Somatic Effects

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THE text of that part of my discussion which may look like a sermon may be taken from a little book by Wendell Johnson, and runs to the effect that a fool is one who knows nothing but answers—while the wise man knows what the questions are (1956).

It is perhaps not generally recognized that, as a result of current scientific interest in all aspects of radiation biology, some serious questions are being asked—with respect to the effects of very small amounts of a noxious agent—which do not appear to be wholly answerable in the near future, have no true parallel in toxicology, and in a sense represent a departure from past thinking.

The present unanswerability of these questions lies in the fact that they ask, in addition to empirical data, for a basic understanding of the aging process and of the common denominator, or denominators, of the carcinogenic equation, which we simply do not have and must develop techniques and modes of thought to answer.

The theoretical approach to these things is being tried, and gives hope that a true theoretical branch of biology may be within our grasp. In contrast to present day theoretical physics, it has at present a Newtonian simplicity of fundamental concept. Its failure to come more rapidly to fruition has a number of roots: the essential, and nearly indivisible, complexity and inter-

* Work performed under the auspices of the U. S. Atomic Energy Commission.

action of many processes; the inaccessibility of many semirefined theoretical treatments to empirical testing; and perhaps not least, the reluctance of the biologist—and of his sponsors—to embark on costly and protracted experimentation for the determination of scanty but decisive data.

Geneticists have perhaps been fortunate in that their basic material exists in the form of single cells containing single molecular determining factors which have only a small measure of interaction, and in that the general rules can be studied in small organisms of which enormous numbers can be reared to produce data of high statistical refinement. We are witnessing, at the present time, a movement in the direction of testing the beautifully simple concepts of genetic change against the much greater complexity and adjustability of somatic changes in multicellular organisms. It is most important at this time that points of view be closely and understandingly shared between biologists in such fields as physiology, pathology, and genetics.

Much of the present confusion about somatic effects of low-level irradiation has a natural historical basis. The mere fact that a tolerable or permissible dose has been asked for has suggested that there may or ought to be a real threshold for damaging effects; indeed, this has been generally assumed in toxicology as a whole. The moment it is suggested that the threshold may not exist, we find ourselves in a totally new situation. We must now make our judgments as to the propriety of an exposure on a basis of calculated risk, by using an equation many of whose constants are unknown, and even (as I hope to show) whose form is not established. In developing this, it will appear that we are forced to formulate similar questions about many of the other hazards of everyday life.

The basic question in regard to somatic effects is the extent to which we are concerned with hazards which, if they exist, cannot possibly be demonstrated to exist because they are relatively so small.

This is not exactly an analog of the uncertainty principle in

physics. The point here is not necessarily that the act of observation disturbs the thing being observed, so much as that other factors which we have not been able to control create a noise above which the phenomenon cannot be heard. The practical result is in analogy, then, to what is taking place in physics: we now ask ourselves questions which necessitate instruments of a magnitude or experiments of an extent not formerly considered in the armamentarium; also a more careful use of the theoretical approach (and I would emphasize that this is opposed to speculative or interpretive thinking). We must have better data, more kinds of data, and a sounder appreciation of what the data may really mean.

Here is where the practical man—the doctor or health physicist—tends to clash with the theoretical man. The practical man is asked and expected to give an answer before adequate data are present. The adjectives that are to modify this answer are such as "safe," "permissible," or "tolerable," and are always such as to satisfy a human, social, or ethical requirement. This is an unpredictable and sometimes rapidly shifting context and is colored by man's basic insecurities and anxieties. It is and must be unscientific, the more so when it gets into the area of low-dose effects, where at once one becomes confused as to whether the question is whether anything happens, whether anything detectable happens, or whether anything "intolerable" happens.

It may not be surprising that recent questioning of the low-dose somatic radiation effects has come largely from geneticists. This is not so much because genetics gives us a fairly reasonable conviction that certain effects follow a straight line, as that it is in the field of genetics that we find it is possible for certain things not to be detectable, yet to have serious results. Thus, although immediate genetic effects at Hiroshima and Nagasaki were undetectable or nearly so, we have some reason to believe that the sort of recessive mutations produced there might, if produced on a sufficiently large scale, result eventually in very serious consequences to mankind as a whole. This aspect of the dominant-

recessive relationship in genetics, which protects us from seeing many effects immediately, must indeed lead us to a very conservative approach to the problems to which such a situation may apply. In somatic effects, this applies particularly to those things which do not happen immediately, or which happen to a very small part of the population: effects on longevity, or tumors.

I will limit my discussion of "low-dose" effects to the effects occurring at a level where certainty is at a minimum, to try to explain why we know so little, and possibly what might be done about it.

In order to make predictions as to what rare or slight effects may occur within this area of uncertainty, we must have some idea as to what type of quantitative relation exists between dose and effect. This implies that the effect is one that can be given an unequivocal number, like the average or median time of death of a group of animals, or the proportional number developing tumors, or (since these observations get into an inconvenient number of dimensions and thus out of hand) the *rates* at which these things are estimated to occur.

Having established such a simple, quantitative measure of the effect, we test it against dose in order to see what the relation is at levels where the effect can be validly measured. We may then hope to extrapolate this into the unknown area empirically or from our rationalization as to what sort of function describes what we see. Certain likely relationships would be as follows:

1. There is a true threshold, a dose below which no effect occurs. This is rationalized through assuming that a certain degree of general malfunction or disorderliness must be produced before the effect can occur. As a special deviation from this there may be a relative threshold, above which the effect is very much more likely to occur. Such responses are generally familiar to physiologists and pharmacologists.

2. The effect is essentially a linear one, each equal increment in dose yielding an equal increment in response. Its rationalization is epitomized by the word "hit"—each hit produces one such

response, or perhaps more strictly, a given probability of a visible response. This is familiar to the geneticist as the mechanism of the point mutation. While the genetic fact has not actually been established by experiment in the low-dose range (below 25 r, to be exact), it is amply justified by much else that we know about the nature of mutations, as well as by the additional fact that in many cases the *rate* at which the dose is administered appears to have no relation to the response.

3. The response is a curvilinear one in which it accelerates with increasing dose. This will, in general effect, be intermediate between the first two. It may be rationalized in ways too many to enumerate here. In a simple instance, two hits may be required to occur, perhaps within certain limits of space and time; in this case the effect rises as the square of the dose and is likely to decline where the dose rate is slow. If we measure death rate against the lapse of time—we call this "aging"—we find, after some obvious extraneous factors are allowed out, a rather strictly exponential relation. Something like this is also seen where the rate of development of tumors is measured against time: the well-known increasing susceptibility of the aged to tumors. Here, however, in spite of the great mass of available data, we cannot be certain whether the relation is best described as exponential or as a power function, since we are perforce looking at a small part of the projected curve, and we do not know enough about tumor genesis to construct a very reliable working hypothesis.

4. To make the story a little less incomplete, I will include the possibility of a reverse curve, one in which the effect becomes saturated. This occurs, of course, at high radiation doses where hits become so numerous that many are wasted. To take quite a different example, you see something of the sort in allergic response, where a single pollen grain may do a greater proportion of the damage than several will do—also, a killed cell cannot respond in any case. The fact that low radiation dosages are always with us suggests that small increments are not likely to act in this way; however, while we must discard this mechanism

from further discussion owing to lack of evidence, it should not be forgotten.

Since linear theories of radiation effects on aging and on tumors have had prominence recently, I shall base the following discussion on them. Certainly, they afford us the most conservative reasonable approach to the practical problems of protection, even as they put the decision-maker squarely on the spot of facing up to a tremendously complicated mass of ethical, social, and scientific considerations.

The two serious somatic effects of radiation at moderate levels, which, it is thought, might have a linear relation to dose even at low levels, are the induction of neoplasms and shortening of the life span. It has been suggested that both of these phenomena might be results of mutations of somatic cells, quite analogous to genetic mutations in germinal cells.

As regards induction of cancer and allied states, this is a very tempting hypothesis, since it can explain in a simple way the appearance *de novo,* as it were, of a new type of cell bearing some resemblance to those of the parent tissue, but with the new characteristic of proliferating with "autonomy" or indifference to the ill-understood rules determining proper behavior of tissue cells. The somatic mutation as the origin of cancer was suggested as long ago as 1919 by R. C. Whitman; it was early appreciated by H. J. Muller, who, in his classical paper on artificial transmutation of the gene (1928) suggested that x-ray cancer might have a mutational basis. It has been dealt with from diverse points of view by such thoughtful investigators as L. S. Strong, J. C. Mottram, Francis Carter Wood and W. F. Dunning, and more recent students of ascites tumors and isolated cell cultures. It has been given consideration by most of those who have gained fairly precise quantitative data on carcinogenic responses. Attempts have been made, as often as not unsuccessful, to correlate the carcinogenicity with the mutagenicity of various agents.

Before going into experimental data, I should like to mention, on a purely theoretical basis, some thoughts previously developed

which make the pristine somatic mutation theory a little difficult to manage. Let me introduce my proposition by pointing out some marked similarities and differences between mice and men. The two species have remarkably similar tumor incidences, within their respective life spans, as indicated by the fact that in well-tended colonies of each, the proportions dying of the various types of tumors is constant within less than an order of magnitude. Their responses to radiation, in the form of cancer, are also quite comparable. Yet the mouse lives between $1/30$ and $1/40$ as long as man, and has no more than about $1/1000$ as many cells of any given type. If cancer is due to a single somatic mutation (which implies that a single hit on any one of a vast number of cells may determine a unit response), we are forced to conclude that man's cells are less susceptible to this sort of deleterious response by something like a factor of 100,000. If we insert a theoretical correction factor that the two species have an equivalent mutation rate *per generation* rather than *per year*, we are still off by a factor of at least 1000. This is illustrated in Table I with constants that have been assumed on the basis of estimates from various experimental data.

TABLE I

Estimation of relative mutation rates for leukemia based on somatic point-mutation theory

	Man	Mouse
Number of proliferating myeloid cells	10^{11}	10^{7}
Leukemia rate per roentgen		
per year	10^{-6}	10^{-4}
total	10^{-5}	10^{-4}
Cell mutation rate		
per year	10^{-17}	10^{-11}
total	10^{-16}	10^{-11}

Other possible explanations may be given to cover up this discrepancy between the species. One is that the carcinogenic response is a power function (just as spontaneous cancer may well be a power function of time) implying that a number of separate random events have to take place. If this required number were, say, two more in man than in the mouse, this would explain the difference but would give a very curved line relating dose to effect. The other—that the tumor prefers to arise in an aging or otherwise disorganized tissue—would agree with the parallelism of age and cancer susceptibility and would suggest a rationale for some sort of near threshold.

Support for the latter view is gained from the fact that many tumors are seen experimentally to arise through mechanisms that are quite indirect; thus, lymphatic leukemia and like tumors, which are induced very readily in mice by x rays, are prevented by administering bone marrow cells or by shielding a small part of the body, measures which alleviate the overall damage to the blood-forming system. The idea of arresting the process at some stage before the sick tissue develops irreversibly into a tumor is intriguing many students of the disease at the present time.

It might further be mentioned that few, if any, direct experiments on carcinogenic effects of any agents have shown or even clearly suggested a linear relation to dose. The studies of Upton and colleagues (1954) on leukemia in irradiated mice show that it is clearly not so in one form of leukemia, but may be (based on very small numbers) in another. It is noted from the data shown, that one control group showed no myeloid leukemias at all—something which emphasizes the wanton variability of such biological data.

Another theoretical objection to the linear theory is that dose rate has very important influence. The data on beta ray cancer of the skin obtained some years ago at Oak Ridge (Raper, 1947, 1951) show very clearly that by protracting the dose, an enormously larger dose is required to produce tumors. In ultraviolet light exposures, on the other hand (where a mutation might be

presumed to exist), Blum (1950) has found it necessary to expose his animals repeatedly to get any tumors at all; and then it is the induction time, rather than the number of tumors, that depends on dose.

To pass now to the human evidence on leukemia production by radiation, may I make it clear that large doses of radiation are well known to be leukemogenic; in fact, the leukemia rate in physicians practicing radiology is several times higher than in other physicians. In this case, we do not know what sort of average dose radiologists as a whole have received, let alone anything about individual dosages (Warren, 1956).

Studies have been made of leukemia following irradiation of the thymus in infancy (Simpson, Hempelmann, and Fuller, 1955). Since the purpose of the radiation was to produce an involution of the thymus, this has no direct bearing, probably, on the low-dose question.

Two studies offer an opportunity to look at the dose-effect relationship. The most detailed is the study of Court-Brown and Doll (1957) of leukemia in men previously irradiated over the spine for spondylitis. Although they have no cases following really low doses, the dosage spread is great enough to allow a curve to be drawn. Plotting the incidences against either the total-body or the spinal dose, we see a markedly curved relationship. By excluding a number of cases who received x ray extraspinally in addition to spinally, however, they find a relationship which can be described as linear. It seems here that the data may be given various interpretations. The authors favor a linear relation, but only as a "working hypothesis."

Leukemias occurring in various areas of Hiroshima and Nagasaki have shown a marked increase in those persons exposed close to the hypocenter (Wald, 1958). Unfortunately, the data so far available have been given in broad, 500-meter sectors, where the dosage range is very large. The critical area is that from 1500–2000 meters, where nine cases occurred. Figure 1 shows the extremely great variation in dose within this sector. It is noted that

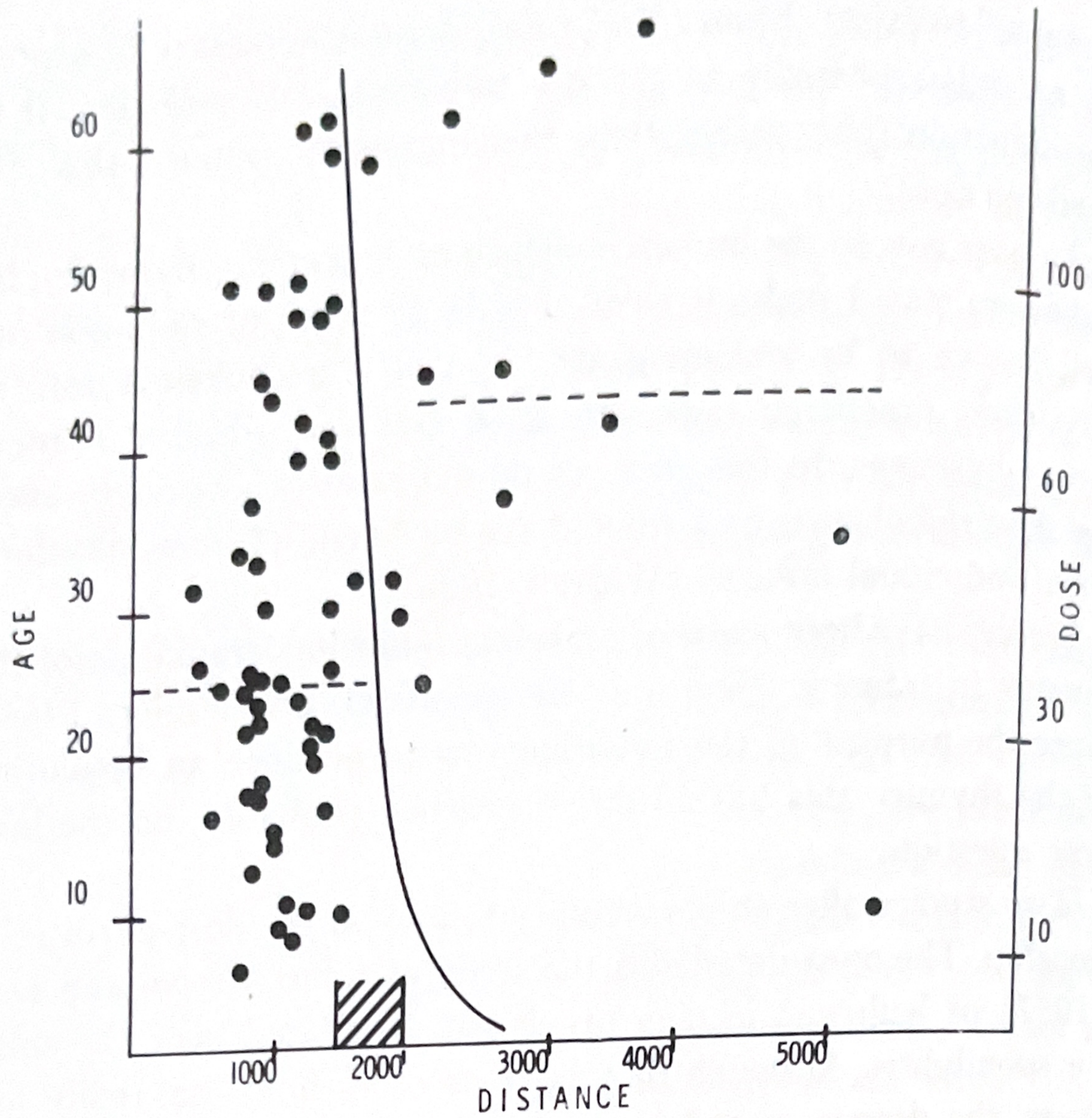

FIG. 1. Distribution of cases of leukemia occurring in Hiroshima and Nagasaki (solid circles) by age and distance from the hypocenter; and relation of radiation dose (rads) to distance in meters (continuous line). (Based on preliminary data.)

the ages at which leukemia occurs are lower in the areas where radiation is an important factor. It is also found that a very high proportion of the leukemia cases in this area had reported initial severe radiation complaints, and this suggests that perhaps this group received higher doses than was usual in the area.

A study that gives a great deal of promise of important information on low-dose effects is that of Dr. Alice Stewart (1956), who is in the process of completing a survey of all children under 10 having leukemia and cancer in England and Wales during a 3-year period. Preliminary reports indicate that antenatal radiog-

raphy (presumably mostly pelvimetric measurement by x ray, practiced on a little less than 10% of cases) is followed by an increase in the probability of developing childhood leukemia or cancer. Although the increment is a small one, so are the radiation dosages presumed to have been encountered. These data provide a very useful addition to our small body of established information on low dosage effects.

Much of this information is summarized in Fig. 2, which is a

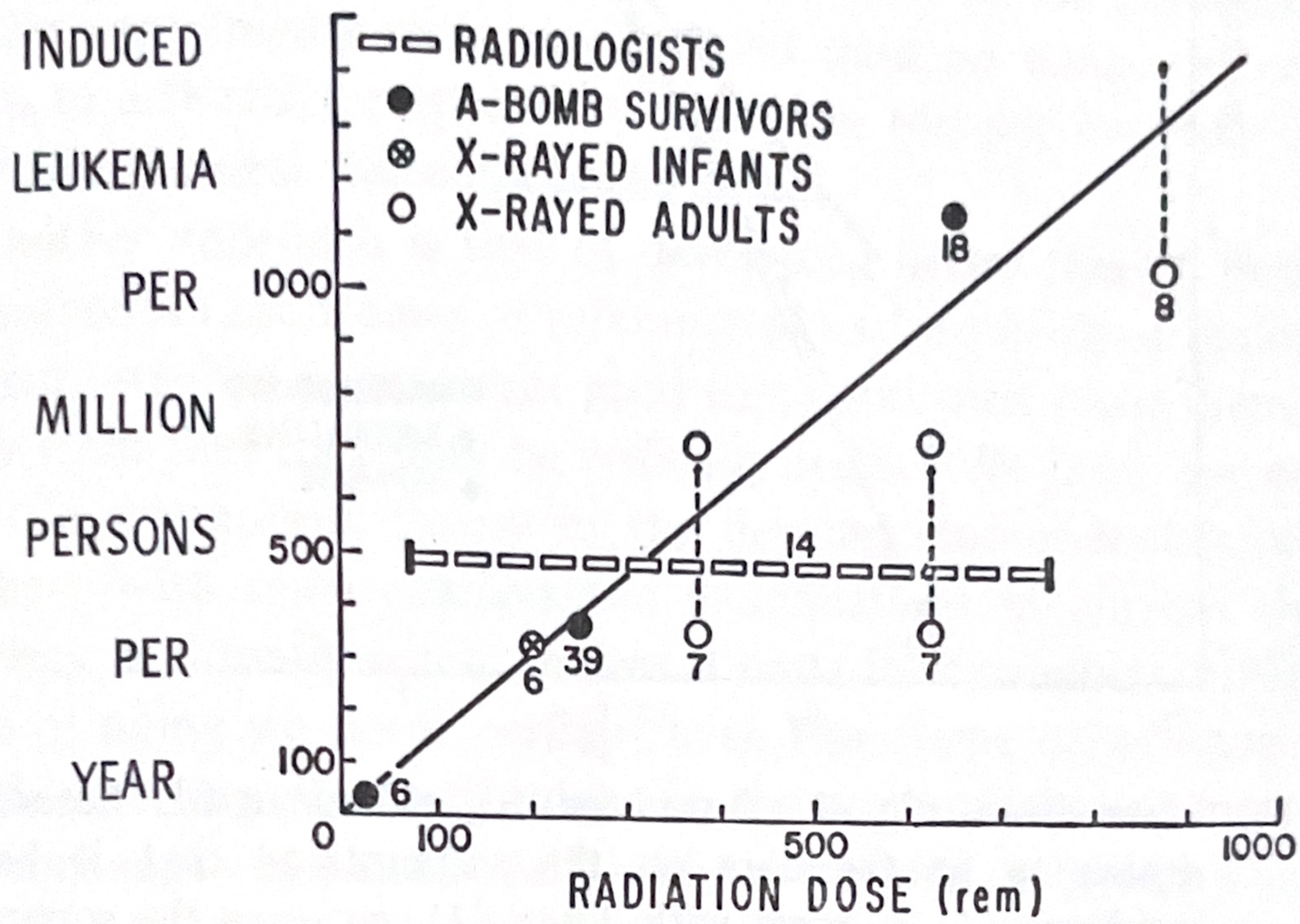

FIG. 2. Relation between annual incidence of induced human leukemia and radiation dose. (From Lewis, *op. cit.*, 1957.)

graph based on one made by E. B. Lewis (1957), in which it was shown that in the range 200–1000 r the data on leukemia induction lie suggestively on a straight line. To show most readily the conformity of alternative hypotheses the data have been transformed to a logarithmic scale and additional lines have been drawn, one hypothecating a threshold at 50 r and the other a square-of-dose relation (Fig. 3). A few corrections of the original data as used by Lewis have been made on the basis of subsequent information.

Of course, it is not a new discovery that various lines may be

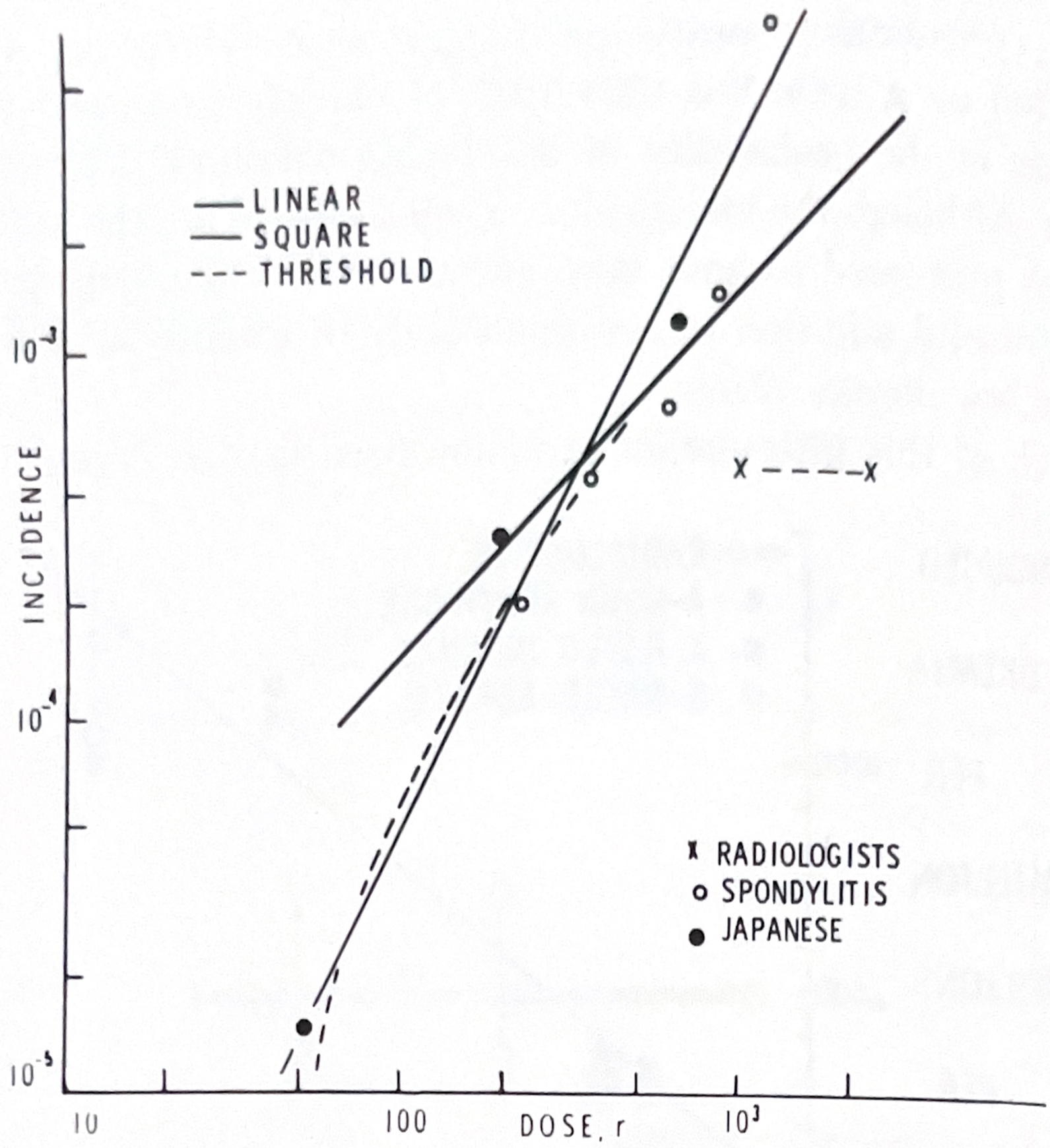

FIG. 3. Data from Fig. 2 plotted on logarithmic grid. Lines are drawn to fit the data on the assumptions that leukemia incidence (1) is linear with dose; (2) varies as the square of the dose; (3) is linear with dose above a 50-rad threshold.

drawn through a few uncertain points. I think, however, that we are in a state where we may profit most by having a number of alternative hypotheses to test. I very much fear that it has been under the pressure of the practical that many of us who ought to know better—and certainly I have been among them—have tended to cling to a satisfactory enough formula and have then forgotten to think the whole problem through. I think that scholarship in science is too precious a thing to abandon in the rush of events in this way.

For lack of time, I will not say a great deal about longevity except to point out that here is a rather similar situation, in that

we are looking at very small differences caused by small amounts of radiation and trying to make inferences as to what will happen as a result of amounts even smaller: such small amounts have, in a number of "classical" experiments, produced rather surprising results that are not in concert with theory. We have here a great deal to worry about.

Work of this sort is inordinately expensive if we are to approach the matter directly. It has already cost a great deal (in the coin of the biologist, although not in that of the physicist) to do the experiments that have yielded data on mouse longevity down to a positive response at about one rad per day, say 3000 times the natural radiation background.

Another approach is that of developing better theory, perhaps considered in the frames of reference of various fields of biological science—trying to construct good ideas and then mold them into such form that they may be critically tested. We have, for example, the mutational theory of the development of leukemia and cancer; with some changes and modifications of current theory we may eventually reach a rational basis for extrapolation. In the case of aging we know perhaps even less. Some of us have been thinking that aging itself might be the accumulation of more and more changes in somatic cells—like mutations or broken chromosomes—up to the point where the cells lose viability. This is still a complicated problem, for example if we consider that the deleterious effect on the life span that is increasingly seen is the deposition of fatty material in the vascular system. Changes in collagen, too, do not seem to be related to mutational mechanisms, although the process could be in some way similar. We must proceed carefully and try to make sense in as careful, sound, and imaginative way as possibly we can.

Much material still is to be gleaned from studies of large human populations. We know, for example, that there is great variation from place to place in the general radiation background and in the type of background (as in radioactive skeletal deposits). In these matters the "noise" of variable vital statistical data get

in our way. This introduces a whole host of problems for the future, especially since in the future, judging from recent interest in low-level radiation, we are bound to become increasingly concerned with all sorts of slight, but perhaps critical, noxious stimuli.

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