autosomal recessive diseases

510. Since the mutation component for autosomal recessive diseases has been estimated to be close to zero in the first few post-radiation generations, the risk of recessive diseases in the first two generations is assumed to be zero.

(c) Chronic multifactorial diseases

511. ***Risk per Gy to the first generation progeny***

$= 650{,}000\ 10^{-6} \times 1 \times 0.02 \times (0.02 \text{ to } 0.09)$

P 1/DD MC PRCF

$\approx$ 250–1200 cases per million

Since the mutation component in the early generations is estimated to be about the same, i.e. 0.02, the estimate of risk to the second generation is the same as shown above.

(d) Developmental abnormalities

512. The risk of developmental abnormalities to the first generation progeny is the same as calculated earlier for conditions of radiation exposure in every generation, i.e. about 2,000 cases per million per Gy. Under the assumption that s is in the range from 0.2 to 0.5, the risk to the second generation can be of the order of about 400 to 1,000 cases per million per Gy.

3. Summary of risk estimates

513. Table 45 (top portion) presents a summary of the (rounded) risk estimates for the first and second generation descendants of a population exposed to low-LET, low-dose or chronic radiation in every generation. All the rates are expressed per Gy of parental irradiation and per million progeny. It shows that, for the first generation, the risk is of the order of about 750 to 1,500 cases for autosomal dominant and X-linked diseases (compared to 16,500 cases per million live births of naturally occurring ones) and zero for autosomal recessive diseases (compared to 2,500 cases per million live births of naturally occurring ones).

514. For chronic multifactorial diseases, the risk is of the order of about 250 to 1,200 cases (compared to 650,000 cases per million of naturally occurring ones). The estimate of risk for congenital abnormalities (about 2,000 cases compared to 60,000 cases per million live births) is based on mouse data. Note that no separate estimates are presented for chromosomal anomalies, since these effects are assumed to be subsumed in part under that of autosomal dominant and X-linked diseases and in part under congenital abnormalities. Overall, the predicted risks for the first generation (3,000–4,700 cases per million progeny per Gy of parental irradiation) represent about 0.41% to 0.64% of the baseline frequency (738,000 per million). The risks to the second generation, as expected, are higher and yet constitute only about 0.53% to 0.91% of the baseline frequency. Note that for congenital abnormalities complete selection has been assumed (i.e. none is transmitted; s = 1) and consequently all the cases are new.

515. The bottom portion of Table 45 shows the estimates of risk contained in the UNSCEAR 1993 Report [U4]. As will be evident, (a) the estimates of the baseline frequency of Mendelian diseases was lower in 1993; (b) the estimates of risk for these diseases was also made using a doubling dose of 1.0 Gy but did not take into account the potential recoverability of radiation-induced mutations in live births; and (c) it was not possible then to provide risk estimates for multifactorial diseases.

516. Table 46 summarizes the estimates for the first two post-radiation generations of a population that has sustained radiation exposure in one generation only. It is clear that the first generation risks are the same as those given in Table 45. With no further radiation, the risk of autosomal dominant and X-linked diseases declines as a result of selection. For chronic multifactorial diseases, since mutation component remains low for several generations, the risk in the second generation remains about the same as that in the first generation. The risk of congenital abnormalities is assumed to be of the order of 400 to 1,000 cases per million per Gy.

4. Strengths and limitations of the risk estimates

517. For the first time, the Committee has been able, in this Annex, to incorporate advances in human molecular biology into the conceptual framework of genetic risk estimation and to present risk estimates for all classes of genetic diseases. In considering these risk estimates, it is instructive to examine the assumptions that have been made, the consequent uncertainties, and more specifically, whether the estimates are likely to be over- or under-estimates. The first of these assumptions, namely, equal sensitivity of both sexes to radiation-induced genetic damage, was dictated by the view that the mouse immature oocytes may not constitute a suitable model for assessing the mutational response of human immature oocytes. If, for example, the human immature oocytes are less sensitive than stem cell spermatogonia to induced mutations, then the sex-averaged rate of induced mutations would be lower (i.e. the doubling dose will be higher, which means lower relative mutation risk). At present it is not possible to address this issue.

518. The average spontaneous mutation rate estimate (the numerator in doubling-dose calculations) is based on 26 disorders encompassing some 135 genes. Obviously, it would have been ideal to calculate an average rate based on rates of mutations for all the diseases included in the

estimate of P, the baseline frequency. This was not possible. One can only speculate at present on the extent to which the estimate of the average rate will change when mutation rate data for all the genes become available.

519. The average induced rate of mutations (the denominator in doubling-dose calculations) is now based on 34 mouse genes including 4 loci at which dominant mutations have been frequently recovered; there are, however, other loci at which dominant mutations have been recovered rarely, but the data are very sparse. Analysis of variations in the locus-specific rates of the loci included in the computations indicates predominance of loci at which induced mutations are rare. The Committee's conjecture at present is that the estimated average induced rate may be biased upwards (i.e. may be an overestimate), but until more information becomes available, it is difficult to examine the validity of this conjecture.

520. For autosomal dominant and X-linked diseases, the Committee has used a mutation component value of 0.3 for the first generation; this estimate was obtained from an analysis of a set of autosomal dominant diseases for which selection coefficients have been published in the literature (recall that the first generation mutation component is equal to the selection coefficient). Considering the fact that for a substantial proportion of autosomal dominant diseases included in the estimate of the baseline frequency, P, onset is in middle age or later (i.e. after the age at reproduction), one can infer that the selection coefficients are likely to be smaller. So the average first generation mutation component will be lower. Consequently, the use of the assumption MC = 0.3 is likely to overestimate the risk.

521. An additional uncertainty is the possible overlap between the risk of autosomal dominant diseases and that of those grouped under "congenital abnormalities" which are also predicted to be mainly autosomal dominant. While it is evident that many of the former included in the estimate of P in the risk equation are in fact developmental abnormalities (with effects not always restricted to the bodily system after which the disease is named), the extent of overlap is difficult to gauge at present since the estimates for the two classes have been arrived at in different ways. If the overlap is substantial, then the overall risk of dominant effects may be less than the sum of the risk for these two classes.

522. For estimating the risk of chronic multifactorial diseases, a mutation component value of 0.02 has been used. The estimate actually obtained in the computer-simulation studies on the dynamics of change of mutation component and its relationship to broad-sense heritability (of between about 0.30 to 0.80 for most chronic diseases) is in the range from 0.01 to 0.02, often closer to 0.01 than to 0.02. If the actual mutation components were in fact closer to 0.01 than to 0.02, then the use of MC = 0.02 will overestimate the risk.

523. The concept of potential recoverability of radiation-induced mutations in live births represents one of the logical outcomes of integrating advances in human molecular biology into the framework of risk estimation and has been used for the first time by the Committee (Section VII.D). The limits of the range of 0.15 to 0.30 for potential recoverability correction factors used for autosomal dominant and X-linked diseases represent weighted (i.e. weighted by the incidence estimates) and unweighted (the fraction of genes among the total studied that might be considered to respond to recoverable induced mutations) as judged by the criteria developed for this purpose. When the available information was insufficient to make a proper assessment of potential recoverability (which was the case with 7 out of 67 genes considered), these genes were included under the "potentially recoverable" category, to err on the side of caution.

524. The criteria for potential recoverability of radiation-induced mutations that were developed, however, do not take into account the breakpoint specificities of naturally occurring deletions (which seem related to the nucleotide sequence organization of genes and genomic regions and which render them susceptible to the occurrence of deletions); *a priori*, one would not expect that radiation would be able to faithfully reproduce the specificities of breakpoints that nature has perfected over millennia, at least not in all genomic regions. Should this be the case, even the weighted potential recoverability correction factor would be an overestimate. Only further advances in structural and functional genomics of the human (and mouse) genomes and in molecular studies of radiation-induced mutations in experimental systems might permit the magnitude of potential recoverability correction factors to be defined with greater precision than is now possible.

525. In estimating potential recoverability correction factors for chronic multifactorial diseases, it has been assumed that the probability of simultaneously recovering induced mutations in all the genes underlying a given multifactorial phenotype is the x power of that of mutation at a single locus, where x is the number of gene loci, assumed to be independent of each other, controlling a multifactorial disease. Since one needs to assume a minimum of two loci to consider a disease multifactorial, the PRCF estimates become $(0.15)^2$ to $(0.30)^2$, i.e. 0.02 to 0.09. Current knowledge suggests that the number of loci for well studied chronic multifactorial diseases such as coronary heart disease, essential hypertension and diabetes (Chapter III) is certainly more than 2. This means that the potential recoverability correction factors for chronic multifactorial diseases are likely to be smaller than 0.02 to 0.09, which in turn means that the risk is probably less than about 250 to 1,200 cases per million progeny per Gy that has been estimated.

526. The concept that multisystem developmental abnormalities are likely to be among the quantitatively more important adverse effects of radiation and that, by and large, they would show autosomal dominant patterns of inheritance is used for the first time by the Committee. This is yet another logical outcome of the integration of knowledge and insights from human molecular genetics into the framework of risk estimation. One should hasten to add, however, that although not in this form, the concept was implicit in the use of data on

skeletal abnormalities and cataracts (both are developmental abnormalities) with the "direct method" of risk estimation [U4, U5, U6, U7, U8].

527. For the above class of adverse effects, mutation component, and potential recoverability correction factor cannot be reliably estimated. However, a provisional estimate of risk has been obtained using the available mouse data on induced skeletal defects, cataracts, and congenital abnormalities diagnosed *in utero* (and the doubling-dose method has not been used). The estimate is about 2,000 cases per million live births per Gy to the first generation with the risk to the second generation being lower i.e. 400 to 1,000 cases (depending on the assumed selection coefficient range of 0.2 to 0.5). Under conditions of radiation exposure in every generation, the risk to the second generation is assumed to be equal to the sum of the newly-induced ones plus that due to persistent damage. The assumption of the selection coefficient range of 0.2 to 0.5 requires validation.

528. Considering the fact that the "target" for radiation action is the whole genome and that genes involved in developmental pathways are in the hundreds (if not thousands) distributed throughout all the chromosomes, the estimated magnitude of the risk of developmental defects *per se* (which is not strikingly different from that for autosomal dominant and X-linked diseases) is surprising and even counter-intuitive. One explanation for this apparent discrepancy is that the risk estimate for autosomal dominant and X-linked diseases may be an overestimate (for reasons stated in paragraphs 523–524) and that for adverse developmental effects, it may be an underestimate for at least two reasons:(a) in mouse studies not all abnormalities (especially those affecting the internal organ systems could be fully ascertained and (b) although a substantial proportion of the induced congenital abnormalities in the mouse are lethal after birth, this may not be true of induced congenital abnormalities in humans.

529. It can be argued, however, that a significant proportion of mutations or deletions in developmental genes is recessive, i.e. heterozygotes do not manifest the abnormal developmental phenotype. Some support for this line argument comes from homozygosity tests of radiation-induced specific locus mutations in mice which uncovered the existence of this class of mutations that were not detected by phenotypic analysis (e.g. [R12]).

530. One can envisage other explanations, which are not mutually exclusive, for the relatively low rate of induced developmental defects: (a) the structural and functional constraints associated with the recoverability of induced multi-locus deletions (which are assumed to constitute the main basis of induced developmental abnormalities), including those imposed by the simultaneous induction of at least one inviable deletion elsewhere in the genome, along with viability-compatible deletions) are such that only a small fraction of the latter may result in live births; (b) the low estimated rate is a reflection, although not in any direct sense, of the fact that the coding sequences constitute only about 3% of the genome, the remainder being made up of non-coding sequences; therefore, although damage induction by radiation may not entirely follow the 1:30 ratio of coding versus non-coding sequences (and which must certainly be true of multi-locus deletions), relatively more damage may be sustained by non-coding regions with presumably no adverse phenotypic effects; and (c) it is due to some kind of functional redundancy that must be present in developmental networks.

531. Notwithstanding the uncertainties discussed in this Section, the Committee believes that in its judgement, (a) the risk estimates presented for the first two generations in this Annex adequately reflect the current state of knowledge in this evolving area and (b) further advances in human molecular biology and experimental radiation genetics will enable more precision to be achieved than is now possible.

5. Genetic risk at the new equilibrium between mutation and selection for a population that sustains radiation exposure in every generation

532. The population genetic theory of equilibrium between mutation and selection that underlies the use of the doubling-dose method predicts that, under conditions of a permanent increase in mutation rate, the mutation component will reach a value of 1 at the new equilibrium for both Mendelian and multifactorial diseases. In other words, if there is an x% increase in mutation rate, there will be an x% increase in disease frequency at the new equilibrium. So, in principle, the equation used for estimating risk (namely, risk per unit dose = $P \times 1 / DD \times MC \times PRCF$) can be used, assuming MC = 1 for all classes of genetic disease for which the doubling-dose method is used.

533. For autosomal dominant and X-linked diseases, using $P = 16{,}500\ 10^{-6}$, 1/DD = 1.0, MC = 1 and PRCF = 0.15 to 0.30, one can predict that the risk at the new equilibrium will amount to some 2,500 to 5,000 additional cases per million live births per Gy. For autosomal recessive diseases, MC in the first few generations is zero (and consequently no potential recoverability correction factor was estimated); however MC = 1 at the new equilibrium. If the potential recoverability correction factors estimated for autosomal dominant and X-linked diseases are assumed to be applicable to recessive diseases as well, then with $P = 7{,}500\ 10^{-6}$ (and all the other quantities remaining the same), the prediction is about 1,100 to 2,200 additional cases per million per Gy. For chronic multifactorial diseases, with $P = 650{,}000\ 10^{-6}$ and PRCF = 0.02 to 0.09, the estimate becomes, about 13,000 to 58,500 additional cases per million per Gy. For congenital abnormalities, an estimate of risk at the new equilibrium is very difficult to obtain in view of the fact a progressive increase in genetic damage in the genome over time may dramatically increase the magnitude of selection such that individuals affected with

these developmental abnormalities may not survive to reproductive age to transmit the damage. For all classes of genetic diseases, the time it takes to reach the new equilibrium is critically dependent on the magnitude of selection.

534. Although the calculations shown above illustrate the kind of predictions that are potentially possible, the Committee firmly believes that it is prudent to limit these predictions to the foreseeable future, namely, the first one or two generations. This is because of the reasoning that risk predictions at the new equilibrium imply the totally unrealistic and untestable assumptions that (a) the circumstances (e.g. demographic and health care) of human populations would remain constant over very long periods of time, and (b) the estimates of the various parameters used to estimate mutation component and the other quantities in the risk equation would remain unchanged over tens or hundreds of human generations.

6. Summary

535. In this Section the estimates of parameter values discussed in Section A have been used to estimate the genetic risks of radiation exposure. The doubling-dose method is used for all classes of genetic diseases except for developmental abnormalities, for which mouse data are used. While the emphasis is on risks to the first two post-radiation generations (following irradiation in one generation only or in every generation), some speculations are made on the approximate magnitude of risks at the new equilibrium for the latter radiation scenario. Additionally, the strengths and limitations of the risk estimates are discussed.

536. The estimates (all expressed per Gy of parental irradiation per one million progeny) are the following: for the first generation, the risk is of the order of about 750 to 1,500 cases for autosomal dominants and X-linked diseases (compared to 16,500 cases per million live births of naturally occurring ones) and zero for autosomal recessive diseases (compared to 2,500 cases per million live births of naturally occurring ones). For chronic multifactorial diseases, the risk is of the order of about 250 to 1,200 cases (compared to 650,000 cases per million of naturally occurring ones). The estimate of risk for congenital abnormalities is about 2,000 cases per million live births (compared to 60,000 cases per million live births). Overall, the predicted risks for the first generation (3,000– 4,700 cases per million progeny per Gy of parental irradiation) represent about 0.41% to 0.64% of the baseline frequency (738,000 per million).

537. For a population exposed to radiation in every generation, the risk in the second generation (which includes the risk to the first generation as well) is higher, as expected, and yet constitutes only about 0.53% to 0.91% of the baseline frequency.

C. COMPARISON OF THE PRESENT RISK ESTIMATES WITH THOSE OF OTHER APPROACHES

538. Other approaches to genetic risk estimation are the use of the "direct method" and the use of a mouse-data-based doubling dose of 5 Gy advocated by Selby [S101, 102]. As may be recalled, the Committee first used the direct method in the UNSCEAR 1977 Report [U8] to obtain an estimate of the risk of dominant effects in the first generation progeny on the basis of data on radiation-induced dominant mutations causing skeletal abnormalities in male mice. Subsequently, in the UNSCEAR 1982 Report [U7], the direct method was extended to include dominant mutations that resulted in cataracts. The estimated range of risk was 1,000–2,000 cases per million progeny per Gy for irradiation of males and 0–900 cases per million per Gy for irradiation of females. For irradiation of males, the lower limit of the range was based on data on cataracts and the upper limit, on those on skeletal effects. For irradiation of females, the lower limit of the range was based on the assumption that human immature oocytes would have a mutational sensitivity similar to that of mouse immature oocytes and the upper limit, on the assumption that the human oocytes would have a mutational sensitivity similar to that of mature and maturing oocytes and that it is 0.44 times that of spermatogonia.

539. The various assumptions that were used to convert the data on skeletal abnormalities and cataracts to estimates the overall risk of genetic damage causing dominant phenotypic effects have been discussed in detail in the above and subsequent reports including the UNSCEAR 1993 Report ([U4]; see Table 7 in this Report) and will not be repeated here. In the UNSCEAR 1993 Report, the Committee introduced another component of dominant damage based on data on litter-size reduction (i.e. between birth and weaning) in mice [S20] and other unpublished data bearing on this issue. The estimates for this category of damage were 500–1,000 cases per million progeny per Gy for irradiation of males and 0–500 cases per million progeny per Gy for irradiation of females. [Note that the figures for females are based on the same assumption as that mentioned in the preceding paragraph.] The total risk, estimated by this method therefore was 1,500 to 4,400 cases per million per Gy for irradiation of both sexes (see Table 3 in [U4]).

540. In view of the fact that no new data of relevance to the direct method have become available since the UNSCEAR 1993 Report, this method is not further discussed here. However, the Committee has used the basic mouse data (on skeletal abnormalities and cataracts) that were used with the method (along with those on congenital abnormalities also in mice) to obtain an overall estimate of risk of developmental abnormalities in this Annex.

541. It is instructive to note that, despite the very different assumptions used with the earlier direct method, the estimate of 1,500 to 4,400 cases per million per Gy of dominant effects in the first generation progeny obtained with this

method is of the same order as that of 2,750 to 3,500 diseases per million per Gy (autosomal dominant and X-linked diseases plus developmental abnormalities) given here (Table 46). Although the direct method as used earlier is not emphasized in this Annex as the way forward, the Committee considers it a useful one.

D. GENETIC STUDIES ON SURVIVORS OF THE ATOMIC BOMBINGS IN JAPAN IN THE LIGHT OF THE PRESENT RISK ESTIMATES

542. The main focus of the genetic studies of survivors of the atomic bombings in Japan [N20] had always been a direct assessment of hereditary risks of exposure to the atomic bombs in the children of survivors using indicators of genetic damage that were practicable at the time the studies were initiated; they were not aimed at expressing risks in terms of genetic diseases. As the studies progressed, it became clear that no statistically significant adverse effects (in any of the eight indicators used) could be demonstrated in the children of the survivors. The indicators were: untoward pregnancy outcomes [UPO], deaths among liveborn infants exclusive of those resulting from malignant tumours, malignancies in the F_1 children, frequency of balanced structural rearrangements of chromosomes, frequency of sex-chromosomal aneuploids, frequency of mutations affecting protein charge or function, sex ratio among children of exposed mothers, and growth and development of the F_1 children). The data on five of the indicators (i.e. untoward pregnancy outcomes, F_1 mortality, F_1 cancer, sex-chromosomal aneuploids, and mutations altering protein charge or function), however, were subsequently used to set some limits to the doubling doses with which they were consistent [N20]. These doubling doses were expressed as (a) endpoint-specific "minimal doubling doses" excluded by the data at specified probability levels or (b) the "most probable gametic doubling doses". The latter were 3.4 to 4.5 Sv for chronic radiation conditions.

543. Recalling that in the case of UNSCEAR (a) the risk estimates have been obtained through the use of the doubling-dose method (except for congenital abnormalities); (b) these are expressed in terms of genetic diseases; (c) the estimate of doubling dose is based on spontaneous and induced rates of mutations at defined human and mouse gene loci, respectively; and (d) the reciprocal of the doubling dose is used, as one of the factors in the risk equation to predict risks prospectively. It is obvious that comparisons of the doubling dose used in this Annex with the doubling doses of 3.4 to 4.5 Sv retrospectively estimated in the Japanese studies are inappropriate. The Committee wishes to stress this point here in view of the fact that over the years, the doubling doses have become identified with the magnitude of risk as if they are the only determinant of risk, i.e. a low doubling dose implying a high risk and a high doubling dose implying a low risk, irrespective of the fact that the Committee's calculation procedure and use of the doubling dose in risk estimation are quite different from that in the Japanese studies.

544. Nonetheless, it is possible to make a limited comparison, admittedly crude, between the empirically determined risk of adverse effects manifest as untoward pregnancy outcome in the Japanese studies (the untoward pregnancy outcomes include stillbirths, congenital abnormalities and death during the first week of life) and the risk of congenital abnormalities predicted in this Annex. The regression coefficient for untoward pregnancy outcome in the Japanese studies is $26.4\ 10^{-4}$ per parental Sv (although the standard error for this is as large [$27.7\ 10^{-4}$] as the estimate itself) compared to the total background risk of about $500\ 10^{-4}$ assumed in the calculations As discussed earlier, the estimate of risk for congenital abnormalities (for irradiation of both sexes) presented in this Annex is of the order of $60\ 10^{-4}$ per parental Gy for acute x-irradiation (paragraph 491) compared to the background risk of $600\ 10^{-4}$ (Table 45). Considering the uncertainties involved in both these estimates, one can consider the estimated risk (this Annex) and the risk of untoward pregnancy outcome in the Japanese studies are of the same order. Although this similarity may be due to pure coincidence, it should be realized that the estimate of gonadal dose for this endpoint is only about 0.36 Sv in the Japanese studies, and consequently, the lack of a significant effect is not entirely surprising.

545. None of the other endpoints used in this Annex is similar to those used by Neel et al. [N20] in their doubling-dose calculations (F_1 mortality, F_1 cancers, sex-chromosomal aneuploids, and electrophoretic mutations), and so no comparisons are possible. Note, however, that the first two of these are multifactorial traits (similar to untoward pregnancy outcomes) and their responsiveness to an increase in mutation rate (as a result of radiation exposures) will depend on the magnitude of the genetic (i.e. mutation-responsive) component, which as Neel et al. themselves point out, is quite small. Therefore the rates of induced genetic damage underlying these traits are expected to be small, and increases will be undetectable at the low radiation doses (about 0.4 Sv) sustained by most of the survivors. The reasons for the lack of significant effects in sex-chromosomal aneuploidy and electrophoretic mutations (mobility variants and null enzyme mutants) are different: there is no evidence from mouse studies that radiation is capable of inducing chromosomal nondisjunction (which is the principal basis for the origin of sex chromosomal aneuploidy). *A priori*, one would not expect electrophoretic variants to be induced by radiation to any great extent, as they are known to be mostly due to base-pair changes. Null-enzyme mutants would be expected to be induced but unlikely to be found at the dose level experienced by most of the survivors.

546. In spite of the differences in the endpoints and the way the risks are quantified, the main message from the Japanese studies and the risk estimates discussed in this Annex is basically the same, namely, that at low doses, the genetic risks are small compared to the baseline risks of naturally occurring genetic diseases.

SUMMARY AND CONCLUSIONS

547. No radiation-induced genetic (= hereditary) diseases have so far been demonstrated in human populations exposed to ionizing radiation. However, ionizing radiation is a universal mutagen and experimental studies in plants and animals have clearly demonstrated that radiation can induce genetic effects; consequently, humans are unlikely to be an exception in this regard. Since the publication of the UNSCEAR 1993 Report, several advances have occurred in human genetics, experimental radiation genetics and in modeling efforts. The Committee took into account all these developments in revising the estimates of genetic risks of exposure to low-LET, low dose, low-dose-rate irradiation. The introductory chapter (Chapter I) provides a setting by briefly outlining the advances in human molecular biology and how these, together with those in radiation genetics, permit a restructuring of the conceptual framework of genetic risk estimation and a reformulation of some of the critical questions in the field.

548. The basic molecular aspects of the human genome, genes, their organization are discussed in Chapter II as are the kinds of changes (mutations) that are known to occur spontaneously in single genes and that cause hereditary diseases; these are called Mendelian diseases. Aspects of these diseases covered in this Chapter include: the molecular nature of mutations, the mechanisms by which mutations arise (including some novel ones), and the complexities of the relationship between mutation and disease.

549. Mendelian diseases are classified into autosomal dominant, autosomal recessive and X-linked depending on the chromosomal location of the underlying genes and the mode of transmission. Advances in human genetics have now permitted an upward revision of the estimates of incidence of Mendelian diseases from 1.25% to 2.4% (from 0.95% to 1.50% for autosomal dominants, from 0.25% to 0.75% for autosomal recessives and from 0.05% to 0.15% for X-linked diseases).

550. Until 1993, the calculation of the doubling dose (one of the quantities of relevance for risk estimation) was based entirely on mouse data on spontaneous and induced mutation rates. The data on spontaneous rates of mutations of human genes are considered in Chapter II. These rates differ between the two sexes: the rate in males is higher than in females, and the former increases with paternal age. Since spontaneous mutations rates in humans and mice are unlikely to be similar, the Committee favours the view that the use of a mouse-data-based doubling dose is incorrect and that the use of spontaneous mutation rates in human genes and of induced mutation rates in mouse genes for doubling- dose calculations is the prudent way forward. An additional reason for the above conceptual change is that uncertainties in the calculation of spontaneous mutation rates in mouse genes have now been uncovered, owing to the non-inclusion (in the earlier estimates) of data on spontaneous mutations that arise as mosaics (which generate clusters of identical mutations in the following generation). This issue is addressed in Chapter VI.

551. Human genetic diseases that are interpreted to arise as a result of a complex interplay between genetic and environmental factors are discussed in Chapter III. These diseases are called multifactorial diseases and include the common congenital abnormalities that are present at birth (i.e. cleft lip with or without cleft palate, congenital dislocation of the hip, etc.) and chronic diseases of adults (e.g. coronary heart disease, diabetes, etc.). Unlike Mendelian diseases, these diseases do not show simple predictable patterns of inheritance, but they do "run" in families, i.e. the risk to relatives of an affected individual is several times the risk for a random member in the general population.

552. Congenital abnormalities arise as a result of errors in development and affect an estimated 6% of live births. Chronic diseases affect about 65% of the population. The genetic basis of a chronic disease is the presence of a genetically susceptible individual who may or may not develop the disease, depending on the presence or absence of other risk factors, which may be genetic or environmental. Thus, for these diseases, the more appropriate concepts are "genetic susceptibility" and "risk factors". For example, elevated serum cholesterol levels are among the known risk factors for coronary heart disease, elevated blood pressure for stroke, and elevated blood sugar levels for diabetes.

553. For most multifactorial diseases, knowledge of the genes involved, their number, the types of mutational alterations and the nature of environmental factors is still very incomplete. Data from well studied chronic diseases such as essential hypertension, diabetes, and coronary heart disease, reviewed in Chapter III, permit one to conceptualize the relationships between gene mutations and multifactorial diseases: genetic susceptibility to develop a multifactorial disease resides in two classes of genes, the so-called "polygenes" whose mutant alleles have small to moderate effects on the risk factor trait and "major genes" whose mutant alleles have strong effects. Because polygenes are more common, they contribute to the bulk of variation of risk factor traits in the population at large. In contrast, mutations in major genes, although having a devastating effect at the individual level, are rare and therefore contribute far less to the variability of risk factor traits.

554. One of the models that has been used to explain the transmission patterns of multifactorial diseases and which permits the prediction of risks to relatives of affected individuals (from population prevalences) is what is referred to as the multifactorial threshold model. This model, which relies on principles of quantitative genetics, assumes that numerous genetic and environmental factors contribute to what is referred to as "liability" to develop a disease. Because these factors are assumed to be numerous,

the distribution of liability in the population is normal (Gaussian). Affected individuals are those whose liability exceeds a certain threshold value.

555. The multifactorial threshold model makes use of the properties of the normal curve and enables a number of predictions, such as the risk to relatives of affected individuals. It also enables the conversion of information on the prevalence of a multifactorial disease in the population and in relatives of affected individuals into estimates of correlation in liability, from which a useful statistic called heritability of liability can be estimated. Heritability provides a measure of the relative contribution of transmissible genetic effects to the total phenotypic variability, which has both genetic and environmental components. The multifactorial threshold model, however, is essentially a descriptive model, i.e. it does not address the questions on specific genetic causes or mechanisms of disease susceptibilities or how the disease frequencies in the population will be affected when the mutation rate is increased as a result of radiation exposure.

556. The aim of genetic risk estimation, whether it be for Mendelian or multifactorial diseases, is to predict the effects of a small dose of radiation (which causes an increase in the mutation rate) on disease incidence in the population. Until recently, most of the efforts in this area were focussed on Mendelian diseases because of the simple relationship between mutation and disease for this class of diseases, the availability of empirical data on induced mutation rates in the surrogate organism chosen for this purpose, namely, the mouse, and the long-established population genetic models which permit inquiry into the dynamics of mutant genes in populations.

557. The population genetic theory used for the above purpose is what is referred to as the "equilibrium theory". This theory postulates that there exists in the population a balance between two opposing forces, namely, mutations that arise in every generation and selection that eliminates some of these mutations, depending on their effects on reproduction (= fitness). The effects of mutations on fitness can vary, ranging from those that cause death before reproduction (and therefore are eliminated in one generation) to those that do not cause death before reproduction in all individuals (and therefore can persist in the population for varying periods of time (because they do not cause death of all affected individuals before reproduction). The main concept here is that the stability of disease frequencies that one sees in a population is a reflection of the existence of an equilibrium between mutation and selection.

558. When a population is exposed to radiation, new mutations are introduced into the gene pool of the population, and these induced mutations are also subject to selection. Thus, when a population sustains radiation exposure in every generation, eventually the population will reach a new equilibrium between mutation and selection at a higher mutation (and thus of disease) frequency. The time in takes (in generations) to reach the new equilibrium and the rate at which the new equilibrium is reached, depend on the induced mutation rate and selection coefficients and vary between different classes of genetic diseases.

559. One of the methods that has been used for risk estimation (and the one used in this Annex) is what is referred to as the doubling-dose (DD) method. It is based on the equilibrium theory mentioned above. The doubling dose is the amount of radiation required to produce as many mutations as those occurring spontaneously in a generation. It is estimated as the ratio of the average spontaneous mutation rate of a given set of genes relative to the average rate of induction of mutations in the same set of genes. The reciprocal of the doubling dose is the relative mutation risk per unit dose. Since 1/DD is a fraction, it is clear that the lower the doubling dose, the higher the relative mutation risk and vice versa. The risk due to radiation is conventionally expressed as the expected number of cases of genetic disease (over and above the baseline incidence). For autosomal dominant diseases, for which the disease frequency is approximately proportional to the mutation rate, the risk is estimated as a product of two quantities:

$$\text{Risk per unit dose} = P \times [1 / DD] \qquad (21)$$

where P = the baseline incidence and 1/DD is the relative mutation risk.

560. Since, as stated in paragraph 557, the disease incidence, P, represents the equilibrium incidence before radiation exposure, the product of P and 1/DD represents the predicted incidence at the new equilibrium. Traditionally, estimates of risk for the first, second, etc. generations were obtained by "back-calculating" from that at the new equilibrium, assuming specific values for the selection coefficient. For X-linked diseases, the procedure is basically the same. For autosomal recessive diseases, while estimation of risk at the new equilibrium is straightforward, the risk to the first few generations is essentially zero, since an induced recessive mutation does not result in disease. For multifactorial diseases (for which there is no simple relationship between mutation and disease), the situation is more complex and depends on the model used to explain the stability of their prevalence in the population.

561. Methods and algebraic formulations have now been developed to predict the risk of any class of genetic disease in any post-radiation generation of interest following radiation exposure either in one generation or in every generation. These constitute the subject matter of Chapter IV. These methods make use of the concept of what is referred to as the "mutation component" (MC), which enables one to predict the relative increase in disease incidence (relative to the baseline) per unit relative increase in mutation rate (relative to the spontaneous rate). With illustrative examples, it is shown that for autosomal dominant and X-linked diseases, mutation component in the first post-radiation generation is equal to the selection coefficient; under conditions of continuing radiation exposure in every generation, mutation component progressively increases to reach a value of 1 at the new

equilibrium. In other words, an x% increase in mutation rate will result in an x% increase in mutation rate at the new equilibrium. For autosomal recessive diseases, while the mutation component at the new equilibrium is also equal to 1, in the first few post-radiation generations, it is essentially zero, indicating that the frequencies of these diseases will not detectably increase in the first few generations. When the increase in mutation rate occurs in one generation only, the first generation mutation component is the same as that in the first generation for a radiation scenario involving radiation exposure in every generation.

562. For predicting mutation component for multifactorial diseases, the multifactorial threshold model discussed in paragraphs 554–555, was modified by (a) assuming a finite number of loci underlying the disease and (b) incorporating mutation and selection as two additional parameters. The assumption of finite number of loci (in contrast to the infinite of loci in the multifactorial threshold model) was dictated by emerging data on chronic multifactorial diseases (reviewed in Chapter III). The incorporation of mutation and selection into the multifactorial threshold model was dictated by population genetic models on the maintenance of polygenic variability in populations, which show that the equilibrium theory can be applied to polygenic traits as well. The resulting finite-locus-threshold model (FLTM) was used to predict mutation component.

563. The formulation of the finite-locus-threshold model and the number of parameters that enter into it are such that the mutation components cannot be expressed in the form of simple equations (unlike the situation with Mendelian diseases). Therefore, using specified values for mutation rate, selection, threshold, etc., computer simulation studies were carried out to study the dynamics of changes in mutation component with time (in generations) and its relationship to heritability (paragraph 555) for two radiation scenarios: radiation exposure in every generation and in one generation only. The results show that under conditions of continuous radiation exposure in every generation and over a broad range of heritabilities (0.3 to 0.8 for most multifactorial diseases), the mutation component in the first several generations is very small, being about 0.02, often smaller. At the new equilibrium (which is reached after many or scores of generations, depending on selection coefficients and assumed increases in mutation rates), mutation component becomes equal to 1 (a situation similar to that of autosomal dominant diseases mentioned in paragraph 560). When the increase in mutation occurs in one generation only, after a transient increase, the mutation component progressively declines to zero. Although the mutation component estimation with the finite-locus-threshold model was originally intended for use in risk estimation for both chronic diseases and congenital abnormalities, they are used only for chronic diseases. The reason for this is explained in paragraph 571.

564. A review is provided in Chapter V of selected aspects of current knowledge of genes involved in maintenance of genomic stability, cell-cycle control, and DNA repair, which, when mutated, cause predisposition to cancers. Collectively, such cancer-predisposing mutations are believed to account for about 1% of cancer cases. Since a proportion of cancer-predisposed individuals may also be sensitive to radiation-induced cancers, the potential increase in cancer risks in a heterogeneous population (i.e. consisting of cancer-predisposed and normal individuals) is discussed using mathematical models and illustrative examples. It is shown that unless (a) the mutant gene frequencies; (b) the proportion of cancers attributable to the mutant genes; (c) the predisposition strength; and (d) radiosensitivity differentials between predisposed and normal individuals are all high, the amount of increase in cancer risks in the heterogeneous population is small compared to one that is homogeneous in this regard.

565. New information is discussed in Chapter VI that has become available since the publication of the UNSCEAR 1993 Report, from human studies of genetic diseases in the offspring of long-term survivors of childhood and adolescent cancer (no significant increases), reproductive outcome in women irradiated during infancy for skin haemangiomas (no demonstrable adverse outcomes) and possible genetic effects of radiation exposure resulting from the Chernobyl accident (none demonstrable). Additionally, data are considered on the induction of minisatellite mutations in human germ cells (in the progeny of those who were resident in heavily contaminated areas in Belarus after the Chernobyl accident) and in laboratory experiments with mouse germ cells. In both, radiation-induced increases were demonstrated, but since these are not protein-coding genes, their relevance for risk estimation cannot be readily discerned.

566. Also considered in Chapter VI are data on mosaic mutations in mice (briefly alluded to in paragraph 550) and the question of their possible relevance for estimating the spontaneous mutation rate. It is concluded that, at the present state of knowledge, the extrapolation of observations on mosaic mutations in a limited number of mouse genes to the human situation is not possible. In view of this and the lack of similarity of spontaneous mutation rates in humans and mice mentioned earlier (paragraph 550), the prudent way forward is to abandon the use of an entirely mouse-data-based doubling-dose estimate and use a doubling dose based on human data on spontaneous mutation rates and mouse data on induced mutation rates.

567. The concepts and data discussed in the preceding Chapters that are used for risk estimation are recapitulated in Chapter VII. Additionally presented are (a) an analysis of human data on spontaneous mutation rates and mouse data on induced mutation rates and the doubling dose based on this analysis and (b) two concepts that have not been used hitherto in risk estimation. One of these has to do with bridging the gap between radiation-induced mutations studied in mice and the risk of genetic disease in humans, and the other argues that multisystem developmental abnormalities are among the principal adverse effects of radiation-induced genetic damage in human germ cells;

both these concepts represent logical outcomes of the integration of the advances in human molecular biology into the framework of genetic risk estimation.

568. The analysis of human data on spontaneous mutation rates (26 disease phenotypes and an estimated 135 genes) shows that the average rate is $2.95 \pm 0.64\ 10^{-6}$ per gene per generation. A similar analysis of mouse data on induced mutations (which now encompasses, besides the morphological specific loci, other genes used in biochemical studies and dominant mutations at 4 loci, a total of 32 defined genes) shows that the induced rate is $0.36 \pm 0.10\ 10^{-5}$ per locus per Gy. The resulting doubling-dose estimate is 0.82 ± 0.29 Gy. The Committee uses a round figure of 1 Gy in risk estimation. Although the doubling dose is the same as that which the Committee has used in the earlier reports, the present doubling dose is supported by more data on defined genes.

569. The concept of potential recoverability correction factor (PRCF) for radiation- induced mutations has been introduced to bridge the gap between radiation-induced mutations studied in mice and the risk of inducible genetic diseases in human live births. It is based on the known differences (in nature, type, and mechanisms) between spontaneous disease-causing mutations in humans and radiation-induced mutations in mice. On the basis of recovered mutations in mouse experiments, criteria for assessing the potential recoverability of radiation-induced mutations were developed and applied to human genes of interest from the disease point of view. The attributes of human genes considered in the assessments are: gene size, location, normal function, known mutational mechanisms, the spectrum of naturally occurring mutations, gene-richness of the region containing the gene of interest, etc.

570. A gene-by-gene analysis of a total of 67 human genes permitted the estimation of the unweighted potential recoverability correction factor (i.e. the fraction of genes among the total studied at which induced mutations may be recovered in live births) and weighted potential recoverability correction factors (i.e. weighted by the respective disease incidences). The estimates are: about 0.15 (weighted) to 0.30 (unweighted) for autosomal dominant and X-linked diseases and no more than 0.02 (weighted) to 0.09 (unweighted) for chronic multifactorial diseases. No potential recoverability correction factor calculations are made for autosomal recessives, since for these, the mutation component is close to zero in the first few generations. For congenital abnormalities, potential recoverability correction factor calculations are not necessary (see paragraph 571).

571. The concept that the multisystem developmental abnormalities are likely to be the principal adverse effects of radiation damage of human germ cells rests on the following observations or inferences: (a) the whole genome is the target for radiation action; (b) genetic damage is induced by random deposition of energy in the cell; (c) the observations that most radiation-induced mutations are multilocus deletions; (d) the knowledge that genes involved in developmental processes are very many and distributed in nearly all the chromosomes; (e) the findings from studies of many microdeletions (i.e. those that encompass multiple contiguous genes on a chromosome) in humans (identified in different chromosomes) that they share some common attributes, namely, mental deficiency, specific pattern of dysmorphic features, serious malformations, and growth retardation; (f) mouse data that support the view that radiation-induced multi-locus deletions in different chromosomal regions are associated with growth retardation and dysmorphic features. The Committee believes that mouse data on radiation-induced skeletal abnormalities, cataracts, and congenital abnormalities can be used to provide a provisional estimate of risk without the need to use the doubling-dose method.

572. Since most radiation-induced developmental abnormalities are predicted to show dominant patterns of inheritance (in contrast to naturally occurring ones, which are interpreted as being multifactorial), the mutation component and potential recoverability correction factor estimates calculated for chronic multifactorial diseases are not applicable to developmental abnormalities. However, as stated in the previous paragraph, since one can now estimate the risk of these effects using mouse data (without the need to use the doubling-dose method), the inability to estimate mutation component and potential recoverability correction factor for developmental effects does not pose any problem.

573. The final Chapter (Chapter VIII) builds on the concepts and estimates of the different parameters summarized in Chapter VII to provide estimates of genetic risks of radiation exposure focussing on the the first two generations. Two radiation scenarios are considered, namely, radiation exposure of the population in one generation only and radiation exposure in every generation. The strengths and limitations of the new risk estimates are also discussed in the Chapter and compared with those presented in the UNSCEAR 1993 Report. Additionally, the lack of significant genetic adverse effects in the studies of survivors of the atomic bombings in Japan are considered from the perspective of the new risk estimates.

574. The estimates of risk for the different classes of genetic diseases (except congenital abnormalities) have been obtained using the doubling-dose method. The estimate of doubling dose used in the calculations is 1 Gy for low dose/chronic low-LET radiation conditions. For a population exposed to radiation in one generation only or in every generation, the estimates of risk to the progeny of the first post-radiation generation are the following, all expressed as the number of cases per Gy per million progeny: autosomal dominant and X-linked diseases, 750–1,500; autosomal recessive diseases, zero; chronic multifactorial diseases, 250–1,200; congenital abnormalities, 2,000. The total is about 3,000 to 4,700 cases per Gy per million progeny and constitutes 0.41 to 0.64% of the baseline frequency of 738,000 per million.

The figures for Mendelian diseases are roughly similar to those presented in the UNSCEAR 1993 Report.

575. When the radiation exposure is limited to one generation only, the risk to the second post-radiation generation is lower, as expected. If however, the radiation exposure occurs in every generation, the risks are higher in the second post-radiation generation, since these represent risks to the first and second generations.

576. It is argued that while the doubling doses of 3.4 to 4.5 Sv, retrospectively estimated from the Japanese data (showing no significant adverse genetic effects of radiation) are not comparable to the doubling dose of 1 Gy used by the Committee, an approximate comparison of the risk of untoward pregnancy outcomes in the Japanese studies with the risk of congenital abnormalities in this Annex shows that the risks are similar, considering the uncertainties involved in these estimates.

Glossary

Allele	One of several alternative forms of a gene (or DNA sequence) at a specific chromosome allocation. At each autosomal locus, an individual possesses two alleles, one inherited from the father and one from the mother.
Aneuploid	The chromosome number is not an exact multiple of the haploid number; an individual with an aneuploid chromosome number; usually refers to an absence (monosomy) or an extra copy (trisomy) of a single chromosome
Anticipation	A phenomenon in which the severity of a disorder appears to become more severe and/or arise at an earlier age in succeeding generations.
Autosome	Any chromosome other than the sex chromosomes, X and Y; the diploid human genome consists of 22 pairs of autosomes and one pair of sex chromosomes (X and Y in males and 2 X's in females).
Autosomal dominant disease	One that is due to a mutation in a gene carried on one of the autosomes and manifests its phenotype in a heterozygote.
Autosomal recessive disease	One that requires two mutant genes at the same locus (one from each parent) carried in the autosomes for disease expression.
Candidate gene	Any gene by virtue of its property (function, expression pattern, chromosomal location, structural motif, etc) is considered a possible locus for a given disease.
Coding sequence	Those parts of a gene from which the genetic code is translated into amino acid sequences of a protein.
Codon	A group of three adjacent nucleotides that codes for particular amino acids or for the initiation or termination of the amino acid chain.
Congenital abnormality	An abnormality that is present at birth; the term does not have an aetiologic connotation.
Contiguous gene syndrome	A syndrome due to abnormalities of two or more genes that map next to each other on a chromosome; most often caused by a deletion that involves several contiguous genes.
Diploid	A full set of genetic material, consisting of paired chromosomes – one chromosome from each parental set; most animal cells except the gametes have a diploid set of chromosomes (compare *haploid*)
Deletion	Loss of a portion of a gene or chromosome; a type of mutation; a synonym for deficiency.
Dominant allele	One that determines the phenotype displayed in a heterozygote with another (recessive) allele.
Dominant negative mutations	Dominant mutations in which the product of the mutant allele interferes with the function of the normal allele in the heterozygous state.
Doubling dose (DD)	An important concept used in genetic risk estimation. It is defined as the dose of radiation required to produce as many mutations as those which occur spontaneously in a generation. It is calculated as a ratio of the average spontaneous and induced rates of mutations in a defined set of genes.
DNA sequence	The relative order of base pairs, whether in a fragment of DNA, a gene, a chromosome, or an entire genome.
Epistasis	The non-reciprocal interaction of non-allelic genes in which one gene masks the expression of another.
Equilibrium theory	One of the fundamental concepts in population genetics which postulates that mutant alleles are maintained in the population as a result of a balance between mutations that arise in every generation and selection which eliminates them.
Exon	A region of a gene containing a coding sequence. Most genes have several exons separated by introns (non-coding) which are usually longer.

Fitness (also called Darwinian fitness)	The relative ability of an organism to survive and transmit its genes to the next generation.
Frameshift mutations	A mutation that alters the normal triplet reading frame so that codons downstream from the mutation are out of register and not read properly.
Gamete	Mature reproductive cell (sperm or ovum); contains a haploid set of chromosomes (23 for humans.
Gene	The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product.
Genotype	(a) the genetic constitution of an individual; (b) the types of alleles found at a locus in an individual.
Germ-line mosaicism	Presence of two or more cell lines in the gonadal cells; implies risk of transmisssion of mutation present in the gonads to offspring; synonymous with gonadal mosaicism.
Genomic imprinting	A phenomenon in which an allele at a given locus is altered or inactivated depending on whether it is inherited from the father or the mother. Implies a functional difference in genetic information depending on whether it is inherited from the father or the mother.
Haploid	A single set of chromosomes (half the full set of genetic material) present in the egg and sperm cells of animals (compare diploid).
Hardy-Weinberg equilibrium	The concept that both gene frequencies and genotype frequencies will remain constant from generation to generation in an infinitely large, interbreeding population in which mating is at random and there is no selection, migration or mutation. In a situation where a single pair of alleles (*A* and *a*) is considered, the frequencies of germ cells carrying *A* and *a* are defined as *p* and *q*, respectively. At equilibrium, the frequencies of genotypic classes are p^2 (*AA*), 2 *pq* (*Aa*) and q^2 (*aa*).
Heritability	An attribute of a quantitative trait in a population that expresses how much of the total phenotypic variation is due to genetic factors. In the broad sense, heritability is the degree to which a trait is genetically determined; it is expressed as the ratio of the total genetic variance to the phenotypic variance. In the narrow sense, it is the degree to which a trait is transmitted from parents to offspring and it is expressed as the ratio of additive genetic variance to the total phenotypic variance.
Heterozygote	An individual with different alleles at some particular locus.
Homologous chromosome	Chromosome containing the same linear gene sequences as another, each derived from one parent.
Homozygote	An individual with the same allele at the corresponding loci on the homologous chromosomes.
Intron	The DNA base sequence interrupting the protein-coding sequence of a gene; this sequence is transcribed into RNA, but is cut out of the message before it is translated into protein.
Linkage	The tendency of genes (or other DNA sequences) at specific loci to be inherited together as a consequence of their physical proximity on a single chromosome; measured by percent recombination between loci.
Locus (plural: *loci*)	A unique chromosomal location defining the position of an individual gene or DNA sequence.
Major genes	Those with pronounced phenotypic effects as compared with polygenes.
Mendelian disease	One that is due to mutations in a single gene. Depending on the location of the mutant genes (in autosomes or the X-chromosome) and their effects on the phenotype, Mendelian diseases are classified as autosomal dominant, autosomal recessive and X-linked recessive or dominant.
Mendelian inheritance	A pattern of inheritance which obeys Mendel's first law of independent segregation of the alleles at the same locus conveyed by each parent.

Microdeletion	Deletion of a small piece of chromosome or DNA sequence; may or may not be visible at the microscopic level.
Microsatellite	Highly polymorphic DNA markers comprised of mono-, di-, tri- or tetranucleotides that are repeated in tandem arrays and distributed throughout the genome; the best studied ones are the CA (alternatively GT) dinucleotides repeats; they are used for gene mapping.
Minisatellites	Highly polymoprhic DNA marker comprised of a variable number of tandem repeats that tend to cluster near the telomeric ends of chromosomes; the repeat often contains a repeat of 10 nucleotides; they are used for gene mapping.
Missense mutation	Mutation that causes one amino acid to be substituted for another.
Mitochondrial DNA	DNA distinct from nuclear DNA in that it is mostly unique sequence DNA and codes for proteins that reside in mitochondria.
Mosaicism	Presence of two or more cell lines derived from a single zygote; can be limited to somatic cells or to germ cells or can occur in both somatic and germ cells.
Multifactorial disease	A disease that is interpreted to result from the joint action of multiple genetic and environmental factors.
Mutational cluster	If a gonad is a germinal mosaic for a mutation in a given generation, clusters of identical mutant individuals will result in the following generation; this is called a mutational cluster.
Mutation component	One of the important concepts used in risk estimation with the doubling-dose method. It is defined as the relative change (i.e. increase) in disease incidence (i.e. relative to the incidence before irradiation) per unit relative change in mutation rate (i.e. relative to the spontaneous rate). It is not the same as the genetic component of the disease; rather, it quantifies the responsiveness of the genetic component of the disease to increases in mutation rate. If the disease is only partly genetic, since only the genetic component will respond to an increase in mutation rate, mutation component for such diseases will be lower than that for a fully genetic disease. If the disease is entirely of environmental origin, the mutation component concept does not apply.
Nonsense mutation	Mutation that changes a codon for an amino acid to a termination or stop codon and leads to premature termination of translation so that the protein is either truncated or absent.
Nucleotide	A subunit of DNA or RNA consisting of a nitrogenous base (adenine[A], guanine [G], thymine [T] or cytosine [C] in DNA, adenine, guanine, uracil [U] or cytosine in RNA.
Oncogene	A gene, or more forms of which is associated with cancer; many oncogenes are involved, directly or indirectly, in controlling the rate of cell growth.
Paternal age effect	Used in the context of spontaneous mutation rates, it refers to the increase in mutation rate with the age of the father.
Penetrance	The frequency of expression of a trait or genotype; the proportion of individuals observed to show a particular phenotypic effect of a mutant gene compared with that expected on the basis of Mendelian inheritance.
Phenotype	The physical characteristics of a cell or organism as determined by the genetic constitution.
Point mutation	A mutation confined to a single nucleotide.
Polygenic inheritance	Inheritance determined by many genes at different loci, each with small additive effects; a simple example is height within either sex; see also *multifactorial*.
Recessive	A trait that is expressed in individuals who are homozygous for a particular allele.
Recessive mutations	Those that produce a specific phenotype when present in the homozygous (autosomal recessive) or in hemizygous state (X-chromosomal recessive).
Sex-chromosomes	The chromosomes that primarily govern sex determination (XX in women and XY in men); the other chromosomes are autosomes.
Sex-chromosomal gene	A gene located on either the X or the Y chromosome. Since the number of genes on the Y chromosomes is small, unless otherwise specified, most often the term implies location of the gene on the X chromosome.

Somatic cells	All cells in the body except gametes and their precursors.
Synteny	The term *synteny* (meaning same thread or ribbon; a state of being together in location as synchrony would be together in time) refers to gene loci on the same chromosome regardless of whether or not they are genetically linked by classic linkage analysis. Although not quite correct, the term is used nowadays to refer to gene loci in different organisms located on a chromosomal region of common evolutionary ancestry.
Telomere	The end of a chromosome. This specialized structure is involved in the replication and stability of linear DNA molecules.
Transition type mutation	A mutation which results from the substitution of one purine by another (A to G or G to A) or of one pyrimidine by another (C to T or T to C).
Transversion type mutation	A mutation which results from the substitution of a purine by a pyrimidine or vice versa.
Uniparental disomy	Situation in which an individual has two homologous chromosomes (or chromosomal segments) from one parent and none from the other
X-linked gene	Gene carried on the X-chromosome.

Table 1
Sizes of human genes
Based on [M1], with additions

Gene	*Genomic size (kb)*	*cDNA (mRNA) (kb)*	*Number of introns*
Small			
α-globin	0.8	0.5	2
β-globin	1.5	0.6	2
Insulin	1.7	0.4	2
Apolipoprotein E	3.6	1.2	3
Parathyroid hormone	4.2	1.0	2
Medium			
Protein C	11	1.4	7
Collagen 1 pro-α-1	18	5.0	50
Collagen 1 pro-α-2	38	5.0	50
Albumin	25	2.1	14
Adenosine deaminase	32	1.5	11
Factor IX	34	2.8	7
Catalase	34.	1.6	12
Low-density lipoprotein receptor	45	5.5	17
Large			
Phenylalanine hydroxylase	90	2.4	12
Breast cancer gene 1 (BRCA 1) [M10]	≈100	5.6	22
Fibrillin [P6]	≈110	≈9.3	64
Giant			
Factor VIII	186	9.0	26
Cystic fibrosis transmembrane conductance regulator (CFTR) [T1]	≈230	6.5	26
Thyroglobulin	>300	8.4	>36
Mammoth			
Dystrophin (Duchenne muscular dystrophy) [K13, R8]	2 500	14	69

Table 2
Molecular nature of mutations in Mendelian diseases
[S4]

Category	*Number of Mendelian diseases caused by*			*Total*
	Point mutations [a]	*Point mutations and length mutations* [b]	*Length mutations and microdeletion syndromes*	
Autosomal dominant	73	18	25	116
X-linked	16	24	8	48
Subtotal	89 (54%)	42 (26%)	33 (20%)	164
Autosomal recessive	111	27	7	145
Total	200 (65%)	69 (22%)	40 (13%)	309

a Base-pair changes.
b Predominantly DNA deletions.

Table 3
Distribution of point mutations in some human genes

Disease	*Gene*	*Genomic size (kb)*	*Number of exons*	*Comments*	*Ref.*
Autosomal dominant					
Osteogenesis imperfecta	*COL1a1*	18	≈50	Nearly over the entire gene	[B2, D2]
Familial hypercholesterolemia	*LDLR*	45	18	Nearly over the entire gene	[H13, S23]
Breast and ovarian cancer due to BRCA1 mutations	*BRCA1*	≈100	23	Nearly over the entire gene	[C10, F5, F6, L8, M12, S24, T9]
Achondroplasia	*FGFR3*	(≈2.5) (cDNA)	?	G→A at amino acid residue 380 (Gly307 Arg) in the transmembrane domain of the protein most common; G→C at the same residue resulting in the same amino acid substitution in some cases	[M5, R4, S11]
Amyloidosis V; gelsolin gene defects	*GSN*	(≈2.6) (cDNA)	?	G→A (Asp187Asn) is the only mutational event recorded in studies worldwide; the other mutation is G→T transversion at the same codon (Asp187Tyr) in Danish and Czech families	[D8, M1]
Acute intermittent porphyria	*HMBS*	11	15	21 of the 34 recorded mutations in exons 9, 10, and 12 (7 in exon 10 and 11 in exon 12)	[A5]
Autosomal recessive					
Gaucher disease (glucocere-brosidase deficiency)	*GBA*	≈7.6	11	In all exons except 3 and 4; most widespread missense mutations in exons 9 and 10)	[H14, M13]
Mucopolysaccharidosis, type I (glycosidase α-L-iduroniase deficiency)	*IDUA*	19	14	In all exons except 5 and 13; most clustered towards the beginning (exons 1-3) and middle (exons 6-10) of the gene	[S9]
Phenylketonuria (phenylalanine hydroxylase deficiency)	*PAH*	90	13	Distributed nearly over all exons	[E2]
Cystic fibrosis	*CFTR*	≈230	27	In exons 3-5, 7-8, 10-12, and 20-21; paucity of point mutations in exons 6b, 16, 17a, and 24	[T1]
X-linked					
X-linked severe combined immunodeficiency (inter-leukin-2 receptor defect)	*SCIDX1, IL2RG*	4.2	8	In all exons, but most in 2-4	[P8]
Glucose-6-phosphate dehydro-genase deficiency	*G6PD*	≈18	13	In all exons except 9, the smallest, and exon 13, which codes for the carboxyterminus	[V5]
Agammaglobulinaemia, Bruton type	*AGMX1, BTK1*	20	19	Over the whole gene, including in the ATG start codon	[P8]
Lesch-Nyhan syndrome	*HRPT*	44	9	Nearly over the whole gene including some splice sites; about 40% of the point mutations occur in exon 3 in two regions of only 6 bp; exon 5 has 11% of mutations with a 8 bp region	[C11, D27, S25, T10]
Haemophilia A	*FVIII*	186	26	Missense mutations over the whole gene except for exon 14 which codes for the B domain which has no known function; nonsense mutations in exon 1, 7-9, 11, 12-14, 16-19, and 22-26	[A4]

Table 4
Examples of mutations in one gene resulting in more than one clinical disease (allelic heterogeneity) [M1, R52]

Gene	*Chromosomal location*	*Disease*	*Ref.*
CMT1A (PMP22) (peripheral myelin protein 22)	17p12-p11.2	Charcot-Marie-Tooth disease type 1A (CMT1A); hereditary neuropathy for pressure palsies (HNPP), Djerine-Sottas syndrome (DSS)	[B1, C3, P1, R1, S8]
APOA1 (apolipoprotein A1)	11q23.3	Hypertriglyceridaemia, amyloid nephropathy	[F7, N5]
COL2A1 (collagen type 2, α1)	12q12-q13.2	Wagner syndrome, spondyloepiphyseal dysplasia, Stickler syndrome, Kniest dysplasia	[B13, K14, W8]
FBN1 (fibrillin)	15q21.1	Classic Marfan syndrome, neonatal Marfan syndrome, ectopia lentis	[D9]
COL1A1 (collagen type 1, α1)	17q21.3-q22	Osteogenesis imperfecta types I-IV, Ehlers-Danlos syndrome type VII	[B2, S10]
FGFR3 (fibroblast growth factor receptor 3)	4p16.3	Achondroplasia, thanatophoric dysplasia types I and II, hypochondroplasia	[M5]
FGFR2 (fibroblast growth factor receptor 2)	10q25.3-q26	Pfeiffer syndrome, Apert syndrome, Jackson-Weiss syndrome, Crouzon syndrome	[M5]
RET protooncogene	10q11.2	Multiple endocrine neoplasia MEN2A, MEN2B, medullary thyroid carcinoma, Hirschprung disease	[D1, E1, H2, M3, M4, R2]
IDUA (α-L-iduronidase)	4p16.3	Hurler syndrome, Scheie syndrome	[S9]
LIPA (Lipase A, lysosomal acid cholesteryl esterase)	10q23.2-q23.3	Wolman disease, cholesteryl ester storage disease	[A6, K15]
DMD (Dystrophin)	Xp21.3-p21.2	Duchenne muscular dystrophy, Becker muscular dystrophy	[W9]
AR (Androgen receptor)	Xq11.2-q12	Androgen insensitivity syndrome; Kennedy spinal and bulbar muscular atrophy; male breast cancer	[B10, B14, W10]

Table 5
Examples of similar clinical diseases resulting from mutations in different genes
[M1]

Disease	*Gene*	*Chromosomal location*	*Ref.*
Alport syndrome, X-linked	COL4A5	Xq22-q23	[B15]
Alport syndrome, autosomal recessive	COL4A3	2q36-q37	[L9, M14]
Alport syndrome, autosomal recessive	COL4A4	2q35-q37	[L9, M14]
Familial Alzheimer disease, early onset, autosomal dominant	APP	21q21.2	[G4]
Familial Alzheimer disease, early onset, autosomal dominant	E51	1	[R10, S26]
Familial Alzheimer disease, early onset, autosomal dominant	S182/AD3	14q24.3	[R10, S26]
Familial Alzheimer disease, late onset, autosomal dominant	ApoE/AD2	19q13/2	[M59, S26]
Diabetes insipidus, nephrogenic, autosomal dominant	AQP2	12q12-q13	[D10]
Diabetes insipidus, nephrogenic, autosomal recessive	AVPR2	Xq28	[R11, V6]
Diabetes insipidus, neurohyphyseal, autosomal dominant	AVP	20p13	[B16, I12, I3]
Diabetes mellitus, MODY, type II, autosomal dominant	GCK	7p	[S27, V7]
Diabetes mellitus, MODY, type I, autosomal dominant	MODY1	20q12-q13.1	[S27, V7]
Osteogenesis imperfecta, types I-IV, autosomal dominant	COL1A1	17q21.3-q22	[B2]
Osteogenesis imperfecta, types I, autosomal dominant	COL1A2	7q21.3-q22.1	[B2]
Ehlers-Danlos syndrome, type VII, autosomal dominant	COL1A1	17q21.3-q22	[S10]
Ehlers-Danlos syndrome, type VII, autosomal dominant	COL1A2	7q21.3-q22.1	[S10]
Hirschprung disease, autosomal dominant	RET	10q11.2	[E1]
Hirschprung disease, autosomal dominant	EDNRB	13q22	[P9]
Epidermolysis bullosa, Dowling-Meara type	KRT5	12q	[S28]
Epidermolysis bullosa, Dowling-Meara type	KRT14	17q12-q21	[S28]
Usher syndrome	USH1A	14q32.1-q32.3	[C14]
	USH1B	11q13.5	[C14]
	USHIC	11p15.1-p14	[C14]
Retinitis pigmentosa, autosomal dominant	RP1	8p11-q21	[C15, M1]
Retinitis pigmentosa, X-linked	RP2	Xp11.4-p11.23	[C15, M1]
Retinitis pigmentosa, X-linked	RP3	Xp21.1	[C15, M1]
Retinitis pigmentosa, X-linked	RP6	Xp21.3-p21.2	[C15, M1]
Retinitis pigmentosa, autosomal dominant	RP9	7p	[C15, M1]
Retinitis pigmentosa, autosomal dominant	RP10	7q	[C15, M1]
Retinitis pigmentosa, autosomal dominant	RP11	19q13.4	[C15, M1]
Retinitis pigmentosa, autosomal recessive	RP12	1q31-q32.1	[C15, M1]
Retinitis pigmentosa, autosomal recessive	RP14	6p21.3-p21.2	[C15, M1]

Table 6
Skeletal disorder phenotypes associated with mutations in the fibroblast growth factor receptor (*FGFR*) gene [M5]

Phenotype/gene	*Hypo-chondro-plasia*	*Achondro-plasia*	*Thanato-phoric dwarfism*	*Pfeiffer syndrome*	*Apert syndrome*	*Jackson-Weiss syndrome*	*Crouzon syndrome*
Main clinical features							
Short limb dwarfism	+	+	+	–	–	–	–
Cloverleaf skull	–	–	+	+	–	–	–
Underdeveloped midface	–	+	+	+	+	+	+
Craniosynotosis	–	–	–	+	+	+	+
Foot anomalies	–	–	–	+	+	+	–
Hand anomalies	–	–	–	+	+	–	–
Mutations identified [a]							
FGFR1				P252R (7)			
FGFR2				C342R (8) exB acc.ss [b] C342Y T341P D321A	S252W (25) P253R (15)	A344G	C342Y (3) A344A (3) Y340H (2) S354C S347C Y328C C342R C342S
FGFR3	N540K (8)	G380R (192) G375D	R248C (22) K650E (16) S371C				

a Predicted amino acid changes with number of times observed in unrelated individuals in parentheses.
Amino acid designations: P = proline; R = arginine; C = cysteine; Y = tyrosine; T = threonine; D = aspartic acid; A = alanine; N = asparagine; K = lysine; G = glycine; E = glutamic acid; S = serine; W = tryptophan

b Three different point mutations within the acceptor splice site of exon B of *FGFR* were described in five unrelated patients. A recurring synonymous change Ala344 to Ala, within the same exon B in individuals with Crouzon syndrome was shown to activate a new donor splice site within exon B of *FGFR*.

Table 7
Reported instances of uniparental disomy in humans
[S2]

Chromosome segment	*Hetero-/isodisomy*	*Clinical disorder*
*2mat [a]	?	[Developmental delay] [b]
4 mat	i (?)	None
*5 mat	i	None [SMA]
6 pat	i	None
*7 pat	h, i	Silver-Russell (-like) syndrome
*7 pat	i	None [chloride diarrhea]
11pter-p15.4 pat	i	Beckwith-Wiedemann syndrome
11 pat mosaicism	i	Beckwith-Wiedemann syndrome
13 mat	i	None
*13 pat	i	None
14 pat	h, i	MCA/MR syndrome
14 mat	h, i	MCA syndrome
15q11.2-q12pat	h, i	Angelman syndrome
15q11.2-q12pat	h, i	Prader-Willi syndrome
16 mat	h, i	Growth retardation?
*20 pat	i	[MCA/MR syndrome] [a]
21 mat	i	None
21 pat	i	None
*22 mat	i	None
X pat	i	Growth retardation? [a]
X and Y pat	h	None
*XXXX mat	h, i	Severe 48,XXXX

a mat = maternal; pat = paternal; SMA = spinal muscular atrophy; MCA = multiple congenital abnormality; MR = mental retardation.
b Mosaicism for trisomy (monosomy) makes clinical evaluation difficult.

Table 8
Trinucleotide repeat expansions in mendelian diseases
[A2, B8, B29, C80, D7, D24, G15, K10, K12, M7, S15, Z1]

Disease [a b]	*Repeat sequence*	*Repeat number range*		
		Normal	*Premutation*	*Disease*
Fragile X-A (FRAXA)	CGG	5–50	50–200	>200
Fragile X-E (FRAXE)	GCC	6–25		>200
Spinal and bulbar muscular atrophy (SBMA)	CAG	6–39		36–62
Huntington's disease (HD)	CAG	10–35	30–38	27–121
Dentatorubral pallidoluysian atrophy (DRPLA)	CAG	7–23		49–75
Spinocerebellar ataxia 1 (SCA 1)	CAG	6–39		54–75
Spinocerebellar ataxia 3 (SCA 3)/ Machado Joseph disease (MJD)	CAG	13–61		61–84
Spinocerebellar ataxia 2 (SCA 2)	CAG	15–24		35–59
Spinocerebellar ataxia 6 (SCA 6)	CAG	4–16		21–27
Spinocerebellar ataxia 7 (SCA 7)	CAG	7–17		38–130
Myotonic dystrophy (DM)	CTG	5–37		100–4 000
Friedreich's ataxia	GAA	7–22		200–1 700
Oculopharyngeal muscular dystrophy (OPMD)	GCG	6		8–13
Synpolydactyly (SPD)	GCG	15		22–29

a For FRAXA, FRAXE and SCA 1, the repeats are in the 5'-untranslated region of the gene; for SBMA, HD, SCA 3, SCA 7, MJD, DRPLA, OPMD, SPD and Friedreich's ataxia, they are in the coding region; for DM and SCA6, they are in the 3'-untranslated region.

b Not shown in Table 9 is a form of progression myoclonus epilepsy that is due to an expansion of a dodecamer repeat (12 nucleotide repeat expansion) located upstream of the 5' transcription start site of the *GSTB* gene.

Table 9
Summary of baseline frequencies of genetic diseases in humans

Disease class	*Estimates of frequency in 10^4 persons* [a]		*Ref.*
	Previous estimate [U4]	*This estimate*	
Mendelian			
Autosomal dominant	95	150	[C67, C68, S105]
Autosomal recessive	25	75	[C67, C68, S105]
X-linked	5	15	[C67, C68, S105]
Chromosomal	40	40	[U8]
Multifactorial			
Congenital abnormalities	600	600	[C37]
Chronic	6 500	6 500	[C35]

a Frequencies in live births for Mendelian diseases and congenital abnormalities; population frequency for chronic multifactorial diseases, frequency in population.

Table 10
Estimates of the frequency of autosomal dominant diseases in humans

Disease	*Number of genes known or mapped*	*MIM number [M2]*	*Frequency (× 10^4)*		*Age at clinical diagnosis / onset (years)*	*Ref.*
			Live births [C67]	*Population*		
Nervous and neuromuscular systems						
Huntington disease	1	143100	5.0	0.4-0.8	3 to late 70s; 6% of cases with childhood/juvenile onset; others fourth and sixth decade	[H7, M49]
Neurofibromatosis 1	1	162200	4.0	3.5	First decade	[L53, R46]
Neurofibromatosis 2	1	101000	0.3 [a]	-	Severe type: 20 years; milder type: third decade	[E23]
Tuberous sclerosis	2	191092 191100	1.0	0.3-0.6	Childhood and young adults	[H21, O2]
Primary basilar impression	0	109500	3.0	-	Young adults	[C67]
Cerebellar ataxias	7	109150 164400 164500 183086 183090 600223 600224	0.5	0.5	Young adults	[H22, I6]
Dentatorubral pallidoluysian atrophy	1	125370	-	0.04-0.7	First to sixth decade; mean: 32 years	[I7, O3]
Myotonic dystrophy	1	160900	2.0	1.3	Severe congenital form: at birth; classical form: early adult life; mild form: late adult life	[H10, W6]
Peroneal muscular atrophy (Charcot-Marie-Tooth disease)	3	118200 118210 118220	2.0	4.0	Second decade	[P1, S89]
Spastic paraplegia	3	182600 182601 600363	0.5	0.7	Early childhood to adult	[P34, R47]
Facioscapulohumeral muscular dystrophy	1	158900	-	0.4-0.5	Variable: young adult to late adult life	[L49]
Skeletal system						
Diaphyseal aclasis (multiple exostoses)	3	133700 133701 600209	5.0	0.1-0.2	Childhood	[H23, L49, S90, S91, W30]
Thanatophoric dwarfism	1	134934	0.8 0.2-0.5 [a]	-	Birth (neonatal lethal)	[A18, M41, O4, S95]
Achrondroplasia	1	134934	0.2 0.1-1.5 [a]	-	Birth	[A18, M41, S95]
Osteogenesis imperfecta	2	120150 120160	0.4 1-2.2 [a]	-	Birth	[A18, B2, O4]
Ehlers-Danlos syndrome	3	120150 120160 120180	0.1	2.0	Childhood	[S10]
Osteopetrosis tarda	1	166600	0.1	0.5	Childhood	[B70, B66, V2, W30]
Treacher Collins syndrome	1	154500	0.2 [a]	-	Childhood	[D33]

Disease	*Number of genes known or mapped*	*MIM number [M2]*	*Frequency (× 10^4)*		*Age at clinical diagnosis / onset (years)*	*Ref.*
			Live births [C67]	*Population*		
Craniosynostosis (Pfeiffer, Apert, Crouzon and Jackson-Weiss syndromes)	5	101200 101400 101600 123101 123500	4.0 [a]	-	Birth	[C75, W31, W32]
Holoprosencephaly	3	142946 157170 600725	1.7 [a]	-	Birth	[C76]
Van der Woude syndrome (Cleft lip ± palate with mucous pits of lip)	1	173900	0.1 0.3 [a]	-	Birth	[B63, R48]
Kidneys						
Autosomal dominant polycystic kidney [b]	2	173900 173910	8.0	10.0	Most cases in late middle age	[D34, H24]
Von Hippel Lindau syndrome [c]	1	193300	0.3 [a]	-	Second to third decade	[M29]
Intestines						
Familial adenomatous polyposis coli	1	175100	1.0	-	Multiple polyps in colon by age 20 and progression to cancer by age 50 in 90% of cases	[B61]
Blood/circulatory system						
Hypercholesterolemia (FH)	1	143890	20.0	-	50% of heterozygous males have some manifestation of coronary heart disease by age 50; in females this occurs 10-15 years later	[B56]
Hypercholesterolemia due to familial defective apoB-100	1	107730	10-15 [a]	-	Roughly similar to FH	[H51, I11, M30, M31, T19]
Congenital spherocytosis	1	182900	2.0	-	Childhood	[C67]
Antithrombin III deficiency	1	107300	-	2-5	Childhood	[A19, P35, R49]
Familial hypertrophic cardiomyopathy	7	160760 160781 191010 191044 191045 600858 600958	-	2.0	Young adults	[W33]
Williams syndrome	1	130160	1.0 [a]	-	Childhood	[B53]
Velecardial syndrome (DiGeorge syndrome)	1 (?)	192430	2.5	-	Childhood	[C77]
Hereditary haemorrhagic telangiectasia	2	187300 600376	-	1.0	Childhood	[P36]
Ear and eye						
Dominant forms of early childhood pre-lingual deafness	3	601317 601543 601842	1.0	-	Childhood	[P37, V12]
Dominant form of adult-onset deafness	10	121011 124900 600101 600652 600965	-	2.5	Adults	[P37, V12]

Disease	*Number of genes known or mapped*	*MIM number [M2]*	*Frequency (× 10^4)*		*Age at clinical diagnosis / onset (years)*	*Ref.*
			Live births [C67]	*Population*		
Dominant form of adult-onset deafness (continued)		600994 601316 601369 601412 601848				
Dominant forms of blindness (for retinitis pigmentosa)	9	180100 180103 180104 180105 180380 600132 604414 601850 ?	1.0	-	Young adults	[B54, D16, X1]
Retinoblastoma	1	180200	0.3 0.4-0.7 [a]	-	Childhood	[B71, V8, Y3]
Teeth						
Dentinogenesis imperfecta	2	125490	1.0	1.3-1.6	Childhood	[W13]
Amelogenesis imperfecta	1	104500	0.2	0.5	Childhood	[W11]
Breast and ovary						
Early onset familial breast and ovarian cancers	2	113705	10.0 [a]	-	About 30 years	[C21, E6, F14, N6, S93]
Metabolism						
Acute intermittent porphyria	1	176000	0.1	>0.5 10.0 [d]	After puberty	[A20, W34]
Variegate porphyria	1	176200	0.1	-	First decade	[C67]
Others						
Marfan syndrome (skeleton, cardiovascular, ocular)	1	154700	0.4	2.0	Neonatal for a small subset; the remainder first and second decade	[D9]
Waardenburg syndromes (auditory, pigmentation)	2	193500 193510	-	0.1-0.2	Childhood	[F18, R50]
Hirschprung disease (nervous, gastrointestinal)	3	131244 142623 164761	2.0 [a]	-	Childhood	[I8, P38]
Malignant hyperthermia susceptibility (skeletal muscle homeostasis)	5	154275 154276 180901 600467 601888	-	1.0	Childhood	[H25, R51]
Li-Fraumeni syndrome	1	191170	0.2 [a]	-	Invasive cancers by age 30 in 50% of cases	[M24]
Total frequency [(10^4) live births (38 entries)] Total adjusted frequency (10^4 live births)			~92-96 150			

a Additional or new estimate included.
b Also affects liver and cerebrovascular systems.
c Also affects nervous system, eye, and pancreas.
d Northern Sweden.

Table 11
Estimates of the frequencies of autosomal recessive diseases in humans
Unless otherwise stated, most of these diseases have early onset

Disease	*Number of genes known or mapped*	*MIM number [M2]*	*Birth frequency ($\times 10^4$) [C67]*	*Comments*	*Ref.*
Metabolism					
Cystic fibrosis	1	219700	5.0	Varies from ~1.3 10^{-4} in Sweden to ~6.0 10^{-4} in Faroe Islands; very rare in Orientals and African blacks	[S80, T1]
Phenylketonuria, classical	1	261600	1.0	Frequency in United States blacks one third of that in whites; rare in Ashkenazi Jews	[B30, C78, H34]
Cystinuria	1	220100	0.6	High frequency in Israeli Jews of Libyan origin (4 10^{-4})	[S81]
Tay-Sachs disease	1	272800	0.4	High frequencies in Ashkenazi Jews (1.7 10^{-4} to 2.6 10^{-4}) and non-Jewish French Canadians from south eastern Quebec	[A21, G22]
Mucopolysaccharidosis type IIIB	1	252920	0.4	Estimates vary from 0.5 10^{-4} in Germany to 0.2 10^{-4} in Australia to 0.04 10^{-4} in Northern Ireland	[W35]
Mucopolysaccharidosis type I (Hurler syndrome)	1	252800	<0.2	Rare in Ashkenazi Jews	[L16]
Metachromatic leukodystrophy	1	250100	0.2		[G12, G13]
Galactokinase deficiency	1	230200	0.1		[M2]
Galactosaemia	1	230400	0.1		[M2]
Homocystinuria	3	236200 236250 277400	0.1		[M32]
Methylmalonic aciduria	1	251000	0.3 [a]		[C79, L31]
Krabbe disease	1	245200	0.1[a]	Higher frequency in Druze and Moslem Arab villages in Israel	[W2]
Hereditary fructose intolerance	1	229600	0.1[a]		[T8]
Haemochromatosis	1	235200	30.0 [a]	Range: 20-50 10^{-4}; mid-adulthood	[C64, E19, F15, L51]
Neuromuscular					
Spinal muscular atrophy	1	253300	1.0		[P31]
Friedreich's ataxia	1	229300	0.2 [a]	Population frequency 2-4 10^{-4} in several European populations; onset <20 years of age	[C55, L38, P34, R45]
Limb girdle muscular atrophies	6	114241 253601 253700 600900 601411 601954	0.1? [a]		[M33]

Disease	*Number of genes known or mapped*	*MIM number [M2]*	*Birth frequency (× 10^4) [C67]*	*Comments*	*Ref.*
Endocrine glands					
Adrenal hyperplasias	3	201910 202010 202110	1.0 [b]	The estimate for the non-classical (late onset or cryptic) form of 201910 is higher: 3.7% in Ashkenazim, 2% in Hispanics and Yugoslavs, 0.3% in Italians; 202010 and 202110 are less frequent than 201910	[S88]
Red blood cells					
Sickle cell anaemia	1	141900	1.0	Sickle-cell trait (heterozygotes) present in about 8% of the African-American population	[M34]
Hearing					
Severe congenital deafness	10	276903 600316 601386 600791 600792 600971 600974 601071 601072 ?	~2.0	601386 (DFNB3) affects 2% of the residents of an Indonesian village on the north shore of Bali	[F19, P37, V12]
Sight					
Recessive forms of blindness (retinitis pigmentosa loci)	>10	123825 180069 180071 180090 600105 601718	1.0		[D16]
Mental retardation					
Non-specific recessive forms of mental retardation		-	5.0		
Total frequency in 10^4 live births Total adjusted frequency in 10^4 live births			50.8 75		

a Additional or new estimate included.
b For the severe “classical” form 201910.

Table 12
Estimates of the frequencies of X-linked diseases in humans
Unless otherwise stated, most of these diseases have early onset

Disease	*Number of genes known or mapped*	*MIM number [M2]*	*Birth frequency (× 10^4) [C67]*	*Comments*	*Ref.*
Muscular					
Duchenne muscular dystrophy	1	310200	4.0	Range: 2.2-3.0 10^{-4} male births; DMD has early onset and rapid progressive muscle wasting resulting in death in the teens; with BMD, onset in early teens and death in middle age	[B31, E24, N7, V13]
Becker muscular dystrophy	1	310200	~0.5 [a]		
Skin					
Ichthyosis (steroid sulfate deficiency	1	308100	2.0		[S75]
Anhidrotic (hypohidrotic ectodermal dysplasia)	1	305100	~1.0 [a]		[K20]
Blood					
Haemophilia A		306700	2.0		[A22]
Haemophilia B		306900	0.2 [a]		[M35]
Mental retardation					
Fragile-X syndrome (X-linked dominant)		309550	5.0 [a]	Range: 3-10 10^{-4} male births; about 30% female heterozygotes mentally retarded and 10-20% of males in fragile-X pedigrees predicted to carry the fragile-X mutation are normal	[F3]
Non-specific X-linked mental retardation (including fragile-X E and F types)	>10	300031 300046 300047 300062 300077 309530 309540 309545 309548 ?	~1.0	-	[M2]
Eye, ear					
Ocular albinism	2	300500 300600	<0.10 [a]	-	[W12]
Choroideraemia	1	303100	0.10 [a]	Affected males develop night blindness in their teens, followed by progressive construction of visual fields and complete blindness by middle age	[V14]
X-linked nystagmus	1	310700	0.10		
X-linked deafness	5	300030 300036 300039 304500 304700	0.10		
Others					
Fabry disease	1	301500	0.25 [a]		[E25]

Disease	*Number of genes known or mapped*	*MIM number [M2]*	*Birth frequency (× 10^4) [C67]*	*Comments*	*Ref.*
X-linked immune disorders (agammaglobulinaemia, hyper-Igm syndrome, severe combined immunodeficiency)	3	300300 300400 308230	0.25 [a]		[H11, P8]
Hypophosphataemia (X-linked dominant)	1	307810	0.05 [a]		[F20]
Batten disease (juvenile neuronal lipofuscinosis)	1	304200	1.00 [a]	Increased prevalence in northern European populations	[Z2]
Total frequency 10^4 male live births			17.65		
In total births			8.8		
Total adjusted frequency in 10^4 live births			15		

a Additional or new estimate included.

Table 13
Examples of Mendelian diseases with high prevalence and/or enrichment for specific mutations among Ashkenazi Jews
[M2, M6]

Disease	*MIM number [M2]*	*Findings*	*Ref.*
Autosomal dominants			
BRCA1- and *BRCA2*-associated breast and ovarian cancers	113705 600185	Two ancestral mutations (*BRCA1: 185del AG* and *BRCA2 6174 delT*) each appear in the general population at ~1% frequency; a third mutation, *BRCA1 5382 insC*, occurs at a population frequency of 0.11%	[A17, S93, T11]
Idiopathic torsion dystonia	128100	Overall heterozygote frequency: 0.1-0.3%	[R42]
Autosomal recessives [a]			
Tay-Sachs disease	272800	Overall heterozygote frequency 3-4%; a four-base-pair insertion in exon 1 is the most common mutation, found in about 80% of the carriers tested; in the classic infantile form, the disease causes lethality by age 2-3 years	[K9]
Gaucher disease	230800	Overall heterozygote frequency 4-6%; two mutations, a G→A transition at nucleotide 5841 (aspargine to serine) and an insertion of G at nucleotide 84 account for 80% of the mutant alleles; nearly 90% of the homozygotes for the first of these mutations have a mild clinical course	[H9]
Canavan disease	271900	Overall heterozygote frequency 1.7-2%; three mutations, an A→C (glutamic acid 285 alanine), A→C (tyrosine 231 ter), and A→G (IVS-2, -2), account for 98.8% of mutant alleles; homozygotes almost lethal in infancy	[K8]
Niemann-Pick disease, types A and B	257200	Overall heterozygote frequency 1-2%; three mutations, a T→C (leucine 302 proline), del C in codon 330, and a C→A (arginine 456 leucine) account for 65% of the mutant alleles in patients with type 1 disease; homozygotes lethal in infancy	[L14]
Mucolipidosis	252650	Overall heterozygote frequency ~1%; the disease is generally lethal but milder variants may exist	[M34]
Bloom's syndrome	210900	Overall heterozygote frequency ~1%; homozygosity for a six-base-pair delation and a seven-base-pair insertion at nucleotide 2281 in four ostensibly unrelated patients of Ashkenazi Jewish ancestry. Overall, out of 168 cases worldwide, 107 had survived infancy and 93 were alive as of 1996. Of the 61 deceased patients, 50 had died of cancer at a mean age of 26.4 years.	[E26, G14]
Familial dysautnomia	223900	Overall heterozygote frequency ~3%; disease incidence 1 in 3600 live births	[B32, M27]
Factor XI deficiency (clotting factor)	264900	Overall heterozygote frequency 8.1%; two mutant alleles, one causing glutamic acid 117 to ter and another causing phenylalanine 283 to leucine change accounted for 96% of the 86 mutant alleles examined; heterozygotes have a mild bleeding tendency; survival of patients almost normal	[A23]
Pentosuria	260800	Overall heterozygote frequency 2.5-3%; survival of patients normal	[L4]

a A rough guide to the disease frequency for autosomal recessive is as follows: if the disease frequency of a monogenic recessive trait is $1/10^4$, under the assumption of Hardy-Weinberg equilibrium, the mutant gene frequency is $1/10^2$ (i.e., $\sqrt{0.0001} = 0.01$). The heterozygote frequency is $2 \times 0.01 \times 0.99 = 1.98\%$.

Table 14
Examples of Mendelian diseases that are more common in Finland than elsewhere
[D31, P33]

Disease	*MIM number [M2]*	*Approximate number of affected described*	
		In Finland	*Elsewhere*
Autosomal dominants			
Familial amyloidoses, Finnish type; also Meretoja syndrome, amyloidosis V	105120	1000 [a]	<40
Familial benign erythrocytosis	133100	40	?
Autosomal recessives			
Aspartylglucosaminuria	208400	>200	20
Cartilage hair dysplasia	250250	112	80
Congenital nephrotic syndrome (Finnish type)	256300	300	>200
Congenital choroid diarrhoea	214700	40	>60
Cornea plana congenita	217300	60	>20
Diastrophic dysplasia	222600	170	200
Gyrate atrophy of chloride and retina, also gyrate atrophy with ornithine delta amino transferase deficiency	258870	70	<50
Autoimmune polyadrenopathy-candidasis-ectodermal dystrophy (APECED)	240300	63	<50
Mulberry dwarfism	253250	54	<10
Early infantile ceroid lipofuscinosis	256730	107	50
Salla disease (also sialuria, Finnish type)		68	<10
Progressive myoclonal epilepsy	254800	170	>100
Usher syndrome type III	276902	70	<100
X-linked diseases			
Choroideraemia	303100	150	300
Retinaschisis	312700	300	>300

a Estimate; some 300 cases actually diagnosed.

Table 15
Selected "classic"mutation rates for human genes
[V20, V21]

Trait	*Population examined*	*Mutation rate (× 10^6)*
Autosomal dominant mutations		
Achondroplasia	Denmark Northern Ireland Four cities Münster, Germany	10 13 14 6-9
Aniridia 1, 2	Denmark Michigan, United States	2.9-5 2.6
Myotonic dystrophy	Northern Ireland Switzerland, Germany	8 11
Retinoblastoma	United Kingdom; Michigan, United States Switzerland, Germany, Hungary Netherlands Japan France New Zealand	6-7 6 12.3 8 5 9.3-10.9
Acrocephalosyndactyly (1) (Apert syndrome)	United Kingdom Münster, Germany	3 4
Osteogenesis imperfecta types I, II, IV	Sweden Münster, Germany	7-13 10
Tuberous sclerosis (epiloia)	Oxford, United Kingdom Chinese	10.5 6
Neurofibromatosis (1)	Michigan, United States Moscow, Russian Federation	100 44-49
Polyposis of intestines	Michigan, United States	13
Marfan syndrome	Northern Ireland, United Kingdom	4.2-5.8
Polycystic disease of the kidneys	Denmark	55-120
Diaphyseal aclasis (multiple exostoses)	Münster, Germany	6.3-9.1
Sex-linked recessive mutations		
Haemophilia	Denmark Switzerland Münster, Germany	32 22 23
Haemophilia A	Hamburg, Germany Finland	57 23
Haemophilia B	Hamburg, Germany Finland	3 2
Duchenne type muscular dystrophy	Utah, United States Northumberland and Durham, United Kingdom Südbaden, Germany Northern Ireland Leeds, United Kingdom Wisconsin, United States Bern, Switzerland Fukuoko, Japan Northeast England Warsaw, Poland Venice, Italy	95 43 48 60 47 92 73 65 105 46 35-61
Incontinentia pigmenti, Mainz type 2 (Bloch-Sulzberger)	Münster, Germany	6-20
Orofacidigital (OFD) syndrome	Münster, Germany	5

Table 16
Distribution of 49 human X-linked traits according to estimated mutation rates
[C69, S106]

Estimated mutation rate (10^{-6})	*Frequency of traits with this mutation rate*
50	1
20–49	1
10–19	1
5–9	2
1–4	9
0.1–0.9	11
<0.1	24
Total	49

Table 17
Comparison of birth prevalences of congenital abnormalities in Hungary and British Columbia

ICD code [a]	*Type of abnormality*	*Prevalence per 1,000 live births*	
		Hungary, 1970-1981 [C37]	*British Columbia* [b]*, 1974-1983 [B36]*
740-742	Central nervous system	2.2	2.3
743	Eye	0.3	1.2
744	Ear, face, and neck	0.5	1.8
745-747	Heart and circulatory system	7.9	10.5
748	Respiratory system	0.3	1.5
749	Cleft lip with/without cleft palate	1.5	1.7
750-751	Other parts of digestive system	2.8	6.3
752-753	Urogenital system	9.1	9.0
754-756	Musculoskeletal system	31.3 [c]	17.4
757	Integument disorders	0.7	2.4
758	Chromosomal anomalies	1.3	1.3
759	Other unspecified disorders	2.0	0.9
Total		59.9	52.8 [d]
550	Inguinal hernia	11.0	7.9 [d]
227-228	Congenital tumours	0.1	-
Total		71.0	60. 7[d]

a Based on WHO [W20].
b Most of these rates are based on total diagnoses and therefore have been adjusted downward by a factor of 0.8; see Baird et al. [B36] for details.
c Prevalence would be 5.5 if congenital dislocation of the hip were excluded.
d Based on actual cases and not adjusted.

Table 18
Classification by aetiology of congenital abnormalities

Category	*Birth prevalence per 1,000*	*Per cent of total*	*Per cent of those with genetic aetiology (I-IV)*
British Columbia (ICD 740-754) [B36]			
I Mendelian	1.1	2.1	4.1
II Chromosomal	1.8	3.5	6.9
III Multifactorial	23.1 [b]	43.7	86.8
IV Genetics unknown	0.6 [c]	1.1	2.1
Subtotal genetic	26.6	50.4	100
V Non-genetic plus unknown aetiology [a]	26.2 [d]	49.6	
Total	52.8		
Hungary (ICD 740-749) [C60]			
I Mendelian	3.6	5.5	
II Chromosomal	3.0	4.6	
III Multifactorial	45.3	69.7	
IV Genetics unknown	-	-	
Subtotal genetic	51.9	79.8	
V Non-genetic plus unknown aetiology [e]			
Teratogens	2.0	3.1]	
Maternal factors	0.4	0.6] 20.2	
Unknown aetiology	10.7	16.6]	
Total	65.0	100	

a For about 8%, no aetiology of the types I-IV could be assigned.
b Also includes conditions other than those listed under ICD 740-759.
c Sum for the decade (1952-1963) showing the highest rate; these are judged to have a genetic basis, but the precise mode of inheritance could not be determined.
d Arrived at by subtraction from the total.
e For about 8%, no aetiology of the types I-IV could be assigned.

Table 19
Epidemiological features of selected isolated abnormalities in Hungary
[C33]

Congenital abnormality	*Prevalence per 100 births*	*Sex ratio (M : F)*	*Concordance rates [a] for twins (%)*		*Other features*
			Monozygotic	*Dizygotic*	
Anencephaly, spina bifida cystica, and encephalocele	0.29 [b]	1 : 1.5	28.7	0	Regional and seasonal variations in birth frequency; significantly less frequent in Oriental and African peoples and more frequent in Sikhs of Northern India and in Egypt; high still birth and infant mortality rates; higher prevalence among first-borns and with more advanced maternal age
Cleft lip with or without cleft palate	0.10 [b]	1.8 : 1.0	20.0	0	Isolated CL with or without CP has about 1:2 ratio of CL and CL with or without CP; CL three times more common on the left side; higher birth frequencies in Japan and lower ones in African people; higher birth prevalence with advanced maternal age
Congenital hypertrophic pyloric stenosis	0.15 [c]	4 : 1 to 5 : 1	–	–	Lower birth prevalence in African people (5-10 per 10^4), Orientals (1-5 per 10^4), and still lower in Filipinos (below 1 per 10^4)
Ventricular septal defect	0.15 [c]	1 : 1.2	22.2	0	Accounts for 25%-30% of all cases of congenital cardiovascular malformations
Congenital dislocation of the hip	2.8 [c] 1.30 [c, d]	1 : 5 to 1 : 8	83.3	13.6	Higher birth prevalence in Bretagne (France); also in native American and Lapps; higher birth prevalence in winter months, breech deliveries, and among first-borns
Structural talipes equinovarus	0.13 [c]	2 : 1	50.8	3.5	Half the cases of congenital are bilateral; more frequent among twins; pre-term births slightly more common and breech presentations three times more frequent; about three times more prevalent among gypsies
Congenital inguinal hernia	1.14 [c]	9 : 1	46.2	8.3	More common in winter births; predominance of right side involvement; higher with advanced maternal age
Simple hypospadias	0.44 [c, e]	Only in males	28.7	0	Lower birth weights and higher proportion of first-borns among index cases
Undescended testicle(s)	1.35 [c,e] 0.80 [f]	Only in males	15.4	0	More common in boys born between February and June; two thirds of cases unilateral with the right side affected more often than the left side

a Concordance rates published in the literature are different to some extent, but in common with Hungarian data the rates for monozygotic twins are higher.
b Among total (i.e. still and live) births.
c Among live births.
d Recent figure.
e In male births.
f Prevalence at one year of age.

Table 20
Increased prevalence of isolated congenital abnormalities in relatives of index patients
[C33]

Congenital abnormality	*Population prevalence (%)*	*Prevalence in relatives of index patients (%)*			
		Parents (first degree)	*Sibs (first degree)*	*Uncles/aunts (second degree)*	*First cousins (third degree)*
Anencephaly, spina bifida cystica, and encephalocele	0.29	-	2.1	0.19	0.26
Cleft lip with or without cleft palate	0.10	1.9	4.8	0.72	0.33
Congenital hypertrophic pyloric stenosis	0.15	1.4	6.3	0.25	0.72
Ventricular septal defect	0.15	-	1.7	0.69	0.79
Congenital dislocation of the hip	2.8				
Budapest study		2.3	13.8	1.37	6.13
Békés county study		2.1	14.0	1.17	4.72
Structural talipes equinovarus	0.13	2.3	5.6	0.55	1.09
Congenital inguinal hernia	1.14	5.7	10.1	6.03	7.62
Simple hypospadias [a]	0.44	3.7	4.8	0.77	0.48
Undescended testicle(s) [a]	1.35	4.8	6.7	0.62	1.04

a In males only.

Table 21
Influence of sex on the risk to relatives of isolated congenital abnormalities
[C33]

Congenital abnormality	*Sex-specific prevalence*	*Risk to relative (%)*	
		Brother	*Sister*
Anencephaly, spina bifida cystica and encephalocele			
Males	0.22	1.0	2.3
Females	0.36	2.4	2.3
Cleft lip with or without cleft palate			
Males	0.13	11.2	-
Females	0.08	1.3	4.5
Congenital hypertrophic pyloric stenosis			
Males	0.22	4.2	5.3
Females	0.07	20.0	-
Ventricular septal defect			
Males	0.14	0.8	1.8
Females	0.16	2.1	2.5
Congenital dislocation of the hip			
Males Budapest study	1.20	16.0	15.9
Females Budapest study	3.90	6.9	19.9
Males Békes county study	0.81	9.1	33.3
Females Békés county study	5.06	6.7	18.7
Structural talipes equinovarus			
Males	0.17	6.6	1.7
Females	0.08	6.9	10.0
Congenital inguinal hernia			
Males	1.89	12.9	1.8
Females	0.25	5.7	7.7

Table 22
Estimates of heritability of liability in the first-degree relatives of index cases for congenital abnormalities
[C23]

Congenital abnormality	*Estimate of h^2*
Anencephaly-spina bifida	0.52 ± 0.17
Cleft lip with/without palate	0.79 ± 0.10
Congenital hypertrophic pyloric stenosis	0.74 ± 0.18
Ventricular septal defect	0.57 ± 0.22
Congenital dislocation of the hip	0.70 ± 0.07
Structural talipes equinovarus	0.82 ± 0.15
Congenital inguinal hernia	0.53 ± 0.08
Simple hypospadias	0.65 ± 0.18
Undescended testicles	0.51 ± 0.15

Table 23
Epidemiological features and heritability estimates for selected common multifactorial diseases
[C35]

ICD code	*Disease*	*Lifetime prevalence per 10^4 persons*		*Age of onset (years)* [a] [b]	*Age distribution* [c]	*Sex ratio M : F*	*Heritability of liability* [d]
		Hungary [e]	*Other countries* [f]				
242.0	Graves' disease (toxic diffuse goitre)	65 (70)	100 (25–500)	43 (11–70)	I	1 : 4	0.47
250.0	Diabetes mellitus (maturity onset; NIDDM)	407 (291) [g]	480 (190–1 600)	58 (26–70)	I	1 : 2	0.65
250.1	Diabetes mellitus (juvenile onset; IDDM)	20	20 (8–56)	11 (1–25)	N	1 : 1	0.30
274	Gout	18 (-)	30 (13–37)	25 (18–55)	I	15 : 1	0.50
295	Schizophrenic psychoses	85 (10)	100 (70–200)	21 (15–45)	N	1 : 1	0.80
296.0-1	Affective psychoses: unipolar	500 (10)	430 (40–2 000)	38 (15–70)	I	1 : 2	0.60
296.2-5	Affective psychoses: bipolar	100 (10)	100 (7–150)	30 (20–60)	I	1 : 1	0.90
340	Multiple sclerosis	4 (-)	5 (1–13)	33 (10–50)	N	1 : 2	0.58
345	Epilepsy	60 (56)	170 (33–429)	4 (0–70)	D	1 : 1	0.50
365.1-2	Glaucoma (open-angle and primary-angle closure)	160 (-)	160 (80–220)	45 (20–70)	I	1 : 1	0.32
401	Essential hypertension	850 (642)	600 (200–1 000)	58 (10–70)	I	1 : 1	0.63
410-411	Acute myocardial infarction, other acute and sub-acute forms of ischaemic heart disease	359 (582)	500 (200–1 500)	50 (30–70)	I	3 : 1	0.65
454	Varicose veins of lower extremities	1 250 (607)	600 (200–3 560)	30 (20–70)	I	1 : 3	0.70
477	Allergic rhinitis (hay fever)	360 (-)	400 (300–1 000)	25 (5–50)	N	1 : 1	0.43
493	Asthma (extrinsic and intrinsic)	249 (86)	500 (50–900)	35 (1–70)	B	1 : 1	0.70
531-532	Peptic ulcer (gastric and duodenal)	460 (458)	500 (150–900)	45 (30–60)	N	2 : 1	0.65
556	Idiopathic protocolitis (including ulcerative colitis)	3 (-)	5 (4–10)	35 (20–60)	N	1 : 3	0.60
574	Cholelithiasis	94 (36)	100 (40–120)	35 (25–70)	I	1 : 3	0.63
579.0	Coeliac disease	13 (-)	12 (3–25)	1 (1–10)	D	1 : 1	0.80
592.0	Calculus of the kidney (nephrolithiasis)	90 (94)	60 (10–250)	45 (30–60)	I	2 : 1	0.70
691.8	Atopic dermatitis (eczema)	60 (94)	70 (50–80)	18 (10–25)	N	1 : 1	0.50
696.1	Psoriasis	39 (16)	200 (10–400)	20 (10–60)	N	1 : 1	0.75
710.0	Systemic lupus erythematosus	4 (-)	4 (2–7)	34 (13–45)	N	1 : 9	0.90
714.0	Rheumatoid arthritis	131 (602)	270 (50–500)	40 (35–64)	N	1 : 2	0.58
720.0	Ankylosing spondylitis	19 (-)	18 (5–23)	23 (18–35)	N	5 : 1	0.79
732.0	Juvenile osteochondrosis of the spine: Scheuermann disease	1 100 [h] (-)	900 (400–1 500)	12 (8–18)	N	1 : 2	0.56
737.3	Adolescent idiopathic scoliosis	41 (86)	33 (13–64)	13 (10–18)	N	1 : 1	0.88
	Total	6 541 (3 740)	6 367				

a The mean ages of onset are based on Hungarian data and the age ranges of those reported in the literature.
b Value gives mean, with range in parentheses.
c I: increases with age; N: normally distributed; B: biomodel; D: decreases with age.
d Estimates of narrow heritability of liability, based on Hungarian data.
e Values in parentheses are prevalence from a population screening carried out in an administrative unit in Hungary that included 3,707 persons over the age of 14 years and 96% of all inhabitants [U17].
f Value is median with range given in parentheses.
g Value for prevalence is for both diseases 250.0 and 250.1 together.
h Radiographic screening; only about 5% are clinically affected.

Table 24
Classification of blood pressure for adults aged 18 years or older [a]
[J10]

Category	*Blood pressure (mm Hg)*	
	Systolic	*Diastolic*
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Hypertension		
Stage 1	140–159	90–99
Stage 2	160–179	100–109
Stage 3	180–209	110–119
Stage 4	≥210	≥130

a Based on an average of two or more readings on two or more occasions in individuals not taking antihypertensive medications and not actually ill. When the average falls in different categories of systolic and diastolic blood pressure, the higher category applies.

Table 25
Selected estimates of correlation coefficients for blood pressure reported in family studies of hypertension
[B50]

Relationship	*Correlation coefficient*		*Reference*
	Systolic	*Diastolic*	
Monozygotic twins			
NHLBI twin study, United States	0.55	0.58	[F30]
Midwest, United States	0.72		[W27]
Dizygotic twins			
NHLBI twin study, United States	0.25	0.27	[F30]
Sib-sib			
Evans County, Georgia, United States (whites)	0.20	0.17	[H39]
Evans County, Georgia, United States (blacks)	0.14	0.19	[H39]
Midwest, United States	0.23		[W27]
Framington, Massachusetts, United States	0.17–0.23	0.18–0.24	[H38]
Montreal, Canada	0.28	0.29	[B52]
Tecumsek, Minnesota, United States	0.22–0.31	0.14–0.23	[L39]
Parent-child			
Evans County, Georgia, United States (whites)	0.13	0.14	[H39]
Evans County, Georgia, United States (blacks)	0.26	0.17	[H39]
Midwest, United States	0.26		[W27]
Framington, Massachusetts, United States	0.13–0.14	0.17–0.21	[H38]
Montreal, Canada	0.32	0.37	[B52]
Tecumsek, Minnesota, United States	0.20–0.24	0.16–0.19	[L39]

Table 26
Familial aggregation of coronary heart disease

Age	*Study design*	*Sample size*	*Odds ratio* [a]	*P value*	*Ref.*
≥45 years	Case-control	6 509	Father: 2.5 Mother: 1.9 Brother: 1.37	<0.05 NS NS	[P7]
Adult	Case-control	1 375 (blacks)	Father: 6.0 Mother: 2.0 Brother: 3.5 Sister: 2.0	<0.01 <0.05 <0.001 0.09	[R32]
≤70 years	Case-control	3 207	Father: 1.71 Mother: 1.58 Brother: 1.36 Sister: 1.32	NS NS NS NS	[T24]
Adult	Cohort of male twins Cohort of female twins	Monozygotic: 3 298 Dizygotic: 5 964 Monozygotic: 4 012 Dizygotic: 7 730	8.1 (CI: 2.7–24.5) 3.8 (CI: 1.4–10.5)		[M54]
≥45 years	Case-control	1 420 (blacks)	Parent and offspring: 5.30 (CI: 2.51–11.23)		[R23]

a Relative risks in relatives of affected individuals compared to controls.

Table 27
Major classes of human plasma lipoproteins and the associated apolipoproteins
[B62]

Class	*Density (g ml^{-1})*	*Electrophoretic mobility* [a]	*Associated apolipoproteins*
Chylomicrons	<0.94	Origin	A1, A4, B48 [b], C1, C2, C3, E
VLDL	0.93–1.006	Pre-β	B100, C1, C2, C3, E
IDL	1.006–1.019	Broad β	B100, C1, C2, C3, E
LDL	1.0019–1.063	β	B100
HDL	1.063–1.120	α	A1, A2, C1, C2, C3, D, E

a According to the mobility of plasma α and β globulins on agarose gel electrophoresis.
b The apo-B48 protein corresponds to the amino-terminal half of the apoB100 protein; both proteins are products of a single *apoB* gene.

Table 28
ApoE polymorphisms and their effects on total cholesterol levels
[M53]

Allele	*Gene product*	*Typical frequency*	*Average allelic effect on total cholesterol (mg dl^{-1})*
ε2	E2	0.109	–14
ε3	E3	0.760	–0.16
ε4	E40	0.131	+7

Table 29
Effects of a one-time or a permanent doubling of the mutation rate on gene frequency, disease frequency, and mutation component for a hypothetical autosomal dominant disease [a]
[C66]

Generation	*Permanent doubling*			*One-time doubling*		
	Mutant gene frequency	*Disease frequency*	*Mutation component*	*Mutant gene frequency*	*Disease frequency*	*Mutation component*
Initial	0.000020	0.000040	0.0000	0.000020	0.000040	0.0000
1	0.000030	0.000060	0.5000	0.000030	0.000060	0.5000
2	0.000035	0.000070	0.7500	0.000025	0.000060	0.2500
3	0.000038	0.000075	0.8750	0.000023	0.000045	0.1250
4	0.000039	0.000078	0.9375	0.000021	0.000043	0.0625
5	0.000039	0.000079	0.9688	0.000021	0.000041	0.0313
New equilibrium	0.000040	0.000080	1.0000	0.000020	0.000040	0.0000

a The values used in the computation are the following: mutation rate (m) = 1 10^{-5}; selection coefficient (s) = 0.5; initial mutant gene frequency (p) = m/s = 2×10^{-5}; and initial disease frequency (p) = 2p = 4×10^{-5}.

Table 30
Minimum number of loci needed to explain a specified prevalence for various mutation rates and selection coefficients for affected individuals
[D17, I2]

Prevalence	*Mutation rate (10^{-5} per locus)*			*Mutation rate (10^{-6} per locus)*		
	Selection coefficient 0.05	*Selection coefficient 0.20*	*Selection coefficient 0.50*	*Selection coefficient 0.05*	*Selection coefficient 0.20*	*Selection coefficient 0.50*
0.0001	1 [a]	1	2	2	10	25
0.001	2	10	25	25	100	250
0.01	25	500	250	250	1 000	2 500
0.1	250	5 000	2 500	2 500	10 000	25 000

a For $sp/2\mu < 1$, a value of 1 is used.

Table 31
Summary of selected inherited cancer syndromes
[F33]

Syndrome	*Primary tumour*	*Associated cancers or traits*	*Chromosome location*	*Cloned gene*	*Proposed function of gene product*
Dominant inheritance					
Familial retinoblastoma	Retinoblastoma	Osteosarcoma	13q14.3	*RB1*	Cell cycle and transcriptional regulation; E2F binding
Li-Fraumeni syndrome (LFS)	Sarcomas, breast cancer	Brain tumours, leukaemia	17p13.1	*P53 (TP53)*	Transcription factor; response to DNA damage and stress; apoptosis
Familial adenomatous polyposis (FAP)	Colorectal cancer	Colorectal adenomas, duodenal and gastric tumours, CHRPE jaw osteomas and desmoid tumours (Gardner syndrome), medulloblastoma (Turcot syndrome)	5q21	*APC*	Regulation of β-catenin; microtubule binding
Hereditary nonpolyposis colorectal cancer	Colorectal cancer	Endometrial, ovarian, hepatobiliary and urinary tract cancer, glioblastoma	2p16, 3p21 2q32, 7p22	*MSH2, MLH1 PMS1, PMS2*	DNA mismatch repair
Neurofibromatosis type 1 (NF1)	Neurofibromas	Neurofibrosarcoma, AML, brain tumours	17q11.2	*NF1*	GAP for p21 ras proteins; microtubule binding?
Neurofibromatosis type 2 (NF2)	Acoustic neuromas, meningiomas	Gliomas, ependymomas	22q12.2	*NF2*	Links membrane proteins to cytoskeleton?
Wilms' tumour	Wilms' tumour	WAGR (Wilms', aniridia, genitourinary abnormalities, mental retardation)	11p13	*WT1*	Transcriptional repressor
Beckwith-Wiedman syndrome (BWS)	Wilms'tumour	Oranomegaly, hemi-hypertrophy hepato-blastoma, adrenocortial cancer	11p15	*?p57/KIP2 ? Others contiguous gene disorder*	Cell cycle regulator
Nevoid basal-cell carcinoma syndrome (NBCCS)	Basal-cell skin cancer	Jaw cysts, palmar and plantar pits, medulloblastomas, ovarial fibromas	9q22.3	*PTCH*	Transmembrane receptor for hedgehog signalling molecule
Familial breast cancer 1	Breast cancer	Ovarian cancer	17q21	*BRCA1*	Interacts with Rad51 protein; repair of double-strand breaks
Familial breast cancer 2	Breast cancer	Male breast cancer, pancreatic cancer, ? others (e.g., ovarian)	13q12	*BRCA2*	Interacts with Rad51 protein, ? Repair of double-strand breaks
von Hippel-Lindau (VHL) syndrome	Renal cancer (clear cell)	Pheochromocytomas, retinal angiomas, hemangioblastomas	3p25	*VHL*	?Regulates transcriptional elongation by RNA polymerase II
Hereditary papillary renal cancer (HPRC)	Renal cancer (papillary type)	? Other cancers	7q31	*MET*	Transmembrane receptor for HGF

Table 31 (continued)

Syndrome	*Primary tumour*	*Associated cancers or traits*	*Chromosome location*	*Cloned gene*	*Proposed function of gene product*
Familial melanoma	Melanoma	Pancreatic cancer, dysplastic nevi, atypical moles	9p21	*p16 (CDKN2)*	Inhibitor of CDK4 and CDK6 cyclin-dependent kinases
Multiple endocrine neoplasia type 1 (MEN1)	Pancreatic islet cell	Parathyroid hyperplasia, pituitary adenomas	11q13	*MEN1*	Unknown
Multiple endocrine neoplasia type 2 (MEN2)	Medullary thyroid cancer	Type 2A, pheochromocytoma, parathyroid, hyperplasia Type 2B, pheochromocytoma, mucosal, hamartoma Familial medullary thyroid cancer	10q11.2	*RET*	Transmembrane receptor tyrosine kinase for GDNF
Multiple exostoses	Exostoses (cartilaginous protuberances on bones)	Chrondrosarcoma	8q24.1, 11p11-13 19p	*EXT1, EXT2,* *EXT3*	Unknown Unknown
Cowden disease	Breast cancer, thyroid cancer (follicular type)	Intestinal hamartomous, polyps, skin, lesions	10q23	*PTEN (MMAC1)*	Dual-specificity phosphatase with similarity to tensin
Hereditary prostate cancer (HPC)	Prostate cancer	Unknown	1q25, ? Others	Unknown	Unknown
Palmoplantar keratoderma	Oesophageal cancer	Leukoplakia	17q25	Unknown	Unknown
Recessive syndromes					
Ataxia-telangiectasia (A-T)	Lymphoma	Cerebellar ataxia, immunodeficiency, ? breast cancer in heterozygotes	11q22	*ATM*	DNA repair, ? induction of p53
Blooms's syndrome	Solid tumours	Immunodeficiency, small stature	15q26.1	*BLM*	? DNA helicase
Xeroderma pigmentosum	Skin cancer	Pigmentation abnormalities hypogonadism	Multiple complementation groups	*XPB. XPD* *XPA*	DNA repair helicases, nucleotide excision repair
Fanconi's anaemia	AML	Pancytopenia, skeletal abnormalities	9q22.3, 16q24.3 ? two others	*FACC* *FACA*	? DNA repair ? DNA repair

Abbreviations: E2F: a transcription factor;
CHRPE: congenital hypertrophy of the retinal pigment epithelium;
AML: acute myelogenous leukaemia;
GAP: GTPase-activating protein, a negative regulator of the p21 ras guanine nucleotide-binding proteins;
Contiguous gene disorder; alterations in several distinct genes in a particular chromosomal region account for the phenotype seen in patients with the disorder;
Hedgehog: a secreted factor that regulates cell fate determination via its binding to the PTCH protein;
GDNF: glial derived neurotrophic factor.

Table 32
Breast and ovarian cancer families and patients from various populations tested for inherited mutations in BRCA1 and BRCA2 genes
[S93] [a]

Population	*BRCA1*			*BRCA2*		
	Number [b] *with mutations*	*Number* [b] *screened*	*Percentage*	*Number* [b] *with mutations*	*Number* [b] *screened*	*Percentage*
Families with three or more cases of female breast and/or ovarian cancer						
Canada	12	30	40	8	49	16
Finland				8	100	8
France	38	160	24	14	77	18
Germany	9	49	18			
Great Britain	71	339	21	25	290	9
Holland and Belgium	71	517	14			
Hungary	7	32	22	4	32	13
Iceland	1	11	9	7	11	64
Israel	16	34	47	8	34	24
Italy	21	73	29			
Japan	2	20	10			
Norway	3	25	12			
Russian Federation	15	19	79			
Sweden and Denmark	24	106	23	12	106	11
United States	69	179	39	24	94	25
Families with male and female breast cancer						
Hungary	0	6	0	2	33	33
Iceland	0	10	0	9	10	90
United States	2	24	8	12	64	19
Breast and/or ovarian cancer patients not selected for family history						
Iceland				42	497	8
Israel	23	243	9	14	243	6
Italy	4	49	8			
Japan	8	179	4	2	103	2

a The original references are cited in this paper.
b Number of families or patients.

Table 33
Summary of studies suggestive of either higher radiation-induced cancer risks in putative cancer-predisposed individuals or radiation-induced tumour-suppressor or proto-oncogene mutations in tumours
[S32]

Endpoint of study	*Population*	*Study conditions*	*Findings*
Breast cancer	Female blood relatives of ataxia-telangiectasia patients [S57]	Single or multiple fluoroscopic examinations of chest or abdomen; dose to breast 1-9 mGy per exposure	Excess risk 5-6
	Female survivors of atomic bombings [L28, T26]		RR at 1 Gy: 14.6 (for those exposed < age 20); 3 (for those exposed > age 20)
	Patients treated by radiotherapy for cancer in contralateral breast [B34]	655 second breast cancer cases 1 189 matched controls Dose to breast 2.8 Gy average, 7.1 Gy maximum	RR 1.6 (at 1 Gy: 1.2) (for those exposed < age 45); RR 1 (no increase in risk for those exposed > age 45)
	Hodgkin's disease patients [H33]	855 women treated between 1961-1990; mean follow-up 10 years	RR: 136 (age <15); 19 (age 15-19, 20-24); 7.3 (age 25-29)
Second cancers in retinoblastoma patients	Long-term survivors of retinoblastoma with and without radiotherapy [E11]	1 408 patients, mortality compared with population of United States Mean follow-up: 17 years	Significant excess mortality for second cancers, suggesting cancer predisposition for those with RB1 mutations. Children with bilateral retinoblastoma treated with radiotherapy had 3-fold higher mortality than non-irradiated cases, suggesting radiation enhancement of genetic susceptibility.
	Retinoblastoma patients receiving various treatments [D13]	Genetic form of retinoblastoma in 241 of 319 patients treated by radiotherapy in 73 of 95 patients treated by radiotherapy and chemotherapy in 3 of 11 patients treated by chemotherapy in 67 of 457 patients not treated	Cumulative incidence rate of all second neoplasms in those with genetic form of retinoblastoma was 8.5% and of osteosarcoma alone 6.0%. Inherent risk for retinoblastoma survivors for developing osteosarcoma after 18 years (excluding effects of treatment) was 2.2%.
	Bilateral retinoblastoma patients with and without radiotherapy [R18]	137 patients treated by radiotherapy 78 patients not treated Follow-up: 30 years	Cumulative incidence rate of second neoplasms: 35.1% in treated patients 5.8% in untreated patients In treated patients, 24.3% of neoplasms were within the radiotherapy field and 8.1% outside.
	Bilateral retinoblastoma patients and patients with other childhood malignancies (Wilms' tumour, neuroblastoma, sarcomas, lymphoma) treated with radiotherapy [S30]		Peak incidence of second malignancies in fifth and sixth post-therapy years in retinoblastoma patients. Latency period >15 years in childhood malignancy group.

Table 33, continued

Endpoint of study	*Population*	*Study conditions*	*Findings*
Cancer in patients with nevoid basal-cell carcinoma syndrome	Patients with medulloblastoma treated by radiotherapy [S30, S31]		Unusually large number of basal-cell tumours in and near radiotherapy field within 5 years, often less than 1 year
Cancer mortality	Survivors of atomic bombings [S61]		Several-fold higher risk for all cancers except leukaemia in those <10 years at time of bombings; excess relative risk 7.2 in this group for stomach cancer and 1.2 in older age groups. Suggests susceptible subgroup.
p53 somatic gene mutations	Uranium miners with radon-associated lung cancer [T20]		About one third of mutations in 52 miners were transversions at codon 249 (AGG-ATG), which is normally very rare. None of 6 mutations in 12 non-miners was of this type.
	Patients with osteo- and soft-tissue sarcomas previously treated by radiotherapy for different cancers [B35]		All sarcomas of the 7 patients were histologically different from original ones and developed within or at margin of radiotherapy field 6-20 years after irradiation. One possible whole gene deletion, one 8-bp deletion in exon 7 and G→T transversion in exon 7. Abnormal or absent RB protein in another one. These changes could have been radiation-induced or arisen during tumour progression.
Ret somatic mutations	Thyroid carcinoma and fibrosarcoma cells [I13]	*In vitro* irradiation with x rays	Two *Ret*-rearrangements were found, one specific for thyroid cancer and the other a 150 bp insert; induction at high dose (50 and 100 Gy). Same two types of rearrangements found in fibrosarcoma cells.
	Children with thyroid cancers from areas contaminated by the Chernobyl accident [I14]		*Ret* proto-oncogene rearrangements found in 4 of 7 cases of thyroid cancer. One case revealed a p53 loss from a poorly differentiated papillary adenocarcinoma.

Table 34
Mouse models for inherited human cancer syndromes
[V19]

Gene	*Development defect in -/- mice*	*Tumours in +/- mice*	*Tumours in humans*	*Good model ?* [a] *tumours arise in*	
				Mice	*Humans*
p53	Viable (low-frequency exencephaly)	Osteosarcomas Soft-tissue sarcomas Lymphoma Breast/brain cancers	Osteosarcomas Soft tissue sarcomas Lymphoma/Leukaemia	Yes	Yes
RB	Lethal (14–16 days gestation) Erythropoiesis and neurogenesis	Pituitary adenomas	Retinoblastomas Osteosarcomas	Yes	No
APC	Early lethality (before day 7)	Intestinal carcinomas	Colon carcinomas	Yes	Yes
NF1	Lethal (13–14 days gestation) Cardiac defects	Myeloid leukaemia Phoechromocytomas	Myeloid leukaemia Pheochromocytomas Neurofibromas	Yes	Yes
NF2	Lethal (6–7 days gestation)	Sarcomas	Schwannomas Meningiomas Ependymomas	Yes	No
INK4a	Viable	Fibrosarcomas [b] Lymphomas [b]	Melanomas Pancreatic cancer	Yes	No
BRCA1	Early lethality (5–6 days)	No tumours	Breast/ovarian cancer	No	No
BRCA2	Early lethality (7–8 days)	No tumours	Breast cancer	No	No
WT-1	Lethal (13–15 days) Urogenital defects	No tumours	Kidney cancer	No	No
VHL	Lethal (10–12 days) Placental blood vessel defects	No tumours	Renal cell carcinomas Pancreatic cancers	No	No

a The +/- mouse represents a good model for the human syndrome if early tumours arise in +/- mice and the tumour types also occur in the human syndrome.
b Tumours arising in null mice.

Table 35
Estimates of risk of breast cancer obtained using the dominant model of cancer susceptibility
[C41]

Dose (Gy)	*Penetrance: 0.50*			*Penetrance: 0.75*			*Penetrance: 1.00*		
	Relative risk	*Attributable fraction*	α [a]	*Relative risk*	*Attributable fraction*	α [a]	*Relative risk*	*Attributable fraction*	α [a]
1.7% of cancer due to mutation									
Radiosensitivity of predisposed genotypes (R_i) = 10.0; predisposition strength (R_p) = 10.0									
0.5	1.00	0.00	0.83	1.00	0.00	0.83	1.00	0.00	0.83
1.0	1.00	0.00	0.87	1.00	0.00	0.87	1.00	0.00	0.87
2.0	1.00	0.00	0.89	1.00	0.00	0.89	1.00	0.00	0.89
R_i = 10.0; R_p = 100.0									
0.5	1.01	0.01	0.82	1.01	0.01	0.82	1.01	0.01	0.82
1.0	1.01	0.01	0.86	1.01	0.01	0.86	1.01	0.01	0.86
2.0	1.01	0.01	0.88	1.01	0.01	0.88	0.02	0.02	0.88
R_i = 10.0; R_p = 1000.0									
0.5	1.06	0.05	0.82	1.08	0.08	0.82	1.11	0.10	0.82
1.0	1.07	0.07	0.86	1.11	0.10	0.86	1.14	0.12	0.86
2.0	1.08	0.08	0.88	1.13	0.11	0.88	1.17	0.14	0.88
R_i = 100.0; R_p = 10.0									
0.5	1.01	0.01	0.98	1.01	0.01	0.98	1.01	0.01	0.98
1.0	1.01	0.01	0.99	1.01	0.01	0.99	1.01	0.01	0.99
2.0	1.01	0.01	0.99	1.01	0.01	0.99	1.02	0.02	0.99
R_i = 100.0; R_p = 100.0									
0.5	1.05	0.05	0.98	1.08	0.07	0.98	1.10	0.09	0.98
1.0	1.07	0.06	0.99	1.10	0.09	0.99	1.14	0.12	0.99
2.0	1.08	0.08	0.99	1.12	0.11	0.99	1.16	0.14	0.99
R_i = 100.0; R_p = 1000.0									
0.5	1.52	0.34	0.98	1.77	0.44	0.98	2.03	0.51	0.98
1.0	1.68	0.41	0.99	2.02	0.51	0.99	2.37	0.58	0.99
2.0	1.82	0.45	0.99	2.23	0.55	0.99	2.64	0.62	0.99
7.5% of cancer due to mutation									
R_i = 10.0; R_p = 10.0									
0.5	1.00	0.00	0.83	1.00	0.00	0.83	1.00	0.00	0.83
1.0	1.00	0.00	0.87	1.00	0.00	0.87	1.01	0.01	0.87
2.0	1.00	0.00	0.89	1.01	0.01	0.89	1.01	0.01	0.89
R_i = 10.0; R_p = 100.0									
0.5	1.02	0.02	0.82	1.04	0.04	0.82	1.05	0.05	0.82
1.0	1.03	0.03	0.86	1.05	0.05	0.86	1.06	0.06	0.86
2.0	1.04	0.04	0.88	1.06	0.05	0.88	0.07	0.07	0.88
R_i = 10.0; R_p = 1000.0									
0.5	1.25	0.20	0.82	1.37	0.27	0.82	1.49	0.33	0.82
1.0	1.31	0.24	0.86	1.47	0.32	0.86	1.63	0.39	0.86
2.0	1.37	0.27	0.88	1.55	0.36	0.88	1.74	0.42	0.88
R_i = 100.0; R_p = 10.0									
0.5	1.02	0.02	0.98	1.03	0.03	0.98	1.05	0.04	0.98
1.0	1.03	0.03	0.99	1.05	0.04	0.99	1.06	0.06	0.99
2.0	1.04	0.03	0.99	1.05	0.05	0.99	1.07	0.07	0.99

Dose (Gy)	*Penetrance: 0.50*			*Penetrance: 0.75*			*Penetrance: 1.00*		
	Relative risk	*Attributable fraction*	α [a]	*Relative risk*	*Attributable fraction*	α [a]	*Relative risk*	*Attributable fraction*	α [a]
$R_i = 100.0$; $R_p = 100.0$									
0.5	1.23	0.19	0.98	1.34	0.25	0.98	1.45	0.31	0.98
1.0	1.30	0.23	0.99	1.45	0.31	0.99	1.60	0.38	0.99
2.0	1.36	0.27	0.99	1.54	0.35	0.99	1.72	0.42	0.99
$R_i = 100.0$; $R_p = 1000.0$									
0.5	3.27	0.69	0.98	4.41	0.77	0.98	5.54	0.82	0.98
1.0	4.01	0.75	0.99	5.52	0.82	0.99	7.03	0.86	0.99
2.0	4.61	0.78	0.99	6.41	0.84	0.99	8.22	0.88	0.99
38% of cancer due to mutation									
$R_i = 10.0$; $R_p = 10.0$									
0.5	1.10	0.09	0.83	1.14	0.13	0.83	1.19	0.16	0.83
1.0	1.12	0.11	0.87	1.18	0.16	0.87	1.25	0.20	0.87
2.0	1.14	0.13	0.89	1.22	0.18	0.89	1.29	0.22	0.89
$R_i = 10.0$; $R_p = 100.0$									
0.5	1.98	0.50	0.82	2.47	0.59	0.82	2.96	0.66	0.82
1.0	2.25	0.56	0.86	2.87	0.65	0.86	3.49	0.71	0.86
2.0	2.46	0.59	0.88	3.19	0.69	0.88	3.92	0.74	0.88
$R_i = 100.0$; $R_p = 10.0$									
0.5	1.90	0.47	0.98	2.35	0.57	0.98	2.80	0.64	0.98
1.0	2.19	0.54	0.99	2.79	0.64	0.99	3.38	0.70	0.99
2.0	2.43	0.59	0.99	3.14	0.68	0.99	3.85	0.74	0.99
$R_i = 100.0$; $R_p = 100.0$									
0.5	10.02	0.90	0.98	14.51	0.93	0.98	18.99	0.95	0.98
1.0	12.96	0.92	0.99	18.92	0.95	0.99	24.87	0.96	0.99
2.0	15.32	0.93	0.99	22.45	0.96	0.99	29.58	0.97	0.99

a α is the fraction due to radiosensitivity alone.

Table 36
Database for estimating the average spontaneous mutation rate of human autosomal genes associated with autosomal dominant phenotypes and their selection coefficients
[C39, V20]

Disease phenotype	*Estimated value of parameter*		
	Number of loci	*Mutation rate (× 10^{-6})* [a]	*Selection coefficient* [b]
Achondroplasia	1	11.0	0.8
Amelogenesis imperfecta	1	1.0	0
Aniridia	2	3.8	0.1
Apert syndrome	1	3.5	0
Blindness	9	10.0	0.7
Cataracts (early onset)	30	6.0	0.3
Cleft lip	1	1.0	0.2
Deaf mutism	15	24.0	0.7
Dentinogenesis imperfecta	2	1.0	0
Huntington disease	1	5.0	0.2
Hypercholesterolaemia	1	20.0	0
Marfan syndrome	1	5.0	0.3
Multiple exotoses	3	7.7	0.3
Myotonic dystrophy	1	18.0	0.3
Neurofibromatosis	2	70.0	0.5
Osteogenesis imperfecta	2	10.0	0.4
Osteopetrosis	1	1.0	0.2
Otosclerosis	1	20.0	0
Polyposis of intestine	1	10.0	0.2
Polycystic kidney disease	2	87.5	0.2
Porphyria	2	1.0	0.05
Primary basilar impression	1	10.0	0.2
Rare diseases (early onset)	50	30.0	0.5
Retinoblastoma	1	8.7	0.5
Spherocytosis	1	22.0	0.2
Tuberous sclerosis	2	8.0	0.8
Total	135		
Average per locus	-	2.95 ± 0.64	0.294

a Mutation rate estimates apply for phenotypes; for some, the estimates are uncertain (see [C39] for details).
b Estimated from reproductive fitness.

Table 37
Database for calculating rates of induced mutations in mice
The data are from experiments involving irradiation of males (stem-cell spermatogonia) and all the rates are normalized to single acute x-irradiation conditions

System	*Number of loci*	*Average rate per locus per Gy ($\times 10^5$)*	*Reference*
The seven-locus system (recessive visible mutations) (3 and 6 Gy; acute x- or γ- irradiation)	7 [a]	3.03	[C8, L26, P5, P10, R33, R34]
The six-locus system (recessive visible mutations) (6 Gy; acute x-irradiation)	6 [b]	0.78	[L5]
Biochemical loci (recessive, null enzyme) (3 + 3 Gy, 24-h interval; x rays)	12 [c]	0.70 [d]	[C12, P10]
Biochemical loci (recessive, null enzyme) (3 Gy; 3 + 3 Gy 24-h interval and 6 Gy; x rays)	32 [e] 32 32	1.64 0.67 [d] 0.24	[N8] [f]
Biochemical loci (recessive, null enzyme) (3 + 3 Gy; 24-h interval; x rays)	4 [g]	1.24 [d]	[N8] [h]
Dominant visibles (*Sl, W, Sp,* and *T*) [i] (x rays)	4	0.44	See Table 38
Unweighted average	8.74/8 = 1.09 10^{-5} per locus per Gy		

a *a*: non-agouti; *b*: brown; *c*: chinchilla; *d:* dilute; *p*: pink-eyed dilution; *s:* piebald; *se*: short ear.
b *a*: non-agouti; *bp*: brachypodism; *fz*: fuzzy; *ln*: leaden; *pa*: pallid; *pe*: pearl.
c *Ldh1, Tpi, Gpi1, Pgk, G6pd1, G6pd2, Pk, Gr, Mod1, Pgam, Gapdh, Ldr*.
d Normalized assuming additivity of the effect of dose fractionation.
e *Acy1,Car2, G6pd1, Ggc,Es1, Es3, G6pd1, Gpi1, Hba, Hbb, Idh1,Ldh1,Ldh2, Mod1, Mod2, Np1, Pep2, Pep3, Pep7, Pgm1, Pgm2, Pgm3, Pk3, Trf (the identity of the other 8 loci could not be ascertained).*
f Unpublished data of S.E. Lewis summarized in [N8].
g *Hba, Hbb, Es3, Gpi1.*
h Unpublished data of J. Peters cited in [N8] and communicated to the UNSCEAR Secretariat.
i *Sl*: Steel; *W*: Dominant spotting; *Sp*: Splotch; *T*: Brachyury.

Table 38
Dominant visible mutations recovered in the course of mouse specific locus experiments (spermatogonial irradiation)
These experiments were carried out during 1964–1994 at Harwell, England. All rates normalized to single acute x-irradiation conditions.

Expt. no	*x-ray dose*	*Number of progeny*	*Number of mutations at* [a]				*Total*	*Mutations per locus per Gy ($\times 10^5$)*	*Ref.*
			S1	*W*	*Sp*	*T*			
1	6 + 6 Gy (8-week interval)	3 612	1	–	–	–	1	0.58 [b]	[L6]
2	6 Gy	16 735	–	1	–	–	1	0.25	[L5]
3	5 + 5 Gy (4-day interval)	7 168	1	–	–	–	1	0.35 [b]	[C7]
4	3 + 3 Gy (24 hours interval)	7 645	2	–	–	–	2	1.09 [b]	[C8]
5	3 + 3 Gy (24 hours interval)	15 849	1	1	1	3	6	0.35 [c]	[C8]
6	6 Gy	10 897	1	–	–	–	1	0.38	[C8]
7	6 Gy	19 285	1	–	–	–	1	0.22	[C8]
8	1 + 9 Gy (24 hours interval)	10 318	1	–	–	1	1	0.24 [b]	[C9]
9	1 + 9 Gy (24 hours interval)	14 980	–	–	–	3	3	0.50 [b]	[C9]
Unweighted average mutation rate/locus/Gy = 3.96/9								0.44	

a *Sl*: Steel; *W*: Dominant spotting; *Sp*: Splotch; *T*: Brachyury.
b Normalized to single unfractionated irradiation conditions under the assumption of additivity of yields.
c Normalized on the basis of observations of the enhancement of specific-locus mutation frequency (in the same experiment) by a factor of 3 (3H1 strain of mice).

Table 39
Locus-specific rates for radiation-induced mutations in mice
Estimated from the data in Tables 37 and 38

Locus [a]	*Rate (× 10^5 per Gy)*	*S.E. (× 10^5)*
pa	0	0
pe	0	0
G6pd1	0	0
G6pd2	0	0
Ldh2	0	0
Ldr	0	0
Pgk1	0	0
Tpi	0	0
Hba2	0	0
Hbb1	0	0
Hbb2	0	0
Gapdh	0	0
Pk	0	0
Mod1	0	0
Sp	0.04	0.04
W	0.15	0.12
Gpi	0.33	0.33
a	0.45	0.24
T	0.45	0.18
ln	0.67	0.67
Ldh1	0.97	0.69
se	0.97	0.33
Sl	1.31	0.51
bp	1.34	0.95
Es3	1.67	1.67
Hba1	1.67	0.67
c	1.90	0.48
Gr	2.19	1.40
b	2.35	0.52
fz	2.68	1.34
p	2.93	0.56
d	3.14	0.62
Pgam	3.91	1.93
s	7.59	0.89
Average rate (acute x-irradiation)	1.08	0.30 [b]
Chronic irradiation	0.36	0.10 [b]

a In these calculations, two additional loci (*Ldh2* in the experiments of Pretsch et al. [P10] and *Hba2* in the experiments of Peters (cited in [N8]) have been included based on current evidence [L54].

b The standard error of the average rate was calculated taking into account variation of the rates between loci as well as sampling variation of the experimental data for each locus.

Table 40
Approximate decreasing relative rank of genes studied in experimental systems that are responsive to recoverable radiation-induced deletions
[S43]

Rank	*Organism/cells*	*Genes under study*	*Inferred attributes and location of the genes*
1	Mouse	s^+, d^+, c^+, b^+; p^+ *Sl, W, Sp, Ph, T*	Non-essential for survival and flanked (5' and 3' to the gene under study) by genes (genomic regions) that are also non-essential for survival
	Human somatic cell	*HPRT, TK, HLA-A2*	
	Chinese hamster cells	*dhfr*	
	Mouse embryonal carcinoma cells	*aprt*	
2	Mouse	a^+, se^+	Non-essential for survival and flanked by genomic regions of which either the 5' or the 3' region may be essential for survival
	Chinese hamster cells	*aprt*	
3	?		Non-essential for survival but flanked by genomic regions both of which may be essential for survival
4	?		Only small changes (point mutations or small intragenic deletions) are compatible with survival but both the 5' and 3' flanking regions may be non-essential for survival
5	?		Only small changes are compatible with survival and one of the flanking regions is essential for survival
6	Mouse	*H-genes*	Only small changes are compatible with survival; flanked by genomic regions both of which may be essential for survival
	Chinese hamster cells	Na^+/K^+ *ATPase*	
7	?		The known phenotype is due to loss-of-function mutations through dominant negative effects
8	?		The known phenotype is due to specific gain-of-function mutations
9	?		The known phenotype is due to non-conventional mechanisms of origin of disease such as specific expansion of trinucleotide repeats

Table 41
Assessment of recoverability of radiation-induced mutations in human genes that underlie autosomal dominant and X-linked diseases
[S16]

Disorder	*Incidence ($\times 10^4$) [S105]*	*Gene*	*MIM number*	*Chromosomal location*	*Comments*
AUTOSOMAL DOMINANT					
Group 1: Unlikely to be recovered					
Antithrombin III deficiency	2–5	*AT3*	107300	1q23–q25	Type I deficiency due to missense/nonsense mutations; partial/whole gene deletions; gene-rich region (several genes map to the same chromosome band)
Variegate porphyria	0.1	*PPOX*	600923	1q22	Missense and frameshifts; gene-rich region (several genes including MPZ map to the same chromosome band)
Familial hypercholesterolaemia due to ApoB-100 defect	10–15	*APOB*	107730	2p24	Only two specific point mutations affecting LDL receptor binding have been reported
Waardenburg syndrome Type 1	0.1–0.2	*PAX3*	193500	2q35	A small (paired-box) gene with 3 exons; loss of function through haploinsufficiency; gene-rich region (at least four genes map to the same chromosome band)
Type 2		*MITF*	156845	3p14.1–p12.3	Splice site mutations and small deletions; putative gene-rich region
Retinitis pigmentosa 4	0.3	*RHO*	180380	3q21–q24	Mostly missense; gene-rich region
Huntington disease	5.0	*HD*	143100	4p16.3	CAG repeat expansion; very gene-rich region
Achondroplasia [a]	0.2	*FGFR3*	134934	4p16.3	Specific gain of function mutations; gene-rich region
Thanatophoric dwarfism	0.8	*FGFR3*			Specific gain of function mutations; gene-rich region
Treacher Collins syndrome	0.2	*TCOF1*	154500	5q32–q33.1	Missense, nonsense and splice-site mutations and small deletions predicted to result in truncated protein; no large deletions known; gene-rich region
Spinocerebellar ataxias	0.5	*SCA1*	601556	6p23	CAG repeat expansion
		SCA2	601517	12q24	CAG repeat expansion; gene-rich region
		SCA3	109150	14q24.3–q31	CAG repeat expansion; gene-rich region
		SCA6	601011	19q13	CAG repeat expansion
		SCA7	164500	3p21.1–p12	CAG repeat expansion; gene-rich region
Nevoid basal-cell carcinoma	0.2	*PTCH*	601309	9q22.3	A relatively small (34 kb) tumour-suppressor gene in a gene-rich region; most mutations (small deletions) cause protein truncation; no whole gene deletions; loss of function through haplo-insufficiency; gene-rich
Tuberous sclerosis 1	0.5	*TSC1*	191100	9q32–q34	Tumour-suppressor gene; very gene-rich region (several genes map to the same chromosome band)
Best macular dystrophy	?	*VMD2*	*153700*	11q13	Missense mutations in a relatively small gene (16 kb) located in an extremely gene-rich region (several genes map to the same chromosome band)

Table 41 (continued)

Disorder	*Incidence ($\times 10^4$) [S105]*	*Gene*	*MIM number*	*Chromosomal location*	*Comments*
Craniosynostosis — Apert syndrome [a]	4.0	*FGFR2*	176943	10q26	Specific gain of function mutations; gene-rich region
Pfeiffer syndrome		*FGFR2*			Specific gain of function mutations; gene-rich region
		FGFR1	136350	8p11.2–p11.1	Specific gain of function mutations
Crouzon syndrome		*FGFR2*			Specific gain of function mutations; gene-rich region
Jackson-Weiss syndrome		*FGFR2*			Specific gain of function mutations; gene-rich region
Boston-type craniosynostosis		*MSX2*	123101	5q34–q35	Mutation (C to A; pro 148 his) presumed to act via a “dominant positive” mechanism
Acute intermittent porphyria	0.1	*PBGD*	176000	11q23.3	Mostly missense mutations and small intragenic deletions; gene-rich region (several genes map to the same chromosome band)
Dentatorubral pallidoluysian atrophy	0.04–0.07	*DRPLA*	125370	12p13.31	CAG repeat expansion; gene-rich region
Familial hypertrophic cardiomyopathy	2.0	*MYH7*	160760	14q12	Loss of function through dominant negative mechanisms; all genes located in gene-rich regions
		TNNI3	191044	14q13.4	
		TNNT2	191045	1q32	
		TPM1	191010	15q22.1	
		MYL2	160781	12q23–q24.3	
		MYBPC3	600958	11p11.2	
Marfan syndrome [a]	0.4	*FBN1*	134797	15q21.1	Disease due to gain-of-function mutations
Polycystic kidney disease	8.0	*PKD1*	601313	16p13.3–p13.1	Both genes located in very gene-rich regions (several genes map to the same band region)
		PKD2	173910	4q21–q23	
Charcot-Marie Tooth disease (all forms)	4.0	*PMP22*	601097	17p11.2	Specific 1.5 Mb duplication; dominant gain-of-function; gene-rich region
		MPZ	159440	1q22	Most mutations missense; dominant gain of function; gene-rich region
Li-Fraumeni syndrome	0.2	*TP53*	191170	17p13.105–p12	A very well-studied, small (20 kb) tumour-suppressor gene with multiple functions; missense and nonsense mutations; no whole gene deletions; the 17p13 is a very gene-rich region
Osteogenesis imperfecta types I–IV [a]	0.4	*COL1A1*	120150	17q21.31–q22.05	Null mutations cause OI type I (haplo-insufficiency); other events cause types I-IV OI through dominant negative mechanisms
		COL1A2	120160	7q22.1	
Ehlers-Danlos syndrome	0.1	*COL1A1*			Loss of function through dominant negative mechanisms
		COL1A2			
		COL3A1	120180	2q31	
Myotonic dystrophy [a]	2.0	*DMPK?*	160900	19q13.2–q13.1	CTG repeat expansion; very gene-rich region
Familial hypercholesterolaemia	20.0	*LDLR*	143890	19p13.2–p13.1	A large gene in which various types of mutations including deletions and duplications of different sizes have been recorded; very gene-rich region (several genes map to the same chromosome band region)
Malignant hyperthermia susceptibility	<<1.0	*RYR1*	180901	19q13.1	Only missense mutations; gene-rich region (several genes map to the same chromosome band)

Table 41 (continued)

Disorder	*Incidence ($\times 10^4$) [S105]*	*Gene*	*MIM number*	*Chromosomal location*	*Comments*
Group 2: Potential recoverability uncertain					
Von Hippel Lindau syndrome	0.3	*VHL*	193300	3p26–p25	A relatively small (50 kb; 3 exons) tumour-suppressor gene; insufficient genomic context information
Familial adenomatous polyposis coli [a]	1.0	*APC*	175100	5q21–q22	A relatively large tumour-suppressor gene; 5q deletions are known; insufficient genomic context information
Multiple exotoses	1.4	*EXT2* *EXT3*	133701 600209	11p13–p11 19p	A 108 kb long tumour-suppressor gene; not enough information on genomic context Not much is known of genome size or context
BRCA2-associated male and female breast cancers	?	*BRCA2*	600185	13q12.3	A 70 kb tumour-suppressor gene in which most of the mutations are small deletions; rich in AT sequences; moderately gene-rich; information on genomic context insufficient
Hirschsprung disease	2.0	*EDNRB* *RET*	131244 164761	13q22 10q11.2	A small (24 kb) gene; missense and nonsense mutations; loss of function through haplo-insufficiency; deletions which include the EDNRB locus known; insufficient genomic context information One of the proto-oncogenes in which germinal mutations (missense and nonsense) are compatible with viability; loss of function through haplo-insufficiency (in the case of absent or truncated protein) and through dominant negative effects in the case of missense mutations; gene-rich region
BRCA1-associated breast and ovarian cancers	15.0	*BRCA1*	113705	17q21	A large (100 kb) tumour-suppressor gene rich in AT sequences; and Alu repeat sequences point mutations and small deletions mutations (most of which cause protein truncation) known; no whole gene deletions; very gene-rich region
Neurofibromatosis 2 [a]	0.2	*NF2*	101000	22q12.2	A 110 kb tumour-suppressor gene; no whole gene deletions; constitutional translocations with breakpoint in the gene known; gene-rich region
Group 3: Potentially recoverable					
Congenital spherocytosis	2.0	*ANK1*	182900	8p11.2	Deletions of 8p11-p21.1 region known; gene-rich region
Multiple exotoses	2.2	*EXT1*	133700	8q24.11–q24.13	A 300 kb long tumour-suppressor gene; large multi-locus deletions including *EXT1*, *LGGR* and *TRPS1* known; gene- rich region
Aniridia [a]	0.1–0.2	*PAX6*	106210	11p13	A paired box gene located in a subregion of *WAGR* region which also contains the tumour-suppressor gene, *WT1*; micro-deletions known; moderately gene-rich region
Retinoblastoma [a]	0.3	*RB1*	180200	13q14.1–q14.2	A 200 kb long tumour-suppressor gene; constitutional deletions known; not much genomic context information
Tuberous sclerosis 2	0.5	*TSC2*	191092	16p13.3	A 45 kb long tumour-suppressor gene; large deletions account for 5% of cases; deletions involving also the adjacent PKD1 locus known
Neurofibromatosis 1 [a]	4.0	*NF1*	162200	17q11.2	A 350 kb tumour-suppressor gene; variety of mutations including very large (700 kb) deletions; very gene-rich region

Table 41 (continued)

Disorder	*Incidence ($\times 10^4$) [S105]*	*Gene*	*MIM number*	*Chromosomal location*	*Comments*
X-LINKED [b] [c]					
Group 1: Unlikely to be recovered					
Anhidrotic (hypohidrotic) ectodermal dysplasia	0.5	*ED1*	305100	Xq12–q13.1	Missense, splice-site and frameshift mutations; small in-frame deletions; no whole gene deletions; gene-rich region
Fragile X syndrome	2.5	*FRAXA*	309550	Xq22.3	Most cases due to *CGG* expansions
Group 3: Potential recoverable					
Duchenne/Becker muscular dystrophy	2.3	*DMD/BMD*	310200	Xp21.2	Both diseases due to mutations in the very large (2.3 Mb) gene; ~2/3 of mutations are deletions of one or many exons; some duplications and point mutations; deletions in the Xp21.2 region can include *DMD, CGD, XK* and *RP6* loci proximally and *GKD* and *AHC* distally
Ocular albinism	<0.05	*OA1*	300500	Xp22.3	Missense, nonsense and frameshift mutations; patients with microdeletions of *Xp23* (~10 Mb) have, in addition to ocular albinism, short stature, chondrodysplasia punctata, mental retardation and ichthyosis
Steroid sulfatase deficiency (Ichthyosis)	1.0	*STS*	308100	Xp22.32	Most patients have large deletions although point mutations are also known; see also entry 30500 above
Choroideraemia	0.05	*CHM*	303100	Xq21.2	Nonsense, frameshift or splice site mutations; deletions which include CHM and contiguous genomic regions associated with mental retardation and deafness
Haemophilia B	~0.1	*F9*	306900	Xq27.1–q27.2	Compared to *F8* (see below), the *F9* gene is smaller (34 kb); missense, nonsense and splice site mutations; deletions of different sizes (some ~110-115 kb) known; genomic region appears less gene-rich than Xq28
Haemophilia A	1.0	*F8*	306700	Xq28	Large (186 kb) gene; majority of mutations nonsense; deletions from 2 kb to <60 kb and one deletion ~210 kb; extremely gene-rich

a Diseases considered in [S43].
b Disease incidences for X-linked diseases given in [S105] are per 10^4 male births; the figures have been divided by 2 to take into account both sexes.
c Assessment based on whether an induced deletion will be compatible with viability in males.

Table 42
Summary of the assessments of potential recoverability of radiation-induced mutations in autosomal and X-linked genes
[S16]

Group(s)	*Number of genes*	*Unweighted PRCF* [a]	*Incidence (10^{-4})*	*Weighted PRCF* [b]
Autosomal dominants				
1 (unlikely to be recovered)	42	–	46.45	–
2 and 3 (Uncertain and potentially recoverable)	17	0.29	55.90	0.157
Subtotal	59		102.35	
Autosomal dominants + X-linked				
1 (unlikely to be recovered)	43	–	48.95	–
2 and 3 (Uncertain and potentially recoverable)	24	0.36	60.90	0.199
Total	67		109.85	

a Unweighted PRCF, autosomal dominants: 17/59 = 0.29; autosomal dominants + X-linked = 24/67 = 0.36.
b Weighted PRCF, autosomal dominants: (55.9 × 17)/(102.35 × 59) = 0.157; autosomal dominants + X-linked = (60.9 × 24)/(109.85 × 67) = 0.199.

Table 43
Examples of human microdeletion syndromes
[S43, S45]

Chromosome localization	*Designation*	*MIM number*	*Estimated size*	*Ref.*
Well-known syndromes often caused by autosomal microdeletions				
4p16.3	Wolf-Hirschhorn; Pitt-Rogers-Dank	194190	165 kb	[W16]
5p15.2–p15.3	Cri du chat	123450	>2 Mb	[O7]
7q11.23 (including *ELN* gene)	Williams-Beuren	194050	1.5–2.5 Mb	[L22, N2]
7q36	Holoprosencephaly 3	142945	[c]	[P30, P31]
8q24.11–q24.13 (including *EXT1* and *TRPSII* genes)	Langer-Giedion tricho-rhino-phalangeal II	150230	~2 Mb	[H5]
11p13 (including *WT1* and *PAX6* genes)	WAGR [a]	194072	~600 kb	[H6]
11q23.3–qter	Jacobsen	147791	1.5–3.1 Mb	[P23]
15q11–q13 (loss of paternal genes)	PraderWilli	176270	~3.5 Mb	[C28]
15q11–q13 (loss of maternal genes)	Angelman	105830	[d]	[K16, M22]
16p13.3	Rubinstein-Taybi	180849	[e]	[P24]
	Deletion of *PKD1* and *TSC2* genes	–	~100 kb	[B37]
	α-thalassaemia-mental retardation	141750	~120 kb	[L23, W17]
17p13.3	Miller-Dieker [b]	247200	~500 kb	[B53]
17p11.2	Smith-Magenis	182290	1.5–9 Mb	[P25, T6]
20p12–p11.23	Alagille	118450	[f]	[L24]
20p12.11–q11.23	Di George, velocardiofacial, Shprintzen	192430	>1.5 Mb [g]	[B53]
Other reported autosomal microdeletion syndromes				
1p36	?	?	?	[S46]
1q32	Van der Woude	119300	840 kb–4 Mb	[S47]
2p21	Holoprosencephaly II	157170	<1 Mb	[S50]
3p14	?	?	?	[S51]
3q22–q23	Blepharophimosis	110100	?	[F35, W18]
4q12–q21.1	?	?	?	[F8]
5q15–31.1	?	?	?	[C29]
7p21.1	Craniosynostosis (Saethre-Chotzen syndrome)	123100	3.5 Mb–11.6 Mb [h]	[J14]
8q12.2–q21.2	Duane syndrome	126800	?	[C30]
9p22	?	?	~2–3 Mb	[P39]
9q22–q23.1	Gorlin syndrome	109400	[i]	[S58]
10q23.3–q26.2	?	?	?	[P4]
11p11.2–p22 (includes *EXT2* gene)	?	?	?	[B38]
13q32	?	?	~1 Mb	[B39]
14q22.1–q23.2	?	?	?	[L25]
18q21.3–q22.2	?	?	9–26 Mb	[S59, S60]
18q23	?	?	~36 Mb	[C31]
19q13	Diamond-Blackfan anaemia	205900	~1 Mb	[G2]
22q13.3	?	?	≥5 Mb	[W19]

a *W*ilms' tumour, *A*niridia, *G*enitourinary anomalies and mental *R*etardation
b Now considered to be autosomal dominant [M2].
c Not all patients have a deletion; now presumed to be a single gene disorder (*HPE3* gene).
d Not all patients have a deletion; now presumed to be a single gene disorder (*UBE3A* gene).
e Not all patients have a deletion; now presumed to be a single gene disorder (*CBP* gene).
f Not all patients have a deletion; now presumed to be a single gene disorder (*JAG1* gene).
g At least 17 genes.
h While Saethre-Chotzen syndrome patients have been found to have mutations in the *TWIST* gene, a significant proportion of these patients have large deletions in the 7p21.1 region resulting in haploinsufficiency of genes neighboring the *TWIST* gene.
i Not all patients have a deletion; now known to be due to mutations and deletions in *PTCH* gene (MIM 601309).

Table 44
Radiation-induced congenital abnormalities following irradiation of male mice

Mouse strain	*Dose (Gy)*	*Number of*		*Per cent*	*Induced rate per Gy ($\times 10^4$)*	*Ref.*
		Live fetuses	*Abnormal fetuses*			
ICR	0	1 967	8	0.4	-	[N10]
	0.36	163	1	0.6	56	
	1.08	234	3	1.3	83	
	2.16	496	9	1.8	65	
Estimated regression of frequency on dose					68	

Table 45
Estimates of genetic risks from continuing exposure to low-LET, low-dose or chronic radiation

Disease class	*Baseline frequency per million live births*	*Risk per Gy per million progeny in the*	
		First generation	*Second generation* [a]
Estimates in the present document (Assumed doubling dose = 1.0 Gy)			
Mendelian			
Autosomal dominant and X-linked	16 500	~750 to 1 500	~1 300 to 2 500
Autosomal recessive	7 500	0	0
Chromosomal	4 000	[b]	[b]
Multifactorial			
Chronic multifactorial	650 000 [c]	~250 to 1 200	~250 to 1 200
Congenital abnormalities	60 000	~2 000 [d]	2 400 to 3 000 [d]
Total	738 000	~3 000 to 4 700	3 930 to 6 700
Total risk per Gy expressed as per cent of baseline		~0.41 to 0.64	0.53 to 0.91
Previous estimate [U4] (Assumed doubling dose = 1.0 Gy)			
Mendelian			
Autosomal dominant and X-linked	10 000	~1 500	~2 800
Autosomal recessive	2 500	~5	~5
Chromosomal	4 000	240	100
Multifactorial			
Chronic multifactorial	650 000	Not estimated	Not estimated
Congenital abnormalities	60 000	Not estimated	Not estimated
Total	726 500		

a Risk to the second generation includes that of the first (under the continuous radiation conditions assumed) except for congenital abnormalities for which it is assumed that between 20% and 50% of the abnormal progeny in the first post-radiation generation may transmit the damage to the second post-radiation generation, the remainder causing lethality.

b Assumed to be subsumed in part under the risk of autosomal dominant and X-linked diseases and in part under that of congenital abnormalities.

c Frequency in the population.

d Estimate obtained using mouse data on developmental abnormalities and not with the doubling dose method; note also that although the designation "congenital abnormalities" is used in column 1, the risk estimate is based not only on data on congenital abnormalities ascertained *in utero* but also on skeletal abnormalities and cataracts studied at weaning age in the mouse.

Table 46
Estimates of genetic risks from one-generation exposure to low-LET, low-dose or chronic radiation

Disease class	*Baseline frequency per million live births*	*Risk per Gy per million progeny in the*	
		First generation	*Second generation* [a]
Estimates in the present document (Assumed DD = 1.0 Gy)			
Mendelian			
Autosomal dominant and X-linked	16 500	~750 to 1 500	~500 to 1 000
Autosomal recessive	7 500	0	0
Chromosomal	4 000	[b]	[b]
Multifactorial			
Chronic multifactorial	650 000 [c]	~250 to 1 200	~250 to 1 200
Congenital abnormalities	60 000	~2 000 [d]	400 to 1 000 [e]
Total	738 000	~3 000 to 4 700	1 150 to 3 200
Total risk per Gy expressed as per cent of baseline		~0.41 to 0.64	0.16 to 0.43

a Risk to second generation is lower than that in the first because of the assumption that radiation exposure occurred in one generation only; the risk will progressively decrease with time (in generations).
b Assumed to be subsumed in part under the risk of autosomal dominant and X-linked diseases and in part under that of congenital abnormalities.
c Frequency in the population.
d Estimate obtained using mouse data on developmental abnormalities and not with the doubling-dose method.
e Under the assumption that selection coefficient is 0.2 to 0.5.

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