Environmental Radiation and Cancer

No threshold is demonstrable, and incidence may have rising inflection with intensity.

Harold F. Blum

Although there is no longer room for doubt that ionizing radiation may cause cancer in man (see *1*), any estimate of the potential danger, in this regard, of increase in the level of environmental radiation contains an element of uncertainty. This arises from our lack of information regarding the shape of the curve relating dose rate (incident radiant flux) and the incidence of cancer in the population. Without such information we are forced, in any estimation we may make, tacitly to assume a shape for that curve, and in this we are likely to be influenced by our ideas of the mechanism of carcinogenesis, a matter on which there is not general agreement. The assumption of a linear relationship may be justified as a first approximation, but this does not have experimental or other support. This article is presented with the hope that data relating to another kind of environmental radiation —ultraviolet light—may be of service in this regard.

Induction of Cancer by Ultraviolet Light

"Non-ionizing" radiation in the ultraviolet spectrum induces cancers of the skin of experimental animals with quantitative predictability, the long-wavelength limit for this carcinogenic action lying at about 0.32 μ. Sunlight, having its short-wavelength limit at about 0.29 μ, contains a small fraction of these carcinogenic wavelengths, and evidence converges to indicate that this is a principal cause of cancer of the skin in man. The evidence (reviewed in *2*) includes, besides inferences from the experiments on animals, the fact that skin cancers are largely limited to exposed areas—principally the face—and that there is a correlation with latitude such as might be expected if this radiation were the cause. The carcinogenic wavelengths are the same as those that cause sunburn, and it is probable that there is at least an indirect casual relationship between the two processes. The outer horny layer of the skin acts as a protective filter against the sunburn-producing, carcinogenic, radiation, and this is found to be more opaque for negro than for white skin. Correspondingly, skin cancer is relatively rare in the Negro population as compared to the white.

Cancer induction by ultraviolet radiation has been the subject of a good deal of quantitative experiment, and it would seem reasonable to attempt to apply some of the information gained therefrom to the case of ionizing radiation—lacking as we do the comparable information regarding the latter. I have discussed elsewhere various aspects of carcinogenesis by ultraviolet light (*2*); not all of these aspects will be treated here, but only those that seem to bear directly on the present problem. For this purpose it will be unnecessary to adopt any specific hypothesis for the intimate mechanism, although the quantitative evidence regarding carcinogenesis by ultraviolet light appears to exclude some of those that have been proposed.

A Cumulative Process

Figure 1 presents in a general way a relationship that has been found in these experimental studies (see *2* for a detailed description). The curves show the distribution of cancers within a genetically homogeneous population of albino mice (strain A, males) exposed to ultraviolet light at regular intervals until cancer appears. The curves represent the result of dosages ranging in relative value from 1 to 32, each dose being twice the preceding one. The logarithm of the time required to reach a given percentage incidence of cancer in the population follows a normal distribution, and when different dosages are used the curves move along the abscissa without change in shape or slope; this is not the case if the dosage terminates before the cancers appear. The dosage relationship is described for any percentage incidence level by

$$Dt^2/i = \alpha \qquad (1)$$

where D is the dose of ultraviolet radiation delivered at each exposure, i is the interval between these exposures, t is the time to appearance of the cancer (in practice, the time required to reach a volume of approximately 60 mm^3), and α is a constant for the given percentage incidence level. This relationship suggests a continuous, cumulative process —for example, that to be expected for a constantly accelerated growth process. Such a relationship is not easily compatible with the idea of independent periods of induction and growth, nor with abrupt genetic changes, as is implied in the somatic mutation hypothesis (*2*).

Although the doses of ultraviolet radiation were given separately at regular intervals, the dose rate being held constant, the same relationship may be expected to hold if the radiation is given continuously at lower dose rates. In such case we may replace Eq. 1 with

$$I t^2 = \beta \qquad (2)$$

where I is the dose rate—that is, the radiant flux per unit time—and β is constant for the particular incidence level. It is seen that the time to appearance of the cancers is proportional to the square root of the dose rate.

But in the present problem we are concerned with the effect of an increase in the dose rate on the percentage incidence of cancer within the population. Let us refer to Fig. 1, where the vertical line labelled L corresponds to 500 days, approximately the normal average lifetime of these mice. It is seen that the incidence of cancers to be expected within the population during this average lifetime is a function of the time to cancer appearance—that is, the period at the end of which a cancer becomes detect-

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able. The same should be true for any other type of cancer in any other population, whether or not the function has the same form as in the present case. From the diagram we see that the dosage corresponding to curve 4 would produce cancer in about 77 percent of the population, the dosage corresponding to curve 2 in about 13 percent, and the dosage corresponding to curve 1, in a fraction of 1 percent too small to express within the dimensions of the diagram. These curves give no evidence of a "threshold" below which cancer is not induced. On the contrary, they indicate that any dosage may induce cancer in some fraction, however small, of the population. Thus, the experimentally determinable lower limit of carcinogenic effect of this agent—and so far as we know, of any other agent—should be a function of the average life-time of the animals concerned and the size of the population studied. Actually, in the case of carcinogenesis by ultraviolet light, there is some evidence of a slight degree of recovery from the carcinogenic process, and so it is possible that a threshold exists at some very low level. But it is, of course, completely infeasible to determine that threshold if it exists. The data also indicate that recovery is a negligible factor—that carcinogenesis by ultraviolet light is a cumulative process and for all practical purposes may be regarded as essentially irreversible and nonthreshold (*2*).

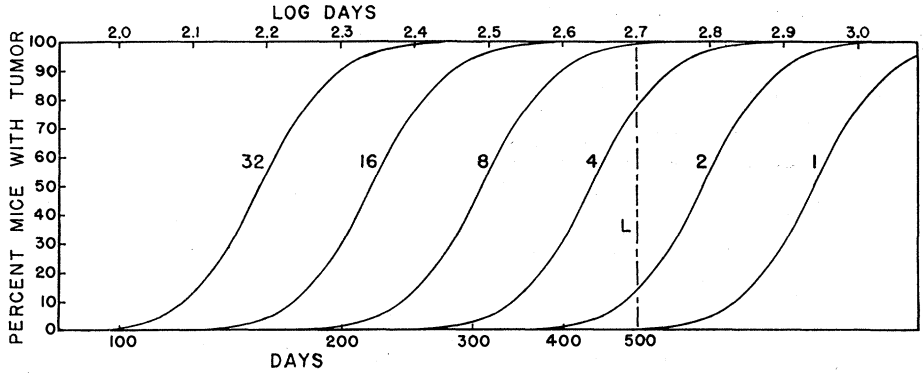

Fig. 1. Percentage incidence versus time to appearance of cancers of the skin of the ears of mice exposed to repeated doses of ultraviolet light, based on experiments described in (*2*). Note that plotting the logarithm of the days to tumor appearance results in a normal distribution of the percentage incidence of tumors. The numbering of the curves indicates relative dosages ranging from 1 to 32, each dose being twice the preceding one. The highest dosage value (32) corresponds to the minimum time observed for a given dosage relationship—that is, when equal doses were given 5 days per week. The vertical line L represents the approximate normal life-time of these mice.

Dose Rate and Percentage Incidence of Cancer

To help in explaining the way in which the percentage incidence of cancer, estimated at the average life-time of the population, varies with dose rate, let us have recourse to the diagram in Fig. 2. Here the curves 1, 2, and 4 of Fig. 1 are represented on a probability grid, which turns the sigmoid percentage curves into straight lines. The units along the ordinate are the commonly used probits, which may be translated directly from percentages by use of an appropriate table. The probit value 5 corresponds to 50-percent incidence, and this may be chosen as the axis. We then write

$$P = \frac{1}{\sigma} [\log t - \log t_5] + 5 \qquad (3)$$

where P is the probit value, read along the ordinate; σ is the standard deviation (the reciprocal of which measures the slope of the curve, and which is constant); and t_5 is the value of t at probit 5.

Rearranging Eq. 2, writing for the specific case of 50-percent incidence (probit 5), and taking logarithms

$$\log t_5 = -\tfrac{1}{2} \log I + \tfrac{1}{2} \log \beta_5 \qquad (4)$$

and substituting in Eq. 3

$$P = \frac{1}{\sigma} [\log t + \tfrac{1}{2} \log I - \tfrac{1}{2} \log \beta_5] + 5 \qquad (5)$$

Holding t constant at the value corresponding to the average life-time (L in Fig. 1), and collecting constants as C

$$P = (\tfrac{1}{2}\sigma) \log I + C \qquad (6)$$

Translating the probit values into percentages and plotting in terms of I, instead of log I, we obtain from Eq. 5 the curve shown in Fig. 3. It is seen that at low percentage incidences the slope of this curve becomes steeper with increase in dose rate. That is, the higher the dose rate from which we start, the greater the increment in percentage incidence of cancer within the population with increment in dose rate. At higher incidences (approaching 50 percent) this tendency is reversed.

Relation to Cancer Induction by Ionizing Radiation

Let us picture what this would mean with regard to cancer induction in man by ionizing radiation if the same sort of relationship held. The steady background dose rate of ionizing radiation coming from cosmic rays and radioactivity in the earth's crust cannot be reduced and may be assumed to be the cause of a certain very low incidence of cancer in the human population. If this rate is raised by a given increment, an increase in cancer incidence is to be expected. A second, equal increment of dose rate should result in a greater increment in cancer incidence than that produced by the first one. Successive increments would thus be increasingly dangerous, until a relatively high incidence of cancer had been reached—in-

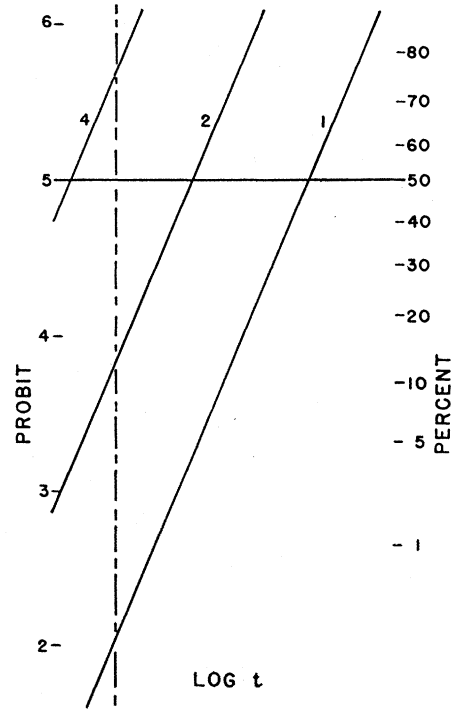

Fig. 2. Curves 1, 2, and 4 of Fig. 1, plotted on a probability grid (probits), which turns them into straight lines.

deed, such incidence as would seem intolerable if the human race is to continue.

A parallel situation should exist in the case of deposition of radioactive strontium in bone, which may cause leukemia and other cancers (*1*). A given amount of Sr^{90} in the bones may be assumed to provide a virtually steady dose rate of ionizing radiation within the body. An added amount of radiostrontium would be expected to raise the dose rate and hence the incidence of cancer; and, again, successive increments would be expected to have increasingly greater effect in the lower incidence range.

But is there any real justification for carrying over the evidence from experiments with non-ionizing radiation? It may be objected that the primary action of these two types of radiation is different, and that, hence, no direct relationship is to be expected. In answer it must be pointed out that the biological effects of these radiations are generally similar, particularly as regards the kinds of quantitative relationships observed, and that we have no evidence to the contrary with regard to cancer. To the best of my knowledge there are no data on experimental carcinogenesis by ionizing radiation that have been obtained in a manner comparable to those with ultraviolet light, nor that will permit a comparable analysis; and until such data have been obtained it seems wisest to accept the parallel. Moreover, carcinogenesis by ultraviolet light has the aspect of a cumulative process, and it seems most likely that the carcinogenic effect of ionizing radiation will turn out to be the same, in which case similar quantitative relationships are to be expected. The normal distribution of cancer incidence found in connection with ultraviolet light appears to be based on the cumulative effect of a number of randomly distributed factors—as may be better appreciated from a more complete analysis of the data and conditions (see *2*). It would not be surprising if the curve relating cancer incidence in man from ionizing radiation did not follow a smooth, normal distribution, as does that found for genetically homogeneous mice exposed to ultraviolet light; the curve might well be skewed in the former case. Nevertheless, any curve resulting from the accumulated effects of a number of randomly distributed factors should have a rising inflection at low incidences, and so the above general analysis should be applicable.

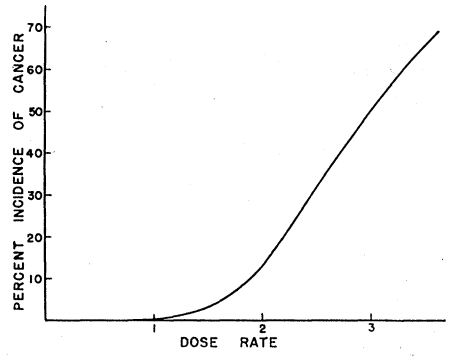

Fig. 3. The effect of dose rate on the percentage incidence of cancer in a population; based on the data illustrated in Figs. 1 and 2.

While much uncertainty must continue to exist, certain things appear clear from the above analysis: There is no definite reason for assuming a threshold for carcinogenesis, and it is infeasible to test the possibility by direct experiment. Thus, there is no justification for assigning a "safe" upper limit for environmental ionizing radiation as regards the genesis of cancer. The assumption of a linear relationship between cancer incidence and dose rate (see *1*) is justifiable only as a tentative first approximation. The curve may be expected to have a rising inflection at low percentage incidences of cancer, in which case estimates based on a linear extrapolation would tend to minimize the effect of increase in dose rate.

It is to be emphasized that what has been said here does not apply to the production of genetic mutations (in the usual sense), which are abrupt, separate events and hence must have a different quantitative relationship to dose rate, but only to the induction of cancer.

References

1. E. B. Lewis, *Science* **125**, 965 (1957).
2. H. F. Blum, *Carcinogenesis by Ultraviolet Light* (Princeton Univ. Press, Princeton, N.J., 1959).

AAAS Chicago Meeting

Raymond L. Taylor

The preparations for any large scientific meeting—even if it is a recurrent yearly event, and one with a basic pattern—are difficult fully to appreciate except by those who have been involved. The annual national meeting of the American Association for the Advancement of Science is particularly complex, uniquely interdisciplinary, and variable with respect to the number and identity of the many participating societies. Typically, all 18 AAAS sections have programs, often symposia one to six sessions in length; some 40 to 50 of the 240 affiliated societies will meet with the Association and sponsor programs varying from single sessions or social events to full-scale national meetings with concurrent sessions extending over four or five days. Several affiliates regularly arrange regional meetings or sponsor special two- or four-session symposia. Another 40 to 50 societies are official cosponsors of the sectional or societal programs of others. Altogether, the AAAS meeting may exceed 300 sessions that range from highly specialized to broad and general ones—arranged, however, so that there is a minimum of conflict for their potential audiences.

The decision of the Board of Directors on the site of the meeting is always made some two to five years in advance. After a survey of the available physical facilities, basic decisions for the meeting and its local committees are made a year ahead. Some of the sectional programs are virtually complete early in the spring, but others, especially those with sessions for contributed papers, are not ready for the printer until early October.

The preliminary announcement of the seventh Chicago meeting [*Science* **129**, 1431 (24 May 1959)] indicated the general scope of this year's con-