ON THE ORIGIN OF CANCER FOCI

AMOS NORMAN, PH.D.

FISHER AND HOLLOMAN have advanced the hypothesis that a critical number of cancer cells is required for the initiation of a malignant growth, and that the cancer cells arise as the result of INDEPENDENT somatic mutations. This hypothesis leads to the equation:

(1) rate of appearance of cancer $\backsim$ (age)$^{n-1}$

where n is the number of cancer cells in a critical-size cancer colony. Equation (1) predicts that, on a log log scale, the rate of appearance of cancer versus age will be a straight line, a prediction that is reasonably well satisfied by at least one type of cancer. Unfortunately, however, almost any function when plotted on a log log scale yields a fairly good straight line; therefore, other consequences of the hypothesis must be tested. It is the purpose of this paper to show that the hypothesis leads to direct contradictions of the data for the incidence of primary multiple cancers, for the mutation rates of human genes, and for the etiology of the best studied cancers.

If a given malignant growth appears with frequency f_1 as the result of mutation in one or more cells, and if another malignant growth arises with frequency f_2, also as the result of somatic mutation(s), then the frequency of both types of cancer in a single individual should be $f_1 f_2$. This follows from the assumption that the mutations are independent. Now typical values for f_1 and f_2 are 10^{-4} (for the age group 40 to 50 years)[1] so that the frequency of two primary cancers should be 10^{-8}; i.e., only one in every hundred million people, or one in ten thousand cancer cases should exhibit two primary cancers. The incidence of more than two primary cancers should be almost unknown. On the contrary, estimates of practicing physicians are that as many as 1 per cent of all cancer cases exhibit multiple primary cancers. This estimate is supported by the large bibliography on multiple tumors.[2] Among the papers listed is one reviewing 207 cases of multiple tumors and one describing a case with four primary neoplasms. The probability for the latter is approximately 10^{-16}, a figure that leads us to expect less than one case of four primary cancers in the whole history of the human race.

A cancer colony apparently consists of about seven cancer cells occupying adjacent sites in a given tissue.[3] Let us be generous and suppose that the seven cancer cells constituting the colony can occur anywhere in a volume of 10^3 cells. Now the frequency of mutation of several human genes is of the order of 10^{-5} per gene per generation.[5] We expect, therefore, that among 10^3 cells the average number of mutant cancer cells (assuming a single gene mutation is responsible for the transformation to a cancer cell) is 10^{-2}. The distribution of cancer cells among the volumes of 10^3 cells each will then be a Poisson distribution. The probability of having seven cancer cells in a volume is then given by

$$P = \frac{e^{-\lambda}\lambda^7}{7!}$$

when λ is the average number of mutant cells per volume. Taking λ as 10^{-2}, we have $P \backsim 10^{-18}$. If there are about 10^9 cells per individual then there are 10^6 volumes of 10^3 cells each, so that the frequency of malignant growths will be about 10^{-12}. This factor is too low by a factor of 10^8. A larger value for λ, the average number of mutations per 10^3 cells, might lead to better agreement. It should be emphasized, however, that this would lead to two difficulties: firstly, it requires a higher mutation rate than has been found in human beings; secondly, if λ is not much less than one, equation (1) no longer holds.

The hypothesis of Fisher and Holloman was advanced to account for the marked age dependence of cancer. It is interesting to note that several diseases are marked by similar age dependence. For example, the incidence of diabetes is strongly age dependent. To be consistent, it would be necessary to advance a somatic-mutation hypothesis for diabetes, but diabetes is an inherited disease[4] and it would

From the University of California at Los Angeles, Los Angeles, California.

Received for publication, January 24, 1952.

become necessary to postulate that what is inherited is a high mutation rate to this disease. In the absence of any supporting evidence such an hypothesis is certainly unnatural as well as barren. Indeed, any simple hypothesis for the origin of almost any disease is somewhat suspect, and this is especially true of cancer in which such diverse factors as hormones, viruses, and carcinogens of every kind all play some role.

REFERENCES

1. ANON.: Cancer Deaths and Death Rates by Age, Sex, and Site, United States, 1948. New York. Statistical Research Section, Medical and Scientific Department, American Cancer Society, Inc. [Mimeo.]

2. ANON.: Multiple Tumors. New York. Medical Library, Medical and Scientific Department, American Cancer Society, Inc. [Mimeo.]

3. FISHER, J. C., and HOLLOMAN, J. H.: A hypothesis for the origin of cancer foci. *Cancer* 4: 916-918, 1951.

4. GATES, R. R.: Human Genetics. New York. The Macmillan Co. 1946.

5. NEEL, J. V., and FALLS, HAROLD F.: The rate of mutation of the gene responsible for retinoblastoma in man. *Science* 114: 419-422, 1951.