Formal Discussion of: Cancer in Man

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Dr. Heston has reminded us of the interacting factors involved in cancer occurrence in mice. So many agents interact to open the threshold that no one factor can be identified as the causative agent in tumor development. Cancer occurrence in man is even more difficult to study.

A genetic background for cancer development in mice has been established by experimentation. This has been made possible by the farsighted decision to breed and set up lines differing in cancer resistance and susceptibility. I have always respected Strong for much of the early effort in this field.

Success with the mice, though, has led to vexation for investigators interested in cancer in man. The layman, misunderstanding genetics, seems to expect a definite genetic pattern in human family histories, or otherwise he may discredit genetics as one factor in cancer development. A few rare kinds of cancer in man have a pattern suggesting a 1-gene involvement. Even in these histories exceptions sometimes occur. Retinoblastoma is referred to as a cancer having a dominant pattern of inheritance, but in some histories the affected child has normal parents. If the case is sporadic, a simple explanation is to say that the case is a mutation. It is not logical to conclude that multiple cases reported in one sibship all arose by mutation when the parents were normal. In genetic terminology the explanation under such circumstances would be a gene with reduced penetrance or, possibly, a varied expression, as yet unrecognized, of the gene.

If the effective agents in mice are comparable to those in man, human cases of cancer may require a number of active genes, in association with nongenic agents. This in fact is to be expected. Gene control may cause a simple change in a cell in the direction of malignancy. The effect, though, is not detectable until later in life. Between the time of the change due to genetic action and the appearance of the cancer, the body has faced environmental agents that, under the conditions indicated here, would be necessary for cancer development. A phenotype is the result of both heredity and environment. Experimental geneticists well recognize that genes, some more so than others, are responsive to environmental agents. Specific environmental conditions can affect the action of a gene or be necessary for a gene to be expressed. Sometimes an environment is of such strength that it is the cause of a variant type, causing a phenocopy of a known hereditary character.

GENETIC BASIS FOR HUMAN CANCER

Although mankind is heterogeneous even in 1 population unit, several investigators have reported data that indicate that cancer occurrence in man has a genetic basis. Comparative studies of monozygous and dizygous twins might be expected to be an effective means for studying the relative effects of heredity and environment. That has hardly proved to be true. Several studies have given evidence that the 2 kinds of twins do not differ significantly where concordance is measured by co-twins having cancers of all sites. Data from some investigations have shown monozygous twins to have higher concordance for cancers of the same site, where twins have been selected because at least 1 of a pair had cancer. Harvald and Hauge (6) made a study of 6893 unselected twin pairs in Denmark. Of these, 1938 had 1 or both of a pair affected. Only a small number of twin pairs who could be used had cancer. Total concordance for dizygous and monozygous twins did not differ significantly when cancers of all sites were considered. Among the relatively few cases of breast cancer, the twin types showed no significant difference in concordance. The results indicate that heredity is not a strong factor, or that environment is a complicating agent.

Twin studies can be used to best advantage only if a long-term longitudinal study is followed. Oliver and Jackson (12) examined the records of 548 twin pairs among relatives of breast cancer probands. They concluded that twins are of little use for a 1-shot study. Most of the twins were too young for study or 1 of a pair had already died or had become lost to the records. After a number of a pair develops cancer, one cannot in justice conclude that the co-twin will remain free of the disease unless the study is carried on for a number of years.

NATIONAL DIFFERENCES

National groups differ in relative frequencies of cancer. Lilienfeld (7) has summarized breast cancer mortality rates for a number of countries, showing that the Japanese have a strikingly low frequency of breast cancer. The findings do not mean necessarily that the genetic backgrounds of the various groups differ so extensively. There can be genetic differences, though, because nonmendelizing groups of men are expected to have gene pools differing at least for frequencies of alleles. Racial differences in incidence of cancer of particular sites have been reported from studies conducted in Hawaii, where multiracial groups are found. The investigators reported that breast cancer incidence in Caucasians is almost 5 times that in Japanese (33.5 versus 7.1/100,000). Gastric cancer occurred with a higher incidence in Japanese than in other groups. The data were not age adjusted.

It is possible that environmental or cultural differences can be the explanations for some national differences in cancer mortality rates. Dungal (2) reported a
very high rate of gastric cancer in Iceland and suggested that diet and particularly the method for preparing food might be important factors.

FAMILIAL TENDENCIES

Stomach cancer is reported to have a familial incidence higher than would be expected on the basis of population risk. References to some of the reports have been given by Oliver (10). Recent investigations of family histories of lung cancer indicate a familial tendency which carcinogens possibly activate; Heston refers to the study by Tokuhata and Lilienfeld.

A genetic basis for a cancer tendency involving the breast has been suggested by the reports of several investigators. Lilienfeld has summarized the reports made by 8 investigators. Six of the studies show an excess of breast cancer in the close relatives of breast cancer probands; the familial rate was about twice the expected rate. Whether this difference represents a hereditary basis or a common environment in the family group, or a combination, is merely argumentative at this stage.

References to several studies of breast cancer occurrence in relatives of cancer and control probands have been cited by Oliver (10, 11). In general, the familial tendency in cancer probands' relatives is higher than that reported for control groups, especially for close relatives of probands.

Mothers of breast cancer probands have a higher frequency of cancer of the breast than would be expected on the population risk. Anderson et al. (1) have summarized the data from several studies and show that 2.5-11.6% of the mothers are affected. An early report by Morse (9) gave frequencies of 6.9% of breast cancer in mothers of cancer probands in comparison with 2.3% in mothers of controls. Our studies (11) show that 6.1% of cancer probands' mothers living past age 30 have developed breast cancer compared with 2.4% of control mothers. Of 291 mothers who did not develop breast cancer, about 20% had died at an earlier age than the breast cancer onset age of the cancer probands. However, this can also be said about 6 of the 19 mothers who had breast cancer.

A desirable study of familial tendency would be to follow the children and grand-children of breast cancer probands. This has been discussed by Anderson et al. (1). As logical as this idea might seem, the possibility of getting a large number of usable probands who could be followed for 2 or more generations is very unlikely. Childless breast cancer cases will not be referred to until another topic is considered. We will look now to the small average number of daughters produced by fertile breast cancer cases.

Of 316 breast cancer patients in our material (5 of whom could not be used for familial tendencies), 71.5% produced children. The childbearers had 590 children, of whom 315 were daughters—an average of 1.39 daughters per childbearer, or slightly less than 1 (0.9965) per breast cancer proband. Both childless and childbearing cases would be involved in selection of probands for possible studies. It would be necessary, therefore, to have a very large number of index cases to get enough female descendants for a follow-up study, if the population is similar to the one we studied. Sons could be used for the study of granddaughters of breast cancer patients. This would be a possible means of transmitting any gene responsible for cancer tendency, but activating factors might be lost. To complete the story, the average number of progeny produced by control cases was almost identical to that for the cancer probands; the 2 sets of index cases also had about the same mean age.

FACTORS ACTivating CANCER

One weakness in our knowledge about the occurrence of human cancer is our lack of information about the effects of agents other than possible genetic factors. A socioeconomic relationship has been referred to by investigators, but this may be tied in with medical care and parity.

Marital status and, for breast cancer, childbearing, and nursing of children are factors to be considered. Various reports have been made showing that spinsters have breast cancer more frequently than do women who have married. The age-specific incidence for spinsters continues at a high rate longer than for married women (7). Some studies have indicated that childless married women have breast cancer more frequently than do childbearers.

Macklin (8) made an analysis of parity and breast cancer. Deceased relatives of breast cancer and control probands were used. Relatives who were single women or childless married (ever-married) women in the cancer proband group did not differ significantly in frequencies of breast cancer occurrence. These relatives, though, had a breast cancer frequency significantly higher than that found among cancer probands' relatives who had borne children. Increases in number of children were associated with gradual decreases in proportions of breast cancer, although the step-by-step differences were not significant.

Similar patterns occurred among the relatives of control probands (8). In each instance, though, the cancer incidence for the control group was lower than the frequency for the respective cancer group.

Macklin concluded that genetic factors and parity are both important in determining the occurrence of breast cancer. The 2 sets of factors presumably are additive.

Sex steroids are known to influence the growth of breast and prostate cancer. Chemical agents can induce cancer of the skin and bladder. Carcinogens in the organism may be effective in inciting cancer, in transforming an activated cell into malignancy. Little is known as yet about the action of the carcinogens, why some cells respond and others do not, and what occurs in the cell to bring about the change. Individuals presumably facing the same carcinogenic agent differ in response to the agent. Not all will develop cancer.

Viruses may be effective in cancer occurrence in man just as in mice, as discussed by Heston. If we can apply to man the knowledge we have about mice, individuals or family groups may differ in their genetic ability to respond to the virus, or possibly some lack the co-carcinogenic agent that is necessary to complete the transformation (14). F. Duran-Reynals (3) had the opinion that neoplasia by chemicals and hormones is mediated by viruses.
and that some of the viruses may be of the ordinary, inflammatory type, which could change into or function as neoplastic viruses. Investigations are still necessary to understand the nature of action by viruses associated with cancer occurrence.

**MULTIPLE CANCER FAMILIES**

Some of the problems of human cancer occurrence might be more readily attacked if records of families with multiple cases of cancer of one site are collected and then these families are subjected to full and detailed investigations. This is the closest that we can come to studies made with inbred strains of mice.

Finding families with a number of relatives having breast cancer will not be an easy task. In our records for 311 usable probands, 29.4% had no discoverable cancerous relatives, including all sites except possibly skin cancer. Limited to breast cancer, 67.7% of the cases were sporadic; relatives included grandmothers and cousins. Only 64 probands (20.4%) had close relatives who had developed breast cancer (11). The low fertility of cancerous women has the effect of decreasing the number of multiple cancer families, as has been stated. Ninety of 316 cancer patients were childless. A daughter of a noncancerous aunt, though, may develop cancer because she has the proper combination of agents and the necessary genes, which were less complete in the aunt, who therefore failed to develop cancer.

Multiple cancer families do occur, and not all can be dismissed by an assumption that the aggregation is due to chance. Aggregations are often found only in specific branches of kinships.

Gardner and Stephens (4) reported 1 kinship in which 8, and possibly 9, breast cancers occurred among 71 relatives, all confined to 3 branches from 8 siblings. Later they discovered 1 other breast cancer in the group. The frequency is higher than was to be expected for the Utah population death rates from breast cancer occurring in the same period of time. Woolf and Gardner (15) reported 8 breast cancers in descendants of 1 breast cancer case.

Hagy (5) investigated the relatives of 1 proband and found among them 6 cases of gastric cancer. The frequency among all of the proband's relatives was low, but the records show that the 6 occurred only in the proband's paternal side of the kinship. Among this branch of the kinship, 19 were age 40 years or older, and the 6 cases give a frequency of 31.6%.

Multiple cancer histories of particular sites have been discovered by other workers, but often no attempt has been made to use them for the potential value they have. Any effort put forth to discover multiple case histories must be great. Proof will have to be established for every relative reported to have had cancer and also for those who supposedly have never had cancer (10, 11). Probands often lack accurate information even about their close relatives. To counteract this defect, the investigator must go to the relatives for information. In order to make the family history available to someone who may want to compare, say, factors effective in breast cancer occurrence, the collected histories should be put on record and the family records should be kept on file for other use.

Until we have more evidence suggesting that different genes (assuming a genetic basis) as well as other agents are responsible for cancers occurring at different sites, investigators should collect and keep complete and accurate records of members of families having histories of multiple-site cancers. One gene could be effective in causing changes in cells of different tissues with other activators responsible for transformation to what we call malignancy. Different tissues may be acted on by a single gene. In Drosophila, there is 1 gene that causes cessation of differentiation in at least 4 parts of the developing body. This gene, therefore, has a pleiotropic effect. Here the term pleiotropism refers to the end product. It is possible that 1 biochemical change due to action of the gene is responsible for the multiple effects on the phenotype.

Cancer is most certainly a change in cells that is the result of interaction of multiple agents (14). Multiple cancer histories of 1 site, at least, will permit studies of the effects of cultural patterns on cancer occurrence; cultural patterns of relatives who are affected and not affected should be more similar than those of nonrelatives. Gene actions on the biochemical level, abnormal cell metabolism, and other conditions causing cancer or resulting from cancer can be studied in a group having similar hereditary backgrounds.

**REFERENCES**


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