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Animal Radiation Data and Their Relevance to Man*

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This broad topic has received repeated treatment in the literature over the past 30 years. For the purpose of this conference, it will suffice to outline in general terms the conclusions reached by examination of experimental animal data without extensive documentation of these data. The documentation is readily available in the literature and the reader is referred to the following: Moskalev and Streltsova (1964); Casarett (1965); Van Cleave (1968); Upton (1964, 1966, 1968). More recent treatment of this topic has been published by Storer and Bond (1971), as well as in the 1972 Report of the Scientific Committee on the Effects of Atomic Radiation Annex G, "Experimental Induction of Neoplasms by Radiation," and Annex H "Radiation Carcinogenesis in Man".

In addition to limitations on the amount of documentation, the author will restrict the discussion to the following: 1) whole body exposure to external radiation, where there is a relatively uniform dose to all cells of the body, thus permitting an accurate determination of dose to the susceptible tissue or cell populations, 2) late somatic effects, thus excluding genetic effects and the hematologic disorders seen within approximately 90 days following radiation, and 3) induction and acceleration of neoplasms, which is the most significant late effect following exposure to low level radiation.

One of the principal problems we face in extrapolating experimental data to man is the variability in type and sensitivity of tumors induced by radiation in different species and even among different strains of the same species. For example, it is well known that mice are highly susceptible

to induction of certain types of hemopoietic neoplasms, principally thymic lymphoma, as well as female endocrine organ tumors (i.e. ovarian, pituitary, and breast) (Upton, 1966). Swine, on the other hand, are susceptible to induction of liver, intestinal and uterine tumors (Brown and Johnson, 1970), and burros show no evidence of tumor induction by whole body radiation (Brown, Johnson, and Cross, 1965). Man appears to be most susceptible to induction of certain forms of leukemia (i.e., acute and chronic myelogenous and acute lymphatic) and thyroid carcinoma (UNSCEAR, Annex H, 1972). Even among strains of the same species such variation is common. While mice of the RFM strain are highly susceptible to induction of thymic lymphoma and myeloid leukemia, C₃H mice rarely develop these diseases following whole body radiation and C57BL mice are intermediate between the other two strains in incidence of thymic lymphoma but do not develop myeloid leukemia (Walburg, unpublished data). With such variation evident, it seems highly unlikely that a single adequate model exists which will permit direct quantitative extrapolation to man of experimental data on radiation carcinogenesis.

How, then, can such experimental data be useful in estimating man's risk to neoplasia from radiation? In general, there are three possibilities as previously outlined by Mole (1970): 1) directly applicable models, 2) useful qualitative generalizations, 3) useful quantitative generalizations. While there do not appear to be any directly applicable models, there are some qualitative observations which appear to be independent of species and their genetic or environmental influences. These will be outlined

subsequently. An example of useful quantitative generalizations would be the relation of cell replication rates to probability of tumor induction following ^{of} radiation for a given tissue. If this relationship were independent of strain and species, then determination of cell replication rates in human tissue could be used to predict tumor incidence in man for that tissue. While no such quantitative generalizations are obvious at present, they are of sufficient importance to require a continuing search, for as the mechanism of radiation carcinogenesis is clarified, quantitative generalizations may also be identified.

To return to the useful qualitative generalizations seen in experimental radiation data, they are as follows. (See UNSCEAR, Annex G, 1972 for documentation).

1. Radiation causes shortening of the mean life-span.
2. Such life-shortening can be explained as principally due to induction and acceleration of neoplastic diseases especially for low doses and low dose-rates of radiation.
3. Dose response curves are characterized by an increase in incidence with increasing dose to a maximum followed by a decline as the dose continues to increase. Where a tumor system is easily induced by small amounts of radiation (e.g., thymic lymphoma in mice, breast tumors in rats), an absolute threshold (i.e., a dose below which there is no effect) has not been demonstrated due to the large numbers of animals required for statistical proof, but for more resistant tumor systems an absolute threshold seems to be established (e.g., kidney tumors by local organ irradiation in rats, skin tumors by local irradiations in rats).

4. High LET radiation (e.g. fission neutrons) is more effective for a given dose than low LET radiation (e.g., gamma rays).
5. For the same total accumulated dose, high dose rates are more effective than low dose rates.
6. Low LET radiation is more sensitive than high LET radiation to this dose-rate effect (No. 5).
7. Juvenile animals are generally more susceptible than adults to induction of neoplasms.

If these generalizations occur independent of species, then irradiated human populations should respond similarly. The irradiated human population most similar to the experimental populations discussed above is the Japanese atom-bomb survivors. Contrary to most other human populations studied, this population was not selected because of illness or a single parameter such as occupation and it received whole body exposure rather than localized irradiation. The following generalizations apply to this population as well. (See UNSCEAR, Annex H, 1972 for documentation).

1. Radiation causes life-span shortening.
2. This life-shortening can be explained on the basis of induced or accelerated neoplasia.
3. The dose-response curve for leukemias is similar to those seen with the experimental animal data.
4. Differences in the induction of leukemia between the irradiated populations of Hiroshima and Nagasaki can be explained on the basis of increased efficiency of the radiation from the bomb

exploded at Hiroshima, radiation which contained a larger component of neutrons than was experienced by the Nagasaki population.

5.-6. There ^{is} ~~is~~ no dose-rate data available from this population.

7. Young members of the irradiated population appear to be more sensitive to the induction of thyroid carcinoma than their adult counterparts.

Thus, in human populations exposed to whole body radiation there do not appear to be any peculiar responses that would invalidate the qualitative generalizations developed from experimental animal data.

In general, combination of the scanty data from irradiated, human populations and the application of these qualitative generalizations has resulted in the best estimates of risk to man by radiation. Turning to the specific problem of estimating the risk to man of radiation emanating from implanted nuclear powered medical devices, several points must be emphasized.

1. There is no evidence that data for late somatic effects of radiation from any single animal model system, not even the non-human primates, can be extrapolated quantitatively to man.
2. Since we are dealing with low levels of radiation which result in small (but not necessarily unimportant) risks to induction of neoplastic diseases, large numbers of animals are required to statistically validate the level of risk involved.
3. Induction of neoplasia occurs characteristically late in life, requiring studies throughout the entire life-span of the population at risk.

It seems clear that the risk of inducing or accelerating neoplasms by radiation emanating from implanted nuclear-powered medical devices cannot be determined by implanting these devices (or "radiation equivalent sources") in a few non-human primates and examining them for pathology within two to five years. While these studies may be valuable for determining the amount of "acute" pathology such as tissue necrosis, aneurism, etc., it is the risk for induction of neoplasms that needs estimation. ~~Such risks can be determined best by applying the entire spectrum of knowledge available concerning radiation-induced neoplasia~~
If the quality of a radiation, its dose-rate and the dose to a susceptible ^{data} tissue are known, application of these/to the entire body of knowledge on radiation carcinogenesis in man and animals will yield a reasonable estimate of risk.

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