



The incidence of hereditary disease in man

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The Medical Research Council's Committee on Protection against Ionising Radiations (PIRC) has the responsibility for advising Council on the risks of ionising radiations. PIRC last reported on the risk of radiation-induced hereditary disease in 1960 when Council published its second report on 'The Hazards to Man of Nuclear and Allied Radiations'. Any new estimate of this risk would require up-to-date information on the natural incidence of hereditary diseases in man. Therefore PIRC decided to organise a forum meeting at which could be discussed the frequencies of hereditary disease, their severity, the extent to which they are maintained by new mutations, and their transmissibility. The meeting was held at the Council's Offices on 16 March 1976. It was chaired by Professor P. E. Polani, FRS, and attended by 35 people (Appendix). Abridged versions of the seven papers presented at the forum are printed in the following pages; the conclusions reached during discussion were as follows.

To estimate the risk of hereditary damage from ionising radiation, the genetically determined diseases to be considered are those whose frequency is closely linked to the mutation rate as estimated using the incidence in live-births. These disorders, most of which are serious, include those arising from chromosome number anomalies (about 5 per 1000), the dominant monogenic disorders (about 7 per 1000), and some of those resulting from chromosomal structural rearrangements (about 2 per 1000), giving a total frequency of about 14 per thousand live births. The concept that a dose of radiation might double the natural mutation frequency might be applied to such disorders.

If for chronic irradiations with X- or γ -rays the doubling dose is 100 rad, 140 cases of these hereditary diseases would occur in one million people of pre-reproductive age exposed to 1 rad.

The question of whether multifactorial disorders should be considered in assessing the risks of ionising radiations is one of semantics, for if multifactorial diseases are maintained by mutations, they are essentially monogenic. For example, there are

genetic and environmental components in the aetiology of ischaemic heart disease and a fraction of the total incidence is actually maintained by new mutation because this fraction is a monogenic disease, for example so-called essential familial hypercholesterolaemia. With regard to polygenic conditions in general, there is still dispute over the extent to which an increased mutation rate would affect their frequency. If they are largely maintained by new mutation it would not be unrealistic to employ the doubling dose concept.

The dominant monogenic conditions have special importance in assessing radiation effects. The relation between mutation rate and birth frequency is relatively direct, the theoretical equilibrium birth frequency being the product of twice the mutation rate and the mean persistence in terms of generations of each mutant gene. Any increase in mutation rate will be reflected at once by an increase in the birth frequency of fresh cases of such dominant conditions born to unaffected parents. Recessive monogenic conditions must also be considered. However, many believe that the more frequent of these diseases are (or were recently) maintained at their frequency level by heterozygous advantage rather than by new mutations. Moreover, the interval between the occurrence of a recessive mutation in a gene and the birth of the affected subject may be lengthy—centuries or even millenia. It is now becoming possible to visualise ways of controlling the frequency of recessive gene disorders, that is the future carriers will be identified and where appropriate offered prenatal screening. Therefore, in the future the incidence of recessive gene disorders is likely to change.

Reference

Medical Research Council (1960). *The Hazards to Man of Nuclear and Allied Radiations*, 2nd Report, Cmnd. 1225. HMSO, London.

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List of Participants at the Radiobiology Forum on the Incidence of Hereditary Disease in Man

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- Dr Julie Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex.
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