Dose, Effect Severity, and Imparted Energy in Assessing Biological Effects

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Abstract. Because of the widespread efforts in cancer radioepidemiological studies to attach a value of absorbed dose to each exposed individual, the notion seems to have become prevalent that dose plays an essential role in the medical determination of the diagnosis and prognosis of the individual. This view is enhanced by the fact that, while the present quantities and units for radiological physics were developed in the context of the acute effects of large exposures to radiation, e.g., in radiotherapy where they still apply well, these same quantities and units have been used, without modification, to apply to cancer radioepidemiology in the context of low level irradiation. A principle purpose of the present communication is to show that, in medicine, dose plays a limited role even in the deterministic application of therapeutic agents, and that diagnosis and estimates of prognosis in medicine are based, not on dose, but on the severity of effect on, or damage to the organ or organs involved in a particular medical condition. Thus it is "going backward" to view estimates of the severity of effect, e.g., the fraction of cells with abnormalities, or killed, as a "biological dosimeter," rather than as a quantitative estimate of the severity of effect.

The use of biological indicators is of maximum value in noncancerous disease or injury in which the severity of an effect causative for organ failure and a consequent quantal, e.g., a lethal response in the individual, can be measured with increasing accuracy by modern medical techniques. A common scale for the measurement of almost any type of effect on any organ is 0.0 to 1.0 (0.0 to 100%), with 100% meaning complete functional failure and certain death if the organ is vital. The opposite extreme is cancer, in which, particularly with low level irradiation, there is no detectable effect directly relevant to cancer causation, the severity of which will provide an individualized, medical-type diagnosis or prognosis. However, this situation is beginning to change with the rapid development of molecular biology and genic change profiles that may make individualized prognostic estimates possible. However, because neither radiation nor other carcinogens leave "markers," the impact of these changes with respect to low level irradiation must be left open.

Introduction

Before biological effects and responses of any kind can be assessed objectively, it is necessary to review and discuss the various levels of biological organization at which these can occur. In Figure 1 is shown a number of levels, most of which are both interlocking and recursive. This means that most of the levels can be regarded as a potentially responding system, composed of potentially damaged elements located one or more levels lower on the scale. However, it also means that the identical level can be regarded as a population of elements, severe damage to which may cause a quantal response in their parent system located one or more levels higher up on the scale.

In the past, when the dose to a system has been unknown or only poorly known, an observable biological endpoint such as chromosome aberrations in cells, has been used frequently as a "biological dosimeter." In other words, because the number of cells with a given aberration determined in an individual is a function of dose, a given level of response can be used to obtain an estimate of the dose received. The implication is that it is the dose to the individual

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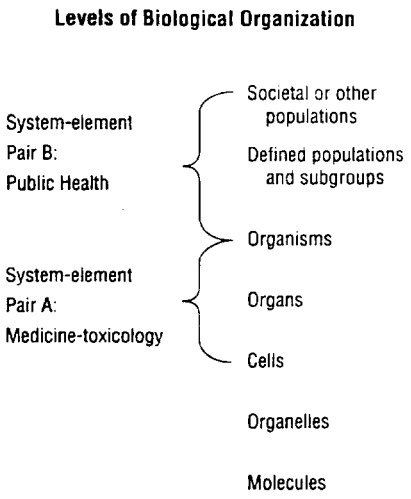

Fig. 1. Levels of biological organization, which are both interlocking and recursive. Thus any given level, e.g., organ-organism can at once serve as a system, the vital elements of which are cells (system-element Pair A), and the elements of a larger system, a defined human population (system-element Pair B).

that must be known for proper diagnosis and prognosis. In what follows, it is the intent to show that this approach is the reverse of the historical and normal course of events in medicine, i.e., it is the severity of organ effect that is used ultimately for diagnosis and prognosis. This holds even if the dose of an offending agent has played a causal role in the abnormal condition requiring medical attention, and often even when therapy has been started with an initial dose of a medicinal agent.

To elaborate, the fraction of organ cells killed or the number of chromosome aberrations in cells can be indicators of the severity of biological effect in the organ. Under proper conditions, one can then use this information as an indicator of the likelihood that the biological system of interest will respond quantally. Even if a dose of a causative offending agent has been estimated, there is no need to go back to that dose for purposes of diagnosis or prognosis. However, the severity of effect has varying degrees of usefulness, depending upon how closely the effect observed can be causally related to the probability of a quantal response of the organ system. Thus an effort will be made to specify the conditions under which a biological indicator can be directly relevant.

As an initial example, only early acute effects from and responses to radiation exposure will be used e.g., early mortality in the mammal. Here biological indicators must be and are used extensively and with a high degree of precision. Late effects, particularly cancer where the approach becomes more problematical, will then be discussed.

The Two Constituent Curves

To illustrate the normal role of severity of organ effect in diagnostic medicine, it is first shown that the usual acute dose mortality response curve, e.g., for x- or gamma rays delivered to the whole body, can be broken down into two separate curves. For the usual curve (Fig. 2), acute mortality in, e.g., the mouse, the fraction of animals responding quantally (dying), is plotted against the absorbed dose to obtain the usual threshold, sigmoid function. The first derivative of this curve yields a gaussian-type distribution, that is often associated with the distribution of sensitivities of the individual animals [1]. It is now well accepted that the usual 30 day mortality is due to complications resulting from depletion of the stem cell population in the bone marrow of the animal, i.e., with reference to Figure 1, the bone marrow is the system of interest, the relevant elements of which are the stem cells (system-element pair A, in Fig. 1).

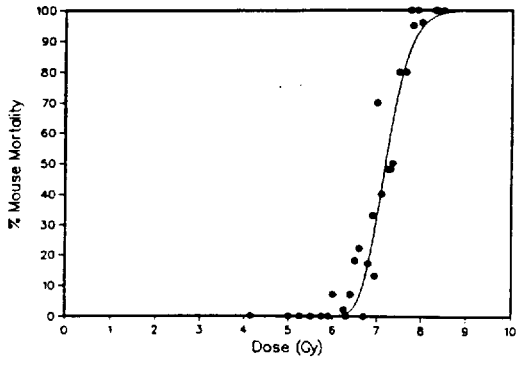

Fig. 2. A conventional dose-quantal response function, for which the (fractional) number of animals responding lethally is plotted against the dose of the agent, radiation energy (250 kVp x-rays). These data were derived from mice of the CBA/Ca (BNL) strain.

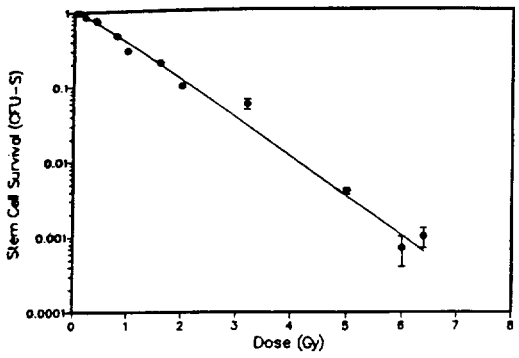

Fig. 3. A conventional plot for the log of the fraction of surviving colony-forming units-spleen (CFU-S) (hematopoietic stem cells) as a function of dose. The fitted function intersects the ordinate at a value somewhat above unity indicating that the curve may have a small shoulder.

The first constituent function of the dose-response curve in Figure 2 is shown in Figure 3. This is simply a "dose-effect" curve, for stem cell survival, obtained by using the *Till* and *McCullough* spleen colony assay. The curve represents composite data obtained over the course of years by the hematology group in the Medical Department at Brookhaven. Of the many such curves that have been obtained with photons, most appear to have no "shoulder." However, occasionally a small shoulder may appear to be present. The function is dotted from about 6 Gy on because of technical difficulties associated with having to inject large numbers of bone marrow cells in order to detect the few remaining viable stem cells.

In Figure 4, and with reference first to the left ordinate only, one sees ("cell survival" curve) the same function plotted in Figure 3, but now on arithmetic rather than semi-logarithmic coordinates. However, also shown is the inverse of this curve, representing the severity of effect on the relevant organ, the bone marrow. When the fraction of the remaining stem cells becomes quite low, on the order of less than 1% (meaning that the effect on the relevant organ, the bone marrow, is severe indeed), the more sensitive animals begin to die, forming the initial part of the mortality response curve indicated on the right ordinate.

It is then obvious that the mortality rate among the cellular elements of the organ system can be used as a "biological indicator," which

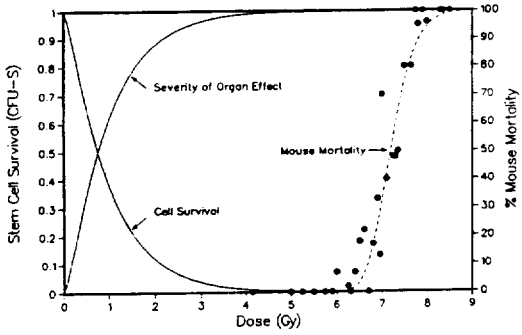

Fig. 4. Plot showing the relationships among the curves for stem cell survival, severity of organ effect and mouse mortality rate, all as a function of dose.

permits one to obtain a quantitative measure of the severity of effect on the parent organ system. The results of thus using severity of effect as the independent variable is shown in Figure 5. Note that the scale for severity of effect is simply the fraction (or percentage) of stem cells killed, which must of course saturate at 1.0 (100%). The resulting curve is extraordinarily steep; however, this is merely a matter of scaling. If one expands the scale (Fig. 6), the S-shaped curve is regained.

It is then also obvious that the severity of effect can be used as the independent variable, in terms of which the mortality rate of the animals may be described and thus predicted. It becomes clear that, if one does have a quantitative

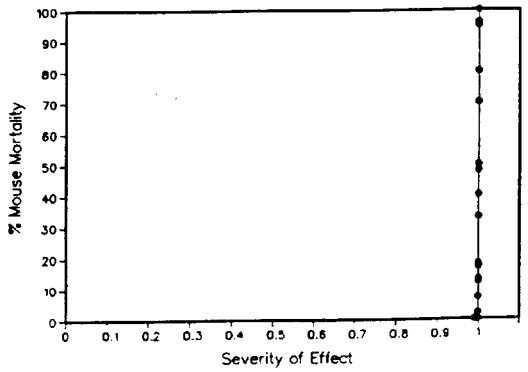

Fig. 5. The second constituent curve, for mouse mortality as a function of the severity of effect on the bone marrow. Note that the line is indistinguishable from linear, but does deviate slightly from the vertical.

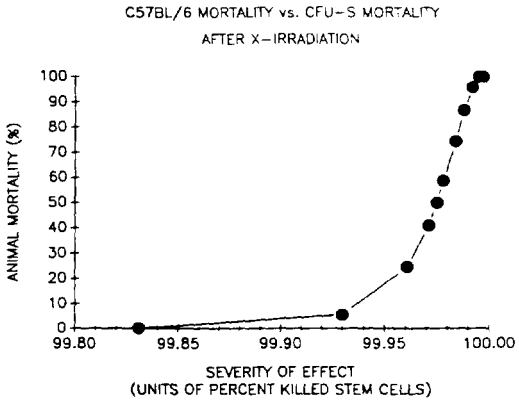

Fig. 6. The same data shown in Figure 5, but plotted on an expanded scale to show that the steepness of the curve in Figure 5 is due only to scaling and not a decrease in the variance.

measure of the severity of a relevant, causal effect on the population of elements, the fate of the entire organ-organism system can be described and predicted: dose need play no role at all.

The above separation of the usual mortality response curve into two constituent curves serves to illustrate several points. Although the dose response curve in Figure 1 is frequently used in medicine and veterinary medicine, and in their subdisciplines of pharmacology and toxicology, it is in a therapeutic mode only, and not for diagnosis. For example, in medicine, when a patient is first seen medically, the cause of the patient's complaint, or indeed what the offending agent may be, is usually unknown or poorly known. Thus no dose is involved. This is true even in the case of accidental poisonings. Here the physician may ask for an estimate of the amount of offending agent that was received by the patient; however any estimates given are taken as being extremely unreliable, and thus of little aid in assessing the gravity of the situation. Thus they are largely or entirely ignored.

The physician immediately begins with a history, physical examination and laboratory procedures to determine what offending agent, if any, is involved, which organ or organs is most likely damaged, and the severity of effect on those organs. It is on the basis of these findings alone, i.e., the severity of the effect, that the physician comes to a tentative, and then increasingly firm decision as to which organ or organs are most affected, and the severity of damage. It is upon this basis that diagnosis, prognosis, and the type and extent of therapy is determined. Again, dose plays no role at all, until the severity of effect is determined and medications or other corrective measures are under consideration.

As a specific example, one may take coronary heart disease and the degree to which a given segment of a coronary vessel has been occluded. Here the severity of effect is measured on a scale of 0 to 1 to indicate the fractional (percent) amount of narrowing of the lumen.

A second example may be more relevant. In 1954, following the detonation of a large atomic weapon, a number of Marshall Islanders were exposed to large doses of external penetrating gamma rays, as well as internal emitters, principally radioactive isotopes of iodine [2]. A team of principally naval physicians, including *Drs. E. P. Cronkite, V. P. Bond,* and *R. A. Conard,* was assembled to determine the medical condition of those dosed and to take actions necessary relative to these exposures. It was realized by the medical team that there might well be estimates of dose provided on arrival in the Marshall Islands. Considerable discussion took place in the aircraft on the way out to the Marshall Islands, with respect to what, if any, use should be made of these estimates. The agreement was unanimous that, although such estimates would be welcome, they would play a minimal if any role in definitive action taken with respect to the care of the patients. Instead, all medical and laboratory studies thought to be relevant and possible would be done. Any definitive action with respect to prognosis and care would be made on the basis of the severity of the effect found in any organ, whether the severity was that expected from the dose estimates.

It then becomes obvious what the criteria for a biological indicator must be, for it to be of maximum use in diagnosis and prognosis. Clearly the indicator must be largely if not entirely causative of whatever degree of organ failure is present. Also, the function for the severity of effect versus quantal response of the system must be monotonic (usually S-shaped), and it must saturate at 1.0 (i.e., 100% severity means total failure of the organ, and thus, if the organ is vital, death of the patient). To the degree that the indicator of biological effects strays from these criteria, the less useful it is for prognosis and therapy.

The advantages of using the biological indicator, rather than an estimated dose of the offending agent, if known, are substantial. First, one has direct information on the "proximate" cause of organ function impairment and its severity, which permits greater confidence with respect to estimating prognosis and prescribing corrective measures. Also, to a large degree, the biological indicator is independent of the exact nature of the agent that may have caused the affect of a given severity, the quality of the radiation (if that is the offending agent), and the time rate at which the offending agent was delivered. All that the organ system "cares about" so to speak, is the degree of damage that it has sustained, and it matters little exactly what circumstances led to the extant biomedical condition.

The above discussion indicates why a great deal of effort has been and is going into improving methods of indicating the severity of effect, whatever the offending agent may be, for virtually every organ system in the body. The efforts involve biochemistry, molecular biology, physiology, immunology and a number of sophisticated instruments including SPECT, PETT, and MRI. It is only in radiotherapy, in which radiation is used as the therapeutic agent after other means have been used to make the diagnosis and estimate the prognosis, that dose is used. This serves to reinforce the thesis that dose at best plays only an initial and tentative role, certainly in the process of diagnosis and medical evaluation, and even in therapy.

Although bone marrow damage was used above as example of the use of severity of organ effect, the principle holds for any noncancerous disease or injury, be it acute, subacute or chronic. The scale is always 0.0 to 1.0 (0.0% to 100%). It represents the quantification of a "biological indicator."

Biological Indicators for Cancer?

The physician can, of course, usually diagnose a cancer that has developed to the point of being detectable, and can take various measures to diagnose the precise type of cancer, the degree to which it has extended or metastasized, and thus the prognosis with different types of therapy. However, at least until very recently (see below), there have been no biological markers of any kind which permits the physician (or anyone else), in the absence of an overt diagnosable cancer, to say whether a given individual will actually develop a cancer that may well be lethal. This is true even if it is known that the patient has been exposed to radiation or a chemical carcinogen, and has sustained detectable damage. Thus, all that a physician can do after examining the patient carefully and finding no overt cancer, is to so state (occasionally, some "precancerous" lesions, of varying prognostic value, may be detected by biopsy).

Furthermore, even should that patient later develop a malignancy, there are no findings which would permit the physician to say that the particular tumor developed from exposure to any specific carcinogenic agent. Cancers leave no "marker" indicating what particular carcinogen was causative. Also, the baseline or "normal" incidence of cancer is quite high, i.e., some 1 out of 5 deaths in the United States is from cancer, and some one third of all persons will have experienced cancer in their lifetime, even though they may die of other causes. Thus, it is not possible to deal with cancer in the same cause-effect fashion outlined above, which is so useful for essentially all other diseases.

It is for the above reasons that the occurrence of cancer must be treated as a public health and not a medical problem. Here epidemiological methods are used to determine whether there is a statistically significant increase in the number of individuals with cancer in a carcinogen-exposed population, as compared to that in a carefully matched population that has not been so exposed.

It has been determined that essentially all human cancers studied are monoclonal, and thus single cell in origin. Thus any given cancer can be regarded as simply a marker for a cell that has been damaged genetically, so as to cause it to become carcinogenic and still capable of forming a clone of like cells that will become manifest as an overt cancer. Thus, with respect to studying mechanisms of carcinogenesis, it is necessary to do molecular biology and related studies at the subcellular level to see which gene changes may be involved in the cause of a particular kind of cancer. Thus it is possible that tests can be devised that would permit a physician to tell an individual patient that he or she has an increased probability of developing a cancer of a specific type. In some cases, exact probabilities may be determinable.

However, few successes have been achieved to date, and these not with radiation-exposure associated diseases. A notable exception is retinoblastoma, which requires two gene changes of which one may be inherited. Thus, finding one or both of these genes permits one to say that the patient has a definitely increased probability of developing the disease, or already has it. Similar findings may become available with respect to other malignancies, e.g., breast cancer in women. Although it is beyond the scope of this paper to deal with the progress that is being made in this area (see other papers in this symposium), the approach of course has the potential of completely altering the situation with respect to being able to provide an individual-specific (i.e., medical) severity of effect diagnostic and prognostic probability.

An added problem exists with respect to the causative agent, be it radiation or otherwise. With cancers and radiation, the criterion for radiation causation has been the appearance of the disease, e.g., a given form of cancer, in excess numbers among the atomic bomb survivors. What criteria for an agent being causative or contributory is to be used in general for diseases other than cancer and agents other than radiation?

As noted above, markers such as chromosomal abnormalities have been used to give some indication of the dose of radiation received by individuals, and in the population. However, there has been little correlation between the type and number of chromosomal aberrations in any given individual, and the probability of that individual developing cancer.

In the context of the atomic bomb survivors, both the incidence of radiation attributable cancers and persistent chromosomal changes such as reciprocal translocations have been studied (*T. Straume*, personal communication). In Figure 7 is shown a plot of both the excess incidence of reciprocal translocations in bone marrow cells and the incidence of leukemia, as a function of the estimated DS86 dose. One can see that, although the relationship is initially curvilinear, the chromosomal aberration incidence tracks very closely the estimated dose. Thus, as expected (Fig. 8), the incidence of cancer (shown for solid tumors only), is a linear function of the "severity of effect" as indicated by the number of reciprocal translocations.

This approach is useful, because it does have the advantages noted above in connection with

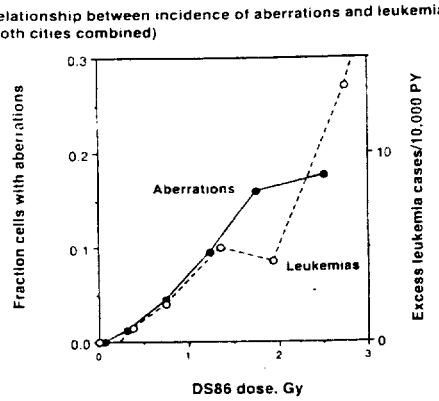

Fig. 7. Plot showing how well both the fraction of cells with chromosomal aberrations and the excess leukemia incidence track the dose to the atomic bomb survivors, particularly in the dose region up to about 1.5 Gy.

noncancer diseases, i.e., the relationship is essentially independent of LET, dose rate and shape of the original dose-response curve. However, this use of "biological markers" cannot in any way be compared to their high precision use, described above, with noncancer disease. The principal reason is that, while chromosome aberrations are due to intracellular DNA changes, and while their increase may well be proportional to whatever gene change or changes may be directly causative with respect to a given cancer, neither the fraction of cells with at least one observable chromosomal aberration, nor the total

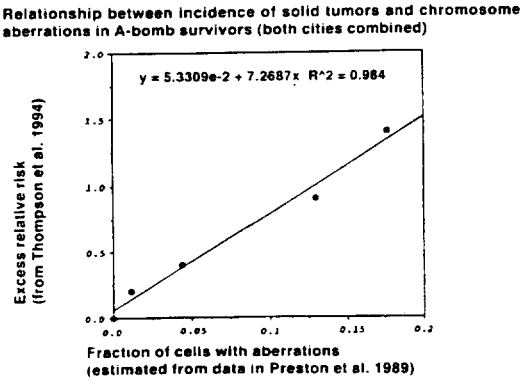

Fig. 8. Plot showing the linear relationship between the fraction of cells with chromosomal aberrations and the excess relative risk of solid tumors.

number of aberrations per exposed cell, is a measure of the severity of effect that has prognostic value for any individual exposed person. Furthermore, the sensitivity of the method is low: differences cease to be significant below perhaps 0.1 or .15 Gy. Thus these approaches cannot be used to provide significantly more information than does dose, with respect to the probable fate of any given irradiated individual.

Nonetheless, Figure 7 does illustrate clearly the important point that a "biological dosimeter" does not require conversion to dose to be useful in predicting excess in the incidence of cancer in an exposed population. One can, if the system is appropriately calculated, readily determine the expected excess incidence directly from the biological indicator of the severity of effect.

Thus, for the present, and no doubt for some time in the future when the situation may be changed entirely by increased knowledge gained through molecular biology and related approaches, potential cancer cannot be approached on a medical basis, i.e., from the standpoint of determining the severity of effect on an individual as indicated by a causative biological marker, and taking some course of action with respect to advising or treating the individual. Rather, the presence or absence of cancer in individuals must be regarded as a public health problem. With respect to Figure 1, this means that the biological entity of interest must be a defined human population which has been exposed to a carcinogen such as radiation, and the system elements of interest are those individuals who have been exposed and who may develop, or actually have developed, a cancer.

Again, it is useful to use a specific example such as the atomic bomb survivors. In Figure 9 is shown a dose response curve for a selected group of survivors, some 40,000 total [3]. Shown is the excess incidence of cancer as a function of absorbed dose (Fig. 1, system-element pair B). This function is often assumed to be "linear and without threshold." It is on the basis of functions such as this, coupled with the fact that individual cell systems, when irradiated either at low doses or at higher doses, but at markedly reduced dose rates, also are often linear, that gives rise to the so called "linear, nonthreshold hypothesis." The hypothesis states that what happens at low doses can be deduced from what is observed at high doses, and that "any amount of radiation, however small, can be harmful, perhaps lethally so (from induced cancer)."

However, there are serious problems with plotting the data as it has been in Figure 9, which has the same coordinates as does the typical sigmoid-shaped toxicological dose response curve for noncancer effects shown in Figure 2. In medicine, it is only the ordinate, the fraction responding quantally, that must be additive (up to saturation at 1.0), while the denominator, defined as the mean agent concentration, is not additive. The abscissa must be in this form because, in chemical toxicology, as is quite generally understood, the mass of the subject is taken into account, e.g., the subject is weighed, and the quantity ε/m is multiplied by m in order to obtain the absolute amount of agent, ε, to be administered (i.e., ε/m is the mean "quality" of the agent, which must be multiplied by the "quantity" in terms of mass). Only then can the response indicated on the ordinate be observed. However, for absorbed dose on the abscissa of the curve shown in Figure 9, no indication is given that the absorbed dose, ε/m, is to be multiplied by the mass.

Furthermore, it is necessary to keep in mind that the ultimate aim of dealing with any dose response curves for cancer is radiation protection. Here "film badges" are issued to a number of individuals, and these readings must be provided in a collective or cumulative form in order to obtain the total physical insult to the population of interest. Thus, for this reason also, the abscissa in Figure 9 cannot be the nonadditive absorbed dose, ε/m in Gy, but must rather be the additive quantity, ε. Such a function is shown in Figure 10.

An added advantage of a plot such as that in Figure 10 is that the inverse of the slope

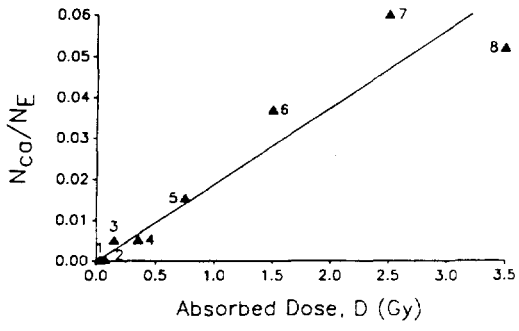

Fig. 9. The fraction of dosed atomic bomb survivors with a solid cancer, as a function of absorbed dose.

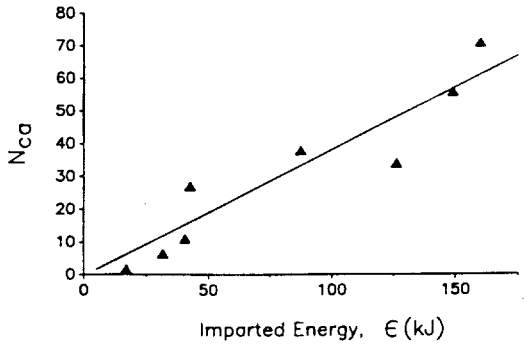

Fig. 10. The actual number of solid cancers among the atomic bomb survivors, plotted against imparted energy.

permits one to obtain a value for the absolute amount of the agent energy that, on average, must be transferred to a population in order to cause one excess cancer [4]. This value is nominally 3 kilojoules (kJ).

The fact that in Figure 10 the ordinate is the absolute number of cancers, and not a ratio that can be interpreted as a probability, points up the other problem with the function in Figure 9—it is not in accord with the levels of organization shown in Figure 1. Public health problems, such as are encountered in radioepidemiology, obviously involve a defined population, and the elements of that system are the number of persons exposed (system-element pair B, Fig. 1). Also, as was discussed earlier, what is of interest is the fraction of the elements of the system dying, and whether this is severe enough to cause a quantal response in the system, i.e., the demise of the population of interest. Therefore, proper under these circumstances is a plot of the same type shown in Figures 5 and 6, which provides the probability of the population showing a quantal response (dying) as a function of the severity of effect. Such a plot is shown in Figure 11.

Although it may seem strange to speak in terms of entire populations or societies dying as a result of the killing off of large fractions of the human elements comprising the society, history is replete with this occurring as a result of wars, epidemics and other unknown causes. During World War II, Tokyo ceased to exist as a city because of mass carpet fire bombing of the entire area. Similarly, with Hiroshima and Nagasaki a large fraction of the population was killed outright by the atomic bomb, and all sanitary and other services were rendered inoperative. These cities also ceased to exist as an entity. However, although acute radiation illness did cause a small fraction of the total deaths in the city, deaths from radiation-induced cancer could not be a factor because excess cancers did not begin to appear until the city was well along to being restored. However, even were there no latent period for cancer, the relatively minuscule numbers of cancer deaths would have precluded it from being a health problem that might threaten the continued existence of the two cities involved. If radiation-attributable cancers could have no effect under these extreme conditions of high-dose and dose rate, clearly they cannot constitute a significant public health problem with the low level radiation now encountered in routine radiation protection practice. Thus low level radiation exposure is not a medical problem at all, and a relatively insignificant public health problem.

Discussion and Conclusions

From the above discussions it is clear that biological markers are not only useful, but are

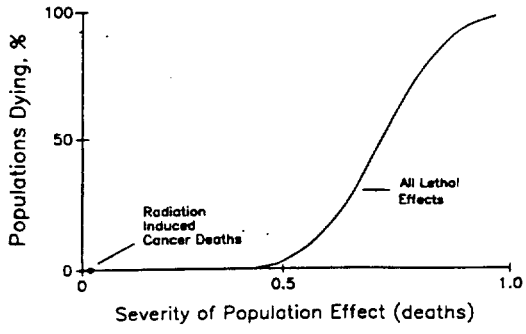

Fig. 11. Plot showing the percent of populations, e.g., cities, dying, as a function of the severity of injury to the cities as measured by the number of persons killed. With reference to Figure 1, here the elements are people and the system is a city. Notice that induced cancer would have played no role in the demise of the cities, even were there no latent period. This lack of importance of cancer as a public health hazard under even these high-dose/high-dose rate catastrophic conditions indicates that, with small amounts of radiation (low level irradiation), it can constitute only a relatively trivial public health problem.