against log-dose, the resulting curve is likely to be sigmoid in shape. This difference between the conditions under which observations on humans and on experimental animals are usually made may, we believe, be responsible for much of the conflict between the conclusions drawn from the two sets of data.

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A significant contribution is achieved by Drs. Armitage, Court Brown and Doll in evaluating some models postulated in assessing the leukæmogenic potency of radiations. Along this line, it appears relevant to discuss some possible interpretations of a linear dose-response, observed over a limited range of leukæmia incidence, as evidenced in the study of patients irradiated for ankylosing spondilytis. Basic assumptions of some theoretical models will be first examined.

It is an experimental fact that a dose d of radiations will induce leukæmia in a proportion P of susceptible individuals. Clearly, among individuals exposed to the same dose, some respond whereas others do not. Consequently individual susceptibility is postulated. Different theoretical models may be obtained, depending on the assumptions made about the susceptibility. In the random-hit hypothesis referred to by Armitage *et al.*, a factor of proportionality k measures the susceptibility. If k is assumed to be *identical* in each individual, it can be shown that the expected proportion P of individuals remaining unaffected (that is, not developing leukæmia) after irradiation with a dose d is $P=\exp(-kd)$. For small doses associated with low incidence of leukæmia, the exponential is closely approximated by the first term of its expansion $1-kd$. Similarly, if k varies from individual to individual within definite limits, the expected proportion of individuals not developing leukæmia at small doses is $1-\bar{k}d$, $\bar{k}$ being the mean value of k (ref. 1). In both cases the expected proportion of leukæmias will be linearly related to dose *over a limited range*. However, if d or the variation in susceptibility becomes large, the discrepancy between the true law and the exponential increases.

It may be assumed that, in addition to random variations, internal and external conditions result in a widespread distribution of susceptibilities of individuals to radiation leukæmia. The susceptibility k is then defined as a variate with some distribution the density function of which is $f(k)$. It can be shown that the expected proportion of individuals remaining unaffected after irradiation with a dose d, is

$$P=\int_0^1 (\exp(-dk)\ f(k)\ dk \text{ (see ref. 1).}$$

If the susceptibility distribution is assumed to be normal or log-normal with dose, the dose-response relationship will be sigmoid. However, as d or the variation in susceptibility declines, the probability of an unaffected individual becomes more closely described by the exponential law and here also, the expected dose-response curve may be approximated by a linear relationship in a limited range of small doses associated with low response. Thus a simple proportional relationship between dose and incidence in the low range may be an approximation to either one of the exponential or sigmoid theoretical models. Conversely, experimental observation of linearity over a small range does not provide conclusive evidence in favour of the random hit type (exponential) or the susceptibility distribution type (sigmoid). It follows that from human experience both models are plausible as observation of leukæmias was limited to a very low incidence[2].

In animal experiments, data on radiation leukæmia are available over a fairly complete range of incidence. None of those distributed on either sides of a median effective dose is in agreement with an exponential model. On the other hand, probit regression curves have been shown to fit the most complete set of experimental results as yet available[3] in mice. Furthermore, numerous host factors have been[4] identified which influence the leukæmic response in irradiated mice in such a way that the probability of developing the disease may, in specific circumstances, vary from almost 1 to 0, regardless of the dose of radiations absorbed. This experimental fact makes it difficult to consider in theoretical models the susceptibility of mice as a variable submitted to purely random influences. It seems appropriate to assume that k actually has a distribution related to some density function. Indeed, probit analysis suggests that the susceptibility of *C* 57 black mice is distributed log-normally. Thus experimental evidence from animals points to the sigmoid model with a susceptibility distribution.

The considerable theoretical and practical implications of the nature of the dose-response relationship in radiation leukæmia make it desirable to postulate a model which will perhaps fit all available data, from human experience as well as from animal experiments. Obviously, the pathogenesis of human radiation leukæmia may not be identical to murine radioleukæmogenesis. No experimental evidence, however, exists that the respective induction mechanisms are fundamentally different in these species. It seems implausible that the complexity of those mechanisms should be less in humans than in pure inbred mice. Therefore it is doubtful whether susceptibility of man to radiation leukæmia may be properly described by a variable the form of which is simpler than that postulated for mice from experimental evidence. In these circumstances, it is reasonable to assume as a working hypothesis that different responses in different human individuals are the result of a distribution of susceptibility or tolerance. In this sense, probit analysis is the appropriate statistical treatment of a quantal response such as radiation leukæmia.

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