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RADIATION IN RELATION TO MUTATION RATE, MUTATIONAL DAMAGE AND HUMAN ILL-HEALTH

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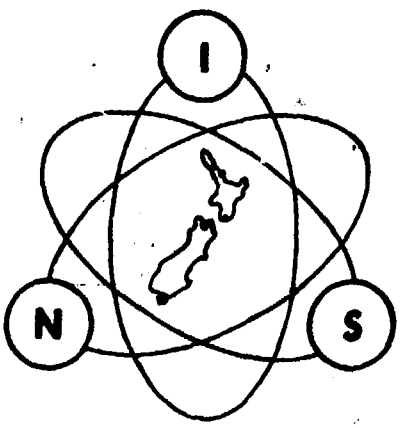

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SUMMARY

The effect of radiation in increasing the frequency of gene mutations is now reasonably understood. We discuss first how an increase in the mutation rate is reflected in the mutational damage expressed in populations. It is shown that the mutational damage, assessed by the loss of fitness in a population or the number of eventual gene extinctions, is equal to the number of new mutations arising per generation or the mutation rate. In a population of stable size, a dose of 1 rem given to 10^6 people leads to roughly 600 gene extinctions when summed over all ensuing generations if the dose is applied to only one generation; this number of extinctions will occur in each succeeding generation if the dose is given to every generation. However, the concept of genetic extinction, although quantifiable, is of limited value in assessing radiation risks since its impact on human ill-health is very speculative. In particular, no estimate can be made of the total cost of effects which are minor in each individual in which they arise, but which, because they are so minor, persist in the population for many generations. The best current estimate is for 14-140 obvious defects in the first few generations following exposure of 10^6 people to a dose of 1 rem.

INTRODUCTION

In 1927, Muller demonstrated the ability of radiation to induce gene mutations.[1] Since that time it has become clear that radiation produces mutations of a similar nature to those that occur 'spontaneously'. That is, radiation merely increases the mutation frequency or rate.[2] Estimates of the spontaneous mutation rate in man have been made and are of the order of 10^{-6} per gene per generation.[2,3] It is thought that each individual possesses about 30,000 genes.[3] Mainly from work with the insect Drosophila and mice, estimates have been made of the dose required to double the spontaneous mutation rate.

At present, the dose would appear to be of the order of 100 rem for low dose rate, low LET irradiation.[3] It is also thought, on both experimental and theoretical grounds, that the number of induced mutations will increase linearly with respect to increasing dose. At very low doses or low dose rates, however, repair of pre-mutational damage will reduce the number of mutation inductions relative to any estimate made from high dose, high dose rate exposures.[4] Thus, although still crude, we have some understanding of the effect of radiation upon mutation rate.

An appreciation of radiation hazard, however, requires an understanding of a) how an increase in the mutation rate is reflected in the amount of mutational damage to be expected in both the first few and all subsequent generations, and b) how the mutational damage is manifested, i.e., to what extent will the medical, social, or economic impact of the damage be significant. It is the purpose of this report to discuss a) and b), over which much confusion and misinterpretation can occur. We will find that it is possible to be reasonably definitive concerning the expected mutational damage but that our knowledge of its manifestation is extremely limited and results in the very approximate estimates of genetic hazard found in the literature.

THE AMOUNT OF MUTATIONAL DAMAGE

First it must be made clear that mutational damage cannot be directly equated to the harm to future generations. Any particular mutational damage can have an effect on the individual receiving it ranging from the totally insignificant to the catastrophic. This will be amplified later. The amount of mutational damage is affected by i) changes in population size, ii) mutation rate, and iii) selective forces acting on mutants. It is traditionally assessed in one of two ways.

1. Fitness: This is a purely Darwinian concept of one 'type' being inferior to another. The inferiority (or loss of fitness) could be measured in many ways but the most meaningful

is the ability to survive and be fertile. As mutations are generally harmful, the individuals carrying a mutant will be made 'inferior' to the normal. The degree of inferiority is given a parameter, s, varying from 0 to 1. A value of 0 implies no loss of fitness or fertility; a value of 1 implies a complete inability to reproduce; a value of 0.05 implies the production of 5% fewer offspring than the normal. Thus, $^1/_s$ becomes equivalent to the number of generations that the mutant will persist in the population. s can be seen, therefore, as the fraction of the mutant removed per generation or as a measure of selective forces acting on the mutant. Note that the less detrimental the mutant to an individual (i.e., $s \to 0$), the more generations will carry the mutant.

Mutational damage in a population as expressed by loss of fitness (inferiority compared to a population without mutations) assumes a population at genetic equilibrium and measures the loss of fitness in a single generation due to all previously accumulated mutations.[5] Genetic equilibrium implies that the number of new mutations arising per generation is balanced by the loss of old mutants. If m is a gene mutation rate (i.e., the number of mutants per gene per generation), then the rate of mutation of that gene in an individual is 2 m per generation since each individual has two of each gene. Recalling that s is the fractional elimination of a mutant per generation, at equilibrium we find $2m = sx$, or $x = {}^{2m}/_s$, where x is the average number of the particular mutant carried per individual. Since the mutant carries an inferiority factor of s in the individual carrying it, the loss of fitness suffered by the average individual is xs, which is equal to 2 m at equilibrium.

2. Genetic extinctions: The previous approach considered the damage in one generation at equilibrium. Here equilibrium is not assumed but we measure all future damage from the mutants that arise in one generation.[6] The assumptions are only that the population is of constant size and that the mutants arising are small in number compared with the total number of genes and are harmful. Damage is measured as the

number of genetic extinctions or the number of genes which will eventually be removed from the gene pool through the premature death or decreased fertility of individuals bearing the mutant. Since the mutants are assumed harmful, the conclusion is simply stated. All the mutants which arise in a generation are gradually removed in succeeding generations. Thus, the total number of extinctions equals the number of mutants in the starting generation, or 2 m for a given gene per person (Of course, new mutants are continuously arising so we never remove all mutants but achieve some equilibrium.) Although selection, or s, is the driving force for the extinctions, the total eliminated is independent of the value of s, which only affects the rate of elimination. Mathematically, if we start with 2 m mutants we remove 2 ms in the first generation and $2\ m\ (1-s)^{i-1}s$ in generation i. Over all succeeding generations we lose 2 ms $[1 + X + X^2 + \ldots.]$ where $X = 1-s$. Thus, we lose $2\ ms \times \frac{1}{1-X}$ or 2 m mutants eventually, regardless of s.

The two approaches given above are very different but lead to the same conclusion, viz. the mutational damage for a given gene locus is equal to the gene mutation rate, 2 m per person. Total mutational damage carried in the population is the sum of the mutation rates over all genes.

In figures 1 and 2 we see the effect of an increase in the mutation rate, for simplicity a doubling, on the mutational damage. Figure 1 illustrates the effect of a doubled rate for just one generation. The number of mutants per individual initially is 2m/s but when the rate is doubled, that generation carries an extra 2 m mutants per individual. With the return of the mutation rate to normal the number of mutants per individual must return to normal and 2 m extra genes must eventually be eliminated. The rate of elimination will depend upon the fierceness of selection. If the increase in the mutation rate is permanent, then a new equilibrium must be set up in which the average number of mutants per individual is 2 x 2m/s. Since equilibrium is maintained by a balance between new mutations and the elimination of old mutants, each generation at the new equilibrium must suffer a rate of loss of old mutants which is greater than the loss

originally sustained by 2 m. The time taken for establishing the new equilibrium will depend on how quickly selection acts. Thus, the total number of extra genetic eliminations over all time from an increase in the mutation rate in a single generation equals the number of extra genetic eliminations occurring in a single generation when the new equilibrium is established after a permanent increase in the mutation rate of the same magnitude (e.g., 2 m in both cases above).

The above considerations assume that the harmful effects are expressed in the heterozygote (an individual who has a mutant at a given locus in one set of chromosomes but the normal gene in the other, complementary set; someone with the same gene (either normal or mutant) at both loci in the two sets of chromosomes is a homozygote). The assumption will obviously be valid when the mutant is dominant. In the case of the numerically superior recessive mutations, it is assumed that the coming together of two recessive mutations in a homozygous individual does not contribute towards elimination and that the harmful effects are brought about in the heterozygous carriers. Tests with Drosophila show that there are, in fact, minor, deletorious effects in the heterozygote.[3] Since mutations are so rare, it would take many, possibly hundreds, of generations for the homozygote to occur. It would take only a small selective force against the heterozygote to cause elimination of the mutant recessive gene before it could be fully expressed. Obvious recessive diseases appear to be less frequent than dominant diseases despite the greater frequency of recessive mutations[2,3] and the idea that only dominant effects need be considered appears valid.

We may estimate the expected genetic eliminations from 1 rem given to each of 10^6 people in a generation as follows:

Number of spontaneous new mutants per generation $= G.N.2m$

where G = total number of genes per individual = 30,000

N = No. of individuals = 10^6

m = spontaneous mutation rate per gene per generation = 10^{-6}

2 = No. of sets of each gene

If the mutation rate is doubled by 100 rem absorbed, then 1 rem is assumed to cause an increase of 1/100 of the spontaneous rate.

Thus, 1 rem to 10^6 people induces $30,000 \times 10^6 \times 2 \times 10^{-6} \times 10^{-2} = 600$ new mutations and there will be this many extra genetic eliminations spread over all ensuing generations if the dose is applied only to one generation, or in each generation if a permanent dose of 1 rem per generation is applied. This estimate depends on the value taken for m (10^{-6}). BEIR[2] quotes a possible range of $0.5 - 5 \times 10^{-6}$.

THE IMPACT OF THE MUTATIONAL DAMAGE

No assessment of the genetic hazards of radiation is complete without an attempt to relate the mutational damage to some observable detriment such as ill-health or economic cost. Notable recent attempts to do this have included the BEIR[2] and UNSCEAR[3] reports, but it has become obvious that this is an area in which our knowledge is scanty. The next section briefly outlines the difficulties.

The simplest situation concerns effects which are controlled by a single gene site. If a mutation at this site is strictly dominant, then its effect will most likely occur in the first succeeding generation and certainly within the first few, say 5, generations. A permanent doubling of the mutation rate will clearly double the number of these effects which must depend upon newly arising mutations in each generation. However, if the mutation is recessive, its full expression will be delayed until two carriers of the mutant mate. As suggested earlier, it is probable that full expression will never occur but that the mutant will be eliminated gradually via the action of minor effects on the fitness of the carriers.

Many human characteristics obviously have a heritable component in that they run in families but they do not obey simple Mendelian behaviour, i.e., they do not act as if they are a response to a single gene. This may be due simply to irregular expression of the gene or because the trait is a

response to not one, but several, genes (polygenic). Examples are physical dimensions and some mental characteristics. It is impossible to predict accurately the effect of an increased mutation rate on such characteristics. Finally, there are mutations which appear to be unfavourable with respect to the normal but are maintained because of particular environmental considerations. A classic example is the mutant gene for sickle cell anaemia which remains prevalent in malarial areas because of the resistance of the carriers of the gene to malaria. In such cases, the incidence of disease cannot be simply related to the number of mutations recurring in each generation.

In view of the above complexities, it is not possible to make more than a crude assessment of the actual ill-health to be brought about by radiation exposures. For these reasons also the idea of genetic eliminations as a measure of genetic risk is no longer regarded as adequate.[2] The BEIR and UNSCEAR reports specifically decline to evaluate the effect of the small decrease in viability of the carriers of recessive mutations. However, both reports admit that just because the effects are so minor (e.g., a greater susceptibility to minor ailments, loss of vitality) the effects will persist longer and affect more individuals in total than the more severe, handicapping mutations. Overall such effects may cause the greatest cost to society but that cost is indeterminate. Experiments in which each of many generations of mice have been exposed to radiation, in fact, show no decrease in ability to survive or develop normally in the later populations.[7] However, it is recognised that the end points used are rather crude and that the presence of deletorious effects cannot easily be ruled out by such experiments. The reports do give an estimate of the amount of ill-health that can be expected as <u>obvious</u> defects in individuals within the first few generations. 1% of all liveborn are assumed to inherit a defect due to a dominant, single gene mutation and this percentage will increase in direct proportion to the mutation rate. The average persistence of such mutants might be five generations. In addition, a crude estimate can be made of the

extent to which recessive genes affect the heterozygote or the fraction of complexly inherited diseases which have mutations recurring in succeeding generations (i.e., the extent to which such traits behave as if they were due to a dominant gene). The two reports both estimate that a maximum of about 2% of liveborn will be affected in this way. However, both BEIR[2] and Newcombe[8] point out that many geneticists would feel this to be far too high an estimate. BEIR suggests a lower limit of about 0.2% of liveborn and 10 generations for the persistence of such mutants. Newcombe also believes that dominant, single gene diseases are greatly over-estimated, suggesting that recent evidence from British Columbia is more in keeping with an incidence of 0.1%, rather than 1%, the figure quoted by BEIR and UNSCEAR which derives from a single study in N. Ireland in 1959.[9] Thus, the range of current diseases in the population which depend upon new mutations recurring in each generation is about 0.3 - 3% of liveborn. Assuming a generation is 30 years and a birth rate of 15,000 per 10^6 people per year, we obtain 30 x 15,000 x 0.3 - 3% = 1350 - 13,500 obvious defects per generation in a population of 10^6 normally. Since 1 rem per generation is thought to increase the number of new mutations per generation by 1%, we obtain a range for extra defects of 14 - 140 for this exposure. The defects will occur over about 5-10 generations if the exposure is only for a single generation. If the exposure occurs in each generation then within a few generations this number of extra defects will occur in each generation.

This report has not considered radiation induced chromosome anomalies (gross changes in the whole chromosome rather than a change in a single gene on the chromosome). Data given by UNSCEAR lead to the conclusion that 1 rem to a stable population of 10^6 will induce roughly two defective liveborn in the first or second generation and around 30 abortions. All the effects occur in the first or succeeding generation and there are no minor long lasting effects.

REFERENCES

1. H.J. Muller, Science 66, 84 (1927).

2. Report to the National Academy of Science by the Committee on the Biological Effects of Ionizing Radiation, Chapter V, (1972).

3. United Nations Scientific Committee on the Effects of Atomic Radiation. Vol. II, Effects, Annex E (1972).

4. For a review see INS-R-195.

5. J.B.S. Haldane, Amer. Nat. 71, 337 (1937).

6. H.J. Muller, Amer. J. Human Genet. 2, 111 (1950).

7. J.F. Spalding, M.R. Brookes and G.L. Tietjen, Genetics 63, 897 (1969); H.B. Newcombe, Genetics 16, 239 (1971).

8. H.B. Newcombe, Proceedings of the Fifth International Congress of Radiation Research, Seattle, Washington, July 1974. Edited by O.F. Nygaard, H.I. Adler and W.K. Sinclair; Academic Press, Inc., p. 937 (1975).

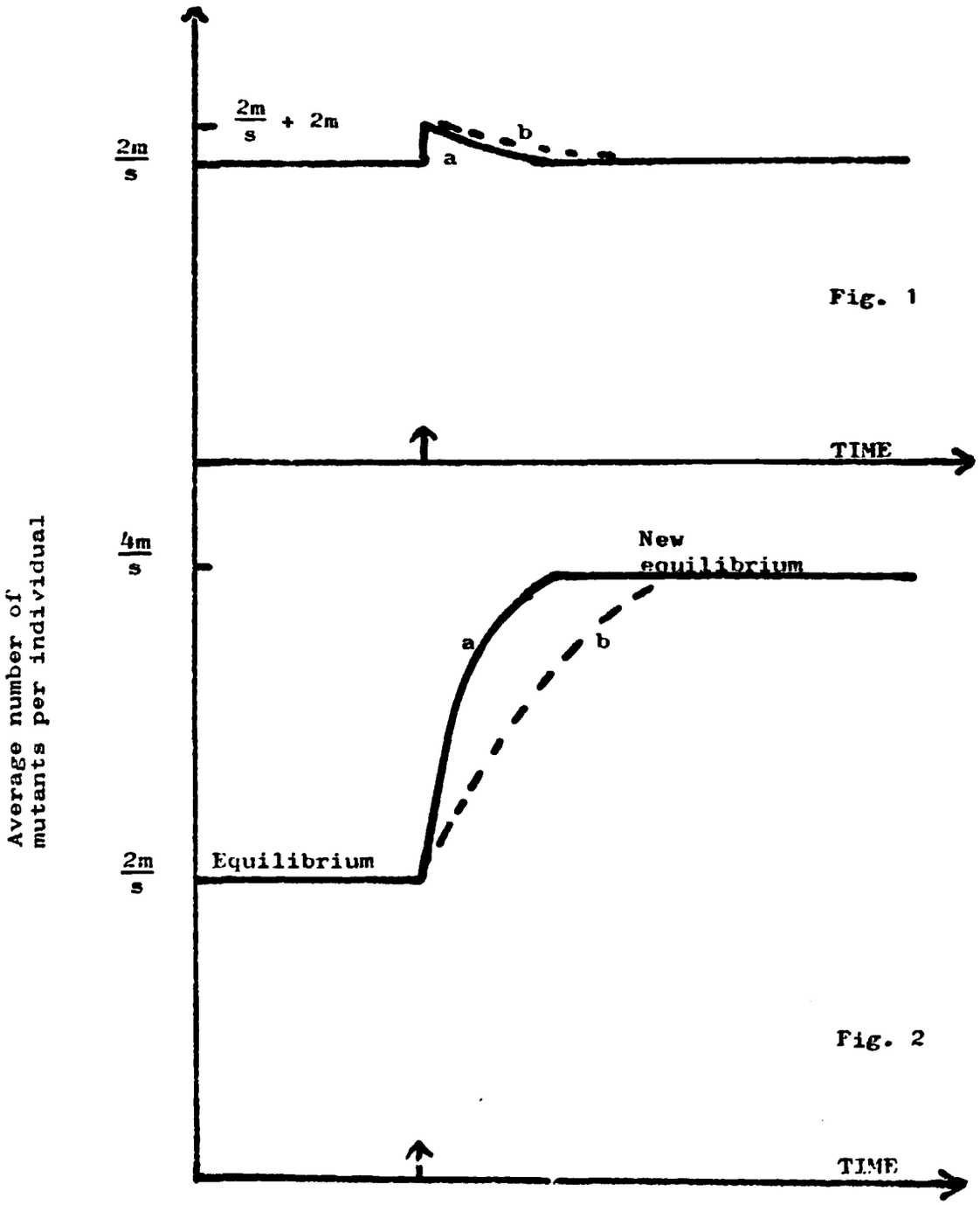

Fig. 1

Fig. 2

The mutation rate is doubled at ↑ for a single generation (fig. 1) or permanently (fig. 2). Lines marked a and b are for a mutant which is more and less detrimental respectively.