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Linking Chemistry to Industry

St. Louis
New York

18 MARCH 1960
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 $2 \times 10^7$ 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 inexcusable 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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