Health, has raised the possibility that stilbestrol may remain in treated meat in some changed form. He advocates banning the drug from animal feed.

Robert K. Enders and Carl G. Hartman, U.S. Department of Agriculture consultants, testified before the Delaney committee about the deleterious effects of stilbestrol and its ability to make meat retain water. Enders called the practice of using it for this purpose "an economic fraud."

The Livestock Reporter reported that cattle buyers had down-graded by as much as 5 cents a pound cattle fed with stilbestrol. These cattle were described by buyers as deformed, covered with fat, and "undesirable."

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Perception of Apparent Motion

Walter and Francis Kaess have shown [*Science* **132**, 953 (1960)] in their exemplary experiments that toads have perception of apparent motion. One could also say it this way: that experiments can be so devised that conditions of movement-perception required for the feeding of a toad can be fulfilled without the actual motion of either toad or food.

These experiments also bring additional evidence for something else. When the toad is placed on a 1-, 2-, and 3-day food deprivation schedule, it will not feed on food in front of it unless movement of food, or at least the conditions of food movement-perception, are fulfilled. Thus the drive of hunger, like other familiar drives, can be satisfied only within a distinct, particular configurational frame. As Tinbergen has shown [N. Tinbergen, *The Study of Instincts* (Oxford Univ. Press, London, 1951)], drives are not amorphous vague impulsions in living things but specific tension systems in search of specific configurations.

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Life Shortening and Production of Tumors by Strontium-90

The recent report by V. E. Archer and B. E. Carroll [*Science* **131**, 1808 (17 June 1960)] includes two figures that are intended to demonstrate that the degree of life shortening and the production of tumors increase linearly with increasing absorbed dose of radiation from strontium-90. Since the data they used were those I had published in *Science* and elsewhere, I am obliged to call attention to several features of their analysis that may influence the acceptability of their conclusions.

The basic alteration applied by Archer and Carroll in their analysis concerns time, and by this alteration they changed *injected millicuries per kilogram* to *millicurie-days per kilogram*. Their approach was in the proper direction, but they oversimplified by using average survival time, and their values would have been more accurate if they had employed the power function for retention. The necessary data and formula have been published in an Argonne National Laboratory Report by S. A. Tyler (No. 5841, p. 132, 1958).

There is no question but that a correction for the time during which the radiation dose accumulates is required for a complete evaluation of the long-term toxicity of any internal emitter. With the present state of knowledge, however, we do not know over what period of time the dose should be integrated. One major problem concerns the length of the latent period between injection and neoplastic change since any radiation received after a tumor has been induced is wasted as far as that tumor is concerned. Another concerns the relative contributions of dose-rate and total accumulated dose to the response, whether it be tumor induction or life shortening or any other effect. But this is not the place to discuss the variety of complications that stand in the way of accurately assessing the absorbed dose that is responsible for a particular response. Nor is this the place to discuss the series of studies now in progress that should help resolve these complications. Archer and Carroll state: "It is hoped that Finkel will calculate an accurate dosage for the different groups in rads." That is my hope as well. However, until this can be done, I feel that we add very little by playing with numbers. Actually, the survival data uncorrected for continuing exposure fit a linear dose-response curve just about as well, or as poorly, as Fig. 1 in Archer and Carroll's report.

What is true for the survival data, however, is not true for the osteogenic sarcoma data. The incidence of malignant bone tumors increases approximately as the square of the injected dose. Since the higher incidences are associated with shorter survival times, correction for continuing exposure makes the curve even steeper and, consequently, more nonlinear. Archer and Carroll's Fig. 2, however, presents an apparently linear relationship between tumor incidence and millicurie-days. This result was obtained by a combination of two fundamental errors.

The first error was the inclusion with the osteogenic sarcomas of a variety of

tumors, some of which have not been observed to change in frequency after Sr^{90} administration. As a result the baseline of tumor incidence was raised substantially. For example, the values for reticular tumors used by Archer and Carroll, which were the incidences observed 625 days after injection, varied in a dose-independent fashion between 25 percent and 38 percent among the control mice and those that had received up to 200 μc/kg (Archer and Carroll's 11.7 millicurie-days). On the other hand, the incidence of malignant bone tumors ranged in a dose-dependent fashion from 0 to 13 percent. Consequently, the reticular tumors masked the true relationship between osteogenic sarcomas and these lower doses.

The second error concerns the higher doses, and it involved failure to recognize the fact that, as the dose of radiation increased, the osteogenic sarcoma response approached 100 percent but could not exceed it because the unit of response was the tumor-bearing animal, although the number of tumors per animal continued to rise steeply. Therefore, there is no justification for drawing the line between the values at 18.8 millicurie-days and 29.3 millicurie-days. The terminal point might better have been the former. Saturation at 100 percent could have been avoided by using the tumor rather than the tumor-bearing animal as the statistical unit. The required data appear in Argonne National Laboratory Report No. 5841, to which Archer and Carroll referred. This, in fact, was done in part when the various tumor types were combined. If this procedure had been followed through properly, the tumor incidence in Fig. 2 would have been 2.4 per mouse at 18.8 millicurie-days and 4.4 per mouse at 29.3 millicurie-days. No manipulation of these points can produce a linear dose-response curve.

There is a growing trend in radiobiology to develop a theory and then to search for the published data that with a little treatment will support it. Other hypotheses that may equally well be satisfied by the data are no longer given any consideration. If we are to discover how ionizing radiation in general, and Sr^{90} in particular, influences a mammalian population, we should attempt to sharpen our understanding of the mechanisms involved and not simply pass over them with broad a priori assumptions and generalizations.

My original paper did not prove that the dose-response curve was not linear, or that there was a threshold. It did, however, point out that such an interpretation is entirely possible. For reasons pointed out above, the type of analysis presented by Archer and Carroll adds very little to our understanding of the subject.

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Miriam Finkel's letter correctly points out some of the defects in our knowledge of the effects of internal emitters on animals. We fully agree with her that a better understanding of the mechanisms involved is needed. When new facts are elicited, they should be checked for compatibility with all current theories. Our article supplemented that of Finkel with regard to this checking.

The first of two "fundamental errors" cited by Finkel is really a difference of opinion as to suitable analytical approaches. She rejects our grouping of several different tumors, "some of which have not been observed to change in frequency after Sr^{90} administration." We included all of the "probably malignant" tumors of the specified kinds which occurred in both control and experimental groups. If the frequency had been the same in the control as in the experimental groups, the resulting curve would not have been affected by such grouping. When more tumors of a specific type (or types) occur in the experimental group than in the controls (greater than statistical limits of randomness), it may fairly be assumed that the treatment has been instrumental in producing the extra tumors—and in changing the frequency. The average frequency of each of the tumor types used by us in our Fig. 2 is greater among

the animals to which Sr^{90} was administered than it was among the controls. Since Sr^{90} was the only known tumor-inducing agent administered, these extra tumors of varied types must then be attributed to Sr^{90}. Why then, is it not perfectly legitimate to group them together when assessing the malignant tumor-inducing activity of Sr^{90}?

The primary reason that we grouped several tumor types was that the number of mice used was too small in several of the groups to provide a sufficient number of tumors of a given type to be of statistical significance. When grouped, they appear to become meaningful, as illustrated in our Fig. 2. A secondary reason for grouping them is that once an animal develops one malignant tumor its chances of living long enough to develop a second are decreased. It is reasonable to suppose that when total malignant tumors reach a certain frequency, the relative frequency of individual types may be changed automatically. It was felt that grouping of tumor types might minimize this effect, even though it cannot be eliminated. An example of this interaction between tumor types may be seen in Finkel's work (Argonne National Laboratory Report No. 5597) in the 200, 440, and 880 μc/kg groups. As the incidence of osteogenic sarcomas rises from 18 to 73 and 91 percent, the incidence of reticular tissue tumors falls from 38 to 34 and 15 percent. One might therefore be misled if he confines his attention to a single tumor type. One might also be led to underestimate the total tumor-inducing potency of an agent if this interaction is not considered.

Finkel's example of reticular tumors purporting to illustrate a lack of change after Sr^{90} administration may be misleading. Her data show a small but definite increase of reticular tissue tumors among Sr^{90} treated animals. Among 150 control animals the frequency was 25 percent. Among the 690 Sr^{90} treated animals represented in our Fig. 2, the frequency averaged 30 percent. This increase occurred in spite of the shortened life span and in spite of the increased frequency of sarcomas among the Sr^{90} groups—both of which factors appear to decrease the observed frequency of reticular tissue tumors.

We concede that the second "fundamental error" pointed out by Finkel is a minor error, but one which has no material effect on the results. The terminal point in our Fig. 2 at 29.3 millicurie days, as Finkel suggests, is probably too low. It is low not only because of the saturated response which she details, but because of the depressing effect of a high sarcoma rate on the frequency of other tumors. The

graph in Fig. 2 is only slightly affected by omission of this point.

We agree, from a theoretical standpoint, with Finkel when she states that it might be better to use the tumor rather than the tumor-bearing animal as the statistical unit. However, we must also agree with Wollman [*J. Natl. Cancer Inst.* **16,** 198 (1955)] that this is a very difficult unit to use for the following reasons: (i) new tumors may appear over such a wide range of time intervals after treatment that the experimental animals may die from the first tumor before all potential tumors are detected; (ii) if the tumor metastasizes, it may be difficult to distinguish between a metastasis and a tumor of independent origin; and (iii) the early tumors may coalesce, resulting in an underestimate when scoring late. The first of these two objections would be especially applicable to the sarcomas, and the second would be especially applicable to the reticular tissue tumors.

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Reprint Exchange Center

All of us who consider the scientific reprint as a valuable research and teaching tool, and as a necessary part of our personal reference libraries, have experienced the frustration which accompanies the reply to a specific request indicating that the author's supply of reprints has been exhausted. At the same time, we are all largely guilty of harboring reprints which are no longer pertinent or useful. In addition, we frequently shelve, indefinitely, reprints which were never of any real interest to us and which came into our possession by means unknown or forgotten. In short, many thousands of reprints are taken out of circulation permanently every year, their purpose for existence defeated, when they should be available to those who could make serious and profitable use of them.

It would seem that a free reprint exchange center could be created with the cooperation of interested scientists. Such a center would accept the voluntary contributions of reprints from individual and institutional files, catalog them, and, in turn, make them available to other scientists in response to general or specific requests without charge.

Although I am certain that there are agencies, institutions, and individuals better equipped by virtue of experience, finances, and facilities to undertake such a program. I would, nevertheless, be happy to attempt to establish such a cen-