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Review article

Risk calculations for hereditary effects of ionizing radiation in humans

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Summary. A prediction of the extent to which an additional dose of ionizing radiation increases the natural germ cell mutation rate, and how much such an increase will affect the health status of future human populations is part of the service that human geneticists are expected to offer to human society. However, more detailed scrutiny of the difficulties involved reveals an extremely complex set of problems. A large number of questions arises before such a prediction can be given with confidence; many such questions cannot be answered at our present state of knowledge. However, such predictions have recently been attempted. The 1988 report of the United Nations Scientific Committee for the Effects of Atomic Radiation and the fifth report of the Committee on Biological Effects of Ionizing Radiation of the US National Research Council have presented a discussion of the human genetics problems involved. Empirical data from studies on children of highly radiation-exposed parents, e.g. parents exposed to the atomic bombs of Hiroshima and Nagasaki, or parents belonging to populations living on soil with high background radiation, have been mentioned in this context. Whereas precise predictions are impossible as yet because of deficiencies in our knowledge of medical genetics at various levels, the bulk of the existing evidence points to only small effects of low or moderate radiation doses, effects that will probably be buried in the "background noise" of changing patterns of human morbidity and mortality.

The problem

The fact that energy-rich radiation can induce mutations had previously been suspected, but was established first by Muller (1927) in *Drosophila melanogaster* and by Stadler (1928a, b) in barley and maize, after Mavor (1924) had shown the induction of nondisjunction by radiation. "Classical" radiation genetics developed, based on these results (Lea and Catcheside 1942; Timofeéff-Ressovsky and Zimmer 1947; Hollaender 1954–56). When DNA was identified as the universal genetic material, it soon became obvious, and was confirmed by overwhelming genetic evidence, that, in principle, the genetic material of all living beings is susceptible to radiation-induced damage. Since the pioneering studies mainly of Paula Hertwig in the 1930s (Hertwig, 1935, 1938a, b, 1940) and, especially, of W. L. Russell beginning in the 1950s (Russell, 1952, 1954, 1957, 1964a, b, 1965), the mouse has become the predominant object of studies designed for elucidating the special conditions of radiation effects on the mammalian genome, and on subsequent generations in mammals (see Vogel et al. 1969). In the late 1960s, we drew the following conclusions that were derived from studies of animals (predominantly mice) but that might also apply to human beings. (1) Radiation at a relatively low dose leads to a sterile phase because of death of most spermatogonia; the testicular tissue is later repopulated by repeated division of a few, especially resistant, A spermatogonia. (2) In the male mouse, the majority of the visible chromosomal aberrations, that are present in the F_1 offspring are induced in the presterile phase, i.e. in postmeiotically irradiated male germ cells. Hence, a considerable risk for chromosomal aberrations in the next generation after irradiation of a human male may be assumed mainly if conception occurs less than about 6–8 weeks after irradiation. (3) In the female mouse, chromosomal anomalies may be induced, most of which lead to the death of the zygote at a very early stage of development (= early abortions in humans). The same is true for chromosomal aberrations that are induced in male germ cells and that are present in the zygote. (4) The hours around fertilization are especially susceptible to the induction of aneuploidies, especially the loss of single chromosomes, e.g. the X chromosome. (5) Acute irradiation with a relatively high radiation dose leads to a considerable increase of recessive mutations in both sexes. (6) A strong dose rate effect was observed in spermatogonia and in oocytes: chronic irradiation induces only about one third of the recessive mutations that are induced by acute irradiation. A dose rate effect is also present in dominant mutations; it is

caused by repair mechanisms. (7) Many radiation-induced mutations, especially those induced in postspermatogonial cell stages, were identified as deletions. Many induced recessive mutations were found to be lethal in the homozygous state. (8) Dominant mutations with clear-cut phenotypic effects and full penetrance are induced relatively rarely; dominant effects within multifactorial genetic systems, e.g. mutations affecting the skeleton, appear to be more common. However, before extrapolating this result to humans, the much easier and more detailed assessment of human anomalies compared with those of the mouse should be considered. (9) Most translocations induced in spermatogonia are unable to pass through meiosis; they do not lead to abortions or to malformed children. These conclusions have subsequently been supplemented by other data in experimental animals; these results will be mentioned in the following sections.

Estimates of international committees on hereditary effects of irradiation of human germ cells: rationale of these estimates

These and other data, together with results from direct observations on spontaneous and induced mutations in humans, have been used by international committees to estimate the hereditary effects of radiation in human populations and to predict genetic damage in relation to a certain additional radiation dose. The history of these estimates is described by Sankaranarayanan (1988). These estimates are based on the following concepts:

The indirect (doubling dose) method. This method compares the estimated additional number of mutations of various kinds with their spontaneous occurrence. This is undoubtedly a meaningful procedure, since it puts all estimates in perspective, giving an impression of the practical impact on the health of future generations. A concept used for such an estimate is the doubling dose, defined as the dose that doubles the spontaneous mutation rate. Lüning and Searle (1970) have reviewed such doubling doses for various genetic endpoints, based on radiation-genetic data in the mouse (Fig. 1). From their report, two aspects are obvious. (1) There is an appreciable difference between the estimates of doubling doses for various endpoints (dominant and recessive "point mutations" leading to defined phenotypes, dominant mutations affecting the skeleton, recessive lethals, and chromosomal translocations leading to semisterility. (2) The confidence intervals of estimates are very large. The last of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) reports published so far (1958, 1962, 1964, 1966, 1969, 1972, 1977, 1982, 1986, 1988) have used a doubling dose of 1 Sv (100 rem) for irradiation at low dose rates (= irradiation over long periods of time). This estimate was based mainly on data from the classical studies of Russell (1952, 1954, 1957, 1964a, b, 1965) and others on 7 recessive test loci in mice. As mentioned above, irradiation with identical radiation doses but at high dose rates (= acute irradiation) leads, according to the same experiments, to more than twice the number of mutations, and hence, to a much lower doubling dose (about 0.4 Sv after irradiation of spermatogonia).

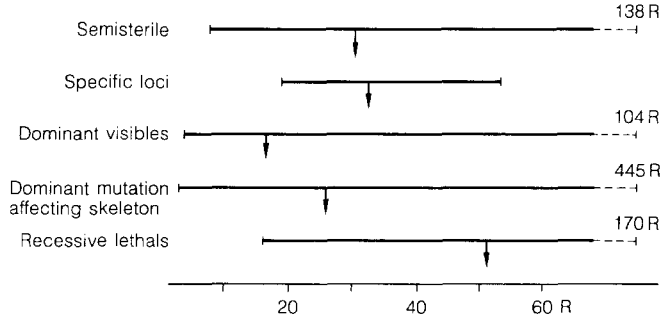

Fig. 1. Doubling dose and 95% confidence intervals for genetic endpoints in the mouse (acute radiation) (Lüning and Searle, 1971)

The problem of the doubling dose has often been discussed, e.g. by Neel and Lewis (1990). These authors have compared doubling doses from more comprehensive mouse data with those estimated from human data. For various experimental systems in the mouse, they arrive at a doubling dose of about 1.35 Gy (Sv) for acute (high dose rate) and approx. 4 Gy (Sv) for chronic (low dose rate) irradiation, with wide confidence margins. Hence, these estimates are higher (and, therefore, point to a lower genetic impact) than those used in the reports of UNSCEAR and the Committe on the Biological Effects of Ionizing Radiation of the US National Research Council (BEIR; 1990).

The doubling dose estimate of 1 Sv has two practical advantages: it is simple, and it indicates that an order of magnitude is implied, not a precise figure. However, it contains two bold extrapolations: from a small set of mutations to all kinds of genetic effects manifested in the next generation, and from the mouse to humans. Both extrapolations will be mentioned repeatedly in the following; the latter has especially raised extended discussions. The following formula is used (Denniston 1982) to provide an estimate with the indirect method:

$$\text{Induced burden (per unit of radiation)} = \frac{\text{spontaneous burden}}{\text{doubling dose}} \times \text{mutational component}$$

The definition of the "mutational component" is straightforward when all instances of a certain state or disease have a clear-cut genetic foundation and are caused by a new mutation. Its determination becomes very difficult in complex diseases. It requires two steps. In a first step, the incidence of a disease condition in human populations has to be determined. This step should be followed by a second, viz. an estimate of the mutational component, i.e. the fraction of instances in each generation that are caused by new mutations. This is easy in conditions such as trisomy (Down's or Klinefelter's syndrome) that are caused by a well-defined mutational event in the germ cell of one of the parents. Moreover, individuals carrying these mutations never reproduce. They represent mutational events in the germ cell of one of the parents. It is difficult in dominant or X-linked mutations

that reduce, but do not abolish the fertility of their bearers. It becomes virtually impossible in complex conditions, such as birth defects and multifactorial diseases.

Another problem is posed by the term genetic burden. According to the 1988 UNSCEAR report, the method "aims at expressing the risk in relation to the prevalence" (better: incidence) "of genetic diseases in the general population..." Here the term "disease" raises another question. Are we really interested only in disease states, even if this term is meant to include everything from sterility and early abortion to quasi "natural" death at an old age? What about possible shifts well within the "normal" range of abilities that are known to be in part genetically determined? For example, there is good evidence that heterozygotes of some autosomal-recessive diseases may sometimes show a small downwards shift of I.Q.; this cannot be considered pathological (see Vogel 1984b). Would this not be of interest for the assessment of the radiation risk?

The following discussion will almost entirely be confined to disease states, but the problem of possible shifts within the normal range should be kept in mind, especially, since in modern human genetics and medicine, the limit between health and disease is becoming more and more blurred (see Vogel and Motulsky 1986; Vogel 1990).

The so-called direct method. Ehling (1985, 1989a, b, 1990) has developed a direct approach that is thought to circumvent many of the difficulties encountered in the practical application of the indirect method. According to this author, it is the goal of this method to achieve a direct estimation of the genetic risk expressed in the first offspring generation. It is based on an extrapolation from dominant mutations induced in mice. The number of radiation-induced mutations leading either to anomalies of the skeleton or to dominantly inherited cataracts in the F_1 generation was determined. In Ehling's opinion, these mutations can be compared directly with corresponding mutations in humans. The following formula was used:

Expected number of induced dominant mutations in man	=	Induced mutation frequency in mice	×	Multiplication factor for the overall dominant mutation frequency in man	×	Genetically significant dose in man

According to Ehling, "The mutation rate for dominant cataracts is determined in experiments with mice. The multiplication factor to convert the dominant cataract rate to an overall mutation rate is based on McKusick's catalogue of autosomal phenotypes ... the number of well-established dominant mutations is 1172. The number of well-established cataracts ... is 28. The ratio of total dominant mutations to cataract mutations of 42 is assumed to be the same in man and mouse. This ratio can be used to convert the induced mutation rate of dominant cataracts to the estimation of the overall dominant mutation rate." Similar reasoning is possible for mutations affecting the skeleton (see, for example, Selby 1990).

Ehling applied this method to about 19000 children of Hiroshima/Nagasaki survivors (for studies on these survivors see below). He arrived at an estimate of 17–21 additional dominant mutations that would be expected to be caused by atomic bomb irradiation of their parents.

At first glance, this direct approach seems to be convincingly simple and straightforward. However, there are points of criticism from the viewpoint of the medical geneticist. (1) It is certainly too simplistic to calculate the multiplication factor from the number of different dominant cataracts in humans in comparison with the total number of known, dominantly inherited human phenotypes, mainly since incidences of all these mutations, which are very different, are deliberately neglected. (2) The generation time in mice is much shorter than in humans. Therefore, many of the cataracts seen in humans simply would have no time to develop in mouse. (3) The direct method is no more direct than the indirect one. The indirect method requires two main steps of reasoning. As a first step, it requires determination of the incidence of certain types of mutation and its increase in response to a certain radiation dose, and extrapolation from certain groups of mutations to all mutations. However, in addition, it requires a comparison of the expected number of induced mutations with the "spontaneous" rate; this part of the indirect estimate creates most of the difficulties. At the same time, however, this comparison gives medical and social meaning to the entire procedure, as mentioned before.

Therefore, I shall discuss only results of the indirect (doubling dose) estimates in the following. This does not mean that I regard mutation studies with incompletely or completely dominant effects (skeletal malformations, cataracts, and others) as meaningless for the estimation of genetic radiation effects. Indeed, they may help us to create hypotheses for the elucidation of the genetic basis of many human malformations. Nevertheless, a careful comparison of such effects with anomalies and malformations observed in humans, and the determination of the spontaneous occurrence in the human species and in mice, is necessary. Attempts at widening the spectrum of such dominant effects in mice, and a comparison of radiation effects with those of some chemical mutagens, the molecular mechanisms of which are known, should be encouraged (see Selby et al. 1991).

The two most important estimates

Two committees have published estimates on the amount of the additional mutational burden in relation to a certain dosage of low-level chronic radiation, i.e. radiation with a low dose rate: the UNSCEAR committee and the BEIR committee. Their estimates are compared in Table 1. Both estimates have been modified repeatedly. Here, only the latest estimates are give (UNSCEAR 1988; BEIR 1990).

The two estimates show some similarities, but also interesting differences. A simple difference is that

Table 1. Risk estimates for genetic disease

Estimated increase per *1 Sv* low-dose-rate radiation (UNSCEAR 1988, Table 7, p31)					Estimated increase per *1 rem* (0.01 Sv) low-dose-rate radiation (BEIR 1990, Table 2-1, p 70)			
Disease classification	Current incidence per million live births	Effect of 1 Sv per generation			Type of disorder	Current incidence per million liveborn offspring	Additional cases/10^6 liveborn offspring/rem/generation	
		First Generation	Second Generation	Equilibrium			First generation	Equilibrium
Autosomal dominant and X-linked	10000	1500	1300	10000	Autosomal dominant			
					Clinically severe	2500	5–20	25
					Clinically mild	7500	1–15	75
					X-linked	400	< 1	< 5
Autosomal recessive	2500	5	5	1500	Recessive	2500	< 1	Very slow increase
Chromosomal					Chromosomal			
Due to structural anomalies	400	240	96	400	Unbalanced translocations	600	< 5	Very little increase
Due to numerical anomalies	3400	Probably very small			Trisomies	3800	< 1	10–100
Congenital anomalies	60000	Not estimated			Congenital abnormalities	20000–30000	10	10–100
Other multifactoral diseases	600000	Not estimated			Other disorders of complex etiology			
					Heart disease	600000	Not estimated	Not estimated
					Cancer	300000	Not estimated	Not estimated
					Selected others	300000	Not estimated	Not estimated
Early acting dominants	Unknown	Not estimated						
Heritable tumors	Unknown	Not estimated						
Totals of estimated risk		1700	1400	12000				

UNSCEAR gives its estimates per 1 Sv, whereas BEIR gives it for 0.01 Sv. Therefore, BEIR estimates should be multiplied by 100 for a comparison with UNSCEAR estimates. Moreover, the UNSCEAR tried to give "best estimates", whereas BEIR gave a range. In the following, the evidence on which these estimates are based will be discussed critically.

Autosomal-dominant and X-linked recessive diseases

For this group of hereditary diseases, the two reports agree very well (the fact that X-linked diseases are enumerated separately in the BEIR report, but not in the UNSCEAR report, is numerically unimportant). It is not difficult to establish a baseline and to estimate its mutational component for those autosomal-dominant and X-linked diseases that have a strong selective disadvantage, and the prevalence of which is maintained in the population by an equilibrium between constant mutational pressure and selection. Since Gunther and Penrose (1935) published their mutation rate estimate for tuberous sclerosis, this group of mutations has been used to estimate mutation rates by the so-called direct method (see Vogel and Rathenberg 1975; Vogel and Motulsky 1986), in which the number of sporadic cases in a population is compared directly with the reference population. In instances in which practical difficulties, e.g. illegitimacy or genetic heterogeneity, can be overcome, this method should lead theoretically to reliable results regarding the spontaneous mutation rate and its increase because of a mutagenic agent. Therefore, such mutations have been named sentinel mutations, since they are expected to indicate mutation rate increases caused by a new agent in the environment. Czeizel (1989a, b) has enumerated 15 sentinel anomalies that are thought to be caused by dominant new mutations, and that can be diagnosed at birth or a short time afterwards (Table 2). As previously shown (Strobel and Vogel 1958), such sentinel mutations are too rare to provide easy results with realistic assumptions on mutation rate increases; continuous screening of very large populations would be required.

Potential sentinel mutations make up only a small fraction of autosomal-dominat anomalies and diseases in human populations. In the 1988 UNSCEAR and the 1990 BEIR reports, the incidence of autosomal-dominant (and, in UNSCEAR, X-linked) diseases was estimated to be about 1% of newborns. According to Czeizel (1989a), the incidence of potential sentinel mutations was about 3 per 10000 in Hungary. This is about 30 times lower.

Table 2. Follow-up figures for indicator conditions after the Chernobyl accident. Numbers of live births were 807939, 126708 and 125514, respectively, in 1980–1985, in 01.05.1986–30.04.1987 and in 01.05.1987–30.04.1988 (Czeizel 1989a)

Indicator conditions	Baseline figures (1980–1985)		01.05.1986–30.04.1987		01.05.1987–30.04.1988		Total	
	No.	Per 10000	No.	Per 10000	No.	Per 10000	No.	Per 10000
Sentinel anomalies								
10080 Achondroplasia	38	0.47	4	0.32	7	0.56	11	0.44
10120 Apert syndrome	7	0.09	2	0.16	2	0.16	4	0.16
10620 Aniridia, bilateral	2	0.02	0	–	1	(0.08)	1	(0.04)
12350 Crouzon syndrome	5	0.06	1	(0.08)	2	0.16	3	0.12
12990 EEC syndrome	3	0.04	0	–	0	–	0	–
14290 Holt-Oram syndrome	12	0.15	2	0.16	2	0.16	4	0.16
15450 Treacher-Collins syndrome	3	0.04	1	(0.08)	1	(0.08)	2	0.08
16620 Osteogenesis imperfecta, type I	11	0.14	3	0.24	3	0.24	6	0.24
17470 Preaxial poly-syndactyly, type IV	56	0.69	15	1.18	10	0.80	25	0.99
18360 Split hand and/or foot, typical	3	0.04	1	0.08	0	–	1	0.04
18760 Thanatophoric dwarfism	6	0.07	2	0.16	1	(0.08)	3	0.12
30830 Incontinentia dwarfism	7	0.09	0	–	0	–	0	–
31120 Gorlin-Psaume syndrome	2	0.02	0	–	0	–	0	–
18020 Retinoblastoma	26	0.32	2	0.16	1	(0.08)	3	0.12
19407 Wilms tumor	65	0.80	6	0.47	7	0.56	13	0.52
Total	246	3.04	39[a]	3.08[a]	37[a]	2.95[a]	76[a]	3.01[a]

[a] Preliminary figures

There are some other, mostly rare diseases, the frequency of which in the population is probably maintained by an equilibrium between mutation and selection. Others, such as bilateral retinoblastoma (Matsunaga and Minoda 1988) or haemophilia have been maintained by such an equilibrium in the past, but successful therapy has upset this equilibrium in recent decades. Assuming constant mutation rates, the incidence of such conditions is bound to increase, with no additional mutagenic agent, until a new equilibrium has been reached, unless there are counteracting circumstances, e.g. artificial selection.

However, it is very unlikely that the most common dominant conditions are maintained by an equilibrium between mutation and selection. Monogenic familial hypercholesterolemia (type IIa), for example, is the most common of all well-defined dominant conditions. In heterozygotes, it often leads to coronary heart disease and premature death in middle age; the very rare homozygotes may die early from cardiac infarction. With present-day living conditions in industrial countries, there may be a very small selective disadvantage of the mutations leading to this condition. In the past, however, a small but widespread selective advantage would most easily explain the high frequency of these mutations in present populations; the mechanism of such an advantage could have involved the shortage of certain foodstuffs. At present, its nature is unknown.

Huntington's disease is another example. It also belongs to the most common autosomal-dominant diseases. Recent sudies with closely linked DNA markers have shown that all mutants identified so far may be located at the same gene locus. For this disease, a number of good epidemiological studies exist (Reed and Nell 1959; Wendt and Drohm 1972; see Harper1992). Selective disadvantage of the gene, as measured by the fertility of patients in comparison with the general population, is small (about 5%–10%). Moreover, even this small disadvantage appears to be caused by voluntary restriction of the number of children, i.e. it is artificial. On the other hand, no new mutations have been identified so far beyond reasonable doubt. This suggests that the Huntington mutation might have had a selective advantage in earlier times.

At first glance, the problem might be solved by simply not using such mutations in risk estimates. However, for many dominant diseases, the mechanisms that have caused their present-day incidence are unknown. Moreover, the situation might be still more complicated. Mutation and selection may cooperate. The X-linked fra(X) (fragile X) syndrome is one example. Here, a relatively high spontaneous mutation rate appears to be combined with a selective advantage of heterozygous carriers, leading to an exceptionally high population incidence (Vogel 1984a; Vogel et al. 1985, 1990).

It follows that dominant and X-linked diseases cannot be subdivided entirely into those the incidence of which is maintained by an equilibrium between mutation and negative selection, and others in which a selective advantage under certain living conditions has been the decisive factor. More complicated situations may occur, and the equilibrium conditions may change over time, depending on living conditions.

In earlier UNSCEAR reports, the mutational component of the entire group was estimated as being 15%. In this estimate, the medical geneticists may have been persuasive, having in mind the more severe and debilitating forms of genetic desease. In any case, the estimate is

high. Until more precise knowledge has accumulated, it might be reasonable to retain it. If the situation is uncertain, it is always wise to assume a risk in the upper part of the possible range; the higher the "spontaneous" mutational component, the higher the radiation risk.

Dominant and X-linked mutations in relation to paternal age

In order to consider an increase of morbidity attributable to autosomal-dominant and X-linked radiation-induced mutations in proper perspective , it should be remembered that the "spontaneous" mutation rate is not a natural constant. The best known factor that influences the mutation rate is paternal age. For some autosomal-dominant anomalies, such as achondroplasia, acrocephalosyndactyly, myositis ossificans, the Marfan syndrome, and probably some others, the mutation rate at a paternal age of 40–45 is fourfold to sixfold higher than at a paternal age of 20–25 (see Vogel and Rathenberg 1975). Recently, Modell and Kuliev (1990) have published calculations indicating how much a given shift in distribution of paternal ages in a population would change mutation rates. Published data on achondroplasia, myositis ossificans and acrocephalosyndactyly were used for these model calculations. Table 3 is based on the paternal age distributions in the general populations of various countries. The expected incidence of dominant new mutants is compared with their incidence if all fathers were < 30 years old at the time of birth of their children. The ratios vary from 1.22 in Bulgaria and East Germany in 1980 to 2.67 in Pakistan, 1968. Hence, even a relatively small shift in paternal age distribution, especially an increase or a reduction of "older" fathers, could influence the mutation rate for such paternal age-dependent mutations appreciably, probably much more than any conceivable change in exposure to mutagenic agents, e.g. radiation.

Table 3. Estimated relative mutation rate in European countries (Modell and Kuliev 1990)

Country and year	Fathers > 35 (%)	Relative mutation rate (1 = level when all fathers are < 30
Bulgaria 1980	7.3	1.22
GDR 1980	8.5	1.22
Czechoslovakia 1978	9.6	1.27
Hungary 1980	10.2	1.28
Belgium 1978	11.6	1.33
Scotland 1980	12.0	1.34
Poland 1980	12.1	1.35
Netherlands 1979	12.9	1.38
France 1980	14.9	1.43
England and Wales[a] 1979	15.4	1.44
Finland 1980	16.0	1.45
Denmark 1980	17.6	1.47
Luxembourg 1980	17.8	1.47
Norway 1980	17.6	1.47
Iceland 1980	21.1	1.53
Northern Ireland 1978	19.0	1.53
Switzerland 1979	20.0	1.53
Sweden 1980	23.4	1.53
Malta 1980	19.8	1.54
FRG 1980	22.2	1.57
Spain 1980	23.6	1.64
Italy 1978	24.1	1.64
Greece 1979	24.3	1.69
Spain 1966	33.5	1.69
Pakistan 1968	46.1	2.67

[a] Correlation for infants born out of wedlock makes no difference to the figure

Autosomal-recessive diseases

The 1988 UNSCEAR report gave an increase of 5 instances in the first generation, and 5 in the second generation, with an equililbrium value of 1500 additional cases at equilibrium. The BEIR V report, giving the same figure for basal incidence (2500/1 million), estimated the increase in the first generation at < 1, and remarked in addition: "Very slow increase." The earlier UNSCEAR reports did not attempt to provide any specific estimates, with the exception of the 1972 report that gave an estimate for the first generation, based on adverse effects in heterozygotes as indicated by some studies in *Drosophila*. The new estimate was based on a publication of Searle and Edwards (1986). According to these authors, an extra genetically significant dose of 0.01 Gy of X-rays or γ-rays received by each parent in a stable population would lead to up to 1200 extra recessive mutations. Depending on which other identical alleles they happened to meet, homozygotes would segregate out; the number of such homozygotes critically depends on the breeeding structure of the population, especially the number of consanguineous matings. To arrive at the estimate of Table 1, the authors assumed a rate of 1% first-cousin marriages. They also stated that, with very low inbreeding rates or in the complete absence of inbreeding, manifestations of recessives may spread over enormous time periods: "... if 1000 recessive lethals were randomly distributed over 10^9 individuals mating at random, the proportion surviving per generation would be 0.999999, giving a half life (of a mutation) of over a million years in man."

In populations of industrialized countries, first-cousin matings have gone down to one or a few per thousand in recent decades (see Vogel and Motulsky 1986). Since this reduction is caused, on the one hand, by greater mobility and, on the other hand, by smaller numbers of children (and, hence, the reduction in the number of available cousins), this decrease will probably continue and spread to other populations. However, if consanguinity can be neglected in the future, it is open to question whether effects distributed over thousands of generations should be considered in genetic risk estimates. Gene therapy and/or prenatal diagnosis at the zygote level will eventually become routine, especially for autosomal-recessive diseases with mostly simple enzyme defects.

Another assumption of Searle and Edwards (1986) was a selective disadvantage of heterozygotes. Extrapolating from the *Drosophila* data given by Muller (1950), they assumed an average selective disadvantage of 2.5%. However, these are by no means the only available *Drosophila* data; selective advantages in a considerable fraction of heterozygotes have been shown in other studies (Stern et al. 1952; Wallace 1957).

In humans, amazingly few data on phenotypic deviations in the heterozygotes of autosomal-recessive diseases are available (see Vogel 1984b). As a rule, heterozygotes have about half the activity of normal homozygotes for the product of the gene that is affected by the mutation, in many cases an enzyme. In most situations, this reduced activity will suffice for normal function. Apparently, evolution has provided the human body with a wide safety margin for the preservation of function, even in the presence of smaller deficiencies. When the system involved is put under special stress, however, abnormal phenotypic effects may ensue. Many examples are known (Vogel 1984b). Very few may lead to reduced reproduction of their carriers, i.e. a selective disadvantage. Most of them, such as slight I.Q. shifts, have no relationship, or no culture-independent and therefore constant relationship, with fertility. Some appear to influence health in middle and advanced age, and it is very well possible that susceptibilities to complex and so-called multifactorial diseases are influenced strongly by our individually different patterns of heterozygosities for recessive diseases.

It is possible that radiation-induced recessive mutations may have, on average, stronger phenotypic effects in heterozygotes than "spontaneous" mutations: As shown in the classical studies mainly by Russell (1952, 1954, 1957, 1964a, b, 1965) on the seven autosomal-recessive test loci of the mouse, radiation-induced recessive mutations are small deletions.

Nevertheless, it has to be conceded that the present knowledge of health effects of the heterozygous state for autosomal-recessive diseases is incomplete. Such studies are time-consuming and they require great epidemiological skill and complex logistics. Their results should be important for improving risk estimates, but they are never impressive, mostly showing slight deviations from normal that often cannot be established beyond reasonable doubt. It is not surprising that such investigations are seldom undertaken.

Finally, the background of recessive genes and diseases in human populations is not constant, being even less constant than that, for example, of spontaneous mutations. The reduction of consanguineous marriages has already been mentioned. A second tendency is the breaking up of isolates. Both developments must have led to a sudden reduction of homozygotes for recessive genes below equilibrium frequencies. Disregarding any changes in the mutation rate, on the one hand, and (unlikely) future increase of inbreeding, on the other, a very slow increase of affected homozygotes must be anticipated, until a new equilibrium is reached (for details see Vogel and Motulsky 1986).

In conclusion, any possible effects of additional radiation should be viewed against a complex background. Moreover, these effects will be different depending on future changes in population structure, changes that can hardly be predicted.

Chromosomal diseases

The risks given for chromosomal diseases are, in principle, similar in both reports. The basic figure for structural anomalies or unbalanced translocations is given at 400/1 million by UNSCEAR and 600/1 million by BEIR. Obviously, both estimates are based on well-known population studies on newborns; they do not comprise figures from studies on spontaneous abortions. UNSCEAR gives an increase estimate of 240 for 1 Sv (= the doubling dose), meaning that more than half the unbalanced translocations occur de novo, and that this fraction would be doubled. The BEIR committee was much less definite, but an estimate of < 5 per 0.01 Sv is obviously of the same order of magnitude. The UNSCEAR estimate was based on evidence that about 9% of individuals with unbalanced chromosome rearrangements will survive to birth. However, how many such rearrangements are actually induced? Here, comparative studies in the mouse, rhesus monkeys, marmoset monkeys, and crab-eating monkeys, and in human males have revealed striking differences (see the 1986 UNSCEAR report, Table 21, p 128). Hence, the figure given in Table 1 is a relatively crude approximation. It is the best estimate from many, but sometimes divergent, data. It is based on extrapolations, some details of which might be doubted. One interesting point should be noted: many spontaneously occuring translocations in humans are Robertsonian in type, but it has been concluded from mouse data that radiation does not induce such Robertsonian translocations (Ford et al. 1978).

For numerical chromosomal diseases (mainly trisomies), UNSCEAR gives a figure of 3400/1 million; BEIR gives an estimate of 3800/1 million. Both reports agree that the increase with increasing radiation dose will probably be very small. Adding incidence data in newborns for autosomal and gonosomal numerical anomalies together (see for example, Nielsen und Silessen 1975; Nielsen et al. 1982) gives a figure for incidence without additional radiation that is closer to the higher (3800/1 million) than to the lower figure. The assumption made in both reports that the increase with low-dose rate radiation will be small is based on mouse data. Some of these data have been mentioned in passing in the first section of this review. Recently, a number of studies have been performed in the mouse in wich the effects of ionizing radiation on female and male germ cells have been investigated in detail (Griffin and Taese 1988; Hansmann et al. 1979, 1985; Pacchierotti et al. 1987; Russo et al. 1983; Speed and Chandley 1981; Tease 1982, 1985). Pacchierotti et al. (1987) concluded from their own and other studies that the rates of aneuploidy induction calculated in male and female germinal cells were of the same order of magnitude (about $2\text{–}7 \times 10^{-2}$ per Gy) and were not very different from those reported by various authors for translocation induction in spermatogonia.

Taken as a whole, however, the evidence is not a good as it should be. This has been realized by mouse geneticists, and a comprehensive international research programme for collecting better data is now in progress. As mentioned in the beginning, the oocyte, when irradiated at the time of fertilization, is especially susceptible to chromosome loss, especially loss of the X-chromosome. However, most monosomic human zygotes do not survive early pregnancy; even the great majority of surviving 45 X zygotes are thought not to be attributable to nondisjunction or chromosome loss during meiosis, but to be caused by mitotic events during early pregnancy. Moreover, most trisomies do not survive to birth (Hassold et al. 1981; Hassold and Jacobs 1984). Hence, in view of the well-known high incidence of chromosomal anomalies among spontaneous abortions, any radiation-induced increase of nondisjunction and/or early chromosome loss would lead to an increase in the rate of spontaneous abortion rather than to more chromosomally abnormal newborns, as explained in greater detail in earlier UNSCEAR reports. This conclusion is corroborated by a study in the mouse (Reichert et al. 1984), in which the frequency of chromosomal radiation effects was followed from MI zygotes to early and late embryos. The fraction of chromosomally disturbed germ cells, which was very high at the beginning, was found to be practically zero in embryos surviving to birth.

In the UNSCEAR 1982 report, (Table 8, p 525), 12 studies were listed in which the problem of whether the incidence of Down's syndrome increases after pre-conceptual irradiation of the mothers was addressed. In 4 studies, a significant increase of this syndrome was described, whereas 8 studies failed to show such an effect. In these studies, women were included who had been exposed at some time in their lives to small radiation doses for medical reasons. Obviously, these women are not an unbiased population sample; there is ample opportunity for the action of confounding variables. On the other hand, these data do not allow the dismissal of the possibility that low radiation doses enhance the risk for autosomal nondisjunction in female meiosis, at least under certain conditions (see also the studies of populations living in areas with high background activity in India and China, discussed in a later section of this report).

As mentioned, the estimation of additional risks is meaningful only in relation to the "spontaneous" mutation rate. The "baseline" is especially variable for trisomies, because the "spontaneous" mutation rate increases with the age of the mother; the risk for mothers above 40 is 10–20 times higher than that for 20-year-old mothers (see for example, Hook and Chambers 1977). Therefore, the same conclusion that has previously been derived for paternal age and dominant mutations holds true, in principle: even a small shift in the distribution of maternal ages in a human population (and especially in the fraction of mothers above the age of 35) will alter the incidence of trisomy syndromes at birth much more than any conceivable increase caused by radiation.

In conclusion, the increase of structural and numerical chromosomal aberration among newborns attributable to additional radiation of parents would very probably be minor. Nevertheless, additional evidence from animal experiments would be very welcome.

Congenital anomalies and multifactorial diseases

For these two categories, UNSCEAR and BEIR deviate from each other in the estimation of incidences. UNSCEAR gives a figure of 60000/1 million for "congenital anomalies" and 600000/1 million for "other multifactorial diseases." BEIR estimated "congenital abnormalities" as 20000–30000/1 million. This report subdivided "other disorders of complex etiology" into three categories: heart disease (600000), cancer (300000) and "selected others" (300000). These three figures add up to more than 1 million; hence, they cannot be meant to be mutually exclusive. UNSCEAR did not estimate the increase caused by radiation for any of the two categories; BEIR mentioned an increase of 10 (per 0.01 Sv) in the first generation and a new equilibrium value of 10–100 for congenital abnormalities. Both estimates, however, are extremely unreliable. The problem begins with the estimation of the incidence of congenital anomalies at birth. It continues with attempts at estimating the "mutational component" of these malformations. As to the first step, estimates of incidence, there are many such estimates. Their results show an enormous range of variation, depending mainly on the definition and delineation of the malformations included and the mode of ascertainment. Population screening programmes, often supplemented by additional examination in selected individuals and families, and ad hoc studies are, in most instances, performed not only to determine incidences, but also to obtain possible causes of such malformations.

The ad hoc studies can be subdivided into two groups: retrospective and prospective studies. In retrospective studies, cases with certain malformations are ascertained in a population, and data on the history of the pregnancies and genetic data are collected retrospectively and compared with adequate controls. In prospective studies, pregnancies are monitored from the beginning, and the outcome is registered. The retrospective design is much simpler and less time-consuming and expensive, but is less reliable for the detection of possible causes.

Koller et al. (1983), who conducted such a prospective study in the Federal Republic of Germany, compared their work with others, and noted that, despite basic agreement on principles of definition, there remained a wide range of subjective and observational variation in real ascertainment and classification of single cases. The following parameters are especially important: age of the child at time of observation, single or repeated examination, and the exclusion or inclusion of instances of early death.

In the study mentioned, children were examined within the first week after delivery, after 6 weeks and at 9, 18, and 36 months. Severe malformations were observed in 122 children (1.73% of 7042 children born). Of these, 86 were discovered at birth or within the first three months, and 36 after the first quarter of a year and up to the end of the third year. In addition to these severe malformations, 1761 (24.9% of 6900) children showed "small but

definite" anomalies; "small borderline" anomalies were registered in 2772 (40.2%). This means that about two-thirds of children included in this study were diagnosed as having malformations or anomalies. This study, comprising a relatively small but unbiased number of thoroughly studied pregnancies, shows many of the problems involved in the seemingly simple task of ascertaining and counting newborns and children with malformations and anomalies.

This study can be compared with a population-wide registry of hereditary or partially hereditary diseases in British Columbia (Canada) with a population of somewhat over 2 million (Trimble and Doughty 1974). All liveborn children in the period 1952–1972 were examined; stillbirths were not included. Anomalies were coded using the International Classification of Diseases (ICD) system. A total of 29378 liveborn children (out of 756304) were found to have one or another of the often hereditary anomalies and birth defects registered in this study; among them 15728 had congenital malformations (3.58%). As in the study of Koller et al. (1983), this figure also comprises chromosomal aberrations and diseases with Mendelian modes of inheritance. The incidence estimate of 3.58% is slightly higher than that given in the study of Koller et al. (1983) for severe malformations (1.73%), but much lower than the figure for children with small but definite anomalies (24.9%). In comparing the figures for severe malformations, it should be noted that Down's syndrome is included in the severe malformation class of the Koller study, but not in the British Columbia study. The ethnic origin of the British Columbia population is not so different from the German one. The actual incidences of malformations in the two populations might therefore be regarded as similar. Moreover, both groups used the ICD classification. However, this classification is insufficient for the purposes of medical genetics, because it combines anomalies with different clinical signs and different etiologies. In comparing ICD classes, it may be concluded that the Canadian survey probably contains, within the single ICD classes, milder anomalies than the German survey. The German team has very probably included fewer malformations in its "severe" class, and included many more anomalies in its "small but definite" category than the Canadians in their "malformation" category.

In theory, a system of continuous registration that is complemented by ad hoc studies on special problems, such as genetic data (for example empirical risks in families) or environmental factors (radiation, drugs and environmental chemicals), is the best system for answering questions of incidence and causation. The programme in Hungary, which has been in operation since the early 1960s, appears to be the most informative of this kind.

Hungary, with a population of about 10.7 million, has been registering all newborns (liveborns and stillborns) with congenital malformations since 1962. Reporting is also mandatory for all birth defects detected within the first year of life. This registry is supplemented by the legally enforced autopsy of all deceased children. Additionally, epidemiological ad hoc studies are performed to solve special problems. In Hungary, practically all pregnancies are monitored, and unusual events during these pregnancies, including drugs and X-ray exposures, are noted. In a case where a child carries a malformation or another anomaly, data from that pregnancy are compared with those from suitably matched control pregnancies.

Reports have been published mainly on congenital anomalies (Czeizel and Sankaranarayanan 1984), selected common multifactorial diseases (Czeizel et al. 1988) and mental retardation (Czeizel et al. 1990). Table 4 contains the relative frequencies per 10000 births in Hungary (total births and live births) in comparison with data from a prospective study in the United States (Chung and Myrianthopoulos 1975) and the above-mentioned British Columbia study. The total number of congenital anomalies in the Hungarian study is higher than in the British Columbian study, but much lower than in the US study.

At first glance, this result would suggest that studies based on malformation registers are always incomplete and unreliable. However, this does not explain the major part of the difference. As shown above, the (much smaller) prospective study in Germany was performed with great care; children were re-examined up to the third year of life. Nevertheless, the recorded incidence of severe anomalies turned out to be much lower in the German than in all three other studies, despite the fact that the same ICD categories were used.

A few of these different results suggest real differences in the incidence of some malformations between these populations. For example, Czeizel and Sankaranarayanan (1984) described an especially high incidence of congenital dislocation of the hip in Hungary in comparison with other European populations (Carter 1976). This anomaly is also common in Britanny (France), and might possibly have a genetic basis. On the other hand, recorded incidence may vary with the diagnostic standards used. Other real (but small) differences might be hidden in the information collected and analysed by the various teams, because of differences in classification and inclusion or exclusion of individual cases.

In the reports on the Hungarian data, the authors also attempted to estimate "detriment in terms of years lost and years of impaired life" for the various categories of anomalies. This attempt at quantifying the actual burden inflicted upon the individual and upon human society by congenital anomalies is certainly interesting. In the opinion of the present author, these results are however unsatisfactory for many reasons. Therefore, this approach will not be discussed in detail within this review.

The mutational component of common malformations

The seemingly simple task of determining the incidence of congenital malformations at birth poses some problems, and results from one study to the next may show considerable differences, occasionally because of real differences between populations, but much more often because of differences in ascertainment and classification. In order to predict a possible increase attributable to a specified radiation dose experienced by the germ

Table 4. Relative frequencies (per 10000 births) of congenital anomalies in the United States of America and Hungary (according to Czeizel and Sankaranarayanan 1984)

ICD code	Congenital anomaly	Prevalence[a] per 10^4			
		US, among total births	Hungary		British Columbia, among live births
			Among total births	Among live births	
740–741	Anencephaly and spina bifida	17.4 (42)[b]	16.6	10.3	9.2
742	Other anomalies of the nervous system	35.2 (85)	14.6	11.4	7.9
743	Anomalies of the eye	23.6 (57)	3.2	3.2	7.8
744	Anomalies of ear, face and neck	14.9 (36)	4.7	4.6	6.0
745–747	Cardiovascular anomalies	86.5 (209)	80.8	79.2	42.6
748	Anomalies of the respiratory system	14.1 (34)	2.8	2.8	1.5
749	Cleft palate and cleft hip	27.3 (66)	14.8	14.5	17.5
750–751	Anomalies of the digestive system	61.7 (149)	27.8	27.8	17.6
752–753	Anomalies of the genital organs and urinary system	115.5 (279)	93.7	90.9	27.5
754–756	Musculoskeletal and skeletal anomalies	438.0 (1058)	314.2	312.7	66.2
757	Anomalies of the integument	101.4 (245)	7.6	7.4	2.4
758	Chromosomal anomalies	16.1 (39)	12.6	12.6	14.1
759	Other and unspecified anomalies	12.8 (31)	21.5	20.0	1.9
	Total	964.5 (2330)	614.9	597.4	222.2 (358)[c] (428)[d]
550	Hernia, inguinal	127.9 (309)	110.4	110.4	–
553	Hernia, umbilical	10.8 (26) 350	9.4	8.8	–
	Congenital tumors	6.2 (15)	1.2	1.2	–
	Grand total	1109.4 (2680)	735.9	717.8	–

[a] The US prevalence figures refer to the number of congenital anomalies (and not the number of affected individuals); for the other two, the figures are based on the numbers of affected individuals

[b] The figures given in parentheses (column 4) refer to the numbers of congenital anomalies on which the prevalence estimates (given in column 3) are based

[c] The frequency of 222.2 is for the period 1952–1972 and that of 358 is the authors' minimal estimate (excluding chromosomal anomalies)

[d] The authors' adjusted estimate (excluding chromosomal anomalies)

cells of parents, the "mutational component" of this incidence should be estimated. This involves an estimate of frequency and degree of genetic determination of single anomalies and their modes of inheritance. Furthermore, possible selective disadvantages of such anomalies under the living conditions of earlier times and at present (and, if possible, in populations of industrialized countries, and in developing countries with poor medical systems) should be known. This information is needed to estimate which part of the genetic component of a certain anomaly is lost in every generation, and which is therefore replaced by new mutants. Even then, one would make an estimate of the right order of magnitude only if an equilibrium between mutation and selection actually existed (Haldane's principle; Haldane 1935)

In view of the complex genetic basis of most malformations, such estimates are impossible to date. Therefore, it was a reasonable decision that, in the UNSCEAR 1988 report, no such estimate was attempted. As mentioned, however, the BEIR (1990) report gives such an estimate: about 10 in the first generation and 10–100 at equilibrium for 0.01 Sv of additional radiation. These estimates are based on the assumption that the relevant malformations consist of those caused in part by multifactorial inheritance in combination with a threshold, and in part, by irregularly manifesting dominant mutations. The overall mutational component is estimated to be between 5% and 35%. The upper limit (35%) is then used to estimate the increase as seen in Table 1. For details of this involved estimation process, the reader should refer to the BEIR (1990) report itself. Suffice it to say that the result is very vague indeed. Moreover, the argument is based in part on results of twin studies, which are misleading for congenital malformations, since the incidence of most of them is increased because of the special conditions of monozygotic twin pregnancies (Vogel and Motulsky 1986).

Many congenital malformations have a truly "multifactorial" basis. A few are caused by environmental factors such as teratogenic drugs or, very rarely, irradiation during pregnancy. For many of them, no cause can be identified; they are attributable to an accumulation of random processes during early embryonic development. However, data from radiation experiments in mice suggest that some may also be caused by irregularly manifesting dominant mutation. Their frequency may increase

after the irradiation of parents. For example, Ehling (1966, 1989a, b), Selby (1990), Selby and Selby (1978) and Selby et al. (1991) have shown that irradiation of mouse spermatogonia may lead to the occurrence of a wide array of skeletal malformations. This indicates that genetic variation influencing such malformations may, indeed, have a strong mutational component. It is remarkable, on the other hand, that studies on the associations of malformations with known genetic polymorphisms, such as the ABO blood grous (see Vogel 1970; Vogel and Helmbold 1972; Mourant et al. 1978), have largely failed to point to any such associations. The same is true for disease associations with the major histocompatibility system (Tiwari and Terasaki 1985). Cautious extrapolation from these few polymorphisms to polymorphisms in general may permit the preliminary conclusion that variation within such polymorphisms in the normal range has litte significance for the occurrence of malformations.

The genetic load

The concept of genetic load has been discussed extensively by population geneticists. At least two types of load have been distinguished: the mutational, and the segregational load. The mutational load describes the deviations from optimal fitness in a population caused by recurrent, and mostly detrimental, mutations, whereas the segregational load comprises deviations attributable to the segregation of homozygotes in situations in which heterozygotes have a selective advantage (for details see Crow 1970; Vogel and Motulsky 1986). Both types of load occur, but there have been heated discussions between population geneticists as to which is the more important in humans.

In the event that the above-mentioned mouse data on skeletal anomalies can be extrapolated to humans, and further studies should confirm the absence of associations with genetic polymorphisms, this would point to a predominance of the mutational load with respect to these anomalies. In this case, only non-genetic causes and a mutational genetic component would have to be considered for this group of mutations.

At present, our limited knowledge concerning these problems in humans does not permit a prediction of how much a certain additional radiation dose will enhance the load due to congenital malformations (except those caused by chromosomal aberrations or regularly inherited dominant and X-linked mutations). This task meets with two major difficulties. (1) The present-day incidence of such malformations in human populations is not known with sufficient precision. This difficulty could be overcome if monitoring systems for birth defects were introduced in a few human populations, following the Hungarian example, and if their logistic and diagnostic precision could be optimized. (2) The mutational component of this group of malformations in humans is unknown. Many more studies on the genetic background of common malformations at different levels (clinical, biochemical, and molecular) are necessary to fill this gap. In the absence of an adequate theoretical rationale, empirical data on irradiated population groups may help with regard to preliminary conclusions (see below).

Other multifactorial diseases

The second group of diseases with no well-defined genetic basis (Table 1) are the "other multifactorial diseases" (UNSCEAR) or the "other disorders of complex etiology" (BEIR). As mentioned, UNSCEAR gives an estimate for present-day incidence of 600000/1 million; BEIR gives 1200000/1 million, subdivided into three categories that are obviously not mutually exclusive. So far, both committees have refrained from estimating the increase caused by additional irradiation. This is a wise decision, since no scientific basis can be found at present for such an estimate. On the other hand, this category poses the very questions that human society want answered. How much will the general health status within our society be altered by increased radiation exposure in previous generations? Will this exposure influence our liability for diseases such as coronary heart disease, cancer, diabetes or autoimmune diseases?

The UNSCEAR figure for incidence, 600000/1 million again comes from a Hungarian study (Czeizel et al. 1988). To arrive at this estimate, the simplifying assumption that one individual suffers from only one such condition was made. Moreover, morbidity was considered only up to the age of 70. Before going into details, it is necessary to discuss the conceptual basis of this estimate.

Multifactorial diseases in this group include coronary heart disease, diabetes mellitus (type 1 and type 2), hypertension with its consequences, and the rheumatic diseases. In short, they comprise almost the entire field of internal medicine. In addition, mental diseases and neuroses have to be considered. Such multifactorial conditions are so common that practically all human beings will suffer at one time or another from one or a few of them, to a mild or severe extent. Moreover, under present living conditions in industrialized countries, almost everybody will die sooner or later from one or a few of the diseases within this group. The entire group of common malignant tumours also belongs in this category. Moreover, etiology is usually complex, and may vary from one population to the other, within the same population from one time to the next, and even from one individual to another. These differences mainly depend on environmental factors that have been, and are being, identified by epidemiological research. Diabetes mellitus may be mentioned as one example (Creutzfeldt et al. 1976; Rüdiger and Dreyer 1983). Two common types are distinguished: type 1 (juvenile, insulin-dependent), and type 2 (adult, insulin-independent). Type 1 often starts with a virus infection; there are also associations with HLA types. Incidence does not change markedly with changes in general living conditions. In type 2, monozygotic twin concordance and familial risk are higher than in type 1, indicating a stronger genetic component. However, the incidence of type 2 seems to have differed at different time periods, such as in periods of war and food shortage; in some European countries, it disappeared almost completely during and after the Second World

War. It reappeared when the food supply first became adequate and then abundant. These observations point to a strong environmental, and especially nutritional, component within the etiology. The diabetes example may be used to demonstrate yet another problem: as mentioned, type 2 diabetes is common under present-day living conditions in affluent societies, but was very rare under conditions of food shortage and near-starvation. This leads to the question: what phenotypic effects did the genes presently promoting type 2 diabetes exert in times of food shortage? Neel (1962) suggested the hypothesis that they constituted a "thrifty genotype", i.e. that they caused a better utilization of foodstuffs, thereby facilitating survival under extreme shortage of certain foods. If such or similar hypotheses contain some truth, this means that present-day populations are probably not at equilibrium for genes establishing this genotype. Possibly, there is now some weak selection against this genotype, which had a selective advantage in times of food shortage.

Another question to be considered before the actual data on the incidence of such multifactorial conditions can profitably be reviewed seems to be, at first glance, much simpler, although it is really at least as complex. Who is ill? Where shall the limit be placed between an unimportant genetic variant, the slight and slightly uncomfortable anomaly, and the actual disease? We can consider the diabetes example once again. In earlier times, a diabetic was someone whose urine contained sugar, and who suffered from certain well-known clinical symptoms. Later on, the range of this diagnosis was extended to include individuals who had increased blood sugar, and who were therefore liable to develop the above-mentioned symptoms in the future. Since blood sugar level is a quantitative trait, the question arose regarding the level at which diabetes might be assumed to begin. This very question shows that there is no "natural" limit and no "natural" disease entity "diabetes", the boundaries of which can simply be discovered. Rather, this delineation is a conventinal one within a continuum.

Similar considerations apply to other such multifactorial conditions, as well. There is no "natural system" of multifactorial diseases (see also Vogel 1990). Any statement on incidences and prevalences depends critically on conventions regarding the definition and classification of such diseases. It is extremely difficult, to say the least, to compare different populations, or even to compare different periods of time with respect to the same population.

The Hungarian study mentioned above (Czeizel et al. 1988) comprises incidence estimates for 26 such "multifactorial" diseases that were classified according to ICD, and that were subdivided into three groups: (1) very severe (schizophrenia, multiple sclerosis, epilepsy, myocardial infarction); (2) moderately severe and/or episodal or seasonal (Graves' disease, diabetes, gout, affective psychoses, duodenal ulceration, asthma); (3) less severe (varicose veins, atopic dermatitis, etc.). With the exception of epilepsy, none of these diseases causes death in the age-group 0–19 years, but they are among the leading causes of death in advanced age. Table 5 gives a

Table 5. So-called multifactorial diseases in Hungary (1977–1981) according to Czeizel et al. (1988)

Disease	Lifetime prevalence per 10^4	Mean age of onset (years)	Mean age at death (years)
Group 1			
Schizophrenic psychoses	85	21	59.8
Multiple sclerosis	4	33	55.5
Epilepsy[a]	36	4	41.9
	24	4	41.9
Acute myocardial infarction, other acute and sub-acute forms of ischaemic heart disease	359	50	68.0
Systematic lupus erythematosus	4	34	56.8
Subtotals/means	512		
Group 2			
Grave's disease	65	45	67.1
Diabetes mellitus	427	58[b]	70.4
Gout	18	25	69.9
Affective psychoses	600	36	54.5
Glaucoma	160	55	76.0
Essential hypertension	850	58[b]	74.3
Asthma	249	35	67.4
Peptic ulcers	460	45	68.2
Idiopathic protocolitis	3	35	65.5
Cholelithiasis	94	35	71.6
Coeliac disease	13	1	71.8
Calculus of the kidney	90	45[b]	70.6
Psoriasis	39	20	72.3
Rheumatoid arthritis	131	40	70.3
Ankylosing spondylitis	19	23	67.2
Subtotals/means	3218		
Group 3			
Varicose veins	1250	(125) [c]30	70.3
Allergic rhinitis	360	(120) [c]25	72.6
Atopic dermatitis	60	(20) [c]18	72.2
Scheuermann disease	1100	(55) [c]12	73.2
Adolescent idiopathic scoliosis	41	(8) [c]13	73.2
Subtotals/means	2811	(328)	
Grand totals/means	6541	(4058)	

[a] In the group of epilepsies, there are 2 subgroups: (I) birth onset with severe progression, 20% of the cases and another 20% also with severe progression, the so-called chronic intractable cases; these 40% never start work; and (II) other cases

[b] For these diseases, the mean age at premature retirement is lower than the age at onset because the most severe cases (with onset earlier than the estimated mean age at onset) are prematurely retired at an earlier age than the estimated mean age at premature retirement

[c] Adjusted figures; to take into account the proportion of cases requiring medical treatment (e.g. 10% in the case of varicose veins)

short overview of the results. Such data are certainly extremely useful for many practical purposes, but their use for studying associations with exposure to mutagenic agents, such as radiation, is very limited, because of the following: (1) A major part of morbidity for many of these diseases is not the result of genetic predisposition or inescapable environmental exposure or both, but is a result of voluntary and avoidable behaviour. Type 2 diabetes has already been mentioned; coronary heart disease and gout are other examples. (2) In some of these diseases, the quality of life is not impaired decisively, providing that the individual finds a way of adapting his life-style to the condition. (3) In a broad borderline field, parameters such as the attitude of the society, the number of available doctors, and the health care systems influence whether a disease is diagnosed at all, and how much detriment it causes. All these factors may vary in different populations, and may vary in time within the same population.

The greatest difficulty is however caused by the complexities of the genetic causes of this disease group. Discussing the genetic background of congenital malformation, we have distinguished two types of genetic load: mutational and segregational. As mentioned, there is some evidence that, for example, for the genetic component in the etiology of malformations, the mutational component might prevail. Such evidence does not exist for most of the multifactorial diseases: many of them show associations with genetic polymorphisms, such as the ABO blood groups (Vogel 1970; Vogel and Helmbold 1972; Mourant et al. 1978) and/or the HLA system (Tiwari and Terasaki 1985). Most mutations within such polymorphic systems show no systematic tendency for increasing disease liabilities. In conclusion, to the extent that the segregational load prevails in such multifactorial diseases, no increase of disease liabilites can be predicted as a result of increased radiation exposure.

However, although the arguments for such a negative prediction are weak, this does not mean that the problem should not be investigated. It would nevertheless be hopeless (at least at our present state of knowledge) to study it at the level of morbidity from single "multifactorial" diseases. One parameter that could be studied is life-span. The mean and distribution of age at death are parameters for which relatively hard data are available. Moreover, there are data in the mouse pointing to a negative influence of parental irradiation on life-span (Russell 1957), especially on prereproductive death (Roderick 1964; for references and discussion, see also Neel and Lewis 1990). A serious problem with the use of this indicator in the mouse, a multiparous animal, is the negative correlation between litter size and survival of newborns. There is some hope that, in the course of time, the continuing study of children of people exposed to the atomic bombs of Hiroshima and Nagasaki will provide information with regard to this aspect (see also Yoshimoto et al. 1991). This also applies to the last category in the 1988 UNSCEAR report, "Early-acting dominants – heritable tumors", which has no counterpart in the BEIR V report.

It might be pssible some time in the not too remote future to make a prediction for a section of the entire group of morbidity and mortality, e.g. mortality up to the age of 20. At present, not even this is possible.

Data from children of atomic bomb survivors

The predictions of Table 1 are based mainly on epidemiological data in humans, and on experiments with mice. Results of the only large-scale "experiment" with human beings, the continuing studies of atomic bomb survivors, have been used only occasionally.

On August 6, 1945, the first atomic bomb, an uranium-235 bomb, was dropped over the city of Hiroshima; 2 days later, Nagasaki was hit by the second bomb, a plutonium-239 bomb. In June, 1946, a high-ranking US government committee decided to start a comprehensive research programme "towards the end of learning as much as possible of medical significance from the Japanese experience" (Neel and Schull 1956). A mixed American-Japanese commission, The Atomic Bomb Casualty Commission (ABCC), now the Radiation Effects Research Foundation (RERF), started work in the two cities. J. V. Neel was responsible for the genetic part of this programme, which was to become over 4 ½ decades the only "big science" programme in human genetics. It involved long-term investigations on children who had been born to atomic bomb survivors and who had been conceived after the bombing. An overview of these studies from 1946 to the present, together with a reprint of the most important original reports, has been published recently (Neel and Schull 1991).

At the onset of the study, the following endpoints were chosen: sex ratio (fraction of males among newborns), malformation, stillbirths, birth weight, death during the 9 month period after delivery, anthropometric data and autopsy findings. In later phases of the study, and with the progress of methods in human genetics, this list of endpoints was supplemented by chromosomal aberrations (see Awa et al. 1968, 1987; Awa 1975), mutants ascertained at the protein level, and survival first up to the age of 19 years, and later, up to middle age (Yoshimoto et al. 1991).

Within the two cities, all pregnancies were registered, and data on the radiation history of husband and wife, their reproductive history, and information on the present pregnancy were collected. A short time after delivery, all newborns were examined by a medical doctor, and a random sample of infants was re-examined 9 months later.

Germ cell radiation exposure was estimated using parameters such as distance from the hypocentre at the time of the bombing, sheltering and signs of radiation sickness. A problem essential for the assessment of any biological effects was the estimation of the quality and quantity of radiation emitted by the bombs and received by exposed individuals. These problems were settled only in 1989 (Neel et al. 1989). Neel et al. (1989) gave an average conjoint parental gonad radiation dose (= radiation dose for both parents together) for all parents with increased exposure of 0.4–0.5 Sv. However, the distribution was very much skewed: a few parents received more than the threshold dose, whereas the dose received by many of them was much lower. Statistical evaluation was

Table 6. Numberical gonosomal aberrtions among children of exposed and unexposed parents (from Neel et al. 1989)

	No. with gonosomal aberrations			
	No. of children	Males	Females	Total
Children of exposed parents	8322	12 (0.307%)	7 (0.159%)	19
Children of unexposed parents	7976	16 (0.435%)	8 (0.186%)	24

carried out with great care (see, for example, Neel and Schull 1956, 1991; for a review, see Vogel 1989). Children of unexposed parents in the same two cities were taken as controls.

For most of the endpoints, no significant increase could be detected that could have been interpreted as a radiation effect. A small sex ratio shift (reduction of liveborn males among the offspring of irradiated females because of X-linked recessive lethals and reduction of females in the offspring of radiation-exposed males because of X-linked dominant lethals) seemed to emerge from the first studies (Schull and Neel 1958) but this was not confirmed later after an increase of sample size (Schull et al. 1966). Subsequently, when chromosomal aberrations and protein variants were included in the list of endpoints, no increase was found in the number of numerical gonosomal chromosome aberrations (Table 6), or in the number of protein variants identified by an extended study of parents as new mutants (Neel et al. 1987; Neel and Schull 1991). In the 1981 and 1989/1990 evaluations, major congenital malformations, stillbirth and death during the first week of life were combined under the heading "untoward pregnancy outcome". Regressions of prevalences on individually estimated radiation exposures of both parents were calculated, assuming a linear (one-hit) dose-effect relationship. More than 70000 pregnancies could be analysed. After confounding variables (such as parental consanguinity) had been eliminated, there was an increase of 0.00182 (according to the 1981 report) or of 0.00239 per 1 gonadal Sv according to the 1989 report (Neel et al. 1989, 1990). Calculating the doubling dose from this value requires making an assumption regarding the fraction of untoward outcome that is caused by spontaneous, i.e. not radiation-induced, mutations in the germ cells of both parents. This problem, estimating the "mutational component" in this group of conditions, has been mentioned before. From complex considerations that cannot be repeated here, the authors concluded in 1981 (Schull et al. 1981) that this might have been the case in 1:200 to 1:400 newborns. In order to be on the conservative side (i.e. to over-estimate rather than under-estimate the genetic radiation effects), they chose the second value for their estimate. Using the 1981 value, they arrived at 1.37 Sv as the zygotic doubling dose. In a similar way, the doubling dose for death during infancy or childhood (up to the age of 19) was estimated. It turned out to be 2.94 Sv. In the 1989 and 1990 report, the four variables, viz. untoward pregnancy outcome, pre-reproductive mortality, balanced structural chromosome aberrations and protein mutations, were combined to yield an overall doubling dose of between 1.5 and 1.9 Sv.

All these estimates are lower than those for various endpoints in the mouse (Lüning and Searle 1970). As mentioned, the doubling dose estimate used in the UNSCEAR and BEIR reports was 1 Sv. However, this admittedly very crude estimate relates to chronic irradiation with small dose rates, whereas irradiation by the atomic bombs was acute, with high dose rates. Therefore, one would have expected a higher effect (= a doubling dose lower than 1 Sv if the human doubling dose is about equal to that found in the mouse). As mentioned at the beginning, Neel and Lewis (1990), in a review of mouse data relevant for a comparison with these human data, arrived at higher estimates for the mouse, pointing to a much lower genetic radiation effect (1.35 Sv for acute and about 4 Sv for chronic low dose rate irradiation; this is more in line with the human estimates).

Before Neel and Lewis (1990) published their report, it was often speculated whether the genetic material of the mouse is more susceptible to radiation than that of humans. Now, such speculations no longer appear to be necessary. There might be a difference, but the evidence for it is certainly limited. As mentioned before, "untoward pregnancy outcome" and death within childhood are poorly defined; they embrace many events of very different genetic significance, from severe malformation to traffic accidents. Moreover, the doubling dose estimates depent critically on assumptions regarding the fraction of such events that are caused by spontaneous mutations. The geneticist tends to ask why these particular endpoints were chosen and not genetically better defined ones. The answer is that they were not available. Chromosomal aberrations have already been discussed. The fraction of gonosomal anomalies and balanced translocations was not increased in comparison with the controls (Table 6). Most children with autosomal, unbalanced numerical of structural aberrations (except Down's syndrome) had died by the time the appropriate methods became available. Down's syndrome is no longer mentioned in the more recent reports, but an older report (Schull and Neel 1962) suggests that the number of children with this syndrome was not increased in the irradiated group. Dominant and X-linked sentinel mutations (see Vogel and Rathenberg 1975; Czeizel 1989a, b) could have been the obvious choice for this study, but, despite the size of the catastrophy, the available sample was much too small for the utilization of such rare events (see, for example, Strobel and Vogel 1958). On the other hand, a strong argument in favour of the general parameters used in this study, (pregnancy outcome and early mortality) is that, after all, this is what society wants to know. Precisely this kind of information is asked for, and geneticists have to do their best to provide it.

Tumour diseases

Another interesting study has been devoted to the question whether tumour diseases in childhood and youth

were increased among this cohort of children. Some experimental data in the mouse suggest an increase of malignancies in the F_1-generation after parental irradiation (Nomura 1982). A rationale for such an increase could be provided by recent results on tumour suppressor genes. Retinoblastoma is the best model. About 40% of all instances, among then all bilateral cases, are caused by constitutional heterozygosity of such a tumour suppressor gene; a second mutation in a cell of the appropriate tissue (in this cases, cells of the developing retina) leads to homozygosity in this cell, which now initiates a tumour. The remaining 60% are caused by two somatic mutations in each of the two alleles (see Vogel 1979). The Wilms tumour probably follows the same rule (Matsunaga 1981). If this holds true for many or even most childhood cancers, irradiation of the parents could lead to an increase of the germ cell mutation rate, and hence, to a higher incidence of childhood cancer. With this question in mind, the children of irradiated parents were examined with respect to the occurrence of malignancies up to the age of 20 (Yoshimoto et al. 1990a, b). The series consisted of 31150 children, one ore both of whose parents had received > 0.01 Sv (average conjoint gonad exposure of 0.435 Sv), and two control groups with 41066 children altogether. A total of 92 cancer cases at an age less than 20 was found; 49 in the control group and 43 in the irradiated group. Obviously, the data fail to indicate any increase within the irradiated group. Taken at face value, they even suggest a small decrease. Because of the small number of cases, confidence intervals are large; the negative result would even be compatible with a small increase. The cohorts are being followed up to ascertain any possible increase in the future. So far, however, no such indication has been observed.

Conclusions from the Hiroshima-Nagasaki study

In conclusion, the studies on children of atomic bomb survivors have a very important result. Acute irradiation with moderate doses of ionizing radiation does not produce any major effects on the health of the following generation. Any minor effects that might be produced are so small that they are submerged in the "background noise" of "naturally" occuring mutational effects. In part, this is because of the variable nature of this "background noise". Spontaneous mutation rates, for example, vary depending on maternal and paternal age, frequencies of stillbirth and early deaths are influenced strongly by environmental factors, such as nutrition or infections, and the incidence of malformations may be influenced not only by population structure, for example consanguinity rates (see, Schull and Neel 1965; Vogel and Motulsky 1986), but also by exposure to teratogenic agents during pregnancy.

Other studies on radiation-exposed population groups

Other studies on radiation-exposed population groups will be mentioned only briefly. There are some areas in the world (Kerala, South India; Brazil; Yangjiang County, China), in which natural radioactivity is strongly increased (sometimes 10–100 times the normal levels) because of the high content of radioactive elements, such as thorium and radium, in the soil. In a population of 12918 individuals living in a high-irradiation area of Kerala, South India, 12 individuals with Down's syndrome, and 12 others with severe mental deficiency but without additional malformations were found, compared with no Down's syndrome cases, only one case with severe mental deficiency and malformations, and two cases with severe retardation without additional clinical signs observed in 5938 controls (Kochupillai et al. 1976). The difference in prevalence of Down's syndrome could easily be caused by an ascertainment bias, since the figure in the controls is unusually low. In a severely exposed population sample of about 12000 individuals in Brazil, a significant but marginal increase of chromosome-type aberrations was found in lymphocyte cultures (Barcinski et al. 1975). Comprehensive studies have been performed in China. The population examined consisted of about 80000 individuals. Here, background radiation is about three times as high as in the control district, where it corresponds roughly to that found in most other populations of the world. As a rule, the families had lived for six or more generations in these regions; there was no major difference in the general living conditions between high-irradiation and control areas. Investigations into this population have been proceeding since 1972, and the last report known to us was published in 1990 (Wei et al. 1990). These studies have failed to show any increase in cancer mortality or in the fraction of children suffering from specified genetic defects or diseases compared with controls. Again, the fraction of chromosome abnormalities in lymphocyte cultures was slightly but not significantly increased, and there was a slightly higher incidence of Down's syndrome patients in the irradiated group (Wei et al. 1987) (Table 7). The sample of children was studied in 1975, 1979, and 1985; at the time of examination, they were less than 12 years old. The difference in the raw figures (22 in the high-irradiation group vs 4 among the controls) is impressive. Part of it can be explained by the higher fraction of mothers above the age of 35 in the irradiated group (Table 7). However, even taking this

Table 7. Prevalence of Down's syndrome among children in the irradiated Chinese population, and in the control area (Wei et al. 1987)

Area	Mother's age	No. of children examined	No. of cases with Down's syndrome	Frequency per 10^3 children
High irradiation		25258	22	0.87
Controls		21837	4	0.18
High irradiation	>35	3076	14	4.61
	<35	22222	8	0.36
Controls	>35	970	3	3.09
	<35	20867	1	0.05

Table 8. Radiation and Down's syndrome: epidemiological studies (UNSCEAR 1982). DSM, Mothers of Down's syndrome cases; DS, Down's syndrome; M, mothers; DSP, parents of Down's syndrome cases

Country	Study type	Cases	Outcome
Canada 1961	Retrospective	81 DSM	Significant increase in DS inicidence in exposed mothers (abdominal exposures or fluoroscopy)
1968	Prospective	861 M	Significant increase in DS in exposed mothers
Denmark 1970	Retrospective	?	No significant radiation effect
Japan 1962	Prospective	15034 M	Frequency of DS in the progeny of exposed mothers was less than half of the controls; not significant
United Kingdom			
Scotland 1959	Retrospective	117 DSP	No significant radiation effect
England 1961	Retrospective	51DSM	Non-significant increase of DS in controls
Northern Ireland 1962	Retrospective	197 DSM	No significant radiation effect
England 1970	Prospective	630 M	No significant radiation effect
England 1972	Retrospective	465 DSP	Significant increase in DS in exposed mothers who had received radiation 10 years or more before the conception of the cases
United States			
1965	Retrospective	216 DSP	Significant increase in DS in exposed mothers
1969	Retrospective	61DSM	No significant radiation effect
1977[a]	Retrospective	128 DSP	No significant radiation effect

[a] A follow-up of the 1965 survey above (S19)

factor into account, a higher prevelance of Down's syndrome cases in the radiation-exposed sample remains. Wei et al. (1987) compared this figure with several other statistics from China. They concluded that the prevalence in this group "is a little higher, but within the normal (spontaneous) range." On the other hand, prevalence in the control area is unusually low compared with figures from other parts of the world (see for example, Vogel and Motulsky 1986). The data are however not incidences from examinations of newborns, but prevalences for the age group up to 12 years. Mortality of Down's syndrome children within this age range is very high if sophisticated medical facilities are not generally available. Moreover, the recorded data from China show an amazing range of variation between different population groups. Nevertheless, all the available data for Down's syndrome (Table 8) leave some doubt as to whether there might be some effect of low-dose radiation on nondisjunction.

Recently, there has been one report in which a higher incidence of leukemias and lymphomas in children of employees of the nuclear power plant Sellafield (Great Britain) has been suggested (Gardner et al. 1990a, b; for a comprehensive discussion see Vogel 1991). The study was performed because a certain increase of childhood leukemias and lymphomas had been observed in this area (Gardner et al. 1987a, b). Some of the fathers of the affected children were, indeed, employed in the nuclear power plant (Table 9). However, the figures were very small indeed, the children of fathers employed elsewhere were also affected, and (most important) the received radiation dose of these fathers was very low. Moreover, no increase in other possible radiation effects, such as chromosomal aberrations and dominant mutations, was reported. The increase of leukemias and lymphomas among these children has probably occurred by chance, or has some other cause.

Table 9. Cases of leukaemia and controls where fathers had been employed in the atomic power plant in Sellafield, and radiation dose received before conception (data from Gardner et al. 1990a, b)

Employment of father and dose	Cases with leukaemia	Controls	
		Local	Total area
Not employed in atomic power plant	0	4	17
No report about dose	0	0	1
0.001–0.049 Sv	0	8	6
0.050–0.099 Sv	1	7	3
≥ 0.9 Sv	3	1	0
Total	4	20	27

New approaches for risk assessment: variation at the protein and DNA levels

So far, estimates have been discussed in which radiation effects have been assessed mainly at the level of phenotypes. Indeed, changes in phenotypes are of primary interest to our societies. However, in any attempt at estimating such effects, one is confronted with complex methodological problems, as discussed in the previous sections. Many uncertainties have to be bridged by assumptions and extrapolations. On the other hand, basic research in genetics, and especially in human genetics, is concentrating its efforts more and more on the genes themselves and their products. In order to utilize these new possibilities to test for radiation effects, new approaches have been, or are being, developed at the gene-DNA and protein levels.

Among the children of atomic bomb survivors, quantitative and qualitative protein variations were examined,

Table 10. Protein variants in children of survivors of the atomic bombs (data from Neel et al. 1989, 1990)

Electrophoretically screened gene loci		
	No. of loci screened	New mutants
Proximally exposed cohort	667404	3
Distally (or not) exposed cohort	466881	3

Mutation rates for electrophoretically detected protein mutation and mutations leading to reduction of enzyme activity		
	Mutation rate per locus per generation	95% confidence interval
Proximally exposed cohort	6.0×10^{-6}	$2–15 \times 10^{-6}$
Distally (or not) exposed cohort	6.4×10^{-6}	$1–19 \times 10^{-6}$

using a variety of methods (Table 10). Presumed new mutations were verified by carefully excluding false paternity. As Table 10 shows, no increase in comparison with the controls was observed. For the monitoring of large population groups, another approach has been suggested in which the logistically most difficult part of protein studies, namely contacting the families and collecting the blood samples, can be avoided (Vogel and Altland 1982). In most countries, practically all newborns are screened for inherited metabolic diseases, for example phenylketonuria (PKU). A few drops of blood are put on a special test card that is sent to a screening centre. In the meantime, a method has been developed by which haemoglobin (Hb) and other proteins can be extracted from this card and studied by electrophoretic methods (Altland et al. 1982, 1985, 1987). In a pilot project, blood samples from between 40003 newborns (for Hb variants) and 30659 individuals (for other protein variants), were screened, representing altogether 722719 gene loci. In three instances, the transmission test turned out to be negative, but there was no evidence for non-paternity. These three individuals can be regarded as new mutants. From these data, the following mutation rates were estimated: 5.2×10^{-6} per locus per generation, 2.0×10^{-8} per codon, and 6.0×10^{-9} per base. These data are in good agreement with other spontaneous mutation rates (see Vogel and Motulsky 1986).

In view of the difficulties in assessing mutational effects at the phenotypic and gene-product levels, on the one hand, and the recent progress in studying DNA sequences directly, on the other, it is not surprising that the possibility of studying possible radiation effects directly in the DNA has been explored. A number of approaches were suggested at a symposium held in Alta, Colorado, in 1984 (Delehanty et al. 1989; see also Mendelssohn 1989). The last-mentioned author mainly discussed the following possibilities: (1) Sequence analysis. At first glance, a comparison of the DNA sequences in parents and children would be the most promising approach. Assuming a spontaneous base-pair mutation rate of 10^{-8} and about $6–7 \times 10^9$ base pairs in the diploid human genome, this would mean about 60–70 spontaneous new mutants in a child's genome. Any statistically significant increase could be pinned down to induced mutations. At present, however, sequencing would not be sufficiently precise and much too time-consuming and expensive. Further progress in techniques is awaited. (2) Restriction fragment length polymorphisms. This is also too time-consuming and expensive at the moment. (3) RNAse A and gradient denaturation electrophoresis. (4) Detection of deletions, insertions and rearrangements. Here, a single restriction enzyme digest is used together with a large number of DNA probes. (5) Mini-satellites viz. repetitive groups of short DNA sequences. (6) Polymerase chain reactions provided that this method becomes still more precise than it is at present. (7) Refined cytogenetic analysis by chromosome in situ suppression hybridization (chromosome painting). As mentioned, many, if not most, radiation-induced changes of the genetic material are structural chromosomal aberrations, such as deletions, insertions and reciprocal translocations. Larger changes of these kinds can be ascertained by conventional cytogenetic techniques. More recently, however, techniques have been developed in which cytogenetics has been combined with non-radioactive hybridization techniques. The resolution power of such methods, while not approaching that of sequencing DNA base pair by base pair, is much better than that of conventional cytogenetics (Cremer et al. 1990; Popp et al. 1990). Such methods could also be used for studying human and animal germ cells.

At this moment, methods of DNA analysis are not contributing to risk assessment. Nevertheless, in the future, some of the approaches mentioned above, or others may help to improve appreciably our understanding of genetic radiation risks. However, even now, we can question whether and to what degree such studies will further our knowledge of possible health hazards. After all, human societies are interested not so much in possible DNA changes, but in their effects on the health status of our populations. Some of these hazards will have ill-effects on our health. Therefore, it is fortunate that the RERF group, which examines the children of atomic bomb survivors, works on such methods of hazard assessment, and is now establishing lymphoblastoid cell lines for further study.

Recently, a new phenomenon of gene action during embryonic development has been studied by human and mouse geneticists: genomic imprinting (Hall 1991; T. Vogel 1992). If a different influence of paternal vs maternal genotypes on the developing zygote is really the rule rather than the exception, then paternal and maternal irradiation could also have different influences on the phenotypes of F_1 offspring, even if damage to the genetic material is identical. These are however concerns of the future.

Conclusions

The conceptual basis of genetic risk estimation and some new approaches for genetic screening have been discussed in this review. In addition, the information available on

the baseline of incidence of genetic disease in the population has been considered. Some relatively reliable data are available on chromosomal aberrations and on a few rare dominant or X-linked conditions (sentinel mutations).

Determination of the incidence of congenital malformations at birth is, in principle, possible. However, it requires a sophisticated logistic network that should include, among other aspects, a precise definition of endpoints. To make data from various countries and different time periods within the same country comparable, international coordination is necessary. The Hungarian registry is a good example for such an international screening system.

Even with data from such a system at hand, prediction of an increase in the incidence of congenital malformation attributable to a specific exposure of the gonads to radiation is not yet possible, since this also requires an estimate of the mutational component of this incidence. An estimation of this component requires a much more thorough knowledge of the genetic basis of these malformations, and its interaction with the environment.

With respect to multifactorial diseases, the situation is even more difficult. Their genetic analysis shows an increasingly complex pattern. Systems of intertwined genetic polymorphisms in combination with a great variety of defect mutants are becoming visible. Moreover, there is increasing evidence that the present-day incidence of genes predisposing to such diseases is shaped by natural selection acting via living conditions in the past. During the previous one or two centuries, these living conditons have changed dramatically. Therefore, marked changes in the genetic composition of human populations have to be anticipated, even in the absence of any additional load of mutations caused by ionizing radiation.

The purpose of this review has been to point out the difficulties that are inherent in any attempt at quantitatively prognosticating, for future generations, health hazards caused by additional ionizing radiation. Such predictions, based on extrapolations from animal experiments and on the direct observation of exposed population groups will become possible in genetically simple and straightforward situations, such as in chromosomal aberrations or rare dominant and X-linked diseases. For all other groups of diseases, such an estimate is impossible as yet, and will probably remain so for a long time to come. The studies on children of atomic bomb survivors in Hiroshima and Nagasaki suggest that the ill-effects on the progeny of a single moderate radiation dose will probably be only minor. A more specific statement would be irresponsible.

References

Altland K, Kaempfer M, Forssbohm M (1982) Mass monitoring for changing mutaton rates using blood samples submitted for PKU screening. In: Human genetics, part A: The unfolding genome. Liss, New York, pp 277–387

Altland K, Hackler R, Banzhoff A, et al (1985) Experimental evidence for flexible slope of immobilized pH gradients under computer control. Electrophoresis 6:140–142

Altland K, Eckardstein A v, Banzhoff A, et al (1987) Hybrid isoelectric focusing: adsorption of proteins onto immobilized pH gradient matrices and desorption by carrier ampholytes. Electrophoresis 8:52–62

Awa AA (1975) Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors. II. Biological effects. B. Genetic effects. 2. Cytogenetic study. J Radiat Res (Tokyo) [Suppl] 75–81

Awa AA, Bloom AD, Yoshida MC, et al (1968) Cytogenetic study of the offspring of atomic survivors. Nature 218:367–368

Awa AA, Honda T, Neriishi S, et al (1987) Cytogenetic studies of the offspring of atomic bomb survivors. In: Obe G, Basler A (eds) Cytogenetics: basic and applied aspects. Berlin Heidelberg New York, pp 166–183

Barcinski MA, Abreu MC, Almeida JC de, et al (1975) Cytogenetic investigation in a Brazilian population living in an area of high natural radioactivity. Am J Hum Genet 27:802–806

BEIR (1990) (Committee on the Biological Effects of Ionizing Radiations) Health effects of exposure to low levels of ionizing radiation (BEIR V). National Academy, Washington, DC

Carter CO (1976) Genetics of common single malformation. Med Bull 32:21–26

Cremer T, Popp S, Emmerich P, et al (1990) Rapid metaphase and interphase detection of radiation-induced chromosome aberrations in human lymphocytes by chromosomal suppression in situ hybridization. Cytometry 11:110–118

Crow JF (1970) Genetic loads and the cost of natural selection In: Kojima K (ed) Mathematical topics in population genetics. Springer, Berlin Heidelberg New York, pp 128–177

Chung CS, Myrianthopoulos NC (1975) Factors affecting risk of congenital malformations. I. Epidemiological analysis. II. Effect of maternal diabetes. Birth Defects Orig. Art Series No. 10, Vol XI

Creutzfeldt W, Köbberling J, Neel JV (1976) The genetics of diabetes mellitus. Springer, Berlin Heidelberg New York

Czeizel A (1989a) Hungarian surveillance of germinal mutations. Hum Genet 82:359–366

Czeizel A (1989b) Population surveillance of sentinel anomalies. Mutat Res 212:3–9

Czeizel A, Sankaranarayanan K (1984) The load of genetic and partially genetic disorders in man. I. Congenital anomalies: estimates of detriment in terms of years of life lost and years of impaired life. Mutat Res 128:73–103

Czeizel A, Sankaranarayanan K, Losonci A, et al (1988) The load of genetic and partially genetic diseases in man. II. Some selected common multifactorial diseases: estimates of population prevalence and of detriment in terms of years of lost and impaired life. Mutat Res 196:259–292

Czeizel A, Sankaranarayanan K, Szondy M (1990) The load of genetic and partially genetic diseases in man. III. Mental retardation. Mutat Res 232:291–303

Delehanty J, White RL, Mendelsohn ML (1986) Approaches to determining mutation rates in human DNA. Mutat Res 167: 215–232

Denniston C (1982) Low-level radiation and genetic risk estimation in man. Annu Rev Genet 16:329–355

Ehling UH (1966) Dominant mutations of the skeleton in offspring of X-irradiated male mice. Genetics 54:1381–1389

Ehling UH (1985) Induction and manifestation of hereditary cataracts. In: Woodhead AD et al (eds) Assessment of risk from low-level exposure. Plenum Press, New York, pp 354–367

Ehling UH (1989a) Germ-cell mutations in mice: standards for protecting the human genome. Mutat Res 212:43–53

Ehling UH (1989b) Methods to estimate the genetic risk. Berzelius Symposia XV, pp 141–149

Ehling UH (1990) Mouse mutational data in the estimation of human risk. In: Mutation and the environment, part C. Wiley/Liss, New York, pp 223–232

Ford CE, Evans EP, Searle AG (1978) Failure of irradiation to induce Robertsonian translocations in germ cells of male mice.

In: Conference on mutations. Jahreskonferenz, Zentrallabor für Mutagenitätsprüfung. Boldt, pp 102–108
Gardner MJ, Hall AJ, Downes S, et al (1987a) Follow-up study of children born to mothers resident in Seascale, West Cumbria (birth cohort). B M J 295:822–827
Gardner MJ, Hall AH, Downes S, et al (1987b) Follow-up study of children born elsewhere but attending schools in Seascale, West Cumbria (school cohort). B M J 295:819–822
Gardner MJ, Snee MP, Hall AJ, et al (1990a) Methods and basic data of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. B M J 300:429–434
Gardner MJ, Snee MP, Hall AJ, et al (1990b) Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. B M J 300:423–429
Griffin CS, Tease C (1988) γ-Ray-induced numerical and structural chromosome anomalies in mouse immature oocytes. Mutat Res 202:209–213
Gunther M, Penrose LS (1935) The genetics of epiloia. J Genet 31:413–430
Haldane JBS (1935) The rate of spontaneous mutation of a human gene. J Genet 31:317–326
Hall JG (1990) Genomic imprinting: review and relevance to human diseases. Am J Hum Genet 46:857–873
Hansmann I, Zmarsly R, Probeck HD, et al (1979) Aneuploidy in mouse fetuses after paternal exposure to X-rays. Nature 280: 228–229
Hansmann I, Bartels I, Beermann F, et al (1985) Mechanisms of non-disjunction: facts and perspectives. In: Delarco VL, et al (eds) Symposium on aneuploidy. Plenum Press, New York, pp 417–432
Harper PS (1992) The epidemiology of Huntington's disease. Hum Genet (in press)
Hassold TJ, Jacobs P (1984) Trisomy in man. Annu Rev Genet 18:69–77
Hassold T, Jacobs P, Kline J, et al (1981) Effect of maternal age on autosomal trisomies. Ann Hum Genet 44:29–36
Hertwig P (1935) Sterilitätserscheinungen bei röntgenbestrahlten Mäusen. Z Indukt Abst Vererb L 70:517–523
Hertwig P (1938a) Unterschiede in der Entwicklungsfähigkeit von F_1-Mäusen nach Röntgenbestrahlung von Spermatogonien, fertigen und unfertigen Spermatozoen. Biol Zentralbl 58:516
Hertwig P (1938b) Die Regeneration des Samenepithels der Maus nach Röntgenbestrahlung unter besonderer Berücksichtigung der Spermatogonien. Arch Exp Zellforsch 22:68–73
Hertwig P (1940) Vererbbare Semisterilität bei Mäusen nach Röntgenbestrahlung, verursacht durch reziproke Chromosomentranslokationen. Z Indukt Abst Vererb L 79:1–27
Hollaender A (1954–56) Radiation biology. McGraw-Hill, New York
Hook EB, Chambers GM (1977) Estimated rates of Down syndrome in live birth by one year maternal age intervals for mothers aged 20–49 in a New York State study. Birth Defects 13:123–142
Kochupillai AG, Verma JC, Grewal MS, Ramaligaswami V (1976) Down's syndrome and related abnormalities in an area of high background radiation in coastal Kerala. Nature 262:60–61
Koller S, et al (1983) Risikofaktoren der Schwangerschaft. Springer, Berlin Heidelberg New York
Lea DE, Catcheside DG (1942) The mechanism of the induction by radiation of chromosome aberrations in *Tradescantia*. J Genet 44:216–245
Lüning KG, Searle AG (1971) Estimates of the genetic risks from ionizing irradiation. Mutat Res 12:291–304
Matsunaga E (1981) Genetics of Wilms' tumor. Hum Genet 57: 231–246
Matsunaga E, Minoda K (1981) Use of retinoblastoma and Wilm's tumor as sentinel phenotypes for population surveillance. Gann Monogr Cancer Res 35:127–133
Mavor JW (1924) The production of nondisjunction by X-rays. J Exp Zool 39:381–432
Mendelsohn ML (1989) Potential DNA methods for measuring the human meritable mutation rate. Genome 31:860–863
Modell B, Kuliev A (1990) Changing paternal age distribution and the human mutation rate in Europe. Hum Genet 86:198–202
Mourant AE, Kopec EC, Domaniewska-Sobczak K (1978) Blood groups and disease. Oxford University Press, London
Muller HJ (1927) Artificial transmutation of the gene. Science 66:84–87
Muller HJ (1950) Our load of mutations. Am J Hum Genet 2:111–176
Neel JV (1981) Genetic effects of atomic bombs. Science 213:1205
Neel JV (1962) Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 14:353–362
Neel JV, Lewis SE (1990) The comparative radiation genetics of humans and mice. Annu Rev Genet 24:327–362
Neel JV, Schull WJ (1956) The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki. National Academy Sci Res Counc Publ, Washington, DC
Neel JV, Schull WJ (1991) The children of atomic bomb survivors. National Academy Press, Washington, DC
Neel JV, Satoh C, Goriki K, et al (1987) Search for mutations altering protein charge and/or function in children of atomic bomb survivors. Manuscript (Final report)
Neel JV, Schull WJ, Awa AA (1989) Implications of the Hiroshima and Nagasaki genetic studies for the estimation of the human "doubling dose" of radiation. Proceedings of the 16th International Congress of Genetics, Toronto 1988
Neel JV, Schull WJ, Awa AA, et al (1990) The children of parents exposed to atomic bombs: estimates of the genetic doubling dose of radiation for humans. Am J Hum Genet 46:1053–1072
Nielsen J, Sillesen I (1975) Incidence of chromosome aberration among 11148 newborn children. Hum Genet 30:1–12
Nielsen J, Wohlert M, Faaberg-Andersen J, et al (1982) Incidence of chromosome abnormalities in newborn children. Comparison between incidences in 1969–1974 and 1980–1982 in the same area. Hum Genet 61:98–101
Nomura T (1982) Parental exposure to X-rays and chemicals induces heritable tumors and anomalies in mice. Nature 296: 575–577
Pacchierotti F, Russo A, Metalli P (1987) Meiotic nondisjunction induced by fission neutrons relative to X-rays observed in mouse secondary spermatocytes. II. Dose-effect relationship after treatment of pachytene cells. Mutat Res 176:233–241
Popp S, Remm B, Hausmann M, et al (1990) Towards a cumulative biological dosimeter based on chromosome painting and digital image analysis. Kerntechnik 55:204–210
Reed TE, Neel JV (1959) Huntington's chorea in Michigan. 2. Selection and mutation. Am J Hum Genet 11:107–136
Reichert W, Buselmaier W, Vogel F (1984) Elimination of X-ray induced chromosomal aberrations in the progeny of female mice. Mutat Res 139:87–94
Rüdiger HW, Dreyer M (1983) Pathogenic mechanisms of hereditary diabetes mellitus. Hum Genet 63:100–106
Russell WL (1952) X-ray induced mutations in mice. Cold Spring Harbor Symp Quant Biol 16:327–336
Russell WL (1954) Genetic effects of radiation in mammals. Rad Biol 1:825–859
Russell WL (1957) Shortening of life in the offspring of male mice exposed to neutron radiation from an atomic bomb. Proc Natl Acad Sci USA 43:324–329
Russell WL (1964a) The nature of the dose-rate effect of radiation on mutation in mice. Jpn J Genet 40[Suppl]:128–140
Russell WL (1964b) Effect of radiation dose fractionation on mutation in mouse spermatogonia. Genetics 50:282
Russell WL (1965) Effect of the interval between irradiation and conception on mutation frequency in female mice. Proc Natl Acad Sci USA 54:1552–1557
Russo A, Pacchierotti F, Metalli P (1983) Meiotic nondisjunction induced by fission neutrons relative to X-rays in mouse secondary spermatocytes. I. The response of different cell stages to a single radiation dose. Mutat Res 108:359–372

Sankaranarayanan K (1988) Prevalence of genetic and partially genetic diseases in man and the estimation of genetic risks of exposure to ionizing radiation. Am J Hum Genet 42:651–662
Schull WJ, Neel JV (1958) Radiation and the sex ratio in man. Science 128:343–348
Schull WJ, Neel JV (1962) Maternal radiation and mongolism. Lancet II:537–538
Schull WJ, Neel JV (1965) The effect of inbreeding on Japanese children. Harper & Row, New York
Schull WJ, Neel JV, Hashizume A (1966) Some further observations on the sex ration among infants born to survivors of the atomic bombings of Hiroshima and Nagasaki. Am J Hum Genet 18:328–338
Schull WJ, Otake M, Neel JV (1981) Genetic effects of the atomic bombs: a reappraisal. Science 213:1220–1227
Searle AG, Edwards JH (1986) The estimation of risks from the induction of recessive mutations after exposure to ionizing radiation. J Med Genet 23:220–226
Selby PB (1990) Experimental induction of dominant mutations in mammals by ionizing radiation and chemicals. Issues and Rev in Teratology 5:181–252
Selby PB, Selby PR (1978) Gamma-ray-induced dominant mutations that cause skeletal abnormalities in mice. II. Description of proved mutations. Mutat Res 51:199–236
Selby PB, Woychik R, Smalley L (1991) Use of the mouse skeleton and lens to estimate genetic hazards of radiation and chemicals and to identify effects of transgenes (abstract). 8th International Congress of Human Genetics, Washington 1991. Am J Hum Genet 49[Suppl]:450
Speed RM, Chandley A (1981) The response of germ cells of the mouse to the induction of non-disjunction by X-rays. Mutat Res 84:409–418
Stadler LJ (1928a) Mutations in barley induced by X-rays and radium. Science 68:186–187
Stadler LJ (1928b) Genetic effects of X-rays in maize. Proc Natl Acad Sci USA 14:69–75
Stern C, Carson G, Kinst M, et al (1952) The viability of heterozygotes for lethals. Genetics 37:413–449
Strobel D, Vogel F (1958) Ein statistischer Gesichtspunkt für das Planen von Untersuchungen über Änderungen der Mutationsrate beim Menschen. Acta Genet Statist Med 8:274–286
Tease C (1982) Similar dose-related chromosome non-disjunction in young and old female mice after X-irradiation. Mutat Res 95:287–296
Tease C (1985) Dose-related chromosome non-disjunction in female mice after X-irradiation of dictyate oocytes. Mutat Res 151:109–119
Timoféeff-Ressovsky NW, Zimmer KG (1947) Das Trefferprinzip in der Biologie. Steinkopf, Dresden
Tiwari JL, Terasaki PI (1985) HLA and disease associations. Springer, Berlin Heidelberg New York
Trimble BK, Doughty JH (1974) The amount of hereditary disease in human populations. Ann Hum Genet 38:199–222
UNSCEAR (United Nations Scientific committee on the Effects of Atomic Radiation) Reports 1958, 1962, 1964, 1966, 1969, 1972, 1977, 1982, 1986, 1988. United Nations, New York
Vogel F (1970) ABO blood groups and disease. Am J Hum Genet 22:464–475
Vogel F (1979) Genetics of retinoblastoma. Hum Genet 52:1–54
Vogel F (1984a) Mutation and selection in the marker (X) syndrome. Ann Hum Genet 48:327–332
Vogel F (1984b) Relevant deviations in heterozygotes of autosomal-recessive diseases. Clin Genet 25:381–415
Vogel F (1989) What can we learn from Hiroshima and Nagasaki? Berzelius Symposia XV, pp 119–130
Vogel F (1990) Humangenetik und Konzepte der Krankheit. Sitzungsber. Heidelberger Akademie der Wissenschaften, 6. Abhandlung
Vogel F (1991) Das Problem der Krebsentstehung bei Kindern von Personen, die einer erhöhten Dosis von ionisierenden Strahlen ausgesetzt waren. In: Reimers, Streffer, Messerschmidt (eds) Strahlenrisiko durch Radon. Fischer, Jena, pp 215–224
Vogel F, Altland K (1982) Utilization of material from PKU-screening programs for mutation screening. Prog Mutat Res 3:143–157
Vogel F, Helmbold W (1972) Blutgruppen – Populationsgenetik und Statistik. In: Becker PE (ed) Humangenetik. Ein kurzes Handbuch, vol 1,4. Thieme, Stuttgart, pp 129–557
Vogel F, Motulsky AG (1986) Human genetics – problems and approaches, 2nd edn. Springer, Berlin Heidelberg New York
Vogel F, Rathenberg R (1975) Spontaneous mutation in man. Adv Hum Genet 5:223–318
Vogel F, Röhrborn G, Schleiermacher E, Schroeder T (1969) Strahlengenetik der Säuger. Thieme, Stuttgart
Vogel F, Krüger J, Brondum Nielsen K, et al (1985) Recurrent mutation pressure does not explain the prevelance of the marker (X) syndrome. Hum Genet 71:1–6
Vogel F, Grusio WE, Kovac C, et al (1990) Selective advantage of fra(X) heterozygotes. Hum Genet 86:25–32
Vogel T (1992) Untersuchungen zum genomic imprinting an reziproken F_1-Hybriden der Maus. Medical Dissertation, Berlin
Wallace B (1957) The effect of heterozygosity for new mutations on viability in *Drosophila*: a preliminary report. Proc Natl Acad Sci USA 43:404–407
Wei LX, Zha YR, Tao ZF (1987) Recent advances of health survey in high background radiation areas in Yangjiang, China. In: International Symposium on Biological Effects of Low Level Radiation, pp 1–17
Wei LX, Zha YR, Tao ZF, et al (1990) Epidemiological investigation of radiological effects in high background radiation areas in Yangjiang, China. J Radiat Res (Tokyo) 31:119–136
Wendt GG, Drohm D (1972) Die Huntington'sche Chorea. Thieme, Stuttgart
Yoshimoto Y, Neel JV, Schull WJ, et al (1990a) Frequency of malignant tumors during the first two decades of life in the offspring (F_1) of atomic bomb survivors. RERF TR/4–90
Yoshimoto Y, Neel JV, Schull WJ, et al (1990b) Malignant tumors during the first two decades of life in the offspring of atomic bomb survivors. Am J Hum Genet 46:1041–1052
Yoshimoto Y, Schull WJ, Kato H, Neel JV (1991) Mortality among the offspring of atomic bomb survivors, 1946–85. RERF TR/1–90