IONIZING RADIATION: LEVELS AND EFFECTS

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Annex G

EXPERIMENTAL INDUCTION OF NEOPLASMS BY RADIATION

CONTENTS

Introduction

1. From the time of the initial observations that radiation causes tissue damage and subsequently cancer (66, 67), animal experiments have been designed and carried out (119, 120) in an attempt to understand better the mechanisms of radiation-induced injury and predict the carcinogenic effects of radiation in man. The older literature has been reviewed by Colwell and Russ (28), Furth and Lorenz (53), Furth and Upton (54), and Lacassagne (101, 102). More recently, the Committee has reviewed the subject (182) and reviews have been published by Casarett (19), Moskalev and Streltsova (135), Upton (185, 187) and Van Cleave (201).

2. It is not the purpose of this annex to review exhaustively the literature but rather to evaluate the present understanding of some of the basic principles of experimental radiation carcinogenesis which could lead to a better predictability of radiation effects in man. Direct assessments of the reliability of existing standards for radiation protection in man will not be made, but the review will indicate what useful data exist or could be developed from experiments on animals. It is recognized that radiation is but one of several important ætiological agents known to induce or accelerate neoplasms in man and while many of the principles discussed in this review are of general significance to carcinogenesis, studies on viral and chemical carcinogenesis have in general not been reviewed.

I. The role of animal experiments in predicting radiation carcinogenesis in man

3. While medicine has frequently turned to animal experiments for assistance in solving problems of human disease, the validity of animal models for studying human disease has often been questioned. It is well known that inherent differences exist among the many neoplasms in experimental animals used in the study of radiation carcinogenesis. Not only are the life spans and tumour latencies different, but the type of tumours induced or accelerated by radiation vary markedly from species to species and even from strain to strain of the same species. Such variability leads to considerable difficulty in extending conclusions from experimental animals to man. Nonetheless, the development of neoplasms appears to be qualitatively similar in man and in those experimental animals that have been studied. Thus, the epidemiological data on radiation carcinogenesis in man, when evaluated in the light of conclusions developed from experimental studies, can lead to a better understanding of the risk to man from exposure to radiation. There are three basic methods for developing experimental data which will be useful for evaluation of such risks in man; these are outlined in paragraphs 4-7.

4. The most useful method entails the study of neoplasms in experimental animals that respond to radiation in a manner qualitatively and quantitatively comparable to their counterpart in man. Unfortunately, directly comparable neoplasms are not well documented in radiation carcinogenesis since considerable amounts of data are required from humans to validate the authenticity of the animal data. Perhaps the best documented model system is osteosarcoma induction by ^{226}Ra in beagle dogs (40, 122) but even here considerable uncertainty is involved in producing quantitative inferences applicable to man. Another animal model system is radiation-induced myelogenous leukæmia in RF mice (192), which has many of the qualitative characteristics of human chronic granulocytic leukæmia. No quantitative relations have been demonstrated and some qualitative characteristics of the murine disease, such as its dependence on the microbial environment (209), have not yet been documented in man.

5. Another method of developing experimental data which are of value in estimating the risk of radiation to man is the establishment of useful generalizations as described by Mole (134). Qualitative generalizations are particularly useful when all types of neoplastic diseases show the same patterns in all species. There are three such generalizations apparent from existing data, although some exceptions have been noted in the literature: high-LET radiations (that is, those radiations which deposit large amounts of energy per unit length of track, e.g., fission neutrons, alpha particles) are more effective in inducing neoplasms than low-LET radiations (e.g., x rays, gamma rays); the incidence of such neoplasms generally increases with dose up to some maximum incidence; and for low-LET radiations, lower dose rates are less effective in inducing neoplasms than higher dose rates. These generalizations appear independent of species and hold true for most, if not all, of the radiation-induced neoplasms that have been adequately studied.

6. Quantitative generalizations are not as easily apparent and none are immediately obvious from experimental animal data. Measurements of RBE (Relative Biological Effectiveness, the inverse ratio of the absorbed dose from one radiation type to that of a reference radiation required to produce the same degree of a stipulated effect) vary considerably; the reduced effectiveness of low-dose-rate radiation is also variable; and dose-effect relations are not only quantitatively different but the shapes of the dose-response curves appear to vary from one neoplasm to another. Such quantitative generalizations require either that the characteristic measured not vary with species and type of neoplasm or that it vary according to some fixed relation with some other quantifiable variable such as body weight, metabolic rate, rate of synthesis of DNA, etc. Were such a relationship established, the neoplastic response in man could be predicted by relating it to the non-neoplastic response. Thus every attempt should be made to develop such quantitative relationships.

7. Perhaps the most useful application of experimental animal data is to clarify the mechanisms of radiation carcinogenesis. As early as 10 years ago, currently popular theories on the mechanisms of radiation carcinogenesis were well developed and discussions about how to clarify their relative importance were common (see discussions in reference 69). Although considerable effort has been directed to the problem over the last decade, the mechanisms of radiation carcinogenesis remain obscure. The design, execution, and analysis of definitive studies on radiation carcinogenesis have proved to be extremely difficult. To be conclusive, many of these studies require large numbers of animals which must be examined minutely for pathology at death and the results analysed statistically to adjust for competing probabilities of other causes of death (see paragraph 22). Frequently, scientists designing animal studies with large sample sizes use only survival as an end-point and those carefully analysing pathology at death design experiments with inadequate sample sizes. Few have properly corrected the data for intercurrent mortality before drawing conclusions. However, when combined, consistent reports of an effect obtained with small sample sizes can give weight to useful qualitative generalizations.

8. One of the principal general theories of carcinogenesis is the two-step mechanism proposed by Berenblum (6). Such a mechanism has been considered for chemical carcinogenesis for many years, but only recently have data begun to suggest a similar mechanism for radiation carcinogenesis. Croton oil, a potent promoter of chemically-induced skin tumours, effectively enhances the induction of skin tumours by some (44, 176), but not all (16), types of radiation. It has also been identified as a promoter of murine thymic lymphosarcoma following exposure to moderate doses of x rays (86). The enhancement of radiation-induced thymic lymphosarcoma in mice treated with urethan has been reviewed by Vesselinovitch (205). Berenblum *et al.* (7) have recently shown that x rays, in doses not normally leukæmogenic, serve as an initiating treatment when followed by adequate doses of the promoter urethan, the increase in effect being generally related to increase in radiation dose. A similar initiating effect of radiation has been described for production of lung tumours in mice treated with urethan (23, 108, 227). Interactions of radiation with other carcinogens have resulted either in an increased incidence of tumours (75, 109, 136, 169, 200, 224, 232, 236), or in no change, or in decreased incidence (99, 167, 200, 224), depending on the carcinogen and tumour system studied and the dose and dosage schedule used.

9. Another general theory of interest to the mechanism of radiation carcinogenesis involves the interaction of energy at the intracellular level. Through a series of theoretical considerations and examination of experimental data, Rossi (160) and Kellerer and Rossi (98) have concluded that a number of radiobiological effects are due to primary lesions within the cell nucleus produced by as few as one particle, in the case of neutrons having energies up to about 14 MeV, or by two or more electrons, in the case of x and gamma rays, and, further, that the elemental lesion results from dual damage within a site by inactivation of two loci. These conclusions would predict a much greater reduction in effect at low doses for x and gamma rays than for neutrons, and an RBE that increases inversely with x-ray dose as has been demonstrated for breast tumours in rats (161) (see paragraphs 35 and 41). It is not clear how such events relate to the general mechanisms of radiation carcinogenesis discussed above (paragraph 8) but the implications for dose-effect relationships and RBE for radiation-induced neoplasms must be considered.

10. Theories of the mechanisms of radiation carcinogenesis which best fit the existing data involve both initiating and promoting events. Initiating mechanisms concern immediate events occurring during the interaction of radiation with cellular macromolecules. The principal initiating mechanisms are release or activation of oncogenic virus and induction of somatic mutations, mechanisms which may be, but are not necessarily, exclusive. The principal promoting mechanisms are increase in cell replication and decrease in immune competence, both of which may be operating concurrently but independently.

11. The role of leukæmogenic viruses in radiation-induced murine leukæmia has been reviewed repeatedly (42, 95, 113, 188) and has been thoroughly discussed by the participants of the 1966 Conference on Murine Leukæmia (29). The early work of Kaplan with C57BL thymic lymphosarcoma and of Upton with RF myeloid leukæmia clearly established a viral mechanism as one of the important factors in the induction of

murine leukæmias by radiation. The significance of numerous host and environmental factors (193) in the development of murine leukæmia suggests the importance of viral interaction with a number of other factors. Strain susceptibility in mice may be more closely related to factors other than virus release, since the release of C-type particles has been demonstrated in resistant strains of mice after x-irradiation at doses which do not induce significant amounts of leukæmia (64). An infectious virus capable of inducing osteogenic sarcoma in mice has been isolated (49), suggesting that there may also be a relationship between radiation-induced osteosarcoma and virus release. On the other hand, ^{90}Sr-induced osteosarcomas of CBA mice have few demonstrable virus particles (145, 181) and low antigenicity (147), suggesting that oncogenic virus may not always be involved in the ætiology of these tumours. The importance of virus activation and release for other radiation-induced neoplasms has not been identified and visible viruses ("C-type particles") have not yet been demonstrated after irradiation or in neoplastic tissue of germ-free rats, although germ-free mice have an abundance of such particles (92). Young adult rats are susceptible to leukæmia induction following radiation if injected with rat-adapted passage-A Gross virus but not if treated with radiation or the virus alone (216).

12. Radiation carcinogenesis has also been explained on the basis of radiation damage to nucleic acids and its effect on information contained in the genetic material of the cell (45, 68). The relationship of such somatic mutations to radiation-induction of neoplasms has been recently reviewed by the Committee (183). In summary, the support for this theory derives from the observation that radiation induces both chromosome aberrations and neoplasms and that chromosome changes have been demonstrated in most of the tumours studied. There are few or no quantitative data that would permit correlation of incidence of chromosomal abnormalities (or gene mutations) with incidence of neoplasia following exposure to radiation. Moreover, such a direct quantitative relationship may never be found if the complex, multi-step, pathogenesis suggested for radiation-induced diseases is correct (25, 34).

13. Interest in the immunological reactions associated with neoplasia has been heightened by the discovery of tumour-specific antigens (i.e., surface antigens not present on normal cells of the adult host). Cells carrying these antigens are capable of stimulating an immune response. These observations have led to the concept of immunological surveillance (see annex F, paragraph 247), which proposes a continuing eradication of emerging, potentially neoplastic cells. A thorough review of the current status of the relation of immunity and tolerance in oncogenesis has been published in the Proceedings of the IV Perugia Quadrennial International Conference on Cancer (168). Recent data on tumour-specific antigens and their relation to immunotherapy of cancer have also been reviewed (2).

14. The relation between radiation-induced immunosuppression and radiation-induced neoplasia is reviewed by the Committee in annex F of the present report. There is abundant evidence to show that immunosuppression is not the sole factor in radiation carcinogenesis and the relative contribution of immune suppression to the complex chain of events resulting in radiation-induced neoplasms has not been determined. As with viral and chemical inducers of neoplasia, radiation results in a transient immunosuppression during what is thought to be a critical period in development of neoplastic cells. The selection of radiation-induced murine leukæmia to study this hypothesis may have been unfortunate since the neoplasm arises out of the same tissue that produces antibodies. Increased cell proliferation of the lymphopoietic organs follows radiation-induced immunosuppression and the importance of this to radiation leukæmogenesis has been reviewed (95) (see paragraph 16). The relative importance of these two mechanisms cannot be determined with this model system.

15. Indirect evidence supporting the importance of immunosuppression has been reviewed by Cole and Nowell (26) and includes such general phenomena as immunosuppression induced by carcinogens, including radiation; increased tumour incidence following immunosuppression; and increased ease of transplanting tumours in immunosuppressed animals. It is interesting that the principal neoplasm observed in immunologic deficiency states in experimental animals (26, 100) and man (151) is lymphoma and that the greatest increase of all types of tumours following immunosuppression for organ transplantation in man is reticulum-cell sarcoma (151). Nonetheless, it has been clearly demonstrated that immunosuppression by radiation and other treatments permits more rapid growth of neoplastic cells, results in more metastases, and permits transplantation across weak histocompatibility barriers (2, 26, 100, 168; see also this report, annex F). Therefore, depending on the antigenicity of radiation-induced tumours, immunosuppression may play a significant role in the rate of growth and rate of metastasis of such tumours, and may determine the tumour latency and final incidence, and the rate of survival of irradiated animals.

16. Another important promoting mechanism of radiation-induced neoplasia is increase in cellular proliferation. Some aspects of the relation between cellular proliferation and neoplasia have been reviewed by Reiskin (156). In summary, numerous chemical carcinogens cause a reduction in DNA synthesis and cell division, followed by recovery characterized by increased cell division. Mean duration of the DNA synthetic period remains normal but the number of cells synthesizing DNA increases. These observations are further supported by the generalization that rapidly proliferating tissues are more responsive to carcinogens than their more slowly proliferating counterparts. There are some tissues which are not covered by this generalization, and the exceptional behaviour of some of them, such as intestinal epithelium, may be explained by loss of potentially neoplastic cells through physiological mechanisms (110). Treatments which induce cell proliferation frequently increase the incidence of neoplasms in irradiated tissue as well. Data on the following radiation-induced tumours support the importance of cell proliferation for expression of radiation-induced neoplasms: mammary-gland neoplasms of the rat (52); bone tumours in the shaft of fractured long bones in some (225, 226) but not all cases (59): ^{90}Sr-induced bone tumours in mice following estrogen treatment (144); thyroid tumours in rats following goiterogen treatment (39, 109); thymic lymphoma alone (95, 166) and following urethan treatment (7); kidney cortical adenomas following uninephrectomy (27) and necrotizing doses

of x rays (117); lung tumours following urethan (8) and following exposure to radon in the presence of irritating dusts (21, 152); hepatomas following injection of carbon tetrachloride (24); liver tumours following hepatic deposition of thorotrast (175); and stomach tumours following necrotizing doses of x rays (71).

17. Attempts to clarify the relative importance of these various hypothetical mechanisms have included studies with chemical and cellular protection against the late somatic effects of radiation. Most of these experiments (13, 73, 103, 116, 127) have given conflicting results largely because of small sample sizes, inadequate description of tumour sites and lack of correction for causes of competing mortality. The data, however, do show that isogenic bone marrow is highly effective at preventing radiation-induced thymic lymphoma (97) but less effective at preventing the development of other late-occurring tumours (31). Chemical protective agents are also able to reduce the incidence of radiation-induced thymic lymphoma following single exposures to x radiation (115, 233) and of other leukæmias with fractionated radiation (139). Chemical protection does not appear to be effective against the induction of non-reticular tumours resulting from whole-body exposure to radiation but interpretation of these data is obscured by competing probabilities of other causes of death because these tumours occur later in life. When local irradiation is used, however, there appears to be protection against radiation-induction of kidney (43) and breast tumours (174). More data will be required, however, before experiments of this sort are able to clarify the mechanism of radiation carcinogenesis.

18. In summary, it seems quite possible that all the mechanisms identified above play some role in radiation carcinogenesis, but the relative contribution has not been assessed and may vary from case to case.

II. Importance of radiation carcinogenesis for life-shortening effects of radiation

19. The general principle that radiation-induced life shortening is due not to the induction of specific diseases but to the advancement in time of all causes of death is derived from analysis of two large, carefully designed and executed, studies on the late somatic effects of radiation in mice (105, 106, 194) where the mean age at death for every disease was reduced by x-irradiation. Corrections for intercurrent mortality were made for some of the data (percentage incidence of some specific diseases) but adjustments for mean age at death of the corrected data were not presented. It has been suggested that this consistently-reduced mean age at death for all diseases is a statistical artifact (see paragraph 22), and the importance of serial killing to provide end-points free from alterations due to survival has been emphasized (3).

20. Preliminary analysis of the survival of RFM male mice exposed to 300 roentgens of x rays at 5-6 weeks of age suggests that virtually all the life-shortening effects of the x-irradiation can be ascribed to induction of neoplasia (210). In this experiment it was also shown that radiation did not significantly alter the cumulative survival curve for mortality from reticulum-cell sarcoma when the data were properly corrected for mortality from other causes. It was also noted that the mean ages at death for mice dying with this or other non-radiation-induced diseases were not significantly different when corrected data were used for the calculations but were reduced in the irradiated groups when such corrections were not made (208). Although radiation can reduce the life span of animals by inducing non-neoplastic diseases, the greater importance of radiation-induced neoplasms has been noted in animals continuously exposed to neutrons (132) and ^{60}Co-gamma radiation (60) and in animals carrying internally-deposited radio-nuclides (18) when doses (and dose rates) were low. Additional data from larger experiments will be required to verify the observation that specific diseases, principally neoplasms, are responsible for life-shortening after exposure to moderate to low doses of radiation.

III. Statistical analysis of specific disease incidence in survival experiments

21. Failure to analyse properly data from survival experiments seriously weakens the conclusions that can be drawn. The common rules, including clear statement of hypothesis, proper experimental design (particularly, adequate sample sizes), adequate accumulation and recording of data and statistical analysis of the data with particular reference to testing for significance, must be applied before accepting or rejecting the hypothesis on which the experiment is founded. These rules have been particularly difficult to apply to animal survival experiments because of the duration and biological variability inherent in such experiments, but the rules must be applied nevertheless. The use of computer data storage and retrieval systems coupled with statistical analysis and testing by computer (see reference 63, for example) permit easier handling of these complex data.

22. An additional problem in analysis of survival experiments is posed by competing probabilities of other causes of death. It has long been recognized that the final incidences of late-occurring diseases are seriously affected by mortality rates from early-occurring diseases. Despite this, data obtained at necropsy are usually presented as the observed incidence of a specific disease and the mean age at death of animals dying with that disease. Such incidences are also used for computing RBE and dose-reduction factors due to protraction of radiation and for describing dose-response curves despite recommendations to the contrary (47, 132). The extreme variability of these radiation parameters is due in part to the use of such uncorrected data. Various actuarial techniques are available for correction of mortality from a lethal disease (e.g., 35, 93) and should be used. The Committee has based its conclusions almost exclusively on data which have not been obscured by intercurrent mortality. In most cases this has been accomplished by using data corrected for competing risks, data for diseases occurring early in life, such as thymic lymphoma where perturbations from other diseases are relatively minor, or data from serial-sacrifice experiments. Occasionally, uncorrected data for late-occurring tumours are referred to if the mortality patterns for all causes of death are similar in the groups being compared.

23. Another possible source of error in statistical analysis is the use of the actuarial techniques designed for assessing causes of death (paragraph 22) with non-lethal diseases such as benign tumours. Changes in mortality pattern due to lethal diseases can be shown to alter age-specific incidence rates of non-lethal diseases

such as ovarian cysts and small pulmonary adenomas. Use of appropriate statistical techniques for correction of competing risks in the case of both lethal and non-lethal diseases has been described by Hoel and Walburg (72).

IV. Special problems of internal emitters

24. Considerable animal experimentation has been carried out in the last decade in an attempt to predict the effects of internally-deposited radio-isotopes in man. In assessing the experimental data, there are several difficulties in interpretation which must be considered. The principal problem is the determination of dose to the susceptible cell population. Different isotopes localize in different tissues to different extents—depending on route of introduction, species, age, and other physiological and environmental variables. In addition, deposited radio-isotopes are involved in the normal metabolic and replacement mechanisms of the body which proceed at varying rates in different hosts and environments. Without measurement of dose to the tissue at risk it is difficult to determine such quantitative factors as dose-response curves, dose-reduction factors for protracted radiation, and RBE (see reference 18 for discussion). Recent attempts have been made to measure the dose to various regions of an organ (principally bone). Both theoretical considerations (121, 228) and direct measurement of linear path length with packed lithium-fluoride thermoluminescent dosemeters (177) and quantitative auto-radiography (70) have been investigated. Considerably more data on dose distribution of internal emitters and structural characteristics of tissues from experimental animals and man are required before a confident comparison of effects in experimental animals and man can be developed.

25. An additional problem is that the susceptible cells are exposed to continuous irradiation at variable dose rates depending on the replacement or metabolic changes and physical half-life of the radio-isotope studied. The dose-response relationships of radiation-induced neoplasms are often difficult to determine for internal emitters because the dose and dose-rate effects cannot be isolated from one another, although it has been shown in some cases that the total accumulated dose is more important than the initial dose rate (146, 202). It is clear that when an animal is continuously irradiated (externally or internally) until death, the cumulative dose received by a tissue contains a component of "wasted radiation", i.e., radiation in excess of that required to produce the effect being measured (9, 49, 128). In addition, survival time may be affected by the radiation administered during the development of an ultimately fatal pathological process (49, 134). Because of these indeterminates, it becomes essential to define the parameters involved in assessing quantitative radiation factors. For example, the RBE for external whole-body irradiation describes the relative effectiveness of different qualities of radiation. An RBE for internal emitters, on the other hand, depends not only on radiation quality but also on differences in distribution, dose rate, etc. Dose-effect curves and dose-reduction factors are often calculated on the basis of the "mean skeletal dose", but it appears that for osteoblastic osteosarcomas it is the dose delivered to cells on the surface of the bone that is important (see paragraph 28). It would be helpful if the data from experiments on late somatic effects of internal emitters were presented in a uniform manner by different investigators and if more accurate determinations of dose to the tissue at risk could be performed. As will be discussed subsequently, generalizations drawn from data on neoplasms induced by external radiation seem to apply equally well to data on neoplasms induced by internally-deposited radio-nuclides, suggesting that when dosage patterns are comparable to those for external radiation, internal emitters produce similar results (18).

26. An equation relating known experimental data from animals to the observed effects of ^{226}Ra in man has been used to extrapolate data for other internally-deposited radio-nuclides from animals to man. Thus the ratio of the accumulated absorbed doses of radiation from radio-nuclide X to those from ^{226}Ra that give equal effect in an experimental animal is equated to the ratio of the corresponding doses of radiation in man:

$$\frac{\text{dose from X in animal}}{\text{dose from } ^{226}\text{Ra in animal}} = \frac{\text{dose from X in man}}{\text{dose from } ^{226}\text{Ra in man}}$$

Parameters in the experimental animal can be determined, leaving "dose from X in man" as the unknown for which the equation is solved (41, 49). This equation carries the assumption that the ratio of absorbed doses which produce equal effects for different radio-nuclides will be the same in man and in the experimental animal, independent of promoting host factors which might act differentially, an assumption that at present remains unproved.

V. Tissues at risk

27. As noted in a previous Committee report (182), neoplasia is apparently induced if sufficient radiation is administered to almost any tissue. Induction of neoplasms in various tissues has been recently reviewed (187). The most frequently studied tumours induced by whole-body exposure to external radiation are thymic lymphosarcoma and granulocytic leukæmia in mice and tumours of the endocrine system (particularly of the female) including tumours of the breast, pituitary, thyroid, adrenal and ovary. Considerable attention has also been paid to tumours induced by internally-deposited radio-nuclides including bone, lung and liver tumours. Most of these tumours are common after exposure to doses of radiation in the 100-1.000-rad range. Recent data support the concept that even highly-resistant tissues can be stimulated to form neoplasms. Carcinoma of the œsophagus in mice following ^{60}Co wire implantation (56), bronchial adenocarcinomas in rats following high x-ray doses to the lung (65), intestinal neoplasms in mice following whole-body x- and neutron-irradiation (33), ovarian neoplasms in dogs following fractionated x-ray doses (4), and tumours of the central nervous system following implantation of radio-active pellets (88, 220, 221) have been documented. None of the tumours of the central nervous system have arisen from adult neuronal tissue. As previously noted (182), although neoplasms arise most commonly in proliferating tissues, among different tissues no simple relationship between rate of cellular proliferation and tissue sensitivity exists (85). However, for any one tissue, an increase in cell proliferation appears to increase the incidence of radiation-induced neoplasms (see paragraph 16).

28. The extensive literature on tissues at risk of tumour induction by radiation from internal emitters has been repeatedly discussed (10, 18, 109, 123, 135, 229). In general, neoplastic effects depend on the distribution of the radio-nuclide and its radiation energy, susceptible cells within range of the radiation providing the site of origin of the neoplasm. Particular interest has been focused on the tissue of origin of osteogenic sarcomas. The subject has recently been reviewed (84, 204). The conclusion of these reports and of recent experimental data (211, 215) is that the principal cells at risk are the endosteal pre-osteoblasts and/or osteoblasts, although the site varies with the site of osteonecrosis and its resultant bone resorption and osteoblastic activity (78, 226). The clearest description of events preceding development of a grossly observable bone tumour following treatment with ^{90}Sr has been provided by Nilsson (141). The initial event is cell death followed by increased bone resorption and increase in number of osteoblasts, then by an increase in non-neoplastic fibroblastic and osteoblastic proliferation within the resorption cavities or along the endosteal linings and finally by the development of microscopically and then macroscopically-visible osteosarcomas, both fibroblastic and osteoblastic. This pathogenesis demonstrates the importance of localization of radio-nuclides and, for induction of osteosarcomas, explains the greater effectiveness of surface seekers compared to those radio-nuclides that have a more diffuse distribution in bone.

29. The relative importance of leukæmia and osteosarcoma for radio-nuclides deposited in bone has also received considerable attention. There appears to be a dependence on total accumulated dose, quality and dose rate of radiation, as well as a strain and species sensitivity. Radio-nuclides emitting short-range alpha particles are more effective in producing osteosarcomas than leukæmia (57, 84). Single doses of long-range beta emitters, which expose the endosteum to large doses of radiation in short periods of time, principally cause osteosarcomas (11, 76, 111, 126, 141). On the other hand, leukæmoid reactions and myelogenous leukæmia predominate when long-range beta emitters are administered continuously (57, 76, 111, 126, 231) or in single low-dose injections (12, 142), presumably because of the resultant low dose rates. Rats, dogs, and pigs have a high sensitivity to induction of leukæmia. Mice and rabbits, on the other hand, have a low sensitivity (84, 111) although non-thymic lymphoma can be induced by ^{90}Sr in some strains (87, 143). Even mice, which characteristically have a high incidence of myelogenous leukæmia after whole-body x-irradiation, appear refractory to induction of these leukæmias following ^{90}Sr injection (30).

30. A similar interest exists in defining the sensitive cell population in skin-tumour induction. Although there is no correlation between general skin damage and tumour induction for some radiation (81, 154), careful studies have demonstrated a close correlation between damage to the hair follicles and the induction of skin tumours (1, 17). It has also been shown that development of carcinomas in the mucous membranes of the head of mice injected with ^{90}Sr is preceded by enhanced mitotic activity and dysplasia in the *stratum germinativum* of the epidermis (140).

VI. Dose-effect relations

31. Characterization of the dose-response curves for radiation-induced neoplasms is essential for predicting effects of exposure to radiation at levels too low to examine experimentally (see paragraph 39). The theoretical curves which might be expected and cannot be excluded by presently available experimental data are linear, quadratic, sigmoid, or some other with a slowly-increasing response to increasing dose as shown in figure I (85). The shape of a dose-response curve can be altered not only by differences in radiation quality and related experimental variables but especially by the end-point used as the indicator of response. For example, use of final uncorrected incidences of a late-occurring tumour may give a decidedly different dose-response curve from use of incidences of animals carrying the tumour in mid-life, as determined by serial-killing experiments. Attempts to verify one or another of the initiating mechanisms of radiation carcinogenesis by the shape of the dose-response curve do not appear reasonable in the light of the many promoting influences which appear to be operating from the internal and external environment of the experimental animal.

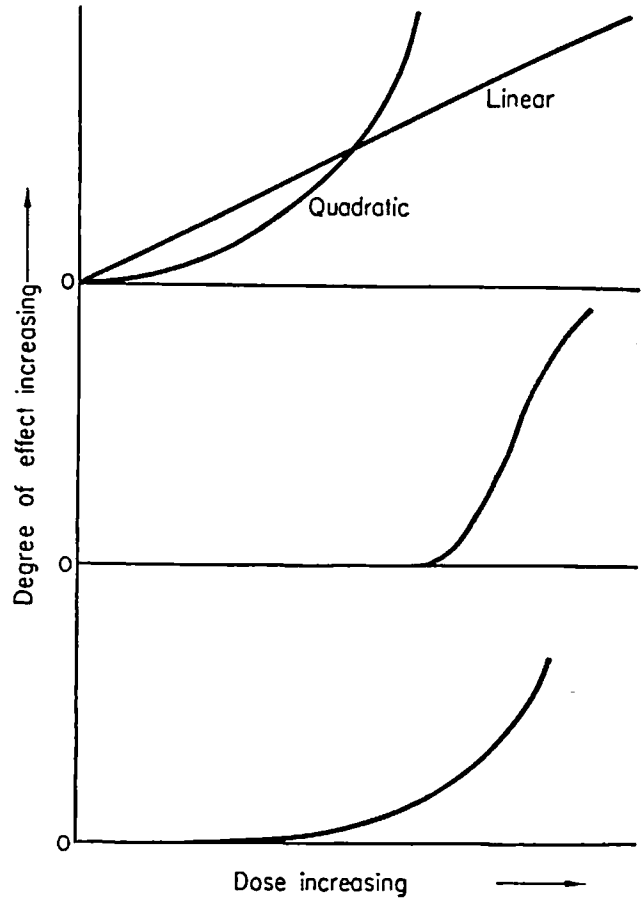

Figure I. Different kinds of dose-response relationship

32. Of particular interest to the selection of appropriate end-points is the question of induction *versus* acceleration. It is generally agreed that if a neoplasm occurs spontaneously with high incidence (e.g., breast tumours in Sprague-Dawley rats), then radiation acts principally by changing the time of onset or latency of the neoplasm. The continuing increase with time in probability of death from a specific neoplasm is often interrupted by death of the animals because of unrelated diseases. Therefore, the final incidence is determined not only by the mortality rate

from the neoplasm of interest but by that from other unrelated diseases as well. Even when neoplasms occur spontaneously late in life with a small but continuously increasing probability, the earlier occurrence and increased incidence of these neoplasms in irradiated populations may be due to acceleration rather than induction. Thus, some measure of acceleration, e.g., the mean age at death corrected for competing probabilities of other causes of death may be a more appropriate end-point than the corresponding final incidence.

33. Whether tumours are induced or are accelerated, one apparent effect of increasing dose is to decrease latency, where this term is defined as "time from application of radiation to observation of neoplastic changes". Such an effect has been noted for rat skin tumours following irradiation with alpha particles and with electrons (17), as well as with fast neutrons and x rays (91); mouse skin tumours after exposure to low-energy beta particles (80); induction of œsophageal cancer in mice following implantation of ^{60}Co wires (212); rat mammary neoplasia following whole-body x-irradiation (172); radiation-induced thymic lymphosarcoma in mice (55, 188); radiation-induced myelogenous leukæmia in mice (192, 234); myelo- and lympho-proliferative diseases of swine following feeding with ^{90}Sr (77); ^{90}Sr-induced bone tumours in mice (141); osteosarcomas induced by alpha-particle radiation in dogs (40) and mice (79); ^{224}Ra-induced ossifying fibromas in mice (59); squamous-cell carcinomas of lung in dogs following inhalation of $^{239}PuO_2$ (150), and skin sarcomas and basal-cell carcinomas in rats following implantation of radioisotope-impregnated Mylar disks (15). When death with a tumour of moderate to long course is the end-point, decreasing latency with increasing dose is not always seen (49). With this end-point, considerable inaccuracy in determination of latency can be expected since the neoplasm originated (and could be observed in radiographs) long before it was observed macroscopically. In all of the examples cited above, except the last, the complications associated with mortality from neoplasms having a long course were not a factor in assessing the latency since determination of early neoplastic growth was made without death of the animal or by serial killing. Where mortality occurred, the course of the neoplasm was short and it appeared early in the life span of the animal.

34. The general character of the dose-response curve consists of an increase in incidence of neoplasms with increasing dose of radiation to a maximum followed by a decline in incidence. The doses at which (*a*) the rise in incidence becomes detectable, (*b*) the maximum incidence is reached, and (*c*) the decline in incidence begins, differ for different neoplasms, species, types of radiation, etc. (figure II). With whole-body irradiation, the limiting factor is often death due to hæmatopoietic failure, and the decline in incidence seen with higher doses can be explained in part by decreased numbers of animals at risk (199). Nonetheless, the fall in incidence of myelogenous leukæmia at higher whole-body doses (192, 234) can in part be explained on the basis of cell killing (62). Certainly there is a decline in incidence of neoplasms with exposure of local areas to high doses of radiation. Such a decline has been seen in the induction of skin (17, 80) and breast tumours (173) by partial-body exposure to radiation from an external source, in the induction of kidney tumours following high doses of radiation to the exteriorized kidney (118) and in the

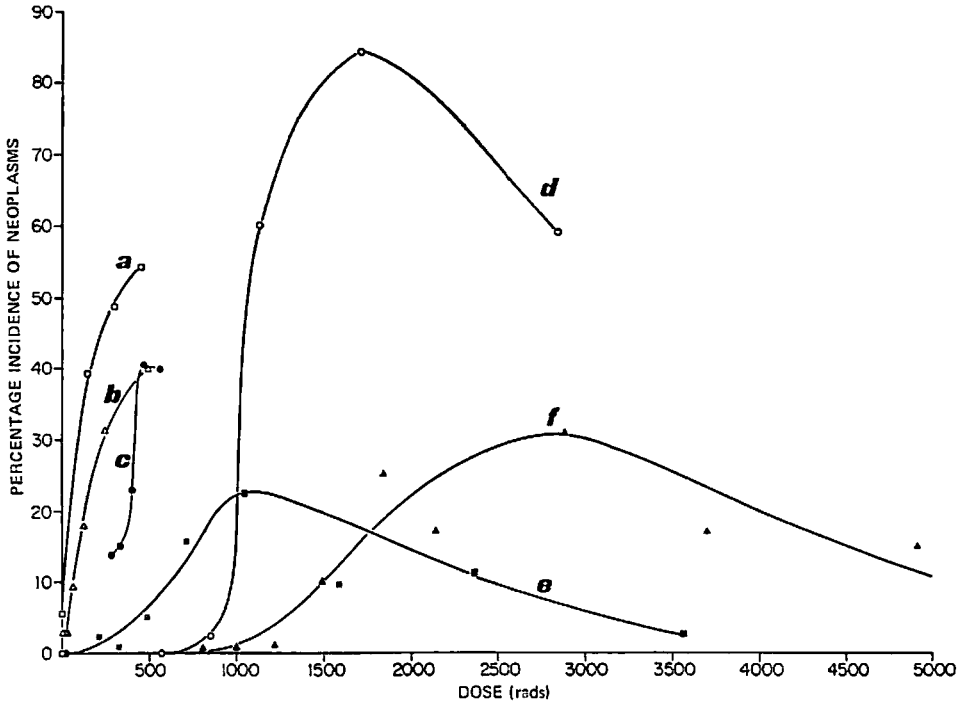

Figure II. Dose-response curves for different types of tumours following exposure to external radiation: (*a*) myeloid leukæmia induced in mice by x rays (199); (*b*) mammary tumours at 12 months in rats by gamma rays (172); (*c*) thymic lymphoma in mice by x rays (96); (*d*) kidney tumours in rats by x rays (118); (*e*) skin tumours in rats by alpha particles (percentage of incidence × 10) (17); (*f*) skin tumours in rats by electrons (percentage of incidence × 10) (17)

induction of bone tumours by internally-deposited radio-nuclides which give rise to high doses of radiation, principally to bone (141). These data can best be explained by cell killing rather than by reduced numbers of animals at risk since little or no mortality of the irradiated animals occurred or the animals were part of a serial-killing study. The doses at which the effect of cell killing begins to reduce the incidence of such tumours are an order of magnitude greater than for myelogenous leukæmia.

35. The dose-response relationship for low doses of external radiation at high dose rates has been described as linear for some neoplasms and curvilinear for others. Data from cell killing and chromosomal-mutation-induction experiments (38) indicate that more than a single event is required to produce the end-points measured. At high dose rates there are often indications that the dose-response curves are linear for high-LET radiation but exhibit positive curvature for low-LET radiation. This is in agreement with the Kellerer-Rossi arguments (see paragraph 9) i.e. with the assumption that two critical events are initiated by a single high-LET particle but predominantly only by two low-LET particles. However, an analysis by Rossi and Kellerer (161) of the dose-incidence curve for mammary neoplasms in the Sprague-Dawley rat indicates that there is lack of linearity at low doses of high-LET radiation. These data suggest also that each tumour arises because of unspecified radiation effects on more than one cell and that extrapolations to low doses are unwarranted. The complications of a multi-step process, however, preclude drawing firm conclusions and these arguments must be tested by examination of more extensive data on radiation carcinogenesis before the validity of the theory can be asserted. It is apparent, however, that repair does not play a significant role in determining the shape of the dose-response curves for single exposures to high-dose-rate radiation, although it is important in the case of low-dose-rate radiation (see paragraph 47).

36. Few experiments have been large enough to provide statistical proof concerning the exact form of the dose-response curves for radiation-induced neoplasms. An apparently linear relationship has been described for the acceleration of mammary neoplasms in Sprague-Dawley rats from x-ray exposures of 25-400 roentgens (172) and preliminary data from a large experiment suggest that the frequency of thymic lymphoma induced in RFM mice by gamma-ray exposures between 10 and 300 roentgens may rise linearly with exposure (190). On the other hand, the x-ray induction of kidney tumours in rats is almost certainly non-linear in the low-dose range (118), and the radiation-induction of skin tumours in rats (17) and mice (80) is probably curvilinear, the response varying with the second or fourth power of the dose. The dose-response curve for myelogenous leukæmia in mice has been described as curvilinear, the response varying with the square of the dose (192). In contrast to the linear dose-response curve seen for thymic lymphosarcoma in RFM mice, the curve for C57BL mice strongly suggests a curvilinear response for the same disease (96). Although the C57BL strain is normally considered to be highly susceptible to induction of thymic lymphosarcoma, it is in reality more resistant to induction of this disease by single, brief x-irradiation than is the RFM strain. These data from experiments with low-LET radiation suggest that the more resistant the tissue to tumour induction, the more likely that the dose response will be curvilinear or sigmoid, and the more sensitive the tissue to radiation, the more likely that linear dose-response curves for tumour induction will be observed. Likewise, linear dose-response curves are seen where the spontaneous incidence of neoplasms is moderate to high, further suggesting that linearity of the dose-response curve is related to sensitivity of tumour induction.

37. As the character of the radiation changes, so does the dose-response curve. X or gamma rays are much less effective at low doses and low dose rates than neutrons. Life-shortening data (197), which can be related principally to the induction of neoplasms (210) demonstrate such differences. For life-shortening due to neutron-irradiation of female RF mice (197), the dose-response curve below 150 rads appears to be linear for both high and low dose rates. The character of the dose-response curve for gamma rays is not as clear, the response to the high dose rate appearing to be linear (as is the case for the thymic lymphosarcoma in this strain), whereas that to the low dose rate appears to be non-linear with marked reduction in effect. For acceleration of mammary tumours in rats, the dose-response curve is non-linear with doses of neutrons up to 50 rads and shows a saturation effect from 50 to 250 rads (207). Considerably more data will be required before the shape of the dose-response curve for neutron-irradiation below the point of saturation can be clearly determined. Change in dose rate also alters the shape of the dose-response curve, but the exact nature of the curve at low dose rates cannot be determined from the limited data available. For both thymic lymphosarcoma and myelogenous leukæmia in RF mice (198) a reduced dose rate of gamma rays results in a dose-response curve similar to that for a high dose rate but with lower peak incidence.

38. The shapes of the dose-response curves for internal emitters, while of importance for predicting effects of such type of exposure at low doses and dose rates, are difficult to interpret because as the activity decreases so does the dose rate. It is clear that for induction of bone tumours by long-range beta emitters, particularly ^{90}Sr, the dose response cannot be linear (125). This effect is attributed to recovery from damage produced by the low-LET radiation when dose rates are sufficiently low. The induction of bone sarcomas by high-LET radiation (i.e. alpha emitters) appears to increase linearly with dose in some cases, but to follow threshold or sigmoid relationships in others. Thus, at low doses, non-linearity was demonstrated for the combined studies of ^{226}Ra, ^{228}Ra and ^{228}Th in dogs (122, 124), and for ^{226}Ra plus ^{228}Ra in humans (162). On the other hand, ^{226}Ra-induced bone sarcomas in CF-1 mice appear to have a linear dose-response curve down to very low doses (49). A similar response was detected with external partial-body x-irradiation (49). The presence of a linear response in this strain of mice may be related to the high (2 per cent) spontaneous incidence of the disease (49). It has also been shown that the RF (30) and the CBA strains (49, 141) are significantly less susceptible to ^{90}Sr-induced bone sarcomas than the CF-1 strain of mouse. As was the case for external irradiation, the induction of tumours in resistant tissue by internally-deposited radio-nuclides appears to be non-linear. The induction of osteosarcomas in most animals (excluding the sensitive CF-1 mouse strain) is a good example of

such non-linear dose-response curves, as is lung-tumour induction by inhaled radio-nuclides (20, 104).

39. There have been many attempts to demonstrate the presence of an absolute threshold for radiation effects. It appears that there is a threshold for very resistant tissues since it requires doses of more than 800 rads in a single brief exposure of the exteriorized kidney to produce kidney tumours in rats (118) and an exposure of more than 35,000 roentgens with local continuous irradiation at high dose rate to produce œsophageal tumours in mice (56). While it has not been disproved that there is an extremely low but slowly increasing response below these effective doses, it seems more likely that induction of these neoplasms occurs only after sufficient tissue destruction and regeneration have occurred, suggesting the existence of a threshold. For more susceptible tissues, however, the threshold, if it exists, is at sufficiently low doses to require massive, expensive experiments to determine its presence. Such efforts should have low priority.

40. On the other hand, the concept of a "practical threshold" has been introduced by Evans (46). This concept is based on the fact that, as dosage decreases, the latency or tumour appearance time increases in some monotonic fashion such that there will be some value of the dose below which the tumour appearance time exceeds the life span. This concept is supported by the suggestion that most, if not all, neoplasms show a decreasing latency with increasing dose (see paragraph 33) and that animals irradiated as adults often die of other diseases before developing long-latency neoplasms because the latency exceeds the remaining life span (see paragraph 51). However, as discussed in paragraph 33, the relationship of dose to latency varies with the end-point for determination of effect. In addition, an accurate determination of the dose at which latency equals the remaining life span requires extrapolation into low-dose ranges where no data exist, which raises much the same problem encountered with the absolute threshold. Further, different values for the practical threshold result when the data are plotted on a semi-log as compared to a log-log plot. It has also been suggested (22) that an extrapolated least-square fit to the MIT human radium data provides a better estimate (and a considerably lower "practical threshold" dose) than the method selected by Evans. Thus, while a "practical threshold" based on latency has some validity, it also appears to have many of the same indeterminants that plague the absolute threshold.

VII. Relative biological effectiveness (RBE)

41. It has been known for many years that low-LET radiation is less effective than high-LET radiation in producing a variety of biological effects including carcinogenesis. Relative biological effectiveness (RBE) was first used by Failla and Henshaw (48) to compare the biological effectiveness of different radiations. Subsequently, RBEs were also used in radiation protection as weighting factors in adding doses of radiations with different qualities (137). It was recognized that the usage of RBE in radiation protection was incorrect (82) and it was recommended that RBE be used exclusively for its original purpose in radiobiology and that the term quality factor be used in the field of radiation protection (83). Thus RBE is now defined as the inverse ratio of the absorbed dose from one radiation type to that of a reference radiation required to produce the same degree of a stipulated biologic effect (138). It has been noted recently that in some instances the RBE increases as the dose decreases because variations in RBE are dependent on the shapes of the dose-response curves. Thus it is necessary to define the curves for both radiations before the RBE can be estimated (figure III). The relationship of RBEs to dose-response curves and their implications for theories of energy interactions at the molecular level have been outlined (98, 160, 179) and are discussed above (paragraph 9).

42. There is no single value of RBE which can be used to predict the relative effects of radiations of different quality in man. A variety of RBEs for different neoplasms in animals, varying from less than 1 to as high as 80, have been reported. It seems certain that much of this variation is due to the use of inappropriate data (e.g., uncorrected incidences) or differences in level of dose or dose rate studied. There are only a few cases where high-LET and low-LET radiations have been compared over a wide range of doses.

43. One of the most extensively studied radiation-induced neoplasms is thymic lymphoma in female RF mice (198). It has been demonstrated that at high doses and high dose rates the RBEs of fast neutrons (196, 198), 14-MeV neutrons (36) and 60-MeV protons (36) are approximately equal to one. This appears to be true over a dose range of approximately 150 to 400 rads of x rays. Between 150 and 25 rads of x rays the RBE for neutrons increases to between 7 and 10 (37). No data exist for RBE below 25 rads of x rays and the shapes of the dose-response curves are unknown at these doses. If both curves become linear, the RBE will remain between 7 and 10. If, as anticipated from theoretical considerations, the neutron curve is linear and the x- or gamma-ray curve is curvilinear at these doses, then the RBE will increase further. The influence of dose rate on RBE has also been studied extensively with this neoplasm and it is clear that neutrons are more effective at lower dose rates than x or gamma rays over a wide dose range. Between gamma-ray doses of 700 and 25 rads, the RBE for fast neutrons increases from between two and four to more than seven, depending on dose rate (196, 198). Since the dose-response curve for neutrons appears to be linear and that for gamma rays curvilinear, higher RBEs might be expected at lower doses.

44. Mammary tumours in Sprague-Dawley rats have also been studied extensively. These data are more difficult to interpret since most of the x- and gamma-ray data come from one laboratory (172) and the data for fission neutrons from another (206). Attempts to determine RBE values from these experiments, which use different techniques and different end-points, have led to values as high as 80 (207). These high values were obtained from the ratio of gamma to neutron doses (400 rad/5 rad) which produce roughly 90 per cent incidence of mammary tumours in Sprague-Dawley rats maintained to death. The accuracy of such determinations is open to question since final incidences uncorrected for competing risks were used and since the final incidence in unirradiated control rats is high (about 50 per cent). Since irradiation results in a dose-dependent acceleration of mammary neoplasia in this strain of rats, the percentage of rats with mammary neoplasms 10 to 12 months after exposure represents the dose-effect relationships more accurately than the survival data. In either case

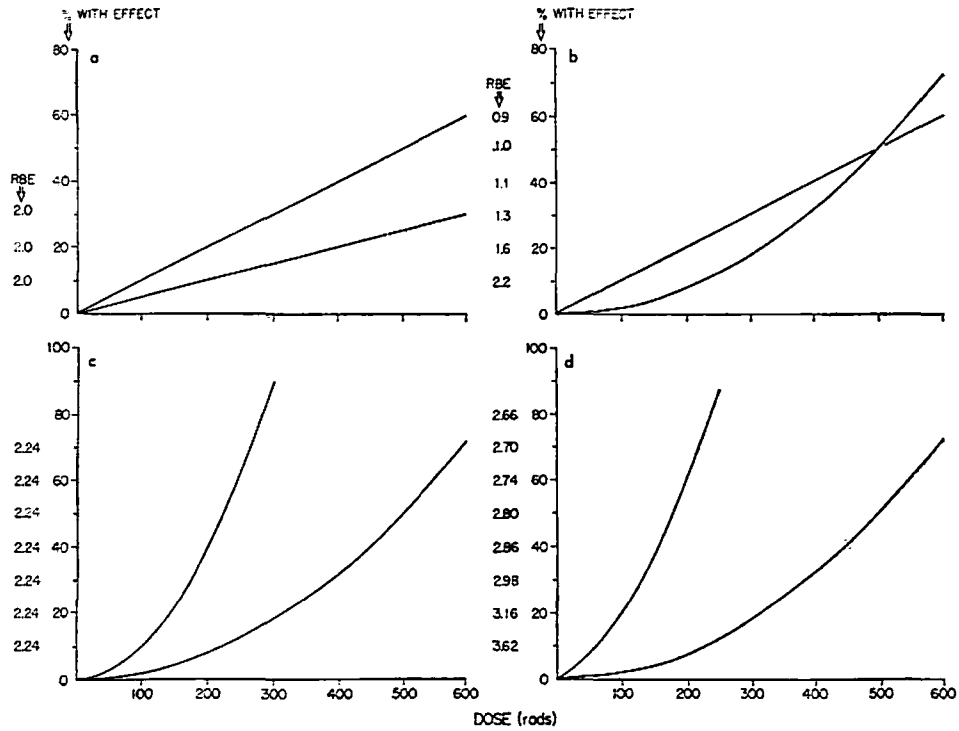

Figure III. Influence of character of dose-response curves on RBE: (*a*) first order (linear) polynomial curves with the same intercept but with different slopes; (*b*) standard radiation, second order (quadratic) polynomial; test radiation first order polynomial; (*c*) second order polynomial curves defined by only two terms, the intercept (which in this case is zero) and the second order term, i.e., $y = cx^2$, but with different second order term constants; (*d*) standard radiation, second order polynomial defined by only the intercept and the second order term; test radiation, second order polynomial defined by the intercept, first and second order terms, i.e., $y = bx + cx^2$

the RBE approaches a value of one between 350 and 400 rads of x rays and increases with decreasing dose (161, 207).

45. Considerable information is also available on the induction of rat skin tumours by cyclotron-accelerated alpha particles and mono-energetic electrons. At lower doses the dose-response curve appears to be curvilinear for both types of radiation, although the alpha particles are more effective and have a more rapid rise in response than the electrons (figure IV). Over the range of doses studied, the RBE of the alpha particles compared to electrons is approximately three and can be considered to increase slowly as the incidence decreases—from 2.3 at 2.0 per cent incidence to 4.3 at 0.2 per cent incidence. Thus within the range of doses for which data for different neoplasms are available, the RBE for high-LET radiation appears to move from one at high doses and high dose rates toward a maximum of 10 at doses between 25 and 100 rads. Estimates at lower doses are not possible since data for calculation of RBE or estimation of RBE by shapes of the dose-response curves are lacking.

46. The relative effectiveness of internal emitters for induction of neoplasia depends not only on the RBE of the particle emitted, but even more strongly on differences in localization, metabolism, transport and size of animal, all of which influence the resultant dose and dose rate to target tissues. For this reason it is not possible to derive quantitative values of RBE for internal emitters for the purpose of extrapolating to man. It can be said, however, that alpha emitters are more effective in producing osteosarcomas (40, 58) and lung tumours (165) than the lower-LET radiations, and the localization patterns of radio-isotopes in bone and the lung play an important role in determining their effectiveness (121, 159, 165).

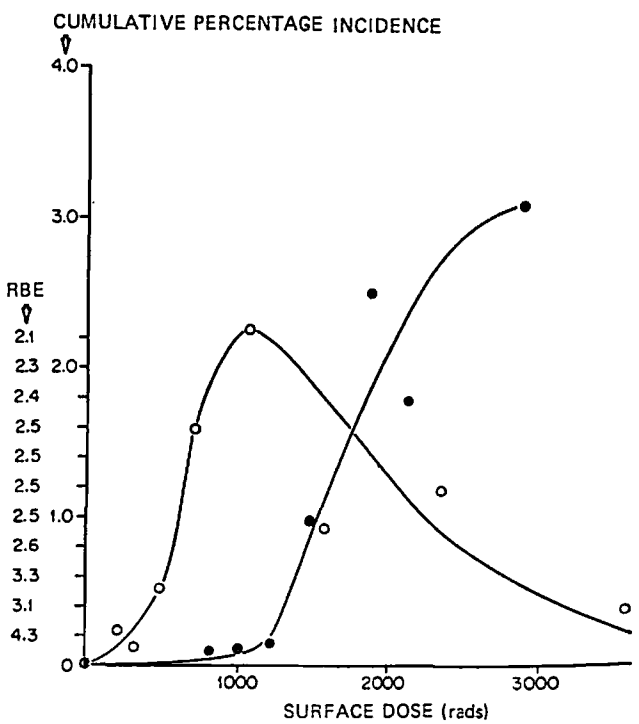

Figure IV. Cumulative percentage incidence of skin tumours at 76 weeks *versus* surface dose of alpha (● - - - ●) and electron (o - - - o) irradiation (17)

VIII. Effect of dose rate

47. It has been known for many years that the dose of ionizing radiation required to produce a given biological effect varies with the dose rate but there are few data on late somatic effects of radiation at low dose rates. Much of the data available relate to life-shortening, which has been reviewed recently by Grahn and Sacher (61). The much smaller body of data on dose-rate effects in radiation carcinogenesis has been reviewed by Upton (185) and the greater dependence on dose rate of low-LET radiation compared with high-LET radiation has been discussed (189). These dose-rate effects can be explained in part by the same mechanism used to explain changes in RBE with dose. If induction of neoplasms by radiation requires that two events occur within a small volume within a sufficiently small amount of time to preclude repair, then low-LET radiations delivered at low dose rates would be expected to result in a low probability of two events occurring simultaneously, and sufficient time might elapse between the two events for repair to take place. With high-LET radiations, the intense ionization patterns yield such a high probability of two events occurring in a small volume at the same time, that even low dose rates would be expected to decrease the effectiveness of high-LET radiations relatively little compared with low-LET radiations.

48. A reduced efficiency of x and gamma rays for production of mouse leukæmia at low dose rates has been reported (164). Dose rates as high as 0.35 rad min^{-1} produce a lower incidence of leukæmia than do dose rates normally employed in "high"-dose-rate exposures (5-100 rad min^{-1}) (129). Thymic lymphosarcoma is more sensitive to this dose-rate effect than is myelogenous leukæmia (196, 217) and induction of both diseases by neutron-irradiation at low doses shows less dependence on dose rate than does induction by x or gamma rays (186, 188, 192, 196, 198). The effect of protraction of dose on the induction or acceleration of other tumours by radiation is less clear, principally because uncorrected incidences have so far been used as end-points. Thus the report that lower dose rates cause an increase in hepatoma incidence (148) can best be explained by increased survival time in the lower-dose-rate group. A significant reduction in ovarian tumour incidence was seen in RF mice irradiated with ^{60}Co gamma rays at low dose rates (184). Although no mortality data accompany the incidence data, it was demonstrated that survival at the lower dose rate was greater than at the higher dose rate (197); thus the reduced incidence cannot be explained on the basis of shortened life span. Since the induction of ovarian neoplasms by radiation has a complex pathogenesis involving the primary event of oöcyte destruction and secondary hormonal stimulation leading to tumour development (see paragraph 53), it is not possible to determine which part of the complex chain of events is affected by the decreased dose rate when tumour incidence is the end-point. No difference in incidence of mammary adenofibroma was noted in Sprague-Dawley rats after gamma-irradiation at exposure rates of 10 R min^{-1} and 0.03 R min^{-1} but the incidence of adenocarcinoma was lower in rats exposed at 0.03 R min^{-1} (170).

49. Numerous studies on fractionation of radiation dose have been performed to determine the amount of reparable injury sustained by the cell, and its translation into radiation-induced disease. Other than the peculiar response associated with induction of murine leukæmia, which is increased by fractionation of radiation dose depending on the schedule of administration (89, 95, 218), most neoplasms occur with lower incidence when doses are substantially fractionated. Such an effect has been reported for skin tumours (81, 157, 235), for ovarian tumours (222), and for the induction of lung tumours promoted by urethan (23, 227). On the other hand, it has been reported that fractionation does not alter the final incidence of mammary neoplasms in rats (230) even when a dose of 500 rads of gamma rays is given in 32 exposures over a period of eight weeks (171). However, since the final incidence of mammary tumours is high in controls, the best measurement of effect is the acceleration caused by the radiation (see paragraph 32). An examination of the data (171) (figure V) shows that at 400 days

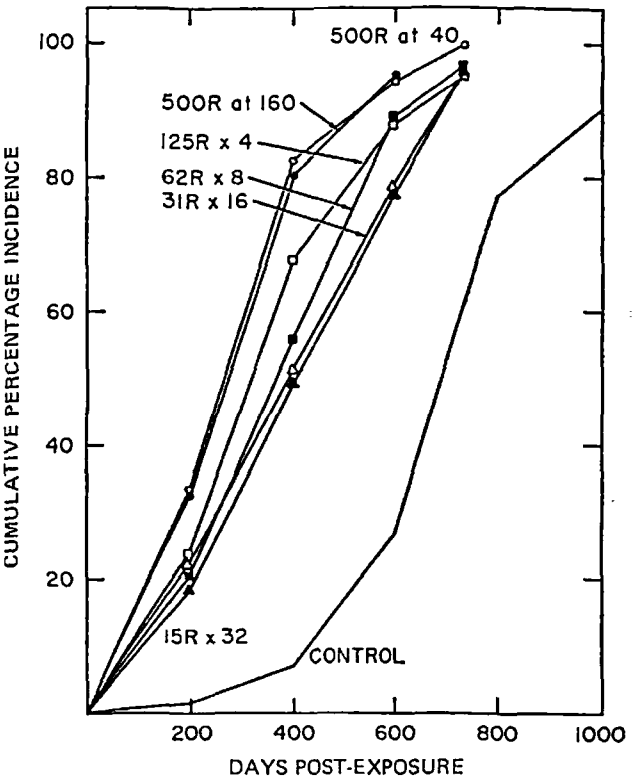

Figure V. Cumulative incidence of mammary gland neoplasia in rats, expressed as a percentage of surviving animals at a given time (rats at risk) having one or more tumours of any histologic type. "At 40" and "at 160" indicate age of rats at time of exposure; "125 R × 4" means that 4 fractions of 125 R were given twice weekly beginning on the fortieth day of age (171)

the cumulative percentage of rats with mammary neoplasms is inversely proportional to the amount of fractionation, with the 32-exposure group showing about 40 per cent reduction. Thus it appears that radiation damage which leads ultimately to neoplasia shows evidence of repair, as do most biological effects of low-LET radiation.

50. The determination of dose-rate effects with internal emitters is a more difficult problem but it is clear that reduction in dose rate reduces the efficiency of tumour induction. Such an effect is seen for induction of bone sarcomas in beagle dogs injected with ^{90}Sr (122). There is a "low-risk" region where bone tumours are not seen despite an accumulation of total

dose in excess of that required for induction of these tumours at higher dose rates. A similar dose-rate effect is seen (*a*) in mice when injected doses of ^{90}Sr are fractionated, giving a reduced maximum dose rate and a decreased number of osteosarcomas (49); (*b*) in mice exposed to different but constant dose rates by continuous ingestion of ^{89}Sr (214), where a reduced dose rate results in reduced incidences of bone sarcoma and hæmatopoietic disease; and (*c*) in lactating mice where the dose rate of ^{90}Sr and the bone tumour incidence are reduced when compared to their non-lactating counterparts (146). In studies on lung-tumour induction by surgically-implanted intrabronchial pellets of ^{106}Ru (104), no difference in lung-tumour incidence was noted between animals exposed at 2.250 rad d^{-1} and those at 422 rad d^{-1}. This is, however, a relatively small dose rate reduction and it would be useful to repeat the experiment with a wider range of dose rates.

IX. Dependence of sensitivity on age

51. The relation of age to the life-shortening effects of radiation (much of which can be ascribed to induction of neoplasms) has been reviewed by Upton (191). In mice, age susceptibility to life-shortening following a single brief exposure to radiation increases to a maximum in juvenile animals, declines until middle age, and increases again in old age (107, 131) (figure VI). The reduced effectiveness of radiation in adult as

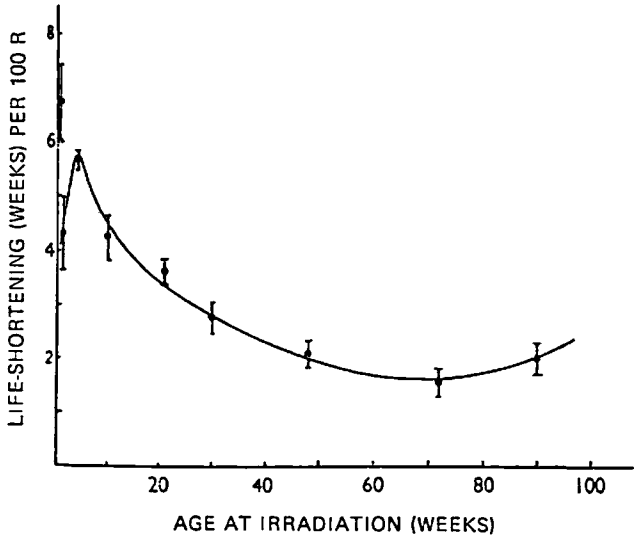

Figure VI. Life-shortening per 100 R exposure as a function of age at irradiation in SAS/4 mice which survived at least 30 days after whole-body exposure to radiation in the LD_0 to LD_{100} range (107)

compared to juvenile animals may be due largely to the failure of adult irradiated animals to survive the long induction period required for expression of the late somatic effects responsible for life-shortening. On the other hand, there is evidence that the susceptibility itself varies with the age at irradiation.

52. The induction of neoplasms is likewise affected by the age at irradiation. Thymic lymphosarcoma, myelogenous leukæmia, and ovarian tumours are particularly sensitive to age effects in mice. In RF mice the sensitivity to induction of thymic lymphosarcoma is low just after birth, increases to a maximum at six weeks of age and declines thereafter, demonstrating low sensitivity after thymic atrophy is far advanced. Myelogenous leukæmia in RF mice also demonstrates a low sensitivity to induction at birth with a slower increase to a later maximum at 10 weeks of age and a slower decline thereafter (195) (figures VII and VIII). Thymic lymphosarcoma in other strains also has

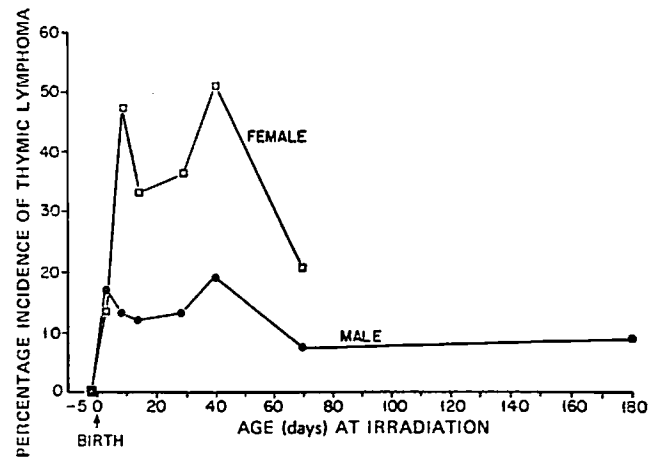

Figure VII. Incidence of thymic lymphoma in relation to sex and age at irradiation (x rays, 300 R) (195)

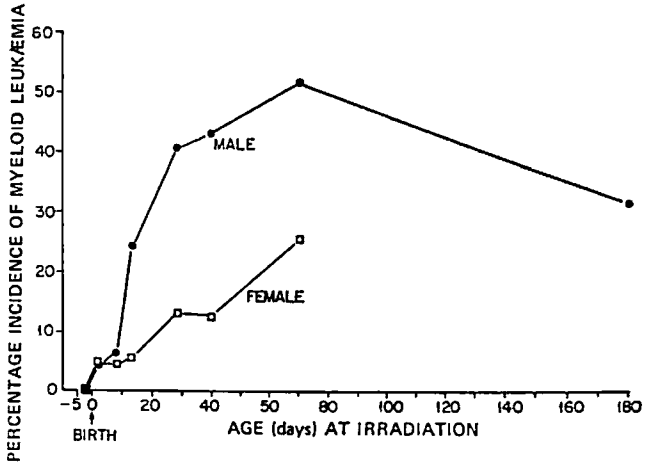

Figure VIII. Incidence of myeloid leukæmia in relation to sex and age at irradiation (x rays, 300 R) (195)

a maximum early in life with subsequent decline (94, 107). Since the latent period and course of murine leukæmias are relatively short, the decline with age cannot be due to insufficient residual life span for expression. X-ray exposures of 50-400 roentgens to RF mice *in utero* at fœtal stages of development when blood formation is localized predominantly in the yolk sac (9½ days after conception), liver (12½ to 14½ days after conception) and marrow and spleen (17½ days after conception) failed to induce leukæmia (185, 191), although these doses are effective in inducing both thymic lymphoma and myelogenous leukæmia in mice of this strain irradiated after birth (198).

53. The incidence of ovarian tumours is dependent on the age at irradiation. Total-body irradiation of young adult mice produces degenerative changes in the ovary with loss of ova of all stages. This radiation

damage enhances the production of gonad-stimulating hormones of the pituitary. While the relative role of this endocrine imbalance as opposed to the direct effect of radiation on cells of the ovary is not clear, the former must be important since intact ovarian endocrine function inhibits the development of tumours in irradiated ovaries (see reference 51). A gamma exposure of 200 roentgens which produces complete sterility in mice exposed at the age of 2 or 12 weeks failed to destroy all ova in ovaries of mouse fœtuses irradiated on the fourteenth or fifteenth days after conception (223). Likewise, doses of radiation which induce a high incidence of ovarian tumours in young adult mice fail to induce such tumours when mice and rats are exposed before birth (155, 195). Immediately after birth, the sensitivity to induction is high (195), reaching a maximum when animals are exposed at 10-20 weeks of age (107, 155) and declining thereafter (32, 107, 155, 158). It is not possible to determine whether the decline in sensitivity with age of irradiation is associated with insufficient life span for expression or with reduced sensitivity of the tissue.

54. The importance of age at time of irradiation has also been demonstrated for the induction of other neoplasms. Kidney adenomas are more easily induced in neonatal than in three-month-old mice (27). Male Sprague-Dawley rats exposed to fast-neutron doses of 215-230 rads show an age-related susceptibility to induction of certain neoplasms (90). Rats irradiated at one month of age were more susceptible to osteochondromas than their three-month-old counterparts. While skin tumours were induced in both groups, those irradiated at one month had a predominance of fibromas while those irradiated at three months had a predominance of basal cell carcinomas. Rats irradiated at three months were more susceptible to cortical carcinomas of the kidney than their one-month-old counterparts.

55. Age-related susceptibility to radiation-induction of tumours by internal emitters has also been reported, and is related to differences in uptake or metabolism of the radio-nuclides. Bone-tumour incidence in young mice (203) and rats (180) is higher than in older animals after treatment with ^{90}Sr; this can be explained on the basis of higher uptake and higher initial dose rate in the younger animals. Similarly, bone-tumour incidence in young rats after treatment with 1 $\mu Ci\ g^{-1}$ of ^{144}Ce was higher than in old rats (114). These results were caused by a lower dose resulting from dilution effects in the rapidly growing rats. Adult rats developed bone tumours at lower injection doses. When dose corrections are made, the differences tend to disappear indicating that the bone cells of young animals are not much more susceptible to induction of neoplasms than those of older animals. Similar results have been noted in man when ^{224}Ra was injected into juveniles and adults; the bone-sarcoma incidence in juveniles was no greater than four times that in adults (178).

56. Fœtal exposure to ^{90}Sr ingested by the mother may be an important factor in the subsequent development of hæmatopoietic neoplasms in miniature swine (149) and ^{32}P administered to pregnant female mice resulted in a significant incidence of leukæmia in female offspring (74). This last result is in contrast to the results obtained with external irradiation (paragraph 52).

X. Differences in sensitivity between strains and between species

57. The role of genetic constitution in long-term survival and induction of neoplasms has been reviewed by the Committee (182) and has since been reviewed by Upton (187). Most of the data on experimental radiation carcinogenesis come from studies with rodents where considerable variation is noted in unirradiated animals, even among different inbred strains of the same species. The spectrum of tumours induced by whole-body irradiation and the amount of life-shortening attributable to these tumours vary considerably with genetic constitution. For example, while the induction of neoplasms by radiation in rodents is well established, none is evident in female burros receiving gamma exposures of 300-550 roentgens despite the occurrence of life-shortening (14). As stated earlier (paragraph 27), almost any tissue will produce a neoplasm if exposed to sufficient radiation. It has also been demonstrated that the different sensitivities attributable to genetic constitution can be overcome if sufficient radiation is administered (212, 213).

58. Different inbred strains of mice differ in their sensitivity to radiation-induction of thymic lymphosarcoma and myelogenous leukæmia (188), but when sufficient radiation is applied in a proper pattern (i.e., fractionated radiation timed to maximize the number of blast cells), some of the differences tend to disappear (153). Species differences exist even among rodents: some strains of rats (130) and guinea-pigs (163, 219) are susceptible to radiation-induced leukæmia, but the Chinese hamster is strikingly resistant (130). Since the Committee last reviewed the subject, additional examples of strain and species differences in sensitivity to induction of various neoplasms have been described. Rats are more susceptible than hamsters to induction of adenocarcinomas of the lung by local external x-irradiation (65); rats are more susceptible than mice to induction of kidney tumours following whole-body x-ray exposures of 500 roentgens (5) but may be less susceptible to large local doses (118); beagle dogs do not show the marked sensitivity of mice for radiation-induction of ovarian neoplasms (4). Different species and strains of animals respond differently to induction of corneal tumours by ultraviolet radiation, with rats, mice, and hamsters being sensitive and guinea-pigs relatively resistant (50). In addition, albino strains of rats are less sensitive than pigmented strains.

59. Considerably less species variation is seen in the spectrum of neoplasms induced by internally-deposited radio-nuclides. Thus, in most species, bone-seeking radio-nuclides cause bone tumours, leukæmias, and squamous-cell carcinomas from tissues in close proximity to the bone. Neoplasms may be induced in other organs when radio-nuclides are deposited there either through direct introduction (e.g., inhalation) or by translocation through physiological mechanisms (e.g., liver with plutonium, pigment epithelium of the eye with radium). This qualitative similarity may be related to the high doses required for induction of many of the neoplasms induced. As was noted in paragraph 57, different sensitivities attributable to genetic constitution can be overcome if sufficient radiation is administered. The qualitative similarity in induction of bone sarcomas by bone-seeking radio-nuclides (122, 125) has been analysed for quantitative similarities among species (133). Although one method of dose calculation (i.e., number of beta particles divided by

body mass) suggests that the radio-sensitivity to tumour induction of the entire endosteum is independent of species, the average skeletal dose required to produce 50 per cent bone sarcomas does vary with the species. In addition, extreme variability in sensitivity among inbred mouse strains suggests that quantitative similarities among species may not exist (30, 49).

XI. Summary and conclusions

60. Comparisons of experimental animal data with human data have been frequent and the Committee is reviewing the most recent data on radiation carcinogenesis in man in annex H of this report. The data reviewed here suggest that the animal systems studied thus far are quantitatively inadequate for determining risk estimates in man. In addition, many of the most commonly studied animal tumours such as thymic lymphoma and ovarian neoplasms of the mouse and mammary neoplasms of the rat appear to have an induction sensitivity far in excess of that seen in man (annex H).

61. On the other hand, there appear to be several qualitative generalizations which may help to interpret the few human data now available:

(*a*) Virtually any mammalian tissue with the possible exception of adult neuronal tissue will give rise to neoplasms if exposed to sufficient radiation;

(*b*) The data from gamma- or x-irradiated animals suggest that for low-LET radiation, while both linear and curvilinear dose-response curves are seen, linear curves in the dose range of less than 100 rads occur principally when the target tissue is highly susceptible to induction of neoplasms by radiation. In man, target tissues which show such high sensitivity to tumour induction by radiation have not been identified except possibly in the fœtus (see annex H). If, as the data suggest, most human tumours induced by radiation arise from relatively resistant tissues, then it could be predicted in the light of experimental animal data that the dose-response curves for such neoplasms will be non-linear in the low-dose range;

(*c*) It is clear, both from theoretical considerations (see figure III) and from animal data, that the RBE for high-LET radiation can vary with dose. A comparison of the dose-response curves for neoplasms induced by high- and low-LET radiation will indicate increasing RBEs with decreasing doses. Estimates of the RBE may be particularly difficult to determine in man where the data at low doses are few, and conclusions about the dose dependence of RBE cannot be drawn until the dose-response curves are defined;

(*d*) Another important consideration is the reduced effect of protracted irradiation as compared to an equal dose administered in a short period of time. While considerably more data are required, the animal data available indicate that both protracted continuous irradiation and fractionated irradiation produce less carcinogenic effect than a single administration of the same total dose, suggesting that such an effect might be expected to occur in man as well;

(*e*) While some exceptions are noted, resistance to radiation-induced tumours is higher in adult than in juvenile rodents and, although some strains of rats and mice are highly susceptible to radiation-induction of leukæmias, fœtal irradiation has failed to induce a significant amount of leukæmias in those strains. The significance of this observation to fœtal irradiation of man must await further studies (see annex H);

(*f*) A difference among species and among strains of the same species in resistance to radiation-induction of neoplasms has been noted, suggesting the existence of considerable genetic control. Such genetic control of tumour induction by radiation makes clear the need for caution in the extrapolation from experimental animals to man. On the other hand, the development of valid qualitative generalizations which appear to apply to mammals of many different species gives hope that quantitative inferences may ultimately be possible.

XII. Areas of major emphasis for future studies

62. While some qualitative generalizations have been derived from animal data which may be useful in understanding the risk of neoplasia following irradiation in man, considerably more data from experiments with a variety of animal species will be required before they can be useful for supplementing quantitative estimates of risks of neoplasms in man. It is particularly important that attention be paid to the determination of the populations of cells that are at risk of neoplastic transformation and the determination of the physical dose to such cells. Where such determinations can be made, it is then essential that experiments be designed in such a way that their results may help in better evaluating quantitative risk estimates for humans. Considerable work is in progress in these three areas for the induction of bone tumours by internally-deposited alpha-emitting radio-nuclides, but other tumour systems must also be studied.

63. Further, the Committee recognizes that there are several broad areas in which we require more information. Among these are studies relating to the mechanism of radiation carcinogenesis. Support or rejection of the various initiating and promoting mechanisms or evaluation of their relative importance will require considerably more data from a much broader spectrum of *radiation-induced* tumours. For example:

(*a*) The role of virus activation as a mechanism in radiation-induction of neoplasms of the hæmopoietic system needs to be extended from the C57BL mouse to other strains of mice and other mammalian species;

(*b*) Similarly, efforts must be made to determine whether viruses which can produce tumours of non-hæmopoietic tissues are activated by radiation;

(*c*) Additional attention should also be given to radiation-induced cell destruction and any subsequent changes in cell repopulation which might temporarily increase the population of susceptible cells. Since different tissues have various susceptibilities to radiation induction of neoplasms, they can be examined for such corresponding changes in cellular kinetics:

(*d*) Likewise, damage and repair of DNA with the production of gene and chromosomal mutations, as well as damage to other biologically important macromolecules, must be related to the production of neoplasia before radiation-induced somatic mutations can be accepted as a cause of the neoplastic effects;

(*e*) Radiation-induced changes in other cell constituents, particularly cellular and nuclear membranes, should also be examined and their relationship to neoplastic transformation determined;

(*f*) The role of radiation-induced immune disorders in neoplasia should be examined with radiation-induced tumours of different tissues;

(*g*) Further clarification of the mechanism of radiation-induced neoplasia may result from studies on disturbances of the neuro-endocrine system by radiation;

(*h*) The effect of radio-protective agents, including both chemical agents and cellular replacement, on radiation-induction of neoplasms may also help to clarify these mechanisms;

(*i*) Another broad area of particular importance to the ultimate understanding of radiation carcinogenesis in man is the role of genetic constitution as a determinant of the susceptibility to induction of cancer by radiation. Studies on the mechanism of gene action in inbred animals are critical to this understanding;

(*j*) Further clarification of the relative importance of dose and dose rate for induction of neoplasms by internally deposited radio-nuclides should be sought through studies on the effect of repeated administration of short-lived radio-nuclides, a procedure analogous to fractionated external irradiation.

64. More data are required to confirm and extend some of the conclusions reached in this report. Most of the experimental animal data derive from studies on a few very sensitive rodent tumour systems. It is essential to study the reduced efficiency resulting from protracted irradiation (dose-rate effect) in other radiation-induced tumour systems, especially less sensitive ones, in a variety of strains and species. In the same sense, it is important to provide data on change in RBE with dose of radiation for a variety of tumour systems, since the applicability of the Rossi-Kellerer theory (see paragraph 9) to the mechanism of radiation-induced damage leading to neoplasia is based on examination of only one such system. The suggestion that shortening of life span by moderate to low doses of radiation (below 300 rads) is primarily due to induction of lethal neoplastic diseases is based on very few data. Expansion of these data is necessary to verify this generalization which can be extremely important for setting risk estimates for human populations. And lastly, the Committee feels that the apparent discrepancy between the rodent data and human data on induction of leukæmia by fœtal irradiation must be studied in additional species which have different rates of maturation of the lymphopoietic system during gestation. All of the studies suggested in this paragraph can be carried out now with existing knowledge and techniques. However, it is essential that such studies utilize the best of statistical approaches to experimental design, as well as careful and proper pathological diagnosis. Analysis of the data must include corrections for competing risks, especially where studies involve late-occurring radiation-induced tumours, which now are those of principal interest.

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