Meeting Report

Workshop on Ataxia-Telangiectasia Heterozygotes and Cancer

There is a common misconception that genetically controlled cancer proneness is synonymous with familial cancer. In fact, there is increasing evidence that cancer-predisposing genes are present in the population at frequencies which may significantly affect cancer incidence yet which do not result in cancer with a high enough probability to give rise to "cancer families." One example may be a gene predisposing smokers to lung cancer which has been suggested to be associated with the gene for debrisoquine metabolism (1). Another example, on which much more information is available, is the autosomal recessive genes for A-T2 in the heterozygous (i.e., carrier) state, which was the main subject of this informal workshop.

Homozygotes for A-T show a rare syndrome with a fascinating variety of aspects. Patients are deficient in immune response, show progressive neurological degeneration and defects in organ maturation, and are prone to develop cancer, particularly of the cells of the immune system (see Ref. 2). Their cells show spontaneous chromosomal instabilities, and there are reports of hypersensitivity to the chromosome-breaking and/or lethal effect of ionizing radiation and certain chemicals such as bleomycin, neocarzinostatin, Adriamycin, and Hoechst 33342. A further addition to this list is phorbol ester (Shiloh, Boston, MA), a tumor promoter that has been claimed to cause endogenous production of free radicals. Such experimental evidence as exists suggests that A-T homozygotes have a defect in the processing (repair?) of DNA that has experienced free radical attack.

In contrast to homozygotes, A-T heterozygotes (found in high proportion among close blood relatives of homozygotes) appear to be normal members of the population. They became of interest, however, following the first study in the USA by Swift (3) which suggested that they too may be cancer prone. A second, more broadly based study by Swift (N. Carolina) is still in progress, but the results to date (based on 225 homozygotes in 140 families) appear to be consistent with the general conclusion of the first study. There is a clear need for information from other populations. An MRC-funded study in the United Kingdom, currently with 58 homozygotes in 52 families, may help but linkage of the data with other studies not yet started may prove to be essential if independent confirmation is to be achieved in a reasonable time period. The currently available data do not enable risk estimates to be made with any confidence for individual types of cancer, but it is clear that the spectrum of cancers among the relatives of homozygotes is different from that of the A-T homozygotes. A speculative explanation is that the profound immunodeficiency of the homozygotes influences the relative incidence of different cancers.

How frequent are A-T heterozygotes in the general population? Swift's current study suggests an incidence of homozygotes of at least 3 per 10^6 live births, but ascertainment is almost certainly incomplete. The highest figure is in Pennsylvania and Michigan (around 8 to 10 per 10^6 live births). An independent estimate of one in 10^5 may be made from the frequency of homoyzygous cousins of homozygous probands with A-T (assuming an outbred population). The United Kingdom study using cases born between 1969 and 1976 also yields a frequency of around 1 per 10^5 (but not all birth dates are yet known and ascertainment is also probably incomplete). The incidence of heterozygotes may be calculated from the same data if one makes assumptions about the number of genes involved and their relative frequency. The consensus view was that 1 to 2% of the population was the most likely frequency of A-T heterozygotes.

The number of genes involved is actually one of the weaker pieces of information. Five or conceivably 9 complementation groups may have been identified, but 4 different techniques have been used, and there has been almost no overlap in the cell strains used thus preventing cross-validation. From experience with other diseases such as xeroderma pigmentosum, it would seem likely that a number of other complementation groups remain to be discovered.

At present, no A-T gene has been cloned or mapped. It would be of considerable help in achieving this if heterozygotes could be identified by means other than parenting a homozygote. Moreover, the information potentially obtainable from the cancer incidence studies would be greatly increased. Perhaps the most significant finding to emerge from a consideration of both published and unpublished data collected from laboratories was that A-T heterozygote cells are indeed distinct from homozygous wild-type cells, chiefly in being slightly more sensitive to lethal and chromosomal damage induced by ionizing radiation and neocarzinostatin. Unfortunately, none of the protocols seem yet accurate or cheap enough to justify attempting to identify heterozygotes in the general population, particularly since there may be other genes conferring a similar phenotype. They are, however, probably adequate for studies on a few large families with known A-T homozygotes in their pedigrees. This should lead to the identification of enough heterozygotes for restriction-fragment-length polymorphism mapping to be possible. An alternative and complementary mapping strategy would be to study sibships with multiple affected individuals.

The outcome of the epidemiological studies currently in progress is likely to be of importance. An appreciably elevated cancer risk in A-T heterozygotes would have significant consequences for cancer epidemiology and public health. It must be emphasized...
that there is no direct evidence that enhanced cancer incidence in heterozygotes is a consequence of a greater susceptibility to DNA damage by exogenous agents such as ionizing radiation, although chromosomal damage in their cultured cells of heterozygotes does show such a susceptibility. If it were to be so, however, there would be a number of important ethical problems to be faced in areas as diverse as radiation protection, carcinogen risk assessment, and genetic counseling.

References

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