Letters

Radiation Carcinogenesis

A number of difficulties lie in the way of accepting Blum's thesis [*Science* **130**, 1545 (1959)] that his data on ultraviolet carcinogenesis in mice and his mathematical deductions therefrom are evidence for the concept that there is no threshold dose for radiation carcinogenesis. It is not simply that he is arguing not from data but from projections of that data into unstudied areas, or that this was done even though direct observation was possible. There is also the fact that other data from his series of studies point rather directly to the opposite conclusion. They not only describe a threshold phenomenon but offer some clues as to quantitation.

As to the first objection, Blum in his Fig. 1 presents the incidence data for varying doses of radiation. According to his figure, halving the radiation dose means that 0.15 is added on to the log of the time necessary for tumor development. According to the chart this relation holds for each halving of dose down to 1/32 of the dose required for most rapid carcinogenesis. The chart is described as being based on experiments described in his recent monograph (*1*). Unfortunately, neither the monograph or the original papers I could find deal with doses corresponding to his two lowest curves, and the third dose level is described as treated partly by extrapolation (*2*). Hence it would appear that the dose ranges on which the question of threshold is based are quite narrow, more so than the diagrams would suggest.

If such information were all that were available to us, there would be some justification for making projections therefrom, even though the tentative nature of the projections would have to be emphasized. Actually this is not the case. Blum makes the point that there is a practical limit on the doses of carcinogenic radiation that can be tested because, with low doses, the time for cancer development will be longer than the life span of the animal. Of course, if the first cancers are not to appear until after all animals are dead, we have a practical threshold if not a biologic one. But further than this, our information need not be as limited as Blum claims. He does not spell it out in his article, but all his figures on dose-time relations are concerned with the time within which cancers appear visible to the unaided eye. Nowhere in his work could I find reference to the power of the microscope to detect cancers much earlier in their course. Given his figures for cell size and rate of growth, a cancer should have a cross section of 100 cells visible under the microscope after an interval one-third that necessary for a gross lesion to develop. This means that doses of irradiation supposedly leading to far more slowly growing tumors than have presently been studied are quite accessible to experimental investigation, so that abstract speculation is neither needed nor appropriate.

But beyond these caveats, there is evidence on threshold existence in other work of Blum himself: his studies on the effect of interruption of irradiation and its resumption after a 30-day rest period (*3*). (The figures for 30-percent tumor incidence are the most convenient to analyze because there was a second interruption of radiation in some series before the 50-percent incidence time was reached.) According to these figures, with uninterrupted radiation it took 95 doses of 2×10^7 ergs/cm^2 to produce visible cancer in 30 percent of the animals. Interruption late in the course of treatment, after 53 doses, meant that only 85 doses were needed for tumor production; the tumors apparently grew during the rest period. This, however, was not the case when the interruption occurred earlier in the course of treatment. When the rest period was given after 33 treatments, there was no progression, and the same total of 95 treatments was needed for cancer production as had been true for the controls. By contrast, when the rest period was introduced still earlier, there was recovery from the first course and more radiation was needed than if there had been no interruption. With the break after 23 treatments, an additional 81 treatments for a total of 104 were needed. And if only three or four treatments were given (the actual number is not clear), more radiation (100 doses) was needed after the rest period than if both the rest period and the first doses of radiation had been omitted.

It seems to me that this evidence for reversibility of the effects of small amounts of radiation bears directly on the question of a threshold. For if there is a dose of radiation low enough so that the exposed tissues recover or become even less than normally sensitive to subsequent radiation, this must be a subthreshold dose by definition. It appears that only above a certain dose level are the effects of radiation irreversible and hence inexorably carcinogenic. Hence, from both negative and positive aspects I find myself unable to accept Blum's thesis that no radiation threshold exists for carcinogenesis.

Extrapolation of this work to carcinogenesis by ionizing radiation presents other problems. It is reasonable to think that there might be parallel quantitative patterns. At least it is hard to imagine that there is no correlation between

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dose and cancer incidence *in the dose range of known carcinogenicity*. The question is whether natural radiation plus fallout brings us into that range, and I see nothing in Blum's work that bears on this crucial point.

JOHN W. BERG
Memorial Center for Cancer and Allied Diseases, New York, New York

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1. H. F. Blum, *Carcinogenesis by Ultraviolet Light* (Princeton Univ. Press, Princeton, N.J., 1959).
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3. H. F. Blum, *ibid.* **11**, 463 (1950).

Before answering Berg's specific criticisms may I point out that my article does not state, as he implies, that there is no threshold for radiation carcinogenesis, but only that it is infeasible to demonstrate one experimentally. As I say in that article, and elsewhere (*1*, *2*), the analysis of data on the induction of cancer by ultraviolet light suggests that a threshold exists but does not permit a value to be set for that threshold, although it must be very low. The argument in the article under discussion is based on the good agreement between extensive experimental data and a quantitative model that is compatible with the concept of acceleration of cancer growth rate under conditions of repeated dosage. Certain extrapolations are made in the article on the basis of this model, but no discussion of the experiments or the model itself was attempted in the brief space available. In objecting to my extrapolations Berg seems to disregard, or to be unaware of, the consistent agreement of the model which I use in my extrapolations with the *whole* of these data, although he cites a reference in which both data and model are discussed at length (*1*).

Although many of Berg's criticisms are directed at points in the basic structure rather than at the content of this particular article, it seems necessary to answer them here. I shall attempt to do so in more or less the order he presents them. Figure 1 in the article is based on the aforementioned model and does not purport to represent specific experiments; it was designed to illustrate the extrapolation to conditions near the end of the life span of the animals, where experiments must necessarily be untrustworthy or infeasible. Curve 1 in this figure obviously represents an extrapolation, since it refers to a time when most of the animals would have been dead. Berg seems to have taken this figure more literally than was intended, since he raises the objection that I do not have experi-

mental data for this particular curve. Citing one of the papers in which some of these data are described (*3*), Berg writes, "the third dose level is treated partly by extrapolation." Apparently Berg is referring to data taken from an experiment in which a dose level which would correspond approximately to curve 3 in Fig. 1 was used. The extrapolation in this case was to the 50-percent incidence level, from measurements representing lower incidences; this extrapolation was made for purposes of comparison, since a more complete curve could not be obtained for this dosage because of normal mortality. So the extrapolation has a better basis than might be inferred from Berg's statement. Actually, the experiments cover rather well the dosage range that it is feasible to study with the animals in question. The fact that one cannot obtain more complete coverage might in itself indicate the infeasibility of setting a threshold, since we can never be sure that cancers which have not come to detectable size before the death of the animals are not present.

Berg does not point out that the validity of the extrapolation represented in Fig. 1 rests on the finding that within the experimental range the shape and slope of the distribution curves does not change with dose or other factors; the reliability of this finding is treated in a later publication (*4*) than the one Berg cites—one which contains further data. The constancy of the incidence distribution curve is illustrated graphically in Fig. 31 of (*1*), where points obtained from over 600 mice are brought into relationship on a composite plot. The curves in Fig. 1 of the article in *Science* are based on this relationship, their positions on the abscissa corresponding to Eq. 1. An important point in the evaluation of the model is that it fits other data in which doses were interrupted (see *1*). If all these data are taken into consideration in terms of the model, I think there is ample justification for the extrapolation that is made in the article under discussion.

Berg is reproachful because studies of the earlier stages of development of cancers were not made with the microscope. But has he taken into consideration the quantitative aspects of such a study? In our experiment the end point was the gross appearance of a tumor of a given volume. Obviously, it would be a great advantage to have reliable data on the growth at earlier, microscopic stages if it were feasible to obtain them. But the time of tumor appearance varies widely among the animals of an identically treated population (see Fig. 1), and one does not know in advance which animal is going to be the first to display a tumor, or how to place any of the animals in

order with respect to the time at which a tumor will appear. We thus face a dilemma; if we wait until a tumor appears we have no measurements of microscopic stages; on the other hand, if we sacrifice the animal before a tumor appears we can have no idea when the tumor would have become microscopically observable had the animal been allowed to survive. If we attempt successive biopsies we are certain to interfere with tumor development, and besides we would not know where to make them. Gross observation shows that more than one tumor may develop on the irradiated area, and that the tumor we ultimately measure is the one of these that grows the fastest (for example, see Fig. 50 in *1*). It is also to be noted that good many of the tumors are mixed (sarcoma and carcinoma), indicating more than one site of origin (*5*). Altogether, the attempt to search out the course of tumor development by microscopic study would seem to have somewhat the aspect of a search for a needle in a haystack.

The decision as to whether it would be advisable to attempt microscopic studies at all—for Berg would apparently attempt them in spite of these difficulties—must depend upon extrapolation back from the time of appearance of tumors. The extrapolation must depend upon the kind of mathematical model one uses. Berg reaches the conclusion that such a study should have been made by means of an extrapolation; this extrapolation, though vaguely stated, would seem to be based on the idea that the tumor has been growing for some time at a constant relative rate. Berg uses the estimates of terminal growth rate which I have made; but if he will examine the original article in which these rate measurements are described (*6*) I think he will find ample indication of the uncertainties involved in such an extrapolation and of its obvious inapplicability. Moreover, the model which we have found to describe the data indicates an acceleration of the relative growth rate of the tumor, in which case the measured terminal rate could not be a valid index of growth at earlier stages when growth must have been slower. From the model it appears that although one may essay to extrapolate to the initial volume at the time the first dose of radiation is given (*1, 7*), extrapolation to intermediate volumes is not possible without information we do not have (*1, 8*).

Berg attempts to demonstrate the existence of a threshold for ultraviolet carcinogenesis on the basis of an interpretation of certain of my data from experiments in which the doses of ultraviolet light were interrupted. He apparently obtained his data by interpolation in curves published in an article about

10 years ago (*9*) in which an approximate model for accelerated growth of these tumors was first developed. It was pointed out that the model as therein developed could account for certain aspects of the data but not for the data of these particular experiments with interrupted dosage. Since that time we have modified the model, without abandoning its essential form, to obtain a model which accounts satisfactorily for *all* these data. Apparently Berg has not consulted Figs. 45 and 47 in (*1*), since he would have found there that all the experimental points fit very well with the new model, and that this renders the calculation he has made quite meaningless. The curves as they stand suggest, although not unequivocally, that there is a slight amount of "recovery" in early stages, which would imply a threshold but certainly at a very low level. As I have said, however, I do not deny in the article the existence of a threshold for radiation carcinogenesis but hold that experimental demonstration of such a threshold is infeasible. I think that a careful consideration of the quantitative aspects of the data and the problem of carcinogenesis will lead others to the same conclusion in this regard that I have reached.

But perhaps Berg has a different concept of threshold than I have, since he writes, "if the first cancers are not to appear until after all the animals are dead, we have a practical threshold if not a biologic one." I must confess that the distinction between a practical and a biologic threshold puzzles me. It is to be noted that normal distribution curves such as those that describe the time of appearance of tumors (see Figs. 1 and 2) are not extrapolable to zero incidence, and the probability of a tumor appearing within such a population at any given time must depend, among other things, upon the size of the population. In such case I cannot see how the failure to observe cancer in a population of, say, 1000 mice within their life span of 1 or 2 years can tell us much about a threshold, in say, the 180 million human beings in the United States with a life expectancy of three score and ten years.

HAROLD F. BLUM

Department of Biology, Princeton University, Princeton, New Jersey
and *National Cancer Institute, Bethesda, Maryland*

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9. ———, *ibid.* **11**, 463 (1950).