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LATE EFFECTS OF RADIATION: HOST FACTORS

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The late somatic effects of radiation fall into two categories; neoplastic and nonneoplastic. The latter result mainly from cell loss, with or without replacement by fibrous tissues, and can be of concern with the high total doses used in therapy. However, after over thirty years of accumulating information about atomic bomb survivors cancer appears to be the only life shortening disease that can be attributed to the radiation exposure of that population (G. W. Beebe et al., RERF-TR 1-77 1978; Kato et al., Radiat. Res. 91: 243, 1982). Experimental results from exposure to low doses or low dose rates support and preceded this finding (D. Grahn et al., Life Sci. Space Res. 10: 175, 1972; H. E. Walburg, pp 145-179, in Advances in Radiation Biology, Academic Press, New York, 1975; J. B. Storer et al., Radiat. Res. 89: 618, 1982). Mice exposed in later life show less radiation-induced life shortening (P. J. Lindop and J. Rotblat, Brit. J. Radiol. 35: 23, 1962), but this age dependency is also strain dependent and reflects a decrease in the contribution of tumors to life shortening (H. I. Kohn and P. H. Guttman, Radiat. Res. 18: 348, 1963).

In this session, papers are presented that deal with the many facets of late effects and therefore also aging, in other words the host of factors that influence the outcome of exposure to radiation.

This contribution will concentrate on the influence of host factors on radiation late effects and in particular cancer. We have chosen this aspect of radiation-induced late effects not just out of contrariness. Currently, there is a great emphasis on the molecular changes involved in initiation but an understanding of the influence of host factors is paramount in the study of mechanisms and in the practical realm of risk estimation and intervention with the process of late effects.

Radiation induces cellular changes that result in initiated cells with a potential to become cancers. Such changes may not be as rare as the incidence of cancer would suggest but the expression of the initiated cells as tumors is influenced, if not determined, by both tissue and systemic factors that are sex--age- and species-dependent.

Host factors and cellular responses.

With the exception of cataract nonneoplastic late effects develop, by and large, as a result of cell loss with or without replacement by fibrous tissue. Such changes that result in loss of function are of importance clinically where high doses are incurred locally (P. Rubin and G. W. Casarrett, Clinical Radiation Pathology, W. B. Saunders, Philadelphia, 1968). Tissue damage may result from direct loss of parenchymal cells or secondarily to damage of the vasculature. Studies of these forms of injury are reported in this session.

Knowledge about threshold doses for late effects for both high dose-rate and protracted exposures is not only of scientific interest but has become of increased importance for protection standards with the introduction of the risk system (Annals of the ICRP, Vol. I, Publication No. 26, Pergamon Press, Oxford, 1977). The risk system allows high doses for localized irradiation. ICRP's recommendation of standards based on risks after exposure of specific tissues assumes a considerable knowledge of the effects of local irradiation. For example, do we know enough about individual variability in susceptibility or the severity of response to establish appropriate threshold doses? How does age at exposure affect the probability of late effects, their time of appearance, their progression and the degree of the effect? It would be difficult to answer these questions precisely on the basis of current knowledge.

Clearly, tissue damage may result from direct radiation-induced cell killing with considerable variations in time to reach discernible loss of parenchymal or of function. Almost all of our knowledge of cell killing and repair in human cells has been derived from aneuploid cell lines and tumor cells such as the ubiquitous HeLa cell. The relatively small amount of data for human cell strains (C. F. Arlett and S. A. Harcourt, Cancer Res. 40: 926, 1980; R. W. Weichselbaum et al., Cancer Res. 40: 920, 1980) show that there are significant differences in such cells compared to cells for stable lines. Unfortunately there are no comparative data for cells studied while still a strain and for the cells after the strain has been transformed to a cell line.

Seed et al. (Exp. Hematol. 10: 232, 1982) have studied survival curves of granulocyte-monocyte progenitors (GM-CFUa) from dogs at different stages of protracted exposures to gamma radiation. The curves for these cells from unirradiated controls and dogs exposed for less than 300 days (short term survivors) have small shoulders. However, the survival curve for the GM-CFUa from dogs that survived longer periods of protracted irradiation were quite different: D_o of 155 $\pm$ 15 to 60 $\pm$ 5 for cells from the short term survivors and a D_q of 45 $\pm$ 15 compared to 9 $\pm$ 2. Since the survivors of the longer periods of irradiation are candidates for leukemia it is of considerable interest if these changes are associated with the early stages of leukemogenesis.

Attainment of unlimited proliferative potential or immortality by cells is central to the carcinogenesis process. The conversion to a cell line or immortality is an initial event in malignant transformation that has not been studied extensively (R. F. Newbold et al., Nature 299: 633, 1982). A knowledge of this conversion in relation to age-sex- and tissue-dependency as well as genetic background seems essential to an understanding of the mechanisms of carcinogenesis.

Host factors in radiation carcinogenesis

Radiation induces the initial necessary cellular alteration for cancer to occur but whether these changes are expressed as a tumor depends on a number of constitutional or host factors. Both human data and experimental evidence suggest that in the case of certain tumor types the secondary factors may be the predominant ones. The data accumulating from the study of atomic bomb survivors show that breast cancer, attributed to the radiation exposure, becomes overt only when the age is reached at which the natural incidence of such cancers begins to rise (M. Tokunaga et al., Lancet 1:

924, 1982). In other words, age-dependent host factors and not the radiation determine the latent period.

Experimental manipulations, particularly of the hormonal system, have shown that changes in the host are either required or hasten greatly the expression of radiation induced lesions (Lick et al., Cancer Res. 9: 532, 1949, K. Yokoro et al., J. Natl. Cancer Inst. 58: 1777, 1977).

There has been increasing acceptance of the idea that cancer induction involves multiple changes in the target cell. Clearly some experimental evidence supports the contention of a multistep process. However, the steps subsequent to initiation may involve host factors independent of further changes in the target cells.

An important question is whether in a particular tumor the long latent period is due to a multistage process in the target cell or whether the length of the period indicates dormancy of the initiated cells. The two processes are not mutually exclusive. The period of dormancy might be ended by exogenous factors or age-dependent changes in the host. The rapid appearance of skin cancers after PUVA treatment in psoriasis patients previously treated many years before with x-rays (Stern et al., New Eng. J. Med. 300: 809, 1979) suggests that dormant initiated cells can occur in the skin. The latent period may include the time it takes for the constitutional factors to become favorable for tumor expression. There is always, of course, a minimum latent period determined by the growth rate and the endpoint used as the indication of a tumor, such as time of appearance or death.

In Table 1 are shown the effects of sex on both the natural incidence and the susceptibility to induction of cancer by radiation. The sex dependency for lethal tumors is itself dependent on the genetic background that determines the prevalence of specific tumor types. However, the presence of the ovaries also clearly affects both the control and induced incidences.

Table 1. Influence of Host Factors on Radiation-Induced Lethal Tumors in Mice

Strain	Sex	Control Incidence %	Irradiated Increase %/Rad
		Influence of Sex	
RFM/Un	Male	59	0.32
RFM/Un	Female	72	0.67
		Influence of Ovary	
BALB/c	Female	83	0.43
BALB/c	Ovariectomized	74	0.22

It should be noted that the increase in incidence of lethal tumors per rad is positively correlated with the natural incidence. This relationship of susceptibility to radiation induction to natural incidence holds for those tumors for which there are adequate data with one notable exception, namely,

myeloid leukemia in CBA mice (I. R. Major and R. H. Mole, Nature 272: 455, 1978). If the susceptiblity to radiation induction for some solid cancers is dependent on the natural incidence it supports the use of the relative risk model for estimates of risk. Furthermore, this apparent relationship underlines the importance of host factors in determining the tissue-strain- and species-dependencies. The susceptibility to breast cancer induction shows marked differences between strains in both mouse and rat but it is not clear how much of these differences reside in the inherited properties of the target cell or depend on other inherent characteristics, particularly in the endocrine system.

The demonstration by Loeb and Kirtz (Am. J. Cancer 36: 56, 1939) that transplants of the pituitary anterior lobe increased the incidence of mammary cancer in mice, and the finding by Desclin (Ann. Endocrinol. 11: 656, 1950) that the pituitary isografts raised the blood level of prolactin, provided a method for investigating the process of tumor development (L. M. Boot et al., in Oncology, Vol. I, Year Book Medical Publishers, pp 434-440, 1970; K. H. Clifton et al., Cancer Res. 36: 3732, 1982). Yokoro et al. (J. Natl. Cancer Inst. 58, 1777, 1977) using prolactin tumor grafts have shown that radiation can initiate cells in the mammary gland that may lie dormant until stimulated to express their malignant phenotype by the hormonal manipulation. The identification and manipulation of the factors that suppress expression of radiation-initiated cells will be as practically important if not as spectacular as any finding about the process of initiation.

A number of host factors influence the induction of murine leukemias by radiation and any description of the mechanisms must account for them. It is not obvious that the currently popular ideas about the role of specific chromosome aberrations in certain types of leukemia are consistent with what is known about host factors. The suggestion that the breakpoints involved in some of the chromosomal rearrangements involve the specific bands to which different c-oncogenes have been assigned has allied the molecular with the cytogenetic findings (J. D. Rowley, Nature 301: 290, 1983). In Fig. 1 it

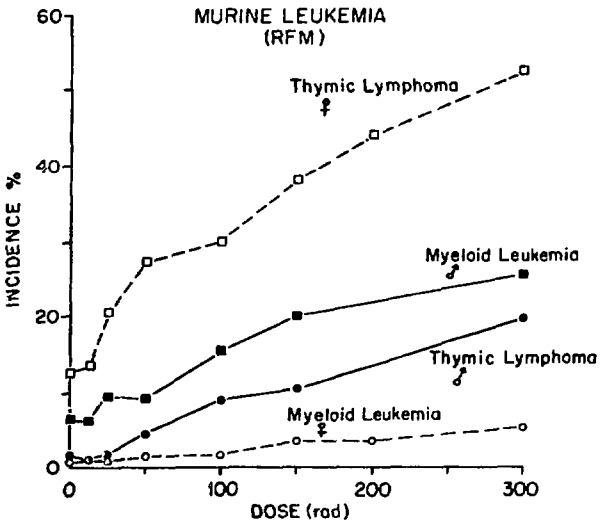

Figure 1: Incidence of thymic lymphoma and myeloid leukemia as a function of dose in female and male RFM/Un mice (data from R. L. Ullrich and J. B. Storer, Radiat. Res. 80: 303, 1979).

can be seen that two distinct leukemias in one strain show quite different sex dependency for both the natural incidence and radiation induction. The induction of murine leukemias is dependent on sex and age. Therefore, if specific translocations are causally related they should also show similar dependencies. There are no data for either the sex- or age-dependency of induction of chromosome aberrations in mice. One human study indicated a negative correlation between age and the yield of dicentrics but no sex-dependent difference (J. Liniecki et al., Int. J. Radiol. Biol. 19: 349, 1971). If it is found that the induction of the chromosome aberrations do not show the same dependencies as the induction of leukemia it must be presumed that sex- and age-dependencies are due to host factors.

Influence of host factors on dose-response relationships

Since the mechanisms of radiation carcinogenesis are different for various tissues it is reasonable that a variety of dose-response curves have been reported. It is probable that many of these differences are due to the factors that influence expression and certainly the shapes of dose-response curves can be changed by treatment with agents that affect expression rather than initiation (R. J. M. Fry, Radiat. Res. 87: 224, 1981).

It can be seen in Fig. 2 that the relationships of incidence to dose are not simple and the shape of the response curves are difficult to explain in terms of biophysical models. In the examples shown we believe that the hormonal imbalance due to radiation inactivation of the ovaries is the most likely explanation for the plateau seen at about 50 rad with gamma radiation and 5-10 rads with fission neutron.

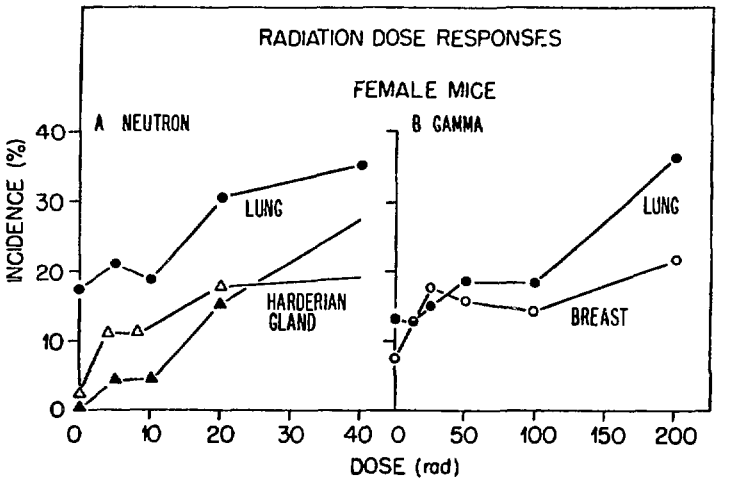

Figure 2: Incidence of tumors in female mice of various strains as a function of (A) neutron and (B) gamma radiation dose.

Three research groups have questioned the widely accepted belief that the target size for cancer induction is certainly not greater than one cell and probably very much smaller. Rossi and Kellerer (Science 175: 200, 1972) maintained that the dose-response curve for the induction of mammary tumors in Sprague-Dawley rats with neutrons was not consistent with the proportionality predicted from microdosimetry. More recently Rossi and Hall (in Radiation Carcinogenesis: Epidemiology and Biologic Significance, Eds. J. D. Boice and J. F. Fraumeni, Jr., Raven Press, New York, 1983) contended that a number of dose-response curves suggested that suppression of transformation occurred and modified both in vitro and in vivo responses. These authors suggest more than one cell must be involved in the induction of cancer by radiation. Mole (in Radiation Carcinogenesis: Epidemiology and Biologic Significance. Eds. J. D. Boice and J. F. Fraumeni, Jr., Raven Press, New York, 1983) came to a similar conclusion because the dose-response curve for the induction of myeloid leukemia by x-rays could only be accounted for by a target size larger than a single cell. Mole suggests that involvement of two adjacent cells not only could accommodate microdosimetric tenets and the D^2 response found for myeloid leukemia induction but also explain the greater carcinogenic effect of high-LET radiation.

Dose-response curves for radiation induction of cancer are usually plotted as the incidence as a function of dose. Since such plots include not only the biophysical events involved in initiation but also the varied factors influencing expression they cannot be used either to deduce the response for initiation or test models of induction of initial events.

The third group of this troika of doubting Thomases (D. W. Van Bekkum and P. Bentvelzen, Health Physics 4: 231, 1982) questioning the single cell concept of radiation carcinogenesis based their argument on the evidence that supported a mechanism that involved more that the one cell. The hypothesis stems from earlier findings of Barendsen (in Radiation Induced Cancer, pp 413-424, IAEA, Vienna, 1969) and Klein (J. Natl. Cancer Inst. 52: 1111, 1974), and contends that transformation takes place as a result of uptake by an irradiated cell of DNA fragments from damaged cells. Incorporation of these fragments, the so-called gene transfer-misrepair process, has a certain probability of malignantly transforming the cell. Such a model is contrary to those based on somatic mutations and also predicts that a threshold must exist at very low doses.

It is clear we need techniques that allow the dissection of the initial events involved in transformation from the effects of the host factors that influence the expression of a malignant phenotype and therefore, the tumor incidence and the shape of the dose-response curve in order to test these hypotheses.

Host factor and analysis of data

All the methods of analysis of data for tumor induction that are in common use assume independence of the occurrence of various types of tumors.

In the case of human data proof that this assumption is justified has not been provided but equally important there is no quantitative estimate of the importance of the assumption to any analysis. J. B. Storer (Radiat. Res. 92: 396, 1982) found both positive (see Table 2) and negative associations (see Fig. 3) between tumors in irradiated female BALB/c mice.

Table 2. Association between tumors in irradiated BALB/c female mice

	Tumor Types				
	Lung	Adrenal Gland	Harderian Gland	Pituitary	Breast
Breast		+	+	+	
Harderian Gland	+	+		+	+

Most of the positive associations were endocrine related and are probably due to the hormonal imbalance caused by radiation damage to the ovary. Unexpected interactions may occur such as changes in time of appearance of lung tumors in mice with pituitary isografts. The increase in the multiplicity of tumor types in irradiated female mice (R. J. M. Fry et al., Environ. Internat. 1: 361, 1978) is also evidence of the lack of independence and the importance of host factors in radiation carcinogenesis.

The explanation of the marked negative associations between reticular cell sarcoma and other reticular tissue tumors is not clear. However, Pierpaoli and coworkers have demonstrated in a series of studies the importance of the endocrine status on development of reticular cell sarcoma (see W. Pierpaoli and A. Meshorer, Eur. J. Clin. Oncol. 18: 1181, 1982).

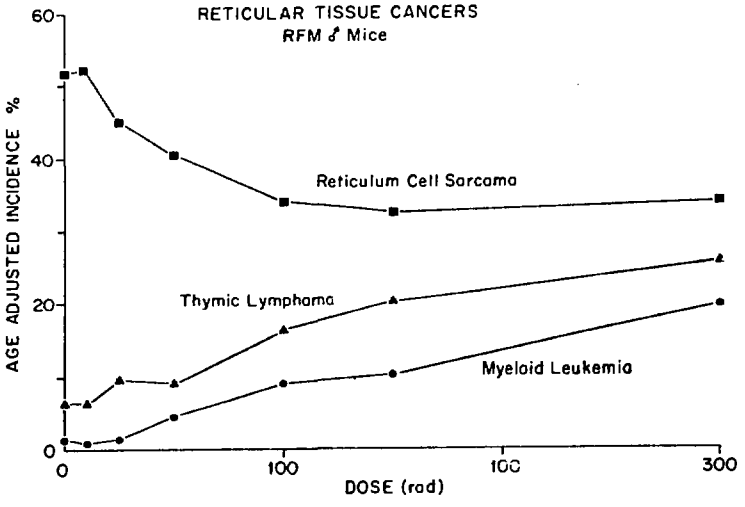

Figure 3: Incidence of reticular tissue tumors in male RFM/Un mice (data from R. L. Ullrich and J. B. Storer, Radiat. Res. 80: 303, 1979).

SUMMARY

There still remains considerable work to be done in the field of non-neoplastic late effects of radiation. For example, experimental model systems seldom have been appropriate for describing the late effects that may occur as the result of exposure at a very young age, in old age, and particularly, in subjects compromised by some other disease. As pointed out by Lett et al. (in Life Sciences and Space Research XVIII, pp 17-28, Pergamon Press, Oxford, 1980), we do not know enough about the progression of late effects. Even the information about cell killing by radiation in different tissues, especially in humans, is far from complete.

Much of the research in radiation carcinogenesis has concentrated on the production of tumors, the dose-response relationships and the mechanism of initiation. But we know little about why some tissues and some members of the population are resistant to cancer induction by radiation. Are the genomes of cells of different tissues sufficiently variant to account for the susceptibilities or does the difference lie in host factors?

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