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SOURCES AND EFFECTS OF IONIZING RADIATION

United Nations Scientific Committee
on the Effects of Atomic Radiation

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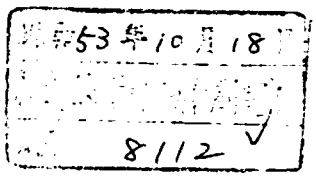

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ANNEX I

Experimental radiation carcinogenesis

CONTENTS

Introduction

1. Induction of neoplasia by ionizing radiation represents one of the first recognized radiobiological effects described in man soon after the discovery of x rays (715). Bergonié and Tribondeau (42) in 1906 in an attempt to rationalize the use of radiation for the treatment of tumours drew the attention of radiologists to this harmful consequence of over-exposure. The first documentation of sarcoma induction after repeated exposure to x rays of an animal's skin followed a few years later (424, 425), and the origin of what is presently known as experimental radiation carcinogenesis may probably be traced back to these classical reports.

2. In spite of some scattered papers which extended the initial observations to practically all common species of laboratory animals and to a variety of different tissues (for good historical reviews see 364, 675, 677), the years that followed until the middle 1940s did not, however, witness the configuration of experimental radiation carcinogenesis as a chapter separate from the field of general carcinogenesis, which was especially concerned at the time with the various aspects of chemically induced neoplasia. Important advances in radiation carcinogenesis were brought about by the experience in man with the reports of radiation-induced lung cancer among uranium miners (577) and of bone sarcoma in dial painters (428). Starting from the middle 1940s on, as a result of the A-bomb experience and within the framework of the renewed interest in biological and radiobiological research, a steady increase in concern and reports on the induction of tumours by radiation has taken place, amounting at present to an estimated few thousand specific bibliographic references. From time to time, the newest acquisitions have been reviewed and the relevant references may be found in Colwell and Russ (125), Furth and Lorenz (208), Lacassagne (362, 363), Furth and Upton (209), Brues (68), Lacassagne *et al.* (364), United Nations (668, 669), Harris (258), Casarett (91), Upton (672, 673, 675, 679), Curtis (140), Van Cleave (697), Casarett (92), Mole (459) and Moskalev and Streltsova (477).

3. Yet, after almost 80 years of arduous research in experimental animals and observations in man, it must be recognized that the complexity of the problem has so far defeated any effort for a reasonable understanding of its numerous implications. The growing concern from the wide-spread use of radiation in industry and medicine (see 562 as a general reference); the progress made in very recent years in all specialized fields of carcinogenesis, with special regard to the role of viruses and their interplay with radiation and to the role of the immune reaction in the development of neoplasia (see 38 for an updated treatise on all aspects of carcinogenesis); the availability of new experimental data in the specific field of neoplasia induction by radiation to be dealt with in the course of the present report: the desirability to keep under close scrutiny the newest development in the experimental animal systems for their implications in human radiation protection; the need to identify areas of special importance where effort might be preferentially addressed in the future (see 564 and 670 as general references); all these, have prompted the Committee to reconsider the information on the induction of neoplasia in experimental animals, after the latest review on the same subject appeared most recently (670).

4. As in the preceding case (670), the present review is not meant to provide an exhaustive and comprehensive treatment of the subject—a very difficult undertaking in view of the vast amount of information available—but a selection of illustrative papers. An effort has been made to identify those reports where the relevance of the hypotheses to the subject, the accurate planning of the experiments, the numerosity of the observation, and the application of careful statistical treatments to the data, render the conclusions amenable to a general interpretation and evaluation. Along these lines, the main scope of the review is therefore that of setting the newest acquisitions in the light of the general problem of cancer induction and of its recent developments, and to identify generalities and regularities emerging from the animal experience that may be of help for the interpretation of the human data.

5. The 1972 report of the Committee (670) has already discussed extensively the scope and the limitations of animal experimentation in radiation carcinogenesis and its role with respect to the interpretation of the epidemiological data. It should again be stressed that animal data are of great value in illuminating the effects in man but may not be used for numerical estimates. They are therefore as such an inadequate substitute for the existing paucity of data in the human species. There are at present insurmountable difficulties in extrapolating between different conditions of exposure, between high and low radiation doses and dose rates in the same species, and even more in the attempts to make generalizations about species having widely different physiological and pathological characteristics. But, partly for pragmatic reasons, owing to the pressing need to project the available data in man to conditions other than those where they were derived, and partly on scientific grounds, in view of the qualitative similarity of cancer induction in man and in other mammalian species, the experimentation on animals has acquired great significance for the understanding of the carcinogenic risk in man. According to the conclusions of the 1972 report (670) which are still valid at present, the contribution of experimental work to the general problem of risk evaluation in man may come about from three main lines of approach.

6. The first and most basic of these lines relates to the clarification of the mechanisms of carcinogenic action. It is obvious that this line still retains its overwhelming value since, in spite of the continuous advancements in our understanding of these mechanisms, we are still far from their detailed comprehension. It must, on the other hand, be realized that research in radiation carcinogenesis is a difficult and slow undertaking, where results cannot be expected within a short time.

7. The second line of approach, discussed by Mole (457), attempts to establish qualitative and possibly quantitative generalizations with respect to a number of

physical parameters (dose, dose rate, radiation quality) and biological parameters (age, sex, weight, body or organ size, metabolic rate, rate of DNA synthesis) which are known or suspected to affect radiation carcinogenesis. This course of action in fact yields useful data, although by no means adequate at present for the quantification of parameters generally applicable to all species with the necessary degree of certainty.

8. Finally, the search for experimental models of carcinogenesis which might respond to radiation in a manner qualitatively similar as in man, has been identified as the third possible objective of well founded experiments. It is thought that knowledge of the relationship of effect with dose and dose rate in such animal models (especially in the conditions relevant to radiation protection) could perhaps allow refinements in our risk estimates for humans, possibly by a consistent factor (564). The development of other models which facilitate the study of relations between tumour induction and such phenomena as radiation-induced cell killing and cell transformation, division and differentiation, could also be useful for that purpose.

I. METHODOLOGICAL ASPECTS OF RADIATION CARCINOGENESIS

A. EXPERIMENTAL APPROACHES

9. The work on experimental radiation carcinogenesis offers unique features that might be considered in a common context, partly to emphasize the difficulties in designing, performing and analyzing radiation carcinogenesis work, partly to draw attention to the many pitfalls that should be taken into account when reviewing results, and partly to warn the reader of the need for caution when generalizing the relevant conclusions.

10. Experiments on radiation carcinogenesis have been performed, especially in the past, on large populations of animals. There were well founded reasons for this experimental strategy, since quantiative assessments of the risk of late effects were needed and the use of large groups of animals was rightly considered as a reasonable, direct solution to the problems of obtaining overall estimates of the risks. The so-called "Greenhouse Experiment" carried out by a task force of scientists and published in its final form in 1960 (688) is probably the best known example of this type of approach involving major scientific efforts and complex organizational problems. The importance of this early experience is outstanding since through it the major long-term effects of irradiation could be documented and basic information about the significance of radiation quality, dose and time factors in mammalian carcinogenesis became available.

11. However, it became gradually apparent that a comprehensive approach involving actuarial, epidemiological and pathological observations of all possible lesions expressed by irradiated animal populations was unsuitable for a detailed investigation of mechanisms. The study of structural and functional modifications at the cellular and subcellular levels during the action of the carcinogenic agent can hardly be carried out on very large groups of animals.

12. For this reason and also because extrapolation of mechanisms between different animal species might perhaps be easier than the extrapolation of rates of induction of diseases which are typical of each species, a different experimental approach has been advocated. The new strategy is perhaps less ambitious since its main scope is to provide answers to very specific questions by designing and testing simplified models of radiation carcinogenesis *in vitro* and *in vivo* (127, 564). The conversion to this new experimental approach will probably be very gradual and in any case will not exclude entirely the traditional large-scale experimentation. Indeed, just as experimental work on model systems was also carried out in the past years, large-scale work may still be necessary in special cases in the future. However, the trend is towards a new equilibrium between both approaches, and only time and experience will allow a definite judgement on their merits.

B. CHOICE OF EXPERIMENTAL ANIMALS

13. From consideration of the available literature it appears that in some cases not enough attention has been paid to the choice of the experimental animals used in radiation carcinogenesis work; this can probably be attributed to unavailability of the relevant specific knowledge at the time when the experiments were planned. The choice of the animal species and/or the strain is however of paramount importance and should primarily be a function of the specific effect to be investigated. In this context, susceptibility of the experimental animal to the particular form of neoplasia under study is often the main consideration. Examples might be offered by the tumours of the kidney to which the rat is particularly susceptible (36, 422) or by the specificity of host-virus relationships in radiation-induced leukaemogenesis in mice (237).

14. In other cases, however, the choice of the animal is primarily dictated by the need to facilitate the extrapolation of the effects by extending the observations to different animal species (730, 638) or by the desire to simulate more closely the exposure of humans by using medium- and large-size mammals such as the dog (545, 622, 435), the pig (281, 278) and the monkey (440, 259). Within each species, however, the characteristics of particular inbred strains with respect to the spontaneous (630, 16, 413) or induced (566) rate of occurrence of special tumour types should also be considered as well as the effect of sex (paras. 68-73) and age at irradiation (paras. 289-300). As a very general proposition and for reasons to be examined later, a good model of carcinogenesis is one where the spontaneous incidence of the neoplastic lesion under investigation is very low in the intact animal and increases considerably after treatment; examples of such systems may be the radiation-induced mammary neoplasia in the young Sprague-Dawley rat (138) or the thymic lymphoma of the C57BL mouse (326). In special instances, however, the reverse condition (high spontaneous incidence of some tumour in normal animals, which is depressed by radiation treatments) may also be of value (135).

C. EXPERIMENT PLANNING

15. When dealing with marginal effects, often on the borderline of significance, it is imperative that the variability introduced by the presence of intercurrent diseases in the animal colony should not mask the effects of the radiation treatment. This calls for high hygienic standards in animal maintenance. It has also been shown (paras. 80-82) that the conditions of the animal intestinal microflora as affected by the living environment may introduce changes in the neoplastic response. Although such effects are probably not relevant to all tumour types, these observations stress the need for a permanent control of the animal facilities in order to allow a precise evaluation of the health conditions of the colony at all times during the execution of the experiments. There is certainly no need here to discuss in detail all procedures connected with animal handling (caging, identification, routine inspection, data collection etc.), but it should be stressed that, in view of the long duration of the experiments, even minor faults in the handling technique might result in the loss of precious data. In large-scale work, information storage, retrieval and processing have been handled by computers (234, 106).

16. Induction of cancer by radiation is a comparatively rare phenomenon, and to be established with the necessary degree of confidence by a comparison between treated and untreated animals this comparison requires therefore the use of fairly large groups of animals, the size of which must be related to the expected incidence of the tumour type and to the accuracy with which the induced change with respect to background incidence is to be assessed. Very large animal populations are particularly required at low radiation doses and dose rates where the incidence of tumours above the spontaneous level is very small and the resolution of the experiments critically depends on the number of animals tested. A good example of the criteria to be followed in the estimation of the sample size in an experiment on tumour induction designed for a particularly well known strain of animals has been provided by Upton *et al.* (681). The situation presented in that report may however be regarded as an extreme one in the sense that seldom are the starting conditions of an experiment so thoroughly defined and also because information is not often sought at such very low dose levels.

17. Calculations of this type may also be performed by other mathematical models (571), but they require, in general, preliminary knowledge of the tumour system to be investigated and, in particular, some background information on the form of the dose-effect relationship and on the latency period of the expected lesions. With regard to sample size, a distinction can probably be made in practice between those experimental series where the primary object is the estimation of tumour induction rates as a function of an independent variable like the dose, and other series concerned with the study of mechanisms, where internal comparisons between groups given different treatments usually allow working with smaller groups (335). The above considerations, however, emphasize the importance of careful planning and the convenience of utilizing animal model systems where basic information on tumour incidence and induction is already available so that previous experience on the model may help in designing further work.

D. DATA COLLECTION

18. The literature reviewed, particularly the earlier reports, show that there has been a tendency by the pathologists to underestimate the need for good planning and for quantitative observations on the irradiated animals and, conversely, that there has been inadequate attention given to the pathology of the induced lesions by radiation biologists mostly concerned with the statistical and epidemiological end-points. This tendency is disappearing in recent papers since it is now clear to all engaged in long-term experimentation that both types of end-point, the morphological and the actuarial, are equally important for a comprehensive evaluation of an experiment. It has also been realized that experiments on late effects, due to their size and cost, are often unique and the best possible use must therefore be made of all the information available. There is no need therefore in the present context to emphasize further the importance of regular animal follow-up and of a thorough macroscopic and histological examination of the animals, particularly at death. Specialized reports are available on this subject to which reference may conveniently be made (133, 106).

19. As far as pathology is concerned, it is important to point out that the object of post-mortem examination is not only to establish the immediate causes of death, but particularly to provide a complete description of the animal's condition at death, for the identification of the various syndromes and lesions brought about by the radiation treatment. In special instances more detailed pathological studies are required, and when the information is obtained at the time of death, it is inadequate for a full description of the time of onset, the rate of development and the final incidence of the various neoplastic lesions. To this end, serial sacrifice experiments are needed (9, 169). In other instances biochemical, microbiological or functional changes must be investigated by destructive tests. Animals for such parallel studies should however be kept separate from the experimental groups on which actuarial observations are made, since withdrawal of animals for sacrifice might seriously affect the estimates of mortality rates in the main experiment (681, 270).

20. Although it is accepted that radiation can induce a great variety of tumours having a wide spectrum of malignancy, the classification of these tumours into "benign" or "malignant" causes endless controversy among pathologists. In fact, the morphological aspects of the tumour cells, their tendency to invade the normal surrounding tissues, their ability to metastasize and to grow into host animals after transplantation, the capacity of the tumour to kill the animal, the immediate cause of death etc., may be assumed to be singly or jointly the criteria to assess malignancy. The present report avoids such a controversial field by referring as much as possible to the nomenclature of tumour types used in the papers reviewed.

21. Recording and classification of the pathological observations may follow extensive (124) or more frequently, compact computerized schemes (520, 106) conveniently adapted to the special needs of the experiments. Special attention should be drawn to the desirability of uniformity in the classification of the various diseases, bearing in mind that late pathological syndromes in animals are often unique to the various species. Efforts for standardization in this field are currently being made on an international scale and to this end cross-reference programmes between specialized laboratories are also desirable (667). Similar criteria of uniformity should also be applied to the conditions of radiation exposure, for which reference is made to general publications (294, 295). Programmes of radiation dosimetry standardization among laboratories specifically active in the field of late effects are also being made and should be continued in order to improve the reproducibility of the physical parameters (550).

E. STATISTICAL ANALYSIS

22. According to Berenblum (38), there are at least four ways of expressing quantitatively tumour induction among treated animals. These are widely used in chemical carcinogenesis work, but are as such inadequate to provide a comprehensive description of the final tumour incidence and incidence rate in radiation work. They are: *(a)* the percentage of animals bearing one or more tumours; *(b)* the average number of tumours per tumour-bearing animal or per treated animal; *(c)* the average and distributional latency times in the appearance of tumours after the application of the carcinogenic stimulus; and finally *(d)* the doses of carcinogen to obtain minimal effective and maximal carcinogenic response in the tumour system under study. The last type of data is precisely what is usually sought in radiation work, that is, the establishment of complete dose-effect relationships; however, the precise assessment of such relationships based on final tumour incidence rate is to a variable extent influenced by the mortality from other diseases in the course of the experiment.

23. In spite of the fact that the effect of competing risks on the induction estimates has been recognized for some time, and that attention has been drawn repeatedly to the possible consequences of not properly allowing for such risks in radiation carcinogenesis work (455, 175), many reports are still found lacking precise actuarial analyses. Appropriate advanced statistical treatments (144, 318) and guidelines to the analysis of tumour and death rates in the presence of competing causes of death are however available (569, 270, 533). Special procedures for the case of continuous exposure to the carcinogenic agent have also been devised (534).

24. A reasonable analysis of the epidemiological and pathological data in radiation carcinogenesis work rests in practice on the following steps. First of all, the construction of the cumulative mortality curve for each experimental group under study, with appropriate estimates of the fifty-per-cent end-points (mean and median) and of their variability. This preliminary step may be carried out by elementary statistical and graphical analysis. Consideration of the general trend of these curves is however inadequate for the identification of possible irregularities in the rate of extinction of the animal population, except in cases where such phenomena are particularly important. Only a second step consisting in a careful study of the instantaneous and cumulative rate of mortality intensity as a function of time, with appropriate corrections for the actual number of animals at risk in any particular time interval (343), will allow the identification of peaks or plateaus in the death rate of the population, which may possibly be traced back to special pathological lesions or syndromes operating in the animals at that particular time. Computation of such death-rate curves at varying time intervals will help to evaluate the importance of these changes, which, especially in small groups of animals, may sometimes be regarded as the spurious result of the system's variability rather than the effect of consistent pathological phenomena. Finally, attention should be focused on any particular disease (or group of diseases) diagnosed, in order to estimate its age-specific rate of occurrence and its final incidence, with appropriate corrections for competing risks (571, 270).

25. It is appropriate to mention at this point that comparisons between different treatment groups in order to derive numerical estimates of tumour induction (such as, for example, in relative biological effectiveness (RBE) or dose-rate-effect studies) should only be performed after elementary criteria of homogeneity between the groups under comparison are satisfied, namely that the mean and median longevity and the rate of mortality of the two animal populations are actually comparable. Unfortunately, reference is seldom made in the reviewed papers to the use of such cautions in the statistical analysis of the data. Calculation of age-specific incidence curves may be considered the only appropriate and complete method of actuarial analysis, since it allows the precise evaluation of both acceleration and true induction phenomena in radiation carcinogenesis (paras. 92, 93). Although the numerical estimates of tumour induction obtained from this type of analysis may not be strikingly different from the results of less refined methods in the case of early-appearing tumours such as the thymic lymphoma, age-specific calculations are absolutely required for all pathological conditions occurring gradually and late in life, such as the malignant solid tumours or the systemic lymphoreticular neoplasms. It is desirable that a more extensive use of these actuarial techniques be made in the future, since they will clarify the conditions under which numerical estimates of tumour induction are actually made.

26. Many aspects of radiation-induced carcinogenesis are closely related to life-span shortening, another important effect of irradiation readily apparent in treated animal groups as a reduction of the mean age at death. There have been discrepancies in the interpretation of this phenomenon and its relevance to tumour induction. On the one hand, the results of experiments where large groups of animals were irradiated with high instantaneous whole-body doses (688, 383) has been interpreted to favour the hypothesis of a non-specific premature ageing of the irradiated animals, since all diseases associated with senescence seemed to appear earlier, with no evidence that life-span shortening could be correlated with any particular cause of death. On the

other hand, as has already been mentioned (para. 19), the use of data derived from post-mortem examinations may be misleading and inadequate to give end-points free from the distortion of the intercurrent mortality (9, 10, 270).

27. Owing to inadequacies of the statistical treatment of the data, the conclusions of these early experiments were thus challenged and the non-specific life-span shortening attributed to a technical artefact (716). Actually, other experimental series where appropriate death-rate analyses have been performed (718) and where the effects of dose fractionation (449), chronic exposure (451, 227) and age at irradiation (451, 749) have been tested, have shown rather conclusively that the concept of a non-specific ageing effect of radiation is no longer tenable. At present, the consensus seems to be that life-span shortening is to be attributed almost entirely to the induction of neoplasia, especially at low doses and dose rates. A non-specific component may however become apparent in the high-dose range (227).

II. MECHANISMS OF RADIATION CARCINOGENESIS

A. GENERAL HYPOTHESIS

28. Since it is the purpose of the present report to discuss the problem of radiation carcinogenesis in the more general context of carcinogenesis as a biological phenomenon, it seems appropriate to review briefly some of the current "theories" of carcinogenesis. It is becoming increasingly clear in view of much experimental evidence that this phenomenon is extremely complex, and therefore one should not expect that early naive concepts postulating, for example, that a tumour might result from the energy imparted to a cell by an ion-pair or solely from a somatic mutation might apply: dosimetric calculations or biological considerations (420) may easily disprove such assumptions.

29. The very low likelihood of an event of neoplastic transformation[1] in relation to the number of possible target cells (429, 459) and the essentially random character of the processes of energy deposition in irradiated tissues have often justified in the past analysis of tumour induction in probabilistic terms. On these bases, mathematical models have been applied to the study of human spontaneous tumours (17, 76) and also to radiation carcinogenesis in man and experimental animals following external irradiation (452, 30, 430) or exposure to internally administered radioisotopes (452, 453, 430). Inferences have also been drawn concerning the shape of the dose-risk curve of relevance to radiation protection (77, 743). In all cases, models of the multi-event type have been supported by the data on neoplastic incidence as a function of time and dose, in the sense that such data are consistent with the general hypothesis that the appearance of a tumour is the final outcome of a succession and/or interplay of rare discrete events. This interpretation would also be in accordance with our notions of the biology of cancer, although it would be unrealistic at present to attribute any precise biological significance to such postulated events.

30. Recently a new interpretation of radiobiological phenomena has been published. This approach is known as the theory of dual radiation action (348). The theory is based on microdosimetric concepts and takes account, not only of the mean absorbed energy of radiation, but also of possible fluctuations of the energy deposited in volumes of micron dimensions. According to the theory of dual radiation action, the primary biological effect takes place only if two events occur in a sensitive volume. The probability of each such event is proportional to the specific energy absorbed in the microvolume. For densely ionizing radiation, a particle traversing the sensitive volume has sufficiently high probability to cause both events. On the other hand, for ionizing radiation with low linear energy transfer (LET), two charged particles are often necessary to provide the pair of events leading to the primary biological lesion. On the basis of these considerations the quantitative theory of dual radiation action has been developed. This theory has been applied to the interpretation of the RBE dependence on dose for a number of biological effects (339), including carcinogenesis (338). Specially interesting for the present report is the consideration of the induction of mammary neoplasia in the rat (575, 613) and of human leukaemia in Japanese A-bomb survivors (576). Remarkable agreement has been shown between the experimental observations and the theory that predicts at the cellular level linear dose-effect relationships for neutrons and curvilinear relationships for low-LET radiations. This approach has obvious implications in practice for the design of new experiments and for the prediction of certain trends of the phenomenon of cancer induction as a function of radiation quality, dose, dose rate, fractionation etc. However, from the point of view of the biological theories of carcinogenesis, the good correlations found, though very suggestive, cannot be taken as absolute proof of the validity of the starting hypotheses. Unfortunately they also do not identify the mechanisms involved.

31. Within the framework of a biomathematical reconnaissance of the most basic problems of carcinogenesis and radiation risks, Mayneord and Clarke (430) have proposed a formulation which relates the dose to the risk of a rare event such as a neoplastic transformation in a population of cells. In spite of the recognized limitations, this formulation has been used to examine a number of practical problems, including the form of the dose-effect relationship, the effect of dose inhomogeneity, the LET, and the estimate of the absolute carcinogenic risk per unit dose. The main value of this contribution lies in the attempt to identify and define the quantities which may be more significant for the analysis of these problems, and as such it is of great interest to the theoretical, experimental and practical aspects of radiation carcinogenesis.

32. In very general conceptual terms, by analogy with the classical experiments on chemically induced skin neoplasia—following, for example, the application of

[1] In the context of the present document the terms "neoplastic transformation" and "cell transformation" are used in a descriptive sense to include all changes that confer upon a normal cell (some of) the properties of a viable neoplastic cell.

benzopyrene and croton oil in optimal doses—the induction of any tumour may be envisaged as the outcome of two independent actions referred to as "initiation" and "promotion" (37). The former is viewed as a fast irreversible process acting on a normal cell and conferring upon it tumorous characteristics. Initiation would precede in time the slowly acting process of promotion but would never result, in the latter's absence, in a growing tumour, since the induced cell might remain indefinitely in a "dormant" state without further division. These different actions may experimentally be resolved in time and quality, since the final yield of tumours is generally a function of the initiator's dose, but their rate of appearance is mainly dependent upon the time and dosage of the promoter.

33. Ionizing radiation, in view of its extreme unspecificity of action on living tissues, cannot be considered as either a "pure" initiator or promoter but shares the properties of both classes, and for this reason it represents a very special carcinogenic agent. In spite of this duality, which might in itself give rise to ambiguous answers, radiation has been tested in a number of experiments in association with chemical carcinogenic substances known to act, under the specific experimental conditions, through initiating or promoting mechanisms. An exhaustive list of references up to 1966 may be found in a review by Kondrateva (356).

B. COMBINED ACTIONS

34. Much of the work on the combined action of chemical carcinogens and radiation was carried out on the skin, the tissue where the two-stage mechanism of carcinogenesis was originally identified (37) and can be more easily tested. Electrons or uv light in association with other carcinogens usually results in a higher yield of tumours than any of the agents administered alone. This applies to methylcholanthrene (113), 7,12-dimethylbenz [*a*]anthracene (171, 639) and 4-nitroquinoline 1-oxide (276). Reversing the order of administration does not change the result in case of beta rays (276) but may lead to an inhibitory effect with uv radiation (640). In the mouse, the tumour induction rate did not change by increasing the interval between the exposure to beta radiation and the subsequent painting with 4-nitroquinoline 1-oxide, showing the persistence of the latent carcinogenic action of radiation (275). The action of croton oil, which is a typical promoter of chemically induced skin tumours, seems uncertain when combined with radiation, since either enhancement of effects with uv (172) and electrons (624) or negative results (233, 71) have been obtained. However, it may be said in very general terms that initiation and promotion have been verified in the case of skin radiation carcinogenesis. The results of combining two independent carcinogenic treatments on the skin might also be interpreted on the base of other concepts of the fundamental processes of carcinogenesis. Some of the previously mentioned experiments (171, 172, 276) would in fact be regarded by others (486) as clear examples of syncarcinogenic summation of chemical and physical agents.

35. The situation appears to be definitely more confused with respect to the induction of tumours in other tissues or to systemic leukaemogenesis. In the case of the lung, urethane (a specific inducer of lung adenomas in mice) has been used in association with x rays with various dose and time schedules and after single or fractionated radiation treatments. A reduction in the percentage incidence and tumour multiplicity per animal has been obtained in one experimental series (200), and this result has been attributed to an inhibitory action by the high radiation dose on the urethane-induced tumours. Recalculation of these data by another group of workers (388) led to an entirely different interpretation. Additive effects were reported by the same authors in another set of experiments. The resulting effect was explained as the end-point of two competing mechanisms, cell killing and cell transformation, whereby, depending on the dose of the two agents, any effect becomes possible. As a further complication, an immunological component might also interfere with these phenomena (116). Mice irradiated *in utero* with a small dose of x rays (36 rad) have shown a significantly increased incidence of lung tumours induced by urethane given after birth (511).

36. Concerning leukaemogenesis, an increased effect with the combined treatment of urethane and radiation seems to be the general finding (337, 41, 154, 376, 40, 707, 216), especially in young mice (40, 707), perhaps due to differences in catabolism rate of the drug with age rather than to changes in the intrinsic susceptibility of target cells (100). However, at least in one case, thymic lymphoma and myeloid leukaemia were found insensitive to the combined action of the two agents (686). Croton oil acts also as an effective promoter of systemic leukaemia (297). Differential actions on the myeloid leukaemia or on the thymic lymphoma have been reported in the mouse by the combination of myleran (695) or novoembichin (12) with radiation.

37. Intragastric administration of 3-methylcholanthrene followed by x-ray (604) or fission-neutron (619) irradiation gave rise to additive effects for induction of mammary adenocarcinoma; however, in another system, brain tumours, where the same chemical was applied locally, beta-ray irradiation resulted in an inhibition proportional to radiation dose (423). As far as other tumours were concerned, no changes were found with respect to x rays alone or in association with 3,4-benzopyrene (348). Dibutylnitrosamine (DBNA) or 4-ethylsulphonyl-naphtalene-1-sulphonamide (ENS) combined with x rays showed no effect on tumours of the urinary bladder but a reduction of mammary tumour incidence (199). A synergistic action on the production of liver and gastric carcinoma by fission neutrons in combination with N,N'-2,7-fluorenylenebisacetamide (2,7-FAA) was reported, but no additivity or potentiation for intestinal tumours (713) was found. Localized x irradiation in association with the same drug administered in the diet accelerated the induction of hepatomas (485), and similar effects were reported with the association of x rays and o-aminoazotoluene (342) and of ^{144}Ce and dimethylaminoazobenzene (DBA) (416). Experiments on additive carcinogenic effects of 9,10-dimethyl-1,2-benzanthracene or 1,2,5,6-dibenzanthracene in association with chronic internal irradiation from ^{90}Sr were also reported (759, 758). Finally, survival and tumour induction were tested in three strains of rats following x-irradiation in

association with urethane. In spite of some interesting differences observed between strains, the overall effect of the joint treatment was not greater than the sum of the separate effects at the dosage level studies (482).

38. In view of the complex pathogenesis of the tumour systems tested, where the conceptual distinction between induction and promotion cannot easily be proven, the conflicting evidences available are consistent with the assumption that associated treatments decrease, rather than increase the induction of neoplasia, in cases where the toxicity of the two combined agents outweighs their additive carcinogenic properties (675). A possible quantitative approach to these problems could possibly come from studies at the cellular level (519 and 518). In embryo hamster cells, for example, the transformation by benzo[*a*]pyrene administered prior to irradiation has shown, both per cell and per total colony, maximum enhancement when the drug treatment was given 48 hours post-irradiation and when the radiation doses range from 250 to 500 rad. At higher radiation doses and at longer intervals between treatments the transformation efficiency actually decreased (149). No definite conclusion with respect to any special tumour model system may therefore be drawn before the dose, dosage schedule, order of administration and modality of the combined treatment with physical and chemical agents are properly and thoroughly explored, which is seldom the case in the works reviewed.

C. "THEORIES" OF RADIATION CARCINOGENESIS

39. The concepts of induction and promotion provide some insight into the possible mode of action of carcinogenic agents, but they don't exhaust the problem of tumour etiology and pathogenesis for which definite biological mechanisms must be traced. To this effect, a good number of theories have been proposed in the past, but most of them were gradually abandoned since none could account for the large array of properties of the tumorous cell. A critical review of most of these theories in a historical perspective has recently been provided by Berenblum (38).

40. At present, only a few of the original theories are still viable and will be discussed in the present report especially for their relevance to the action of radiation. The genetic foundation is common to all of them since it appears at present as the most logical way to account for the irreversibility and the continuity of the neoplastic transformation in the course of cell division. This common molecular genetic basis makes it conceivable that the distinction that is still drawn between the somatic mutation and the viral hypotheses of tumour induction might soon become unnecessary.

41. The somatic mutation theory of cancer induction stems from the notion that tumours are often carrying abnormal mitotic configurations which were originally interpreted as the phenotypic expression of the genetic alteration responsible for cell transformation. Also, the fact that unique chromosomal configurations (201, 290, 722, 213, 444) or biochemical markers (382) are often found in all the cells of primary tumours, as if they would be derived from a single mutated clone, lent support to this theory. However, the fact that aberrant unviable mitoses are often secondary changes or the end-result of excessive tumour growth rather than its cause (353, 354), the gradual realization that mutagenesis at the chromosomal level and carcinogenesis by a number of agents are not necessarily closely linked phenomena, at least in mammals (198), and the notion that carcinogenesis is better explained as a multi-step process involving the interplay of many factors and mechanisms (120, 141, 143), made the theory less appealing, at least at the chromosomal level. At the DNA level, however, the hypothesis of somatic mutation may still be entertained (although with some difficulties in explaining the multi-stage nature of malignant transformation) and could well explain the spontaneous occurrence of cancer as well as its induction by chemical, physical or viral agents. There are as yet no data at the molecular level to validate such a theory in the case of radiation-induced neoplasia, although modern techniques of cell and DNA hybridization and of somatic mutation analysis might render this possible in the future.

42. The refined knowledge of the mechanisms of damage and repair in uv-irradiated eukaryotic cells (see for general references (513)) has developed in recent years in a new line of research. It becomes apparent that, at least in the case of actinic radiation, lesions to cellular DNA and defective repair of this molecule might result in neoplastic transformation of the damaged cells. There are several arguments pointing in this direction and they have recently been discussed at the VIIth International Congress of Photobiology (296). The first argument is the demonstration that exposure of cells to uv results in neoplastic transformation, that the action of a photoreactivating treatment decreases the incidence of transformants and that the initial lesion in DNA is probably the formation of pyrimidine dimers (600). The second is the fact that treatment of the uv-irradiated cells with inhibitors of the repair of photolesions reduces the incidence of tumours produced by uv radiation (756) presumably by decreasing the likelihood of mutations resulting from the misrepair of photolesions in DNA. The third is the detection of defective DNA repair in some human diseases (xeroderma pigmentosum (55) and ataxia teleangiectasia (526)) showing predisposition to malignancy. It should be pointed out, however, that the correlations observed do not represent direct proof that derangements in the repair of DNA lesions might be the primary genetic cause responsible for malignant transformation of the defective cells. Also, although it may be regarded as an attractive general proposition, the model of the misrepair of uv-induced DNA lesions could not as such be acceptable in the case of ionizing radiation, owing to the profound differences in the nature of molecular lesions produced by the two types of radiation.

43. A comprehensive treatment of the numerous viral hypotheses of tumour induction would be unwarranted in the present context and the reader is referred to specialized reviews (237, 38). In experimental radiation work the neoplastic diseases of importance for which sufficient documentation of a viral etiology is available are leukaemia, mammary cancer and osteogenic sarcoma,

and they are discussed in the present report. Since in all of them RNA oncoviruses are implicated, the molecular mechanisms of induction should at present be viewed in the context of one of the hypotheses which postulate the virus to be vertically inherited by the animals and integrated into the cellular genome as a DNA intermediate synthesized on the viral RNA under the action of a specific RNA-directed DNA-polymerase known as reverse transcriptase.

44. The "oncogene" hypothesis (282,139) is founded on the notion of the vertical transmission of type-C RNA virus particles in most animal species. These particles are postulated to act as the potential etiological agents of all forms of cancer, carrying with them the genetic information, transmitted by an oncogene integrated in the genome DNA. Derepression of this information by chemical or physical agents or through spontaneous mutational events would lead to the activation of the oncogenic action. At variance with the oncogene theory, the "protovirus" hypothesis (654, 655) postulates that during normal development RNA is transcribed from a section of DNA of a somatic cell and then transmitted to another cell which may in turn synthesize upon this information, *via* the reverse transcriptase, new DNA sequences to be incorporated into predetermined regions of its genome. This mechanism would be one normally acting in differentiation: cancer would result from the wrong evolution of the protoviruses caused by somatic mutations or by their misplacement in the genome of the cell.

D. ETIOPATHOGENESIS OF RADIATION-INDUCED TUMOURS

45. The most common forms of leukaemia in the mouse are the thymic, the myelocytic and the reticular types. The viral origin has been ascertained only for the first two of them (236, 310), while attempts to isolate a viral agent from reticular neoplasms (253) have not yet been confirmed. Some strains of mouse develop the disease spontaneously, such as the AKR strain in the case of the thymic (237) or the SJL/J for the reticular form (481). After irradiation, leukaemia is found to increase in strains that do not normally show it, and this is most typically the case of the C57BL mouse, which, under suitable conditions of dose fractionation, may develop up to 90 per cent thymic lymphoma (330). Differences have been reported between strains and even among congenic lines of the same strain (317) in the susceptibility to leukaemia induction by radiation. In the course of almost thirty years of work (summarized in 326 and 328), Kaplan and his associates have systematically explored the various conditions affecting the radiation induction of this disease, which is a good example of the complexities of tumour pathogenesis. Reviews on radiation-induced leukaemias and its viral and host factors may also be found in references 325, 126, 167, 407, 674, 678 and 680.

46. Although the thymus was first identified as the target organ for the lymphoid leukaemia type (321), local irradiation of the thymic area (322) or of the upper half of the body (329) was ineffective for induction. Partial-body irradiation may sometimes accelerate the appearance of malignant lymphoma without increase of its incidence (596). Protection against leukaemia incidence was also afforded by shielding of the spleen (367) or the marrow (329) or the lymph node (289) or by transplantation of intact isogenic marrow cells (331) or spleen cells (99). Isologous thymus grafts to irradiated thymectomized mice were shown to undergo malignant transformation (332), and cells of these tumours were found to be of donor and not of host type (333). All this definitely pointed to an indirect induction mechanism which was later to be identified as an RNA oncovirus (377). Advances in the techniques of virus titration (254) made it possible to study extensively, in addition to the morphology of the type-C viral particles, the biochemistry of the purified virus (327), its antigenicity (528, 178), host range (326) and localization (148). It is known that this virus, referred to as Rad LV, is vertically transmitted through the embryo in C57BL mice (327) and that the action of physical and chemical agents is required for its activation and release in young, normally resistant animals (325, 368). Radiation-induced lymphoid leukaemia in chickens through a possible activation of a latent virus (365) and in guinea pigs (697) has also been reported.

47. The initial step in the pathogenesis of radiation-induced thymic leukaemogenesis in the mouse is the release of the viral particles from the injured marrow (247, 238, 304) where they are normally harboured in an oncogenically inert state. In the course of post-irradiation thymic hyperplasia (625, 328, 302, 336, 303), the virus is then taken up by the thymic target cells, identified as the immature lymphoblasts of the outer cortex (376, 53, 90). Since these cells are incapable of giving rise to tumours in the absence of the epithelial-reticular thymic stroma, it is thought that their contact with such a cellular microenvironment is essential for their complete progression to full neoplastic state (327).

48. An important factor in the pathogenesis of thymic lymphoma is the bone marrow, which either by favouring the regeneration of the irradiated thymic cells (331) or by effective scavenging viral particles from the blood stream in the course of the post-irradiation viremia (327), may render their interaction with target cells less probable. Another humoral factor, mediated through the haemopoietic tissue and capable of inhibiting the occurrence of radiation-induced leukaemia, has also been described (379, 380) and identified as a 19S alpha-2-globulin (39). Depression of the host immune response by the whole-body radiation treatment is also an important factor in the pathogenesis of the disease (248, 255). Finally, a range of host factors may influence induction: in addition to the already mentioned genetic constitution, age (320, 251), sex (319) and other endocrine factors (possibly through their action on the thymus) (323, 334, 483, 484) have been shown to interact in various ways with the virus and the radiation exposure in the development of lymphoid leukaemia (747, 746).

49. Information on the viral etiology and pathogenesis in the induction of myeloid leukaemia by radiation in the mouse is far less complete. In the RF strain incidences of up to 25 per cent have been reported after

single doses of radiation, starting from an incidence of less than 1 per cent in untreated animals (67). Age, sex and hormonal effects on the viral transmission of the disease have also been shown (686), as well as changes in the induction rate introduced by environmental factors such as the microbial flora in the mouse colony (720, 719) or by a subsequent re-irradiation (408). These observations clearly point to complex interactions between viral, host, environmental and physical factors which remain to be fully elucidated.

50. A viral agent (241, 35) in association with hormones and other factors (54) is also involved in the induction of mouse mammary tumours by radiation in the strain 020 of mice which do not normally develop such tumours spontaneously (664). The virus has been shown to be widely present in many mouse strains; in some strains however it is released at a young age, with good correlation between the time of release and the onset of spontaneous mammary tumours. On the other hand, in strains releasing the virus late in life, irradiation early in life causes the production of viral antigens (34) and of mammary tumours with infective virus particles (664).

51. It is not known yet whether the viral etiology would also apply to another important model system in radiation carcinogenesis, namely mammary carcinogenesis in the Sprague-Dawley rat. In these animals irradiation leads to induction of tumours which is a function of dose and may go up to 80 per cent (50, 611), starting from a background incidence of less than 2 per cent (138). Sex and hormonal influences are also operating in the mammary carcinogenesis of the rat (63, 138, 615, 609), as well as a number of other modifying factors (608), but primary damage to the mammary gland is necessary for the occurrence of neoplasia (52). Recent biophysical evidence (575) indicate the possible need for interaction between radiation-damaged cells for the production of a viable tumour in this system. Studies have been undertaken to elucidate the effect of genetic strain in radiation-induced mammary carcinogenesis of the rat. Results of an experiment involving Sprague-Dawley, Long-Evans, Buffalo, Fischer-344 and Wistar-Lewis rats strongly suggest the presence of a genetic component (710). Another study (63) on Sprague-Dawley, WAG/Rij and Brown-Norway animals is still in progress.

52. Osteogenic carcoma, a rare form of tumour in the mouse, inducible by bone-seeking radionuclides such as ^{90}Sr (198, 185, 196) has been serially passed by cell-free extracts to isogenic new-born mice of the CF1 strain. In the CBA mouse, on the contrary, ^{90}Sr-induced bone tumours contained very few virus particles, cell-free extracts being ineffective in transferring the neoplasms. A virus termed FBJ (374) is involved in the etiology of bone tumours of the CF1 mouse; its morphology (45) and its interaction with radiation have been described in the mouse (187, 192). It belongs to the class of murine sarcoma viruses (MSV) which may also induce bone tumours in rats and hamsters (632). There is actually evidence that the FBJ virus might require the association of a helper in a complex with murine leukaemia virus (MLV) for its replication (314). Two other viruses inducing bone tumours, termed RBF and FBR, have recently been identified in the mouse (193, 197). Transplantation (199) and immunological evidence (536, 555) seem to imply the extension of the viral etiology also to human tumours.

E. CELL TRANSFORMATION *IN VITRO*

53. There have been attempts for a number of years to study radiation carcinogenesis in cellular systems *in vitro*. There seems to be hardly any doubt that radiation enhances the transformation of animal cells by chemical carcinogens (149, 519, 518) and by a number of infecting DNA viral agents such as polyoma (643), SV_{40} (542) and adenovirus type 31 (114). The existence of a linear relationship between the logarithm of the excess transformation and the dose, with a doubling dose of 200 rad of 250-kVp x rays in the range of 75 to 1200 rad has been reported in one case (542). These data are consistent with the hypothesis that non-lethal damage induced by radiation in cellular DNA might facilitate, in the course of repair, the integration of the viral genome into the genetic material of the host cell. Rescue of lethally damaged cells by the integration of the viral genome has also been considered as a possible mechanism.

54. Induction of a latent leukosis virus in chicken cells (739) and possibly of a murine leukaemia-sarcoma complex in Balb/3T3 cells (541) has also been described. It might be reasonable to assume (although it has not yet been demonstrated) that the activation of an oncogenic virus could be responsible for the induction of neoplasia in fragments of rat mammary tissue irradiated *in vitro* (618, 606). In many reported experiments the criteria used to assess cell transformation were purely morphological, based on the multilayer and irregular arrangement of cells in the transformed colonies, but in other cases malignant tumour growth was actually tested by retransplantation of the transformed cells into the donors (606) or into suitably conditioned, genetically compatible hosts (541).

55. Experimental results have been published on the capacity for transformation of radiation *per se* in the presumed absence of viral agents. According to one group of workers, x-ray-induced transformation is possible and has actually been shown (59): it would result in a change of regulatory mechanisms of the transformed cell lines, such that transformed cells may be contact-inhibited only by a different and not also by the same cell type. In another report, a single x-ray dose of 300 rad resulted in a high proportion of transformed clones in primary and secondary cultures but not in later passages of hamster embryo cultured cells (60). In primary hamster cell cultures, these results were extended down to doses of the order of 1 rad of x rays. A dose-effect curve for transformation of these cells was established, which on a log-log plot increases up to a plateau of approximately 1 per cent transformed clones at doses between 150 and 300 rad. Further increases of dose resulted in a marked decrease of the percentage of transformation. In some cases, in addition to morphological criteria, neoplastic transformation was also tested by the ability of cells to form clones in semi-soft agar or by their agglutinability by concanavalin A and wheat-germ agglutinin (57).

56. On the contrary, exposure of spleen cell cultures (344, 345) under carefully controlled conditions to a range of weekly irradiation treatments up to a total accumulated dose in excess of 15,000 rad of 250-kVp x rays did not result in malignant changes, although the same cell line did turn malignant under the action of methylcholanthene. Urethane alone or in combination with radiation was found similarly ineffective. The conditions affecting the possible failure to show malignant transformation *in vitro* (viability, cell concentration, presence of damaged or unviable cells) were investigated recently (346, 347) on mouse cells. Under certain conditions and on some cell lines, transformation was actually obtained and tested *in vivo*. It was concluded that the presence of large amounts of dead cells and cellular debris, whether induced by radiation or mechanically, in close contact with viable cells is a condition favouring the induction of transformation. This would argue against a direct carcinogeneic effect of radiation *in vitro*. This same conclusion was reached on a different transplantation system of skin carcinogenesis *in vivo* developed in the same laboratory (25).

57. Recently x-ray-induced transformation has also been reported on a C3H mouse embryo cell line (658, 659). In this case the effect was assessed both morphologically and by transplantation of the transformed cells: it did not appear to be mediated by non-specific cell killing. Differences were also noted with respect to the previously reported data (57, 56). In fact, the yield of transformation per surviving cell appeared to increase between 50 and 400 rad and then to level off at higher doses when given to exponentially-growing cells. However in the treatment of plateau-phase cells the transformation frequency was enhanced for doses up to 100 rad. These observations suggest the existence of yet unexplored relationships between the molecular events responsible for neoplastic transformation and those processes controlling cell survival and the kinetics of cell division.

58. Although a certain variability of the results should be expected (in view of the above-mentioned experimental variables, the difficulties of relating morphological changes at the cellular level with the actual malignancy demonstrable *in vivo*, the possible presence and activation of latent tumour viruses, and other biological considerations by which neoplastic transformation can hardly be viewed as an all-or-none phenomenon), the available evidence is too conflicting to allow any firm conclusions. It seems clear, however, that the use of these highly controlled techniques *in vitro* may, in the future, be a powerful tool to disentangle the problem of cancer induction at the cellular level in the absence of other interactions operating at the whole-body level.

F. THE IMMUNE SYSTEM

59. Among the factors which are involved in cancer induction, the immune reaction has gained much attention in recent times. However, since transformation can be obtained by chemical, viral and possibly physical agents in entirely *in vitro* conditions, it must be inferred that immune phenomena play only a secondary role in the development of neoplasia, perhaps associated with the development rather than with the induction of tumours. We shall therefore group this factor under the general heading of the promoting agents. The whole problem of immunity and tolerance in oncogenesis has been discussed at length by Severi (601) and the aspects connected with radiation particularly by Cole and Nowell (121). The Committee also reviewed in 1972 the relevant evidence, both the general concepts (670, Annex F, paras. 247-250) and their specific importance in radiation carcinogenesis (670, Annex G, paras. 13-15). Recent reviews may also be found in Kersey (341), Martin (427), and Weiss (738, 739).

60. Rather than attempting to outline the premisses on which the current hypotheses of immune reactions in oncogenesis are based (375), it seems more appropriate in the present context to review the most recent advances in the field, in the light of these general hypotheses. The discovery of tumour-specific antigens in chemically induced tumours and of tumour-associated antigens as products of the oncogenic viral infection, has led to the general concept that such antigens might be present in all tumours and might be relevant to the tumour evolution.

61. It has been proposed originally by Thomas (660) and later expanded by Burnet (78), that the immune response stimulated by such antigens might actually be effective in controlling and eliminating potentially malignant clones, and that only those clones which escape this mechanism of "immune surveillance" (carried out by the body through cellular (132) and humoral (392) factors) might finally show up as clinically-evident tumours. According to these theories, immune reactions could only be effective in inhibiting tumour growth, but there are data showing that, depending on the stage and intensity of the reaction, stimulation or inhibition of tumour growth may actually result (548, 547).

62. Radiostrontium-induced osteosarcomas were reported to possess tumour-specific transplantation antigens (504), and the degree of this antigenicity, in any case rather weak (464), could be related to tumour histotype (505). Changes in the antigenic constitution of the gastro-intestinal mucosa after a radiation dose which gave rise to tumours in later age were also reported (147). Animal strains carrying vertically inherited RNA tumour viruses react immunologically when injected with such viruses (249, 527). Evidence of the pathological expression of the reaction is found in the kidney of intact non-infected animals: in the course of time, antigen-antibody complexes which have specificity for the murine leukaemia viruses are deposited in the glomeruli and their presence results late in life in nephrosclerosis.

63. This is the case for the AKR mouse (516), for the $B6C3F_1$ mouse (29) and for the RF strain, where analysis of the leukaemia incidence in glomerulosclerotic mice has indicated that immune response may reduce the probability of leukaemia to about one half by comparison with non-glomerulosclerotic animals (752, 753). Viral antigens and infectious virus titres are low in young animals but increase consistently in old age (532,

251), and the reduced immune capacity of aged $B6C3F_1$ mice has been related causally to the subsequent development of lymphatic and non-lymphatic tumours (246). Evidence against this causal relationship has however been produced in NZB/W mice (1).

64. An important factor in radiation-induced leukaemia is the transient immunosuppression caused by radiation with respect to endogenous viruses. Data to support this concept have been reported in the case of the lymphatic leukaemia of the C57BL strain (248, 250) and for the reticular, lymphoid and myeloid leukaemias in the RF strain (753), in which the severity of nephrosclerosis is shown to be inversely related to leukaemia incidence (108). In accordance with this interpretation, stimulation of the immune response should logically result in a reduction of tumour incidence. In fact, treatment of C57BL animals with interferon (379) or with immune and non-immune foreign sera (179) or with methanol extraction residues of BCG (256) under appropriate schedules of administration, actually reduced the incidence of thymic lymphoma. A delayed development and a decreased incidence of ^{90}Sr-induced osteosarcoma was also reported after injection of CBA mice with BCG (506).

65. Effects in line with the above findings were also reported after immunosuppression which resulted in activation of murine leukaemia virus in animals grafted with foreign skin (266), and also in other cases it resulted in a higher incidence of tumours (121, 360, 359). Data have also been reported on the role of immunological factors in the induction of leukaemia in swine by ^{90}SR (279, 202). The role of immunological surveillance against neoplasia and the possible influence of immunodepression have been discussed (203, 24).

66. Radiation-induced immunosuppression is however not the sole immunological factor implicated in the pathogenesis of tumours since the virus itself may depress the immune response. Although there may be uncertainties as to the importance of this latter mechanism in view of the lack of correlation between the immunosuppressive effect and the actual development of tumours (528), it has however been shown rather conclusively that the viral infection *per se* may result in an impairment of the animal's capacity to mount an immunological response to various agents. This is true in the case of both the mammary tumour virus (235) and the murine leukaemia viruses (541, 102). Analyses of the cellular bases of these phenomena point to a great specificity of action. In fact, not only has the virus derived from C57BL mice no suppresive effect on SJL/J animals (602), but in the case of C57BL mice the immunosuppressive effect is expressed at the level of immunocompetent thymus-derived cells (529, 102), while in SJL/J mice the viral infection depressed both thymus- and marrow-derived immunocytes (602).

67. In essence, it might be concluded that there is no doubt as to the presence of an immunological component in carcinogenesis related both to viral or to other etiological factors. The evidence available points rather to an inhibition than to an enhancing action of the immune system on radiation-induced tumour development. The problem is one of ascertaining the actual importance of the immunity among the many factors of cancer induction. The data available however seem to point to a secondary role of the immune reaction in radiation-induced cancerogenesis.

G. HORMONAL ACTIONS

68. Consideration of the hormonal influence on radiation carcinogenesis seems appropriate, since it has been amply documented that the action of hormones may affect tumour induction. This action is not only evident in the cancerization of hormone-responsive organs but may also be present in tumours of other tissues where hormonal control is not readily apparent. Reports on this subject have dealt mainly with radiation-induced carcinogenesis of the ovary, the thyroid, the mammary tissue, the bone and the haemo-lymphopoietic system.

69. X-ray-induced neoplasia of the ovary in the mouse is inhibited by oestrogen treatment (211) and this effect seems to be in accordance with the finding that transformation of irradiated transplanted ovaries is decreased if ovarian function is intact (324). In the rat, local ovarian irradiation produced a high yield of tumours, unaltered by treatment with chorionic gonadotropins (603). Promotion of the sequence of events leading to permanent hyperplasia and/or carcinogenesis of the **thyroid gland** by the thyroid stimulating hormone has been reported in the dog (406) and in other species (389, 159).

70. In the Sprague-Dawley rat the incidence of spontaneous tumours of the **mammary gland** is extremely low in the intact male (615) and approaches 2 per cent in the intact female at 1 year (138). Orchidectomy raises this incidence to 6 per cent (615) and ovariectomy results in a decreased incidence (138). Irradiation with 400 rad of x rays induces breast tumours in 50 per cent of the male (615), and in 79 per cent of the female, rats (138). Ovariectomy produces a decreased yield of tumours in irradiated animals and the implant of normal ovaries restores the incidence to about 80 per cent (138). Thus, the presence of a functioning ovary is required in this system for expression of maximal neoplastic response, although cycling ovarian activity is only a secondary mechanism with respect to the radiation damage to the target organ (52, 606). The effect of thyroid hormones in mammary carcinogenesis is very minor, on the other hand the administration of stilbestrol depresses the neoplastic response to irradiation (614). This latter observation is however at variance with what was reported in the AxC rat strain, where stilbestrol acts synergistically with radiation in producing mammary tumours (598) and the continuous administration of progesterone shows a protective effect against this synergistic action (597). Alterations in the ovarian and pituitary hormonal regulation have also been invoked to explain the changes of mammary tumour incidence in irradiated parabiotic rats (66). The combined action of pituitary isograft and neutron irradiation in $B6CF_1$ mice produced a reduction of the latency period and an increased incidence of mammary tumours. Harderian gland tumours also

showed a shorter latency, a marked increase in incidence and a greater tendency to metastasize. The inductive *versus* promotive role of the pituitary isograft has not yet been ascertained (206).

71. The endocrine functions related to gestation and lactation lead to a significant delay and to a reduced incidence of ^{90}Sr-induced bone tumours in the CBA mouse (495). This effect is probably related to changes in ^{90}Sr retention induced by pregnancy and lactation (503, 568). Treatment with oestrogens, on the contrary, increases considerably bone tumour induction, perhaps through a stimulation of osteoblast repopulation (507). The important role played by the parathyroid hormone was shown in the case of the induction of bone tumours by ^{45}Ca (152, 153). When the action of ^{45}Ca and the hormone are combined, the incidence of osteosarcomas in rats is a factor of about 2 higher than with ^{45}Ca alone. On the other hand, the removal of the parathyroid glands decreases the osteosarcoma incidence by a factor of 3. It appears therefore that the reduction of the hormone level decreases carcinogenesis in bone.

72. Hormonal effects in radiation leukaemogenesis have been reported by many authors. Susceptibility to myeloid leukaemia is higher in male than in female RF mice (694, 686), while the response to lymphoma induction in the same strain is higher in females than in males (694), or about equal in both sexes in the A mouse (436) and in the C57BL (323). Splenectomy reduces susceptibility to myeloid leukaemia but does not alter the induction of lymphoma in the RF (694) and in the C57BL mice (323); thymectomy, on the contrary, does not influence the induction of myeloid leukaemia in the RF (694) but effectively prevents the occurrence of lymphoma in irradiated RF (694) and in C57BL mice (323). As for the action of the gonads, ovariectomy decreases lymphoma incidence and does not alter myeloid leukaemia in RF mice (694) nor does it affect thymic lymphoma in C57BL (323). Orchidectomy has no effect on both types of leukaemia in the RF (694) and on lymphatic leukaemia in C57BL (323). However, in another report, castration has been shown to increase lymphoma incidence and this effect is brought back to normal levels by oestrogen treatment. When administered to intact C57BL animals of both sexes, oestrogens markedly increase the incidence of lymphoma; this effect is not seen in the Balb/C strain (665). On the other hand, the induction of myeloid leukaemia in virus-infected RF mice is inhibited by estradiol treatment (686, 309). Hypophysectomy does not alter the induction of thymic lymphoma by radiation (483). Hypothyroidism inhibits the incidence of this neoplasia in females but not in males implanted with thymic grafts (484). Finally, pregnancy and lactation increase all types of leukaemia in ^{90}Sr-treated CBA mice (495).

73. It is impossible from this long list of scattered observations to draw any consistent conclusion. Clearly, various radiation-induced tumours are differently affected by the animal's hormonal balance in the course of the carcinogenic processes. The effects vary with the tumour system, with the animal strain and sex, and it is therefore likely that the mechanisms of action, at present completely unknown, may be very different in the various experimental conditions.

H. THE ROLE OF CELL PROLIFERATION

74. A discussion of the role of cell proliferation among the promoting factors in radiation carcinogenesis may reasonably be centred around two questions: whether there is any relationship between the rate of tissue renewal and the induction of cancer and whether the phenomenon of cancerization is linked with any specific biochemical or kinetic changes of the transformed tissues. At present, the precise formulation of these questions is very difficult, due to the following considerations.

75. Firstly, cell proliferation often results from the application of a variety of toxic stimuli to any tissue and many physical and chemical carcinogens are toxic to cells: it is difficult therefore to recognize any specificity to the phenomenon of cell division as such. Secondly, the identification of target cells for neoplastic transformation is not always possible and therefore evaluations of kinetic changes on the whole tissue may not be relevant to the target-cell compartment. Thirdly, the usual parameters for the quantification of cellular proliferation in any tissue compartment (mitotic index, labelling index, labelled-mitoses curves, rate of DNA or of specific protein synthesis, etc.) are entirely inadequate to describe the kinetics of the tissue as a whole, including the stem, proliferating, maturing and functional compartments and, in any case, only for a very few animal tissues has such a comprehensive analysis been performed. A series of papers with a detailed quantitative analysis of different cell populations in the course of mouse leukaemogenesis may be pointed out as a first original attempt in this direction (593, 595, 594). Finally, the tissue steady state, which is often the necessary condition for kinetic estimates *in vivo*, is completely disrupted by the application of toxic stimuli and, under such conditions, the description of fine kinetic changes becomes practically impossible.

76. In spite of the above limitations, which substantially confuse the problem, there have been a number of attempts to stimulate by various treatments the cellular proliferation of tissue in order to modify their susceptibility to cancer induction. In the rat, the stimulation of unspecific tissue reactions by stable caesium hydroxide in conjunction with exposure to the daughter products of radon and thoron has resulted in accelerated lung tumour induction (530, 97, 380). Treatments with hormones which are known to stimulate cell division in the mammary gland have increased the yield of breast tumours following x irradiation (207). Treatments of animals with growth hormone increased the incidence of radiation-induced osteosarcomas, and treatment with thyroxine produced a shorter induction period (96). The application of goitrogen substances such as methylthiouracil in association with external x-ray treatment or internal exposure to ^{131}I has produced a higher incidence of thyroid neoplasia (158, 389, 724, 728), and the same observation was made in hamsters (105). In mice, stimulation of osteoblast formation by oestrogens has increased appreciably the incidence of ^{90}Sr-induced bone tumours (507, 508), although bone fracture attempting to enhance tissue proliferation before the application of ^{224}Ra has not significantly modified

bone tumour formation (222). Proliferation of the mucosa of the stomach induced by immunological treatment of the animals has increased the incidence of gastric carcinoma by x irradiation (264).

77. The role of hyperplasia during the post-irradiation regeneration of the thymus is an important factor in the pathogenesis of leukaemia (326, 327, 593, 336, 176): in agreement with this finding, urethane, which also caused injury and regeneration in the thymus (252), has been shown to increase the incidence of thymic lymphoma in association with x rays (40). Stimulation of cell division in mouse liver can increase the yield of various types of radiation-induced tumours: thus, carbon tetrachloride intoxication before or after x rays and neutron irradiation produces a considerably higher incidence of hepatomas (119, 124), and the same applies to a purely proliferative stimulus like partial hepatectomy following gamma or neutron irradiation (740). Urethane in association with x rays produced an increased incidence of lung adenomas (44) and the incidence of neoplasms approached 100 per cent after uninephrectomy in irradiated kidneys (570, 120, 123). Isoproterenol, an agent promoting DNA synthesis in cells of the salivary glands, has been shown to enhance the induction of tumours of these organs when given in combination with x rays (649).

78. Specialized reviews of the cellular and kinetic changes induced by radiation have been published (51, 13). In very general terms, there is nothing in these changes that would point to any specific pattern of cellular and tissue reaction with respect to other carcinogens (561, 27, 553, 38). The assumption that a rapid rate of renewal is a favouring condition for the neoplastic transformation seems therefore unwarranted, without adequate qualifications pertaining to the specific model of carcinogenesis under discussion. Exceptions to this general assumption, sometimes justifiable on biological grounds (393), may be as common as the general rule, and the preceding discussion has made it abundantly clear that the complexities of radiation carcinogenesis hardly point to a simple scheme of mechanism of action.

79. Cellular proliferation is implicit in the notion of promoting action and is clearly necessary for the tumour progression, and the evidence reviewed is generally in accordance with these concepts. However, so far there is no unequivocal evidence that the induction of proliferation in the target cells is a key event in radiation carcinogenesis: on the contrary, there is recent evidence from work in chemical carcinogenesis showing that hyperplastic changes and promoting action are quite independent phenomena (552). In any case, a systematic comparative analysis of events associated with the induction of tumours in target cells would be required before any postulated promotional role of cell proliferation could be fully elucidated.

I. OTHER MODIFYING FACTORS

80. Environmental conditions have been reported to influence the induction of specific tumour types in irradiated animals, through their action on the microflora and possible intercurrent diseases. The response of animals to carcinogenic stimuli, including radiation, may thus be affected to a variable degree by changes in the number of target cells and in cell turnover rates or by immunological factors which may interfere with the expression of carcinogenic damage. These effects have recently been reviewed (717), especially with regard to possible differences in the immunological competence of gnotobiotic and germ-free animals (245). It has been shown rather conclusively that the humoral immunological competence of germ-free and conventional mice is qualitatively and quantitatively very similar (62, 421, 599). In the very old animals, however, a great variability of response is noted, leading generally to a depression of the immune competence both in BC3F1 and in SJL/J mice. The immune competence is minimal in animals affected by lymphoreticular tumours (421, 599), suggesting that in ageing mice such tumours may arise as a result of a decline in their immunological capacity. As with the primary response, the living conditions of the animals do not affect to a great extent the secondary formation of IgG antibody-synthesizing cells (420). Infectious diseases, totally absent in the germ-free state, have little influence on the life span of mice (103, 719). In intact animals the development of spontaneous non-haemopoietic tumours is practically unaffected by the germ-free condition; among haemopoietic tumours, reticulum cell sarcoma incidence is higher in conventional than in germ-free mice, but thymic lymphoma and myeloid leukaemia have similar incidences in both conditions (719).

81. After irradiation, the incidence of myeloid leukaemia is decreased in the absence of microbial flora (719) and this effect is attributed to the reduced myelopoietic cell proliferation in the germ-free animals (720, 717). Radiation-induced lymphatic leukaemia, on the contrary, is not altered under germ-free conditions in Swiss, C3H, C57B1, ICR and C57BL mice (539, 721, 719). There are no qualitative differences in the pathological lesions of gnotobiotic and conventional animals and virus particles are found in germ-free just as in conventional mice (539). The induction of other solid tumours in irradiated animals gives variable results (15, 717). No special features were seen in radiation-induced malignant and benign tumours of the germ-free rat (540).

82. In summary, the data available at present show that the etiology and the pathogenesis of radiation-induced cancer are essentially similar in conventionally reared and in gnotobiotic animals: the host's microbial flora may only play a secondary role in the development of some haemopoietic neoplasms, perhaps through modifications of the immune competence, as in the case of the reticulum cell sarcoma or through the abnormal proliferation of target cell lines, as for myelogenous leukaemia. It seems doubtful that non-systemic tumours may respond to these actions.

83. The need to investigate in more detail specific mechanisms of radiation carcinogenesis and special conditions of practical importance, has often in the past justified attempts to modify tumour induction in irradiated animals by physical, chemical or biological treatments. The relevant work is reviewed in this report,

but owing to the heterogeneity of the conditions and agents employed, no general conclusions are really to be expected.

84. Among the physical treatments, the influence of permanent (466) or of transitory (467) high-altitude exposure has been tested in irradiated RF mice. It was found that the overall incidence of tumours was lower in mice kept at sea level after irradiation for the duration of their life, although thymic lymphoma and granulocytic leukaemia were higher at all radiation doses in these mice. Animals residing at high altitude for only three months after irradiation showed also an enhanced induction of leukaemia owing perhaps to the abnormal stimulation of the bone-marrow stem cells before their full recovery from radiation damage. The combined effects of high or low temperature and radiation were also investigated in the rat (88, 89), but only longevity data without tumour pathology were reported. The carcinogenic action of mechanical damage and x rays on intramandibular tissue of the mouse was also reported (173, 174). Finally, severe metabolic stresses such as starvation, water deprivation or prolonged physical exercise had no additional influence on tumour induction by radiation in the rat (559, 556).

85. In regard to chemical treatments, a number of studies have appeared on radioprotective drugs, but their results appear rather conflicting. Mewissen and Brucer (441) reported a significantly higher incidence of tumours in cysteamine- and cystamine-protected mice, but treatment with another radioprotective chemical (AET) failed to produce any change in the induction of the most common neoplasms of the mouse after whole-body irradiation (129), in ovarian tumour induction by localized x irradiation (129) or in breast-tumour induction in partial-body irradiated rats (616). Protection was reported in the case of kidney irradiation (168). AET alone or mixtures of five different radioprotectors reduced the total incidence of cancers and leukaemias by a factor of about two in mice irradiated with 1350 rad with respect to non-protected animals; complex dose effect relationships might have been operating in this case, since at a dose of 700 rad, the difference between protected and non-protected animals disappeared (418). Protection by cysteamine upon fractionated irradiation was also reported in the case of leukaemia induction (488). Clearly, more experiments are required to clarify this issue.

86. Among the biological treatments tested, parabiosis has been used in order to permit longer survival in animals irradiated with an otherwise lethal dose of 1000 rad of x irradiation. Under these conditions, radiation-induced osteogenic sarcoma was found in about 5 per cent of the animals (732), kidney tumours in about 8 per cent and leukaemia of the irradiated parabiont was lowered, although not to the level of the spontaneous incidence (587). There are indications that parbiosis *per se* may alter the incidence of some forms of cancer in the treated rats. Autologous, homologous and isologous haemopoietic chimaeras were also studied for their susceptibility to tumour induction. The incidence of lymphosarcoma and reticulum cell sarcoma is decreased by spleen shielding (403, 271), lymph-node shielding (289) and bone-marrow shielding (329), 134). The injection of syngenetic bone-marrow cells—but not of homologous marrow (146)—was repeatedly shown to be very effective in protecting the mice from the induction of lymphoma (331, 129), myeloid leukaemia (11) and reticulum cell sarcoma (135). The incidence of other neoplasms was practically unaffected by bone-marrow transplantation (129, 135). Acute loss of blood (2 ml) before exposure (to 270 R) was reported to increase the incidence of tumours in male rats (557). Similarly, an acute anaemic stress has been reported to act as a trigger mechanism for the induction of myelogenous leukaemia in unirradiated (221) and irradiated RF mice (179), but iron-deficient chronic anaemia is ineffective to this end in irradiated Wistar rats (307).

III. PHYSICAL PARAMETERS IN RADIATION CARCINOGENESIS (EXTERNAL IRRADIATION)

A. GENERAL

87. The purpose of this chapter is to discuss the main physical variables influencing radiation carcinogenesis, in an attempt to identify from the vast amount of scattered information in various animal systems common trends in the effect of such variables, and with the aim of assessing their qualitative and, if possible, their quantitative role. Since obtaining precise relevant data in man is extremely difficult, animal experimentation in this field is absolutely necessary to interpret and support the human evidence: this is the reason why such studies, very interesting in their own right for their fundamental implications, are also very important for human radiation-risk assessments, and therefore relevant to radiation-protection development.

88. The relationships of tumour induction with dose, radiation quality, dose rate, fractionation and protection will be examined, with main emphasis on the biological effects themselves and little discussion on the procedures of estimating the values of the physical parameters. It should be realized that technical and dosimetric uncertainties do affect in practice the determination of the physical parameters; they are, however, less important than the uncertainties associated with the biological end-points, probably by an order of magnitude at the doses where the carcinogenic effect is usually studied. Physical parameters will therefore be considered as independent and well controlled variables in the present context, since the variability of the biological end-points outweighs the errors of the physical measurements.

B. DOSE-EFFECT RELATIONSHIPS IN RADIATION CARCINOGENESIS

89. As usual in radiation biology, any attempt to analyze quantitatively the carcinogenic action of radiation must of necessity be based on the observed relationships between the dose delivered to the biological system and the ensuing effect of tumour induction. It should immediately be pointed out,

however, that the establishment of precise dose-effect relationships in animal systems is by no means an easy undertaking and that the interpretation of the relevant data must take into proper account a number of methodological and technical deficiencies encountered in research at various levels. At the most basic level, the virtual absence of adequate *in vitro* techniques is at present the main obstacle to the understanding of the fundamental mechanisms of tumour induction. Essential cellular properties like the susceptibility of single cells to neoplastic transformation, the distribution of susceptibility among cell populations having different division and differentiation potentials, the influence of initiation and promotion actions, the interplay of other cellular effects of radiation such as the loss of reproductive integrity, must somehow be reflected at each dose level in the final number of tumours scored. However, there is no means at present to resolve these phenomena in highly organized tumour models *in vivo* and, consequently, it is to be expected that the analysis of the dose-effect relationships may not be of great help in the study of basic mechanisms.

90. In chapter II it has been shown that after the event of neoplastic transformation has already taken place in one or a few cells, several permissive, enhancing or inhibiting actions may still affect the capacity of these cells to give rise eventually to visible tumour nodules. Thus, the balance between cell production and loss in a transformed clone, the complex immunological relationships between the antigenic stimulation by the newly established neoplastic cells and the immunological surveillance system of the host, and the promoting or inhibiting actions of the endocrine system influence the final yield of tumour nodules and, consequently, the general shape of the dose-effect relationships. Information on these actions is however very inadequate at present to evaluate their relevance.

1. Theory and practice

91. Modern concepts of quantitative radiobiology, as well as practical considerations, must be taken into account when dose-effect relationships for tumour induction are discussed. The most firmly defined concepts of quantitative radiobiology are reflected in the classical hit-and-target "theories". According to these the occurrence of the biological effect under study requires 1, 2 or n "hits" in some "sensitive volume", or "target", of the biological system under consideration.

92. In figure I(a) theoretical dose-effect curves are shown for cases where 1, 2, 10 or 50 events in one target are required for the occurrence of the effect. The doses in figure I are expressed as multiples of $D_{50\%}$, which is the dose inducing effect in 50 per cent of the irradiated specimens. The one-event curve is exponential. However, if the required number of events is larger than 1, the character of the curve changes and it becomes clearly of the sigmoidal type.

93. When the effect under study is the loss of a cell's reproductive ability, the same type of information is represented in the form of the so-called "inactivation curves," plotting the probability of the effect W as a function of dose. If, instead of the probability of the effect, the probability of its absence is plotted ($S = 1 - W$), "survival curves" are obtained. Usually survival curves are shown on semilogarithmic plots. The sigmoidal characteristic of multi-event curves persists in semilogarithmic plots and the "shoulder" of such curves becomes more clearly expressed the larger the values of n.

94. The most interesting part of the dose-effect curve is that corresponding to low doses. In that region of dose, simple one-event exponential relationships are approximately linear and multi-event curves can be approximated by power functions or by power function combinations. These approximations are known as polynomial functions (fig. I(c)).

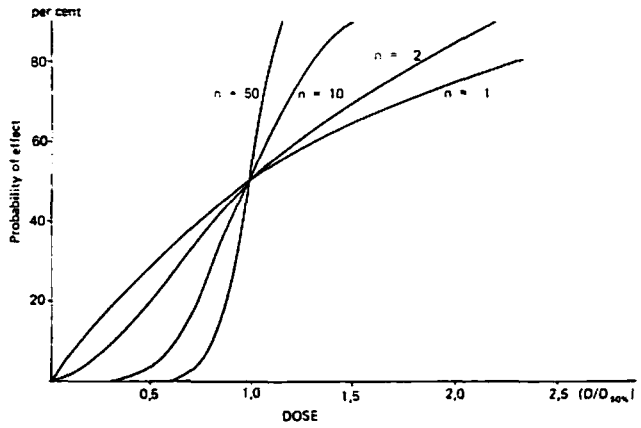
95. An intrinsic peculiarity of multi-event curves is that observable increases of the effect occur only after some definite dose, which can be called the "quasi-threshold dose". In fact, the probability of effect is a monotonically increasing function of dose but the increment up to the "quasi-threshold" is negligible.

96. For a dose-effect relationship with a real threshold, there is no observable effect for doses up to the threshold. In practice, however, the difference between threshold and quasi-threshold relationships cannot be defined. In the case of tumour induction the distinction is made impossible by the high frequency of spontaneous tumours. The variability of tumour incidence in the control group is for example shown on figure I(c) by the shaded band. In this case even a two-event curve would appear to have a threshold D_{qt1}.

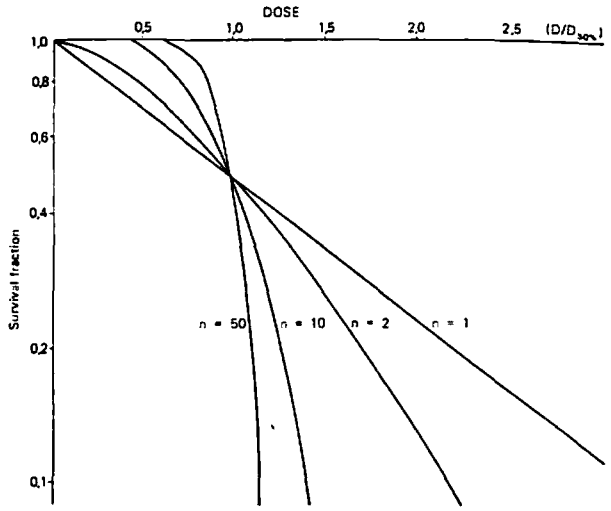
97. Different from the multi-event models discussed so far are the multi-target models which have been used to describe the survival of mammalian cells. These models postulate that several targets must be affected to kill the cell, each of the targets having to receive at least one hit (event) in the most simple case. A "survival" curve corresponding to such a model is shown in figure I(d). The curve is also sigmoidal, but in contrast to the curves shown in figure I(b), this curve becomes exponential for large values of dose. The slope a of the exponential part in a semilogarithmic plot can be characterized by the inactivation dose, D_0 ($D_0 = 1/a$). The intersection of the extrapolated exponential part of the curve with the unity survival line can be considered as a quasi-threshold dose, D_{qt}.

98. Sometimes the relationship between dose and effect is presented in a log-log plot (fig. I(e)). Apart from the fact that this presentation permits the inclusion of a wide range of values, it also emphasizes the variation of the effect at low doses. From the slopes of the straight lines in the log-log plot it is possible to assess the exponents of the power functions involved. In the simplest case a slope of 45° corresponds to an exponent = 1.

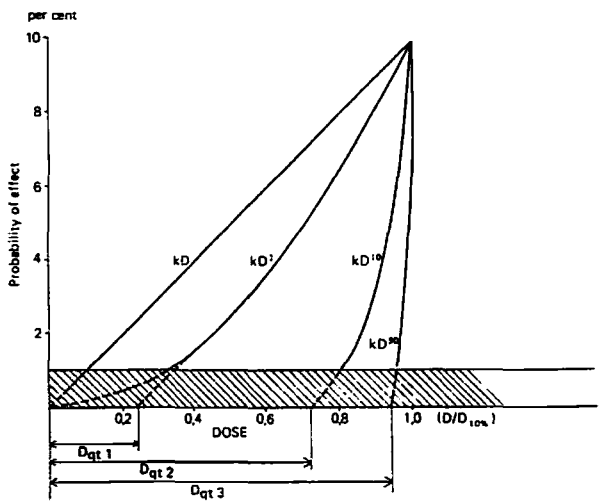
99. It is also of interest to consider a simple model postulating two types of competing processes: *(a)* the process leading to the effect (in this case to tumour); and *(b)* the process leading to cell death and therefore avoiding the manifestation of the effect. The combination of both processes, working in the opposite



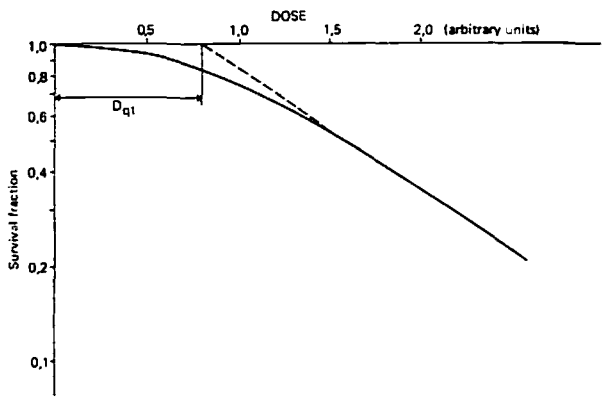
(a) Dose-effect curves relating probability of an effect to the dose expressed as a ratio of dose administered to that yielding 50-per-cent probability of occurrence (D_{50}); n is the number of events required to produce the effect



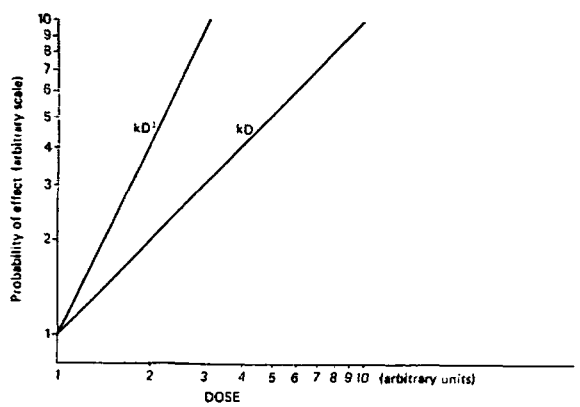
(b) Dose-effect curves relating fractional cell survival to the dose expressed as a ratio of dose administered to that yielding 50-per-cent survival; multi-event model; n is the number of events required by a cell to lose its reproductive capacity



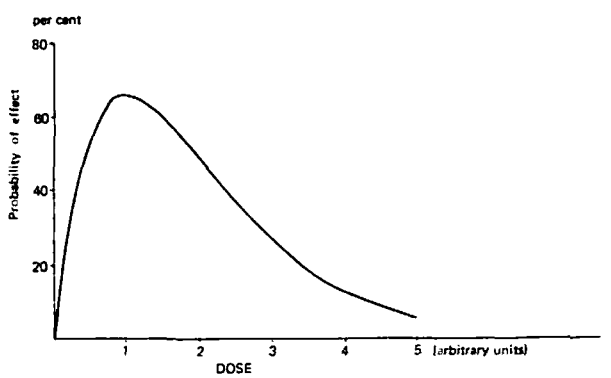
(c) One- and multi-event dose-effect curves approximated by polynomial functions of the power of dose = 1, 2, 10 and 50. "Quasi-threshold" doses for 2, 10 and 50 event curves are also shown (D_{qt1}, D_{qt2} and D_{qt3}, respectively). Dose (abscissa) expressed as a ratio of dose administered to the dose required for 10-per-cent probability of the effect to occur. Shaded area: spontaneous (control) incidence of the effect studied



(d) Typical dose-effect curve for the multi-target model. Fractional survival (ordinate) expressed in a logarithmic scale. D_{qt} = dose corresponding to the "quasi-threshold" reflecting presence of the so-called "shoulder"



(e) Polynomial dose-effect curves (see (c)) presented in a log-log plot for the effects occurring with probability proportional to the first and second power of dose (one- and two-event phenomena, respectively)



(f) Theoretical relationship between dose and probability of an effect (e.g. cancer) resulting from two competing processes: induction of malignant transformation in a cell and killing of the transformed cells.

Figure I. Theoretical dose-effect relationships for effects at the cellular level

directions, leads to a dose-effect relationship with a maximum of the type shown in figure I(f). As will be discussed in paragraph 143, a number of dose-effect relationships found for carcinogenesis are similar to the curve of figure I(f).

100. In experimental work, the most frequently used indicators of carcinogenesis are the mean number of tumours per animal at time t, $R(t)$, and the frequency of animals with at least one tumour, the "incidence" $I(t)$. If Poissonian statistics apply, the two quantities are related by the simple expression

$$I(t) = 1 - e^{-R(t)} \qquad (1)$$

When the two quantities are much smaller than one, it may be assumed that $R(t) \approx I(t)$, and both indicators of carcinogenesis become identical.

101. Several statistical approaches can be used for treating experimental results (571, 613). One approach (613) for the calculation of the mean number of tumours per animal at time t is

$$R(t) = \sum_{i=1}^{n} \frac{1}{N(t_i)} \qquad (2)$$

where t_i is the time of appearance of the tumour number n in the experimental group, and $N(t_i)$ is the number of animals still under observation at time t_i.

102. Either of the quantities $R(t)$ or $I(t)$ may be plotted as a function of dose. $I(t)$ can be obtained out of $R(t)$ by the use of equation (1). The validity of this equation requires that all scored tumours be real primary tumours. To avoid possible complications, it is possible to score only the first tumour of the animal. However, in practice it was shown that there are no statistically significant differences between the results obtained when all tumours are scored or when only first tumours are scored (620).

103. In this review the results will be expressed mainly in terms of the total tumour incidence over lifetime I in per cent. It must be mentioned that such an approach leads to some loss of experimental information, namely the temporal variations of $I(t)$. Another approach is possible (620) where the indicator is the time-integral of $R(t)$

$$P(t) = \int_0^t R(\tau)\, d\tau \qquad (3)$$

By such an approach it is possible to collate all the experimental data for the period of observation. Furthermore, the number of tumours are weighted according to their time of appearance. The quantity $P(t)$, called the "effect period", is expressed in "tumour-days" and represents the mean number of tumours per animal multiplied by the time the animal bears these tumours. The use of the "effect period" should, in principle, decrease the statistical uncertainty of the experimental results.

104. For any approach which may be selected it is also necessary to take account of the influence of the following factors: the competitive risk of other diseases or causes of death (see paragraph 13), the modifications introduced by spontaneous death of the animals or by the serial sacrifice techniques (see paragraph 19), and the possible effect of radiation-induced life-span shortening (see paragraphs 26 and 27). Additionally, the question of tumour acceleration *versus* tumour induction needs separate consideration.

105. A widespread observation which refers generally to all radiation-induced tumours is that their latency time, that is the time from irradiation to the occurrence of the actual neoplastic changes, usually follows some function of the dose and frequently is shorter in highly irradiated animals. Since radiation-induced neoplasms cannot be distinguished from spontaneous ones, the shorter latency could conceptually be interpreted in some cases as an acceleration of the occurrence of the neoplastic diseases rather than as a true induction of new tumours. These phenomena are readily analyzed using curves describing the age-specific cumulative rate of incidence of tumours (see paragraphs 24 and 25), and there are two extreme conditions that may be observed in comparing intact and irradiated animal groups under such circumstances.

106. In the first condition, typical of animal strains having a particularly low spontaneous yield of some tumour type, radiation may act by inducing this tumour within a confined time period, and a good example may be the thymic lymphoma of the C57BL mouse. The probability of observing such a tumour will be essentially zero in the normal animals at all times, but in irradiated animals this probability will gradually increase around the time which is characteristic for appearance of the thymic lymphoma (200-400 days) (330) and will eventually reach a plateau well before the irradiated animal population is extinguished. Clearly, if the appearance of tumours is very unlikely before the normal animals die, the tumours arising at the characteristic age in the irradiated animals may be attributed to a true induction phenomenon brought about by the radiation treatment.

107. The second extreme condition is observed, on the contrary, in animal strains having a high probability of neoplasia in the control population, as, for example, with the mammary neoplasia in the ageing Sprague-Dawley rat. In this case the cumulative incidence of tumours in normal animals will continuously increase with time and this rise will eventually be terminated by the extinction of the whole animal population. In the irradiated animals, however, the rise of the curve will begin at an earlier age and will proceed roughly parallel to or somewhat steeper than the control curve, until all animals die. Such a phenomenon might be interpreted as a radiation-induced anticipation or acceleration in the occurrence of tumours that might possibly have appeared in the normal animals, had they lived long enough.

108. The experimental situations to be dealt with in practice rarely conform to these extreme examples, since, depending on the dose of radiation, both effects of induction and of anticipation or acceleration can

often be observed, even in the same tumour system. For the purpose of comparing the overall effect of different doses or of different experimental treatments, the parameter of importance is the total number of tumours expressed by a population of animals from the time of irradiation to death. An alternate indicator would be the "effect period" referred to in previous paragraphs. In any case, the comparison between groups is often made difficult by the fact that their life spans may be different and also depend on the radiation dose.

109. A reduction of the latency time with irradiation appears to be a rather general phenomenon in most tumour systems studied in many animal species and for all types of radiation. To cite only a few of the many possible examples: In the mouse, skin tumours tend to appear earlier after higher doses of low-energy electrons (285); lung tumours are accelerated but not induced in RF mice (687) and CBA mice (726); the mean ages at death of both male and female LAF_1 animals with thymic lymphosarcoma, non-thymic lymphoma, granulocytic leukaemia, hepatoma, ovarian and mammary tumours decrease progressively with increasing gamma-ray doses (688); myeloid leukaemia occurs earlier at high doses of x or gamma rays in RF mice (685); osteosarcomas (284) and ossifying fibromas (222) induced by ^{224}Ra injection show a steeper rate of induction with increasing isotope dose; the cumulative incidence of bone malignancies at death in CF1 mice after ^{226}Ra treatment is similarly increased in proportion to dose (191); bone tumours (499, 701) and carcinomas of the mucous membranes of the head (496) are accelerated in the CBA strain following intraperitoneal injection of ^{90}Sr; oesophageal cancer after local ^{60}Co irradiation shows an acceleration at increasing doses (733).

110. In the rat, skin tumour appearance is hastened by irradiation with fast electrons and alpha radiation (80) as well as with x rays and fission neutrons (312); the induction of mammary cancer in female Sprague-Dawley rats within one year of ^{60}Co irradiation is progressively accelerated by the dose administered with a possible saturation effect of 500 rad (611); fast neutron and x-ray irradiation show a similar effect within 700 days from exposure (714); the latency time of ethionine-induced liver tumours is decreased by treatment with radiation (653). In the swine, acceleration phenomena in the induction of myelo- and lympho-proliferative diseases are observed after ^{90}Sr feeding (280).

111. In the dog, alpha radiation from ^{226}Ra and beta radiation from ^{90}Sr accelerate the induction of myeloproliferative disorders and of osteosarcomas in proportion to the dose level of the two nuclides (218), and a consistent decrease of the latency time is observed for the induction of malignant tumours of the bone by a variety of bone-seeking isotopes such as ^{239}Pu, ^{228}Th, ^{228}Ra, ^{226}Ra and ^{90}Sr (163). It is to be expected that the time of evolution of the neoplastic disease and also the time of its occurrence with respect to the age of the animals should influence the precision of estimates of the acceleration as a function of dose, and in this respect rapidly killing tumours of high malignancy occurring early in the life span of the animals will produce the most reliable estimates.

2. Experimental dose-effect relationships

112. It seems appropriate at this point to examine in detail the existing data on the dose-effect relationships for the induction of the most common radiation-induced malignancies in various animal species and strains, in order to see whether and to what extent common features and trends can be identified. For this purpose published final cumulative tumour incidence data will be used. These data have inherent limitations due to the fact that corrections for intercurrent competing diseases and death were applied only in some instances. Single exposures of short duration to various types of radiation will be examined in this context, leaving the effects of other radiological factors such as radiation quality, fractionation and dose rate for consideration under separate headings. Some of the most informative experimental series to be discussed have been plotted in figures II-IX. The bars superimposed on the data points in these figures represent the standard errors of the estimates when the necessary information was available.

113. *Myeloid leukaemia.* LAF_1 mice exposed to gamma-ray doses up to 697 rad showed a corrected final incidence of granulocytic leukaemia rising from less than 1 per cent in the control to a maximum of 1.5 per cent in males at 578 rad and of 1.7 per cent in females at 223 rad. At higher doses the incidence seemed to decrease, but the changes observed were on the whole too small to allow any definite statement as to the shape of the induction curve (688). Susceptibility to myeloid leukaemia is higher in the RF strain and fairly complete data are available on the dose-effect relationship (694, 671, 685, 686) (fig. II). When several hundred male mice were whole-body irradiated with x or gamma doses in a single brief exposure early in adulthood, the incidence of myeloid leukaemia was increased from a background level of about 5 per cent to about 40 per cent at 200-300 rad and then declined gradually at higher doses to a level of about 10 per cent at 500 rad (685). In female mice susceptibility was generally lower and attained a maximum of around 20 per cent in the two most complete series available, involving thousands of animals studied by macroscopic and microscopic pathology (685, 107). The peak incidence occurred at 300 rad in one case (685) and at 200 rad in the other (107) after exposure to x rays; exposure to high-energy protons yielded a maximum at around 300 rad (107). In both cases a tendency to decrease with higher doses was reported. Other data on RF male and female mice are in general agreement with the above findings (692).

114. After 5-MeV neutron irradiation in males a plateau incidence of about 40 per cent at 200 rad and a further decline were observed. A lower peak incidence was observed in females (692). After 14-MeV neutron irradiation in female mice a monotonic rise up to 28 per cent at 400 rad was described (145). In summary, after x, gamma, proton and neutron irradiation the overall relationship between incidence and dose appears to be complex. Over the dose range of 0-200 rad of sparsely ionizing radiation the tumour yield has been reported to vary with the square of the dose (671, 685), although the presence of a linear component cannot confidently be excluded (686). Upon neutron irradiation the linear component might be prevailing at the lower doses (613),

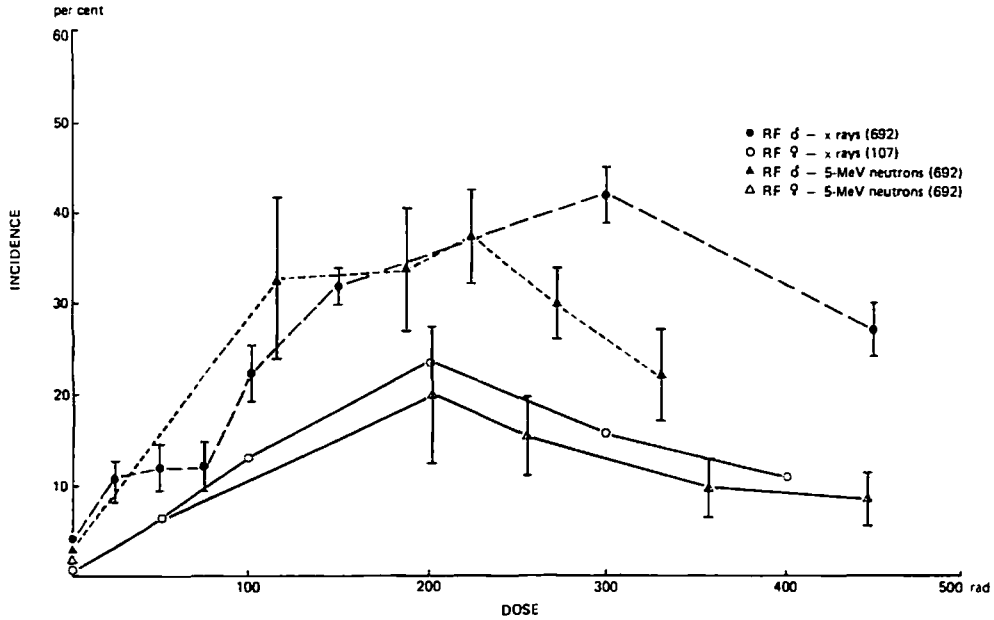


Figure II. Dose-effect relationships for the induction of myeloid leukaemia by x rays and neutrons in RF mice

but the plateau and the later decline are still observed. Some of the data (671) were analysed by Gray (233) and mechanisms were proposed to explain the rise, plateau and ensuing decline; the significance of these mechanisms will be discussed later (see paragraphs 151-154).

115. *Thymic lymphoma* (fig. III). In the RF mouse strain, the incidence of this disease shows a positive relationship with dose for both x rays and 60-MeV proton irradiation up to approximately 300 rad, which might be curvilinear both in male (694) and in female animals (107, 686). A plateau is observed at higher doses up to 400 rad of 300-kVp x rays or of 60-MeV protons (107) or 600 rad of sparsely ionizing radiation (683), but no actual decrease in incidence has been reported. In both sexes, x- or gamma-ray exposures produced a statistically significant increase of thymic lymphoma at dose levels of 200 rad or more. Less consistent effects were described in the case of 5-MeV neutron irradiation (692). After 14-MeV neutrons the incidence increased from 3 per cent in the controls to 19 per cent in the 200 rad group, with a slight decrease at 400 rad (145). The initial rise with dose might be described as approximately linear.

116. In the LAF_1 strain, susceptibility to thymic lymphoma is lower than in the RF in both male and female animals and, within the scatter of the experimental points, the corrected incidence of this tumour appeared to rise until approximately 700 rad with what might be regarded as a roughly curvilinear trend. Within the large variation of the estimates, an approximately linear rise up to a dose of about 140 rad was observed following fission neutron irradiation (688). The susceptibility to thymic lymphoma is however

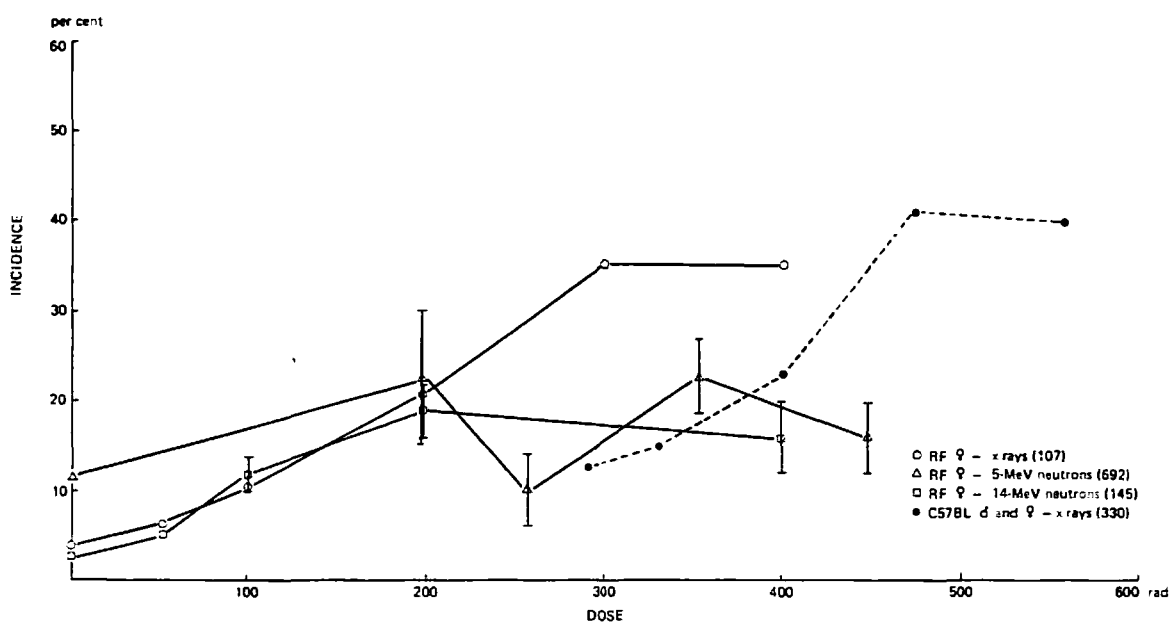


Figure III. Dose-effect relationships for induction of thymic lymphoma in RF and C57BL mice irradiated with x rays and neutrons

maximal in the C57BL mouse where the dose-effect relationship shows a curvilinear trend up to about 450 rad of x rays with an incidence of approximately 40 per cent. An ensuing plateau but no further decline is seen up to about 570 rad (330). It may therefore be concluded that the efficiency of the induction of the thymic lymphoma by sparsely ionizing radiation is greatest in the intermediate dose range between about 100 and 400 rad and lower at doses outside this range, but no clear-cut decline below the peak incidence has been reported. It seems possible that a linear rise at low doses could occur after neutron irradiation and it should be noted that neutron treatment often seems to give a biphasic response with a peak, a trough and a further rise at higher doses, which, if true, would indeed be a very difficult phenomenon to explain.

117. *Reticulum cell sarcoma and other reticular neoplasms* (fig. IV). The dose response relationship in RF female mice shows a continuously decreasing trend

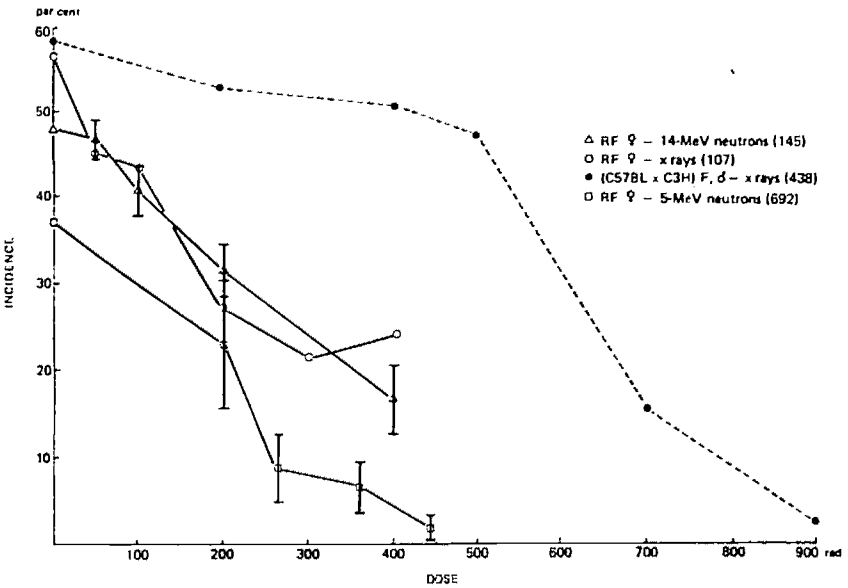


Figure IV. Dose-effect relationships for reticulum cell sarcoma and other reticular tumours in RF (female) and (C57BL X C3H)F_1 (male) mice irradiated with x rays and neutrons

from the control incidence levels of 30-50 per cent (according to various reports) to 15-25 per cent incidences between 300 and 400 rad of x rays (694, 681, 130, 466). The most complete experiment carried out with 330-kVp x rays and 60-MeV protons, suggests that the decrement might be more appreciable at low than at high doses since the incidence tends to level off at about 25 per cent between 300 and 400 rad of both radiations (107). Discrepancies in the pathological classification between non-thymic lymphomas and reticulum cell sarcomas among various workers may have contributed to the considerable variability observed between the reports cited. In the RF male the spread of results appears somewhat smaller and a linear function could possibly be fitted to all data in the interval 0-450 rad of sparsely ionizing radiation (694, 686, 681, 692, 130). The same decreasing trend with dose applies after 5-MeV neutron irradiation in both sexes (692) and after 14-MeV neutron irradiation in females (145), although the slope of the curve appears to be generally steeper with neutrons than with x rays in the same experimental series. Also in the LAF_1 strain, non-thymic lymphoma incidence varies inversely with gamma dose between 0 and 487 rad, with considerable differences between the two sexes (688). The changes induced by x rays in female (101 X C3H)F_1 mice—a strain with a particularly low control incidence of these reticular tumours— were negligible up to 750 rad (129).

118. In male mice of the hybrid strain (C57BL X C3H)F_1 having a spontaneous incidence of reticulum cell sarcoma approaching 60 per cent, radiation had a small effect on the final incidence up to doses of 400 rad of x rays, but higher doses (up to 900 rad in bone-marrow-shielded (134) or in transplanted animals (135)) produced a reduction of tumours to 3 per cent or less. It was pointed out that the final portion of the curve approached the slope of the survival curves of haemopoietic stem cells in this strain of mouse (629). Finally, although induction on non-thymic leukaemia was reported in CBA females irradiated to a dose of 500-rad fractionated x rays, it was also remarked that larger fractional doses tended to reduce the incidence of these neoplasms, an effect which would be in line with all the above data (446). It may therefore be concluded that, within a rather large strain and sex variability, both densely and sparsely ionizing radiation decrease the incidence of reticular tumours in an inverse relationship with dose. It should be pointed out that a decrease of tumour incidence with dose is a rather frequent finding in tumour model systems in which a high spontaneous incidence is encountered.

119. *Lung tumours.* In the case of lung tumours a distinction should be made between whole-body and localized irradiation. Although no complete dose-effect relationship was obtained, a lower incidence of pulmonary adenomas was reported with respect to controls (24 per cent) after treatment with 800 rad and isologous marrow infusion (8 per cent) or after whole-body doses of 290-580 rad of 8-MeV neutrons in LAF_1 mice (514). In the same strain a generally

decreasing dose-effect relationship was observed for lung tumours (essentially adenomas) up to 700 rad of gamma rays: the slope of the curve was steeper in males, which had almost five times as many spontaneous lesions as females (688). Scattered data on pulmonary tumour induction in male LAF_1 mice after single whole-body doses of 300 rad of x rays were also reported by Cole and Foley (116), while 15-MeV electron doses up to about 450 rad produced little change in the incidence of lung tumours in SAS/4 mice of both sexes (325). In the RF female mouse a decreasing trend up to about 400 rad was reported after x-ray and proton irradiation (107) or after neutron treatment at energies of 5 MeV (692) or 14 MeV (145). Some acceleration of lung tumour occurrence but no real induction was also found in RF females after 500-600 R of x rays (687). In male mice of this same strain, graded doses of x rays and 5-MeV neutrons produced an inverse relationship without any apparent difference in slope between the high- and low-LET radiation (692).

120. In an experimental series comprising 1149 male $(C57BL \times C3H)F_1$ animals, the final observed incidence of lung tumours increased from 9 per cent to 15 per cent following a curvilinear function up to 500 rad of x rays and decreased thereafter up to 900 rad down to control levels (137). After lung cancer induction had been reported in rats and hamsters irradiated on the chest with doses of 3 and 4 krad (239), a complete set of data was published more recently, obtained by localized x irradiation of RFM male mice (754) (fig. V). The incidence of pulmonary nodules and the mean number of nodules/mouse scored at 11 months post-exposure showed an increase directly related to exposure (probably following a curvilinear function) up to 1500 R and sharply declined at higher exposures, reaching control level at 2750 R. There can be no question about the significance of these latter data but they are difficult to reconcile with the previous ones obtained by whole-body irradiation in other strains or even in the same strain, since some small increase, rather than the actually observed decrease in incidence would be expected after sublethal doses. Differences in the experimental design or in biological factors could possibly justify the discrepancies (754).

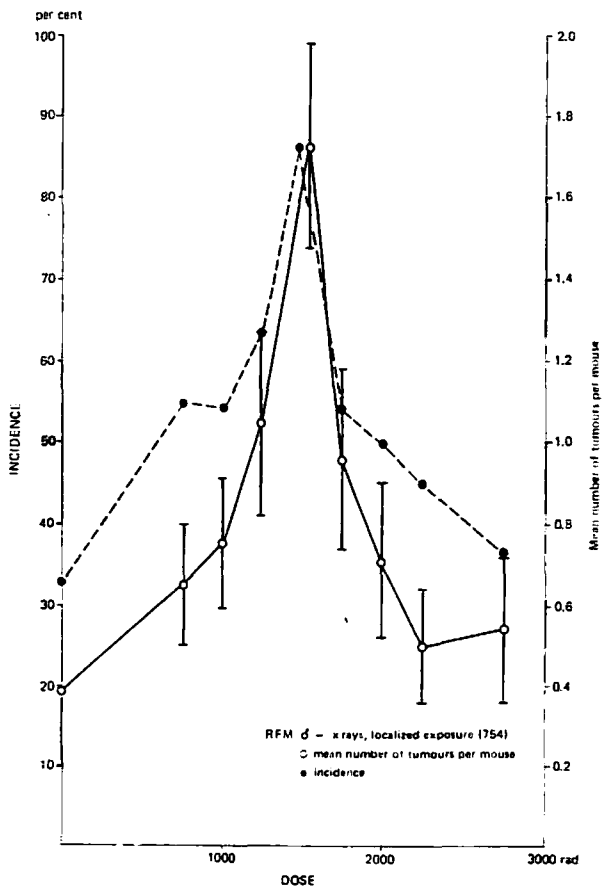


Figure V. Dose-effect relationships for induction of lung tumours in the RFM mouse

121. *Ovarian tumours.* A list of early references on radiation-induced tumours of the ovary is given by Garner (211). The data referred to are very scattered and insufficient for a reconstruction of a tentative dose-effect curve. The incidence of ovarian adenomas increased consistently, over the control level of 11 per cent in LAF_1 mice, after doses of 800 rad of x rays (36 per cent) or of 290-580 rad of 8-MeV neutrons (52 per cent) (514). More complete data were published on gamma-irradiated animals of the same strain (688), showing an increased incidence to about 40 per cent at around 350 rad and an ensuing fall up to 700 rad. The data in the low-dose range seem insufficient to draw conclusions as to the initial shape of the dose-effect relationship. Similar considerations apply to the dose incidence curve for tumours of the ovary in SAS/4 mice (385) and in ddY/F or C3H/Tw animals (355).

122. In the RF strain (fig. VI) acceleration and increased induction of ovarian tumours by single doses of 500-600 rad of x and gamma rays was first reported by Upton, Kastenbaum and Conklin (687). In a more extensive experiment performed with 14-MeV neutrons, the incidence of ovarian neoplasms markedly increased from 15 per cent in the control group to a maximum of 62 per cent at 100 rad, with a plateau at higher doses. The induction rate between 0 and 50 rad might be higher than between 50 and 100 rad (145). The latter observations are in contrast with the results of lower-energy neutrons (692), although in the same series, doses as low as 50 rad of gamma rays consistently increased the incidence of ovarian neoplasms. In this case the dose-incidence relationship followed a sigmoid curve, rising from the control level of 9 per cent somewhere between 25 and 50 rad and reaching a maximum of 45 per cent at 200 rad, declining at increasing doses. Oscillations over a generally decreasing trend were observed further up to 700 rad (692).

123. A similar large increase of ovarian tumour induction was shown in a recent report where 300-kVp x rays and 60-MeV protons were used in single whole-body exposures. The dose-effect curves produced by the two radiations were almost superimposable and showed an extremely high susceptibility without apparent threshold at doses of 50 rad, a further but smaller rise to 100 rad, and a gradual decrease from 100 to 400 rad, the highest dose used (107). Finally, seven different dose-effect relationships at different dose rates were reported for the induction of ovarian tumours by gamma-ray irradiation of the BALB/c mouse. At the highest dose rate of 112 rad/day, a curvilinear

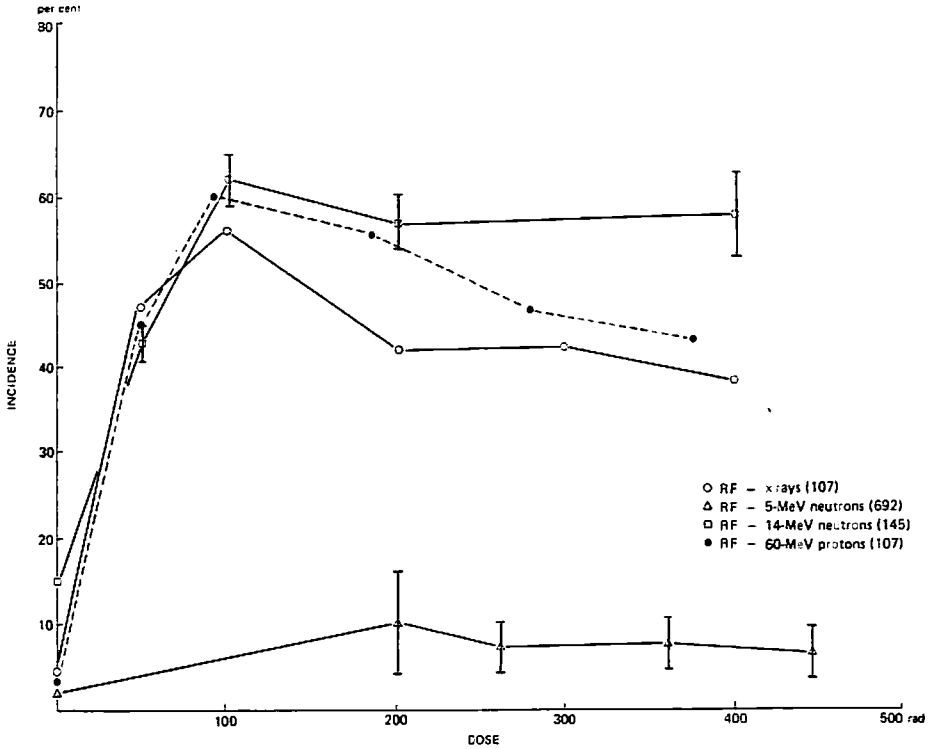


Figure VI. Dose-effect relationships for induction of ovarian tumours in the RF mouse

relationship was found between zero and about 200 rad, with an ensuing plateau up to 390 rad. The non-linearity of the dose-incidence curve was confirmed by the observation that at constant exposure time, the incidence varied as the square of the dose (750).

124. In conclusion, the great majority of the reports seem to confirm that the dose-effect relationship for the induction of ovarian tumours has a very steep rise for doses of radiation between 0 and 50 rad. The maximum yield of tumours is then obtained between 100 and 200 rad and a decrease follows at higher doses. Biological factors such as the strains and radiological variables such as LET and dose rate influence the induction of ovarian tumours.

125. *Mammary tumours.* The RF mouse has a low spontaneous incidence of mammary tumours and is not easily susceptible to the induction of this neoplasia: histological observations on more than 2500 female mice irradiated with x rays or fast protons failed to show any consistent trend with doses up to 400 rad (107). The hybrid $B6CF_1$ mouse also has a low susceptibility to mammary tumour induction by gamma rays or fission neutrons (206). In the LAF_1 mouse, on the other hand, the incidence of breast sarcoma declined monotonically from 15 to 0.5 per cent between 0 and 700 rad, while the observed incidence of carcinoma increased from 1 to 5.5 per cent at around 350 rad and then decreased up to the highest tested dose of 700 rad. The high correlation between mammary sarcoma and granulosa cell tumours of the ovary observed in these studies (688), as well as other data in rats (138) point to a strong influence of hormonal factors in the induction of mammary tumours (see paragraphs 68 to 73). Limited or lifetime whole-body exposures to gamma rays in doses of 30-2100 rad and exposure rates of 0.062-121 R/day were carried out on RAP mice, possibly harbouring a mammary tumour virus. In accordance with other data (see paragraph 70), a similarity of the dose range for ovarian and mammary tumourogenesis but no correlation between the two types of neoplasia was found in this strain. Complex systemic changes in the induction of breast tumours were confirmed (736).

126. The Sprague-Dawley rat is the animal where most studies on the dose-related induction of breast tumours have been carried out (fig. VII). Female animals irradiated with x or gamma rays at the age of about 40 days, were examined during about one year after irradiation for the presence of mammary nodules, which were then excised and histologically diagnosed (614, 611). A fairly good linear relationship with exposure of the observed percentage incidence of tumour-bearing animals or of the cumulative number of tumours per rat was found in the range of 16-250 R for both types of radiation. From this observation it was concluded (50) that a threshold did not exist, the data extrapolating satisfactorily to control incidence. The linear relationship holds (with different slopes) for both the adenofibromas and the adenocarcinomas (611). The response to fission neutrons was examined in the same tumour model system with a range of doses and in this case the animals were followed for the entire life span. The observed percentage incidence of rats carrying mammary neoplasia rose from 48 per cent to 78 per cent after only 5 rad of neutrons and then a plateau with values up to 87 per cent at 150 rad was observed; a further increase of the dose to 250 rad produced a small decline to 76 per cent. A close similarity of response to similar doses of x or gamma rays was also confirmed in these experiments (714). Other data on mammary carcinogenesis in various strains of rats irradiated with single doses of x rays or fast neutrons are to be found in

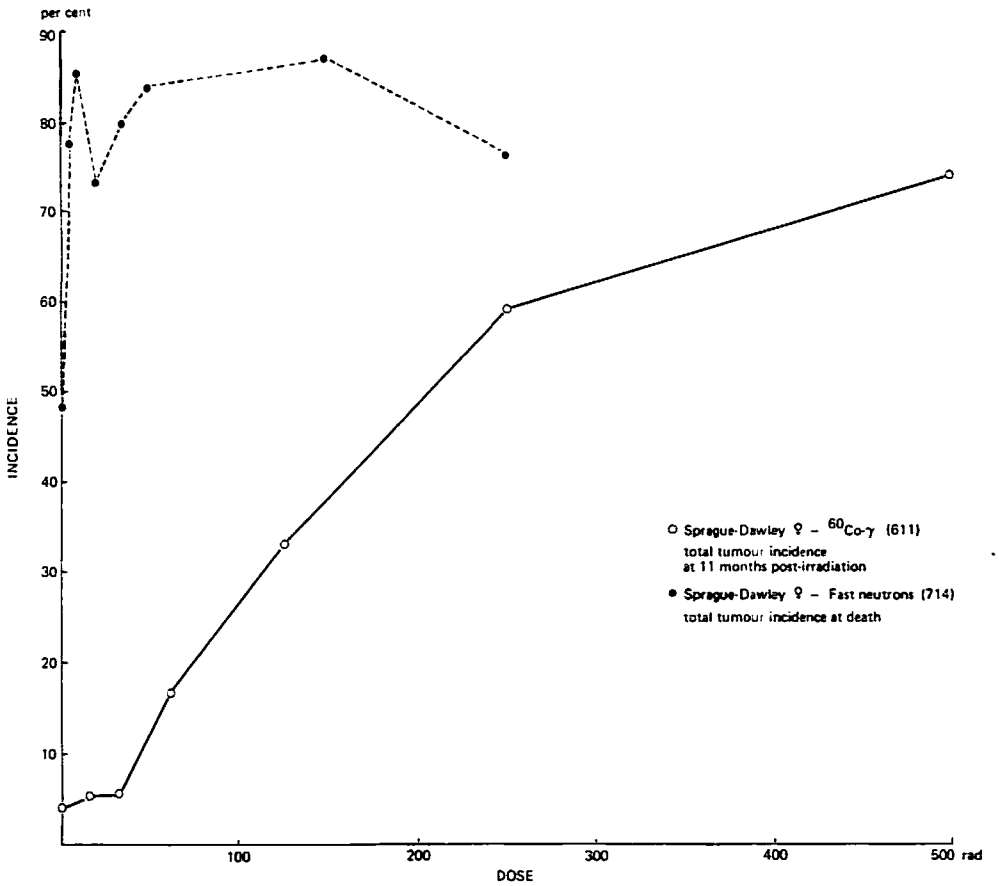


Figure VII. Dose-effect relationships for induction of mammary tumours in the Sprague-Dawley rat irradiated with cobalt-60 gamma rays or neutrons

a paper by Shellabarger (607) or will soon become available from experiments in progress (63, 605). In the dog a lower yield of mammary tumours (10 per cent) has been reported (621, 579) in animals irradiated with a mixed gamma-neutron field, with respect to a control incidence of 40 per cent.

127. The evidence reviewed allows the conclusion that the dose-effect relationship for mammary tumour induction in the rat after x or gamma irradiation appears to be linear down to very low doses. In the mouse the neoplastic response of the mammary gland is more variable, and depends on the strain and on tumour histotype.

128. *Kidney tumours.* Low incidence of kidney neoplasia after whole-body irradiation with x, gamma or proton radiation up to doses in the mid-lethal range have been frequently reported in various mouse strains (351, 36, 688, 107), but no reasonably complete dose-effect relationships have yet been produced. Similarly, in the rat (which is more susceptible to these tumours) most information was obtained after single or only a few doses of x rays (366, 569, 570, 36). A thorough series was however carried out by Maldague (422) with Wistar male rats irradiated locally with x-ray doses ranging from 570 to 14 250 rad (fig. VIII). Spontaneous kidney carcinogenesis in this strain is absent and doses up to 570 rad were ineffective in inducing tumours. A few tumours appeared at 855 rad and the dose incidence curve rose sharply thereafter up to a maximum at around 1700 rad, which may be considered in this strain as the optimal carcinogenic dose, producing tumours in 84 per cent of the animals. The dose-effect relationship declined at doses in excess of 1700 rad down to incidence levels of 5 per cent at the highest dose. Both benign and malignant lesions followed the same general pattern. The initial part of the dose-incidence curve for this type of neoplasia appears therefore to be of the sigmoid type, with a very definite threshold at about 500 rad.

129. *Skin tumours.* The frequency of skin neoplasms in LAF_1 or RF mice irradiated with x or gamma rays, protons and neutrons is only affected to a small extent by radiation up to the mid-lethal dose range (688, 692, 107). Higher doses of localized irradiation are necessary to induce this type of tumour. In CBA mice irradiated with low-energy beta particles, tumours were observed after doses of 750 to 12 000 rad (285). A plot of the number of tumours per irradiated area of skin gave dose-effect relationships of different shape according to the type of the tumours (benign or malignant) and to their origin (dermal or epidermal). Although for some tumours a linear non-threshold response would not be incompatible with the data within the experimental errors, curvilinear relationships seem to fit the data better. A plot of tumour yield per rad, allowing for dose distribution in the skin layers, shows a very rapid increase up to 1650 rad and a considerable fall-off at higher doses for both dermal and epidermal neoplasms (285). A dose-effect curve for the induction of skin tumours in Swiss mice was reported by Albert *et al.* (7) in the range of 500-4000 rad of fast electrons. The initial

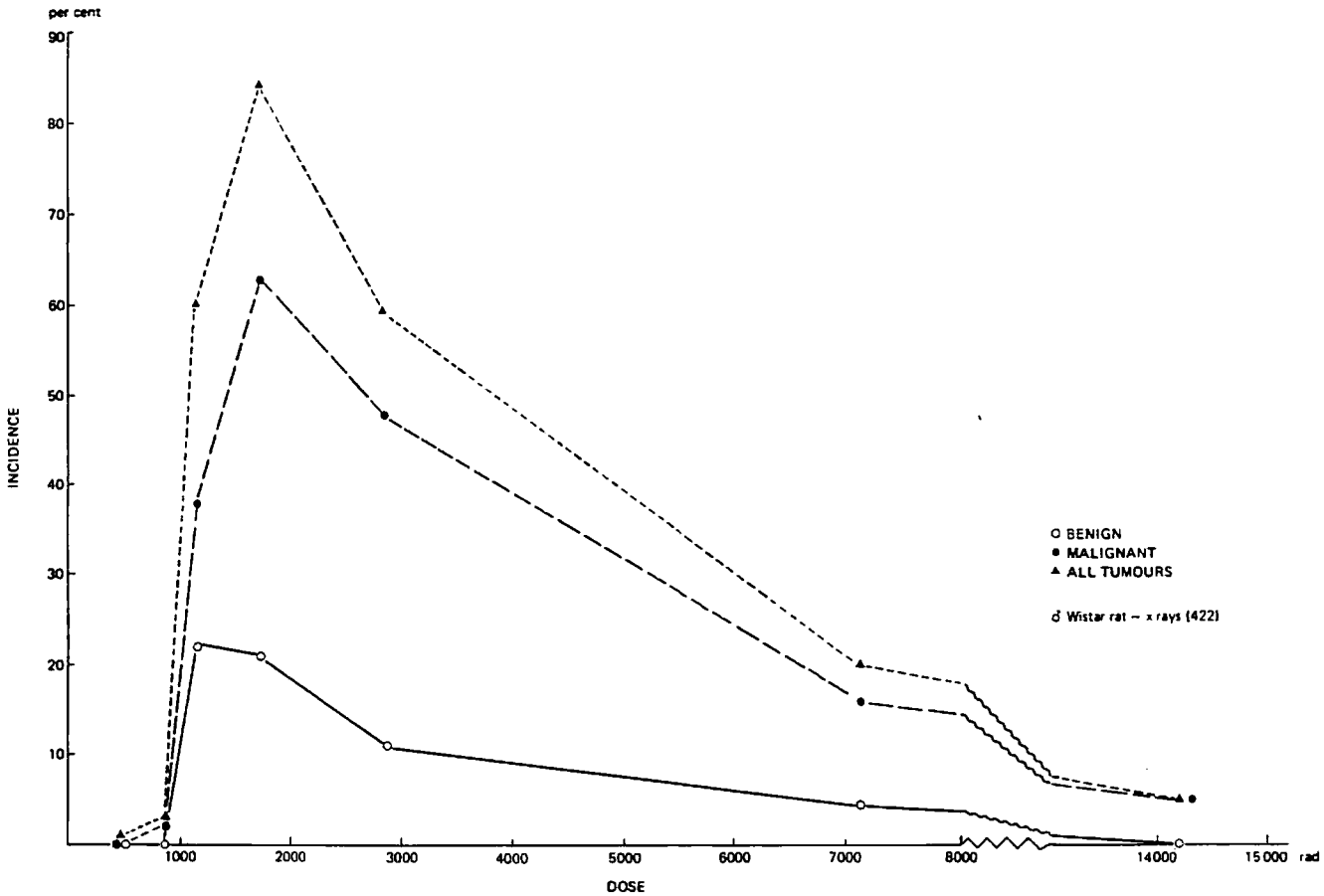


Figure VIII. Dose-effect relationships for induction of kidney tumours after x irradiation of the Wistar rat

shape of this curve appears to be highly curvilinear for both epithelial and connective tissue tumours. There is a peak at around 2500 rad for the induction curve of epidermoid carcinomas, while sarcoma induction constantly rises up to the highest dose. The problem of the relative susceptibility of mice and rats to skin tumour induction has also been discussed in this paper, and the relatively lower susceptibility of the mouse has been attributed to its failure to develop tumours of the cutaneous annexes, which are the predominant type of neoplasms in the irradiated rat skin. Dose-effect relationships for the induction of skin tumours in CD-1 mice by accelerated helium ions of various energies have also been reported (369).

130. In Sprague-Dawley rats whole-body irradiated with two doses of x rays or fast neutrons, a considerable incidence of skin tumours was reported (up to 60 per cent of animals with tumours, starting from a control incidence of about 18 per cent). The data were analyzed carefully on the basis of age-specific incidence rates, but they are insufficient to establish detailed relationships with the dose and type of radiation (94). Good dose-effect curves were obtained, on the other hand, in CD male rats irradiated with the cyclotron-accelerated helium nuclei in the dose range of 210-6950 rad and with high-energy electrons from 910 to 12 300 rad (80) (fig. IX). Tumour incidence per animal increased at the lowest doses of electrons as the fourth power of the dose, levelled off between 2 and 4 krad and gradually declined at doses up to 9 krad, which produced severe skin ulceration. The dose-effect curve for alpha particles showed the same general shape but was displaced towards the origin of the abscissa by a factor of about 3. The low number of tumours obtained at the lowest doses did not allow a definitive evaluation of the initial shape of the dose-effect curve for alpha particles.

131. It seems reasonable to conclude therefore that the initial slope of the dose-effect relationship for the induction of skin neoplasia by sparsely ionizing radiation in mice and rats is curvilinear and that a power function with smaller exponent may apply to densely ionizing particles. A progressively decreasing yield of tumours is observed in both cases at very high doses.

132. *Tumours of the liver and of the gastro-intestinal tract.* Partial data on the occurrence of hepatoma in LAF_1 mice have been published repeatedly (514, 515, 122, 117, 119). Complete dose series were reported by Furth, Upton and Kimball (210) and by Upton *et al.* (688). The latter paper shows that the control incidence of hepatoma in males (22 per cent) is gradually depressed to about 2 per cent after 700 rad of gamma rays from a nuclear detonation. In the female animals, on the contrary, the background incidence of 1.5 per cent is raised to about 8 per cent at 368 rad and again brought back to control levels at 697 rad. The occurrence of hepatomas in the SAS/4 strain is 10 per cent in males and 2 per cent in females and is hardly changed at all by 15-MeV electron doses up to 460 rad (385). In the RF mouse the spontaneous incidence of liver tumours is very low (less than 1 per cent in females and less than 2 per cent in males); radiation does not

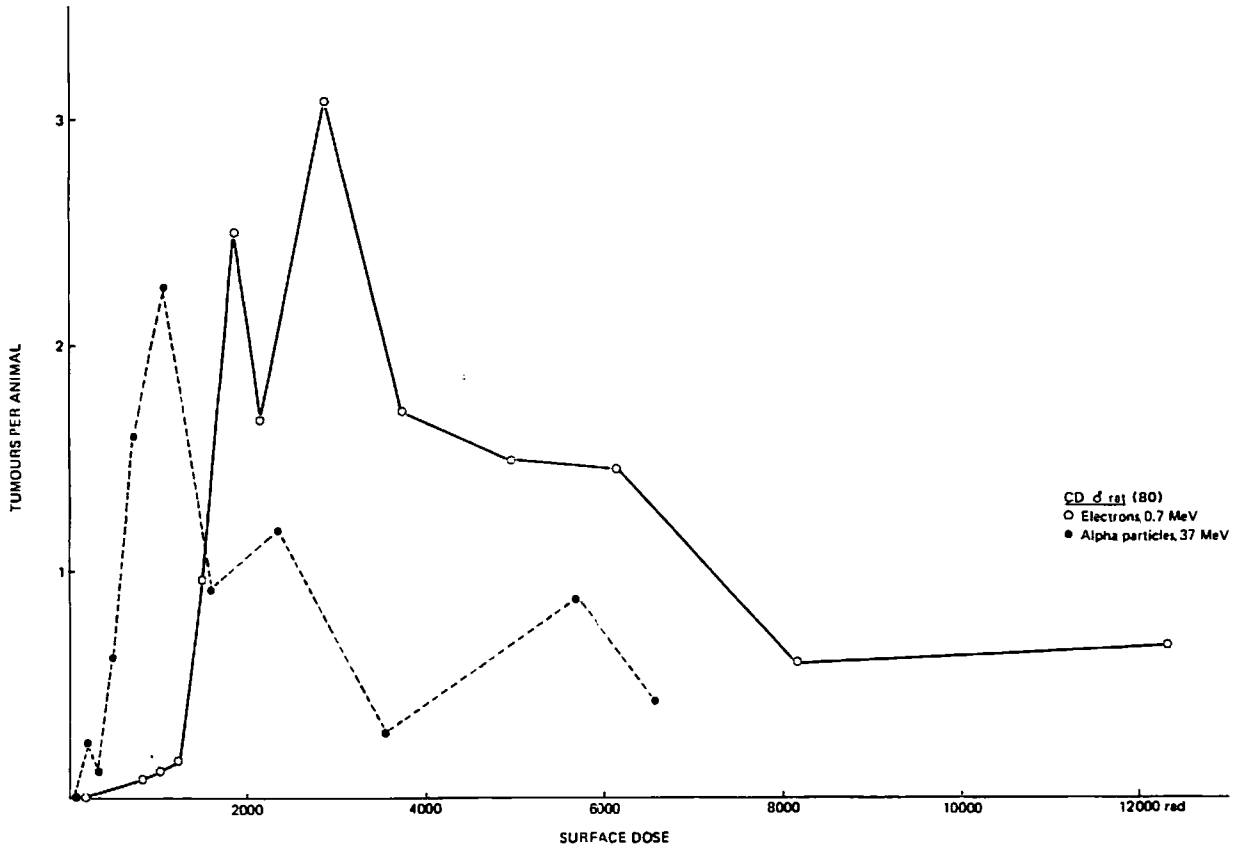


Figure IX. Dose-effect relationships for skin tumour induction in CD rats irradiated with electrons and alpha particles

appear to affect it to any appreciable extent (145, 692, 107). Radiation-induced hepatic tumours in the rat have also been described by Zatsarnaya and Bykorez (760).

133. High localized radiation doses to the various organs are usually required to elicit the formation of tumours of the gastro-intestinal tract (212, 263, 666), but the observation of some tumours at lower doses is not infrequent. The dose-effect data for the occurrence of hyperplastic and tumoural changes of the gastro-intestinal tract in whole-body irradiated mice were reviewed by Cosgrove *et al.* (131) and by Upton *et al.* (684). By combining the three series available of LAF_1 mice exposed to A-bomb radiation (688) and to x rays or neutrons of various energies (514) and CF_1 mice exposed to radiation from nuclear detonations (409), it was concluded that the incidence of gastro-intestinal tumours increased up to a maximum of 5 per cent as a curvilinear function of the dose for both sparsely and densely ionizing radiations, the latter being definitely more effective. Intestinal polyps in dogs and rats following exposure to mixed gamma-neutron beams or feedings of ^{210}Po or ^{144}Ce were also reported, mostly occurring in the large intestine with a tendency to malignant evolution and showing different latencies in the two animal species (367).

134. *Tumours of the bone.* Bone tumour production has been reported in the mouse after partial-body x irradiation of the hind limbs of 70-day-old CF1 females. Results at 442-575 days (194) and at 650 days post-irradiation (185) showed a linear correlation between dose and osteosarcoma incidence (expressed as tumours/mouse) in the exposure range of 250-1000 R. In the rat, irradiation of the knee joint with a radium-iridium source induced a total of 34 osteosarcomas appearing between 300 and 800 days in 116 mice with doses of 3000 rad. The incidence of neoplasia was higher in animals treated with growth hormone; thyroxine treatment reduced the induction period (96, 28). The histological changes and the induction of bone tumours were followed in the hind limbs of 257 rats exposed to x-ray doses of 500-3000 rad. In some cases the highest dose was subdivided into 3 or 6 equal fractions. The greatest number of tumours was found with 3000 rad; one tumour arose in the 500 rad group (32).

135. Male F_1 (Marshall X August) and August strain rats, 6-8 weeks old, were irradiated with 3000 rad of x rays on the right limb or with doses of 1000 rad each at 0, 2 and 4 weeks, or with 6 doses of 500 rad each at 0, 1, 4, 5, 6 and 7 weeks on both limbs, and then observed for 27 months. Twelve tumours were found in 34 rats of the first group within 6 and 12 months; the group receiving 3 doses (15 rats) had only 1 bone tumour; in the group receiving 6 doses, 7 bone tumours developed in 34 irradiated limbs. No significant difference between the 3000 rad group and the 500 X 6 rad group was seen at 27 months (177). A 4-per-cent incidence of osteosarcoma was reported in 125 Wistar rats whole-body irradiated with 600 rad (222) and about 5 per cent of osteogenic tumours were also found in parabiosed rats receiving an x-ray dose of 1000 rad (732). Finally, osteosarcomas developed in rabbits irradiated by gamma rays (500-1400 rad) or by fission neutrons (200-600 rad). The induction period was shorter with neutrons and an RBE value of about

three was proposed. The data however appear too scanty to allow any conclusion about the form of the dose-effect relationship (286). Additional scattered data on bone tumour induction under various conditions may also be found in Upton *et al.* (694, 688, 692), Darden *et al.* (145), Hori *et al.* (274) and Clapp *et al.* (107).

136. *Tumours of the thyroid.* This organ can be irradiated both by external radiation and by the administration of iodine radioisotopes. Data on dose-effect relationships are available in several animal species. In the mouse an extensive series of papers on thyroid damage by radiation reported by Walinder and colleagues have been summarized in reference 723. In the CBA strain, adult animals experience a dose-related increase of the frequency of thyroid tumours following x-ray exposures (500, 1000 and 1500 R) and ^{131}I administrations (1.5, 3.0 and 4.5 μCi). Within this dose range the induction curve is probably biphasic, with a shallow slope at very low doses and an increased slope at higher ones (724). For very high doses, the carcinogenic effect probably passes through a maximum (389, 159). It seems likely that thyroid carcinogenesis may be initiated by radiation and promoted by hormonally stimulated epithelial hyperplasia (725, 104) and that the initial shape of the dose-incidence curve may be the result of the interplay of these factors. The anatomical and functional processes related with ageing of the thyroid gland in CBA mice were described by Walinder *et al.* (727). Other data on mouse thyroid carcinogenesis can be found in Upton *et al.* (688, 692).

137. In the rat, thyroid tumours have been described by Doniach (155, 156, 157, 162) and by Lindsay's group (390, 391, 215, 546). These papers deal with the dose-effect relationships, fractionation effects and comparative studies of x ray and ^{131}I-irradiation effects. A comparison of the carcinogenic effects in rats of ^{131}I (3.2 to 125 μCi, five administrations) and ^{125}I (administered activities four times larger) has been reported by De Ruiter *et al.* (150). Animals were sacrificed two years after injection for scoring of the effects, but the ratio of the administered activities of the two isotopes was found to be too low. In fact, the maximum of lesions (hyperplasia, cysts and tumours) was obtained in the ^{131}I group with the lowest activity injected, while for the ^{125}I the peak induction was at 80 μCi. Some data on tumour induction in dogs irradiated with x rays or ^{131}I were reported by Michaelson *et al.* (443).

138. *Tumours of other organs.* The incidence of these is usually extremely low. As there are few relevant reports referring to varying irradiation conditions and animal strains, and as the doses tested are very few, it is impossible to derive dose-effect relationships for these neoplasms. Often all the control and all the irradiated animals are grouped irrespective of dose in order to reach statistically significant numbers, and under these conditions it is possible to observe in many cases an increased incidence in the irradiated animals. However, the actual significance of these changes is often doubtful. Since reference to these data, however heterogeneous, is sometimes useful, the following list of relevant papers which have been reviewed, subdivided according to the various organs, is provided.

139. Tumours of the pituitary gland have been reported by Upton *et al.* (694, 688, 692) and by Clapp *et al.* (107); of the uterus by Upton *et al.* (692) and Clapp *et al.* (107), of the salivary glands by Glucksmann and Cherry (214) and Takeichi (650); of the adrenal glands by Upton *et al.* (694, 688, 692); of the prostate by Hirose *et al.* (265); of the testis by Upton *et al.* (694, 688), and of the brain (412, 423). Tumours of the harderian gland have been reported by Upton *et al.* (694, 688, 692), by Darden *et al.* (145) and by Clapp *et al.* (107). Most recently Fry *et al.* (206) have reported a considerable increase of harderian gland tumours in $B6CF_1$ mice with doses in the range of 0 to 788 rad of ^{60}Co gamma rays and 0 to 240 rad of fission neutrons in single irradiations. The dose-effect relationships were of the type described in paragraph 143. Analysis of total solid tumour incidences at *all sites*, sometimes as a function of dose but more often after one or a few doses, may be found in the following publications: Upton *et al.* (694, 692) Nowell and Cole (514), Lindop and Rotblat (385), Cole and Nowell (119), Reincke *et al.* (560), Kohn and Guttman (350), Samuels *et al.* (584), Castanera *et al.* (94), Hulse (286) and Vesselinovich *et al.* (706).

3. Conclusions

140. It appears very difficult indeed to identify a common trend of the incidence as a function of dose for all the tumour systems examined experimentally and reviewed in the present report. However, if the discussion is confined to the most commonly observed neoplasms, three major patterns of response have been documented.

141. The first pattern refers to those tumours for which the spontaneous incidence is not significantly changed by the radiation treatment in the low to mid-lethal dose range. This is typically the case for myeloid leukaemia in LAF_1 mice (688), for pulmonary and liver tumours in SAS/4 (385), for mammary tumours in the $B6CF_1$ strain (206) and for mammary and liver tumours in RF female mice (107). The lack of neoplastic response in this dose range does not necessarily imply that these tumours cannot be radiation-induced, but may simply mean in some cases that the dose applied was too low for detectable induction. Actually, increasing the dose to the lung in RF mice well over the mid-lethal range (which gives an uncertain or even a negative response) results in the appearance of adenomas with a peak incidence at 1500 rad of x rays (754) (fig. V). The question remains open in such cases as to the real shape of the dose-effect curve (threshold or quasi-threshold type) but such questions are only of theoretical relevance since for all practical purposes virtually no tumours of this type will be induced at the low doses of interest.

142. In other cases, tumour incidences have been described as having a negative slope in the dose-effect relationship which sets in at the lowest doses and then generally proceeds up to the highest doses tested (700-900 rad). This pattern of response is found for the reticulum cell sarcoma and the non-thymic lymphoma in RF (694, 686, 681, 692, 145, 107) (fig. IV). LAF_1 (688) and $(C57BL \times C3H)F_1$ (438) (fig. IV), for

pulmonary adenoma in RF (692, 145, 107) and LAF_1 (515, 688) and for hepatoma and mammary sarcoma in LAF_1 mice (688). A radiotherapeutic effect on the cells which will eventually give rise to the tumours (in the absence of any significant concomitant induction of new tumours by radiation) is usually invoked to explain the negative slope of the relationship (447, 671). This may well be the case for systemic tumours, where such an interpretation at the single-cell level is supported by ancillary evidence concerning the slope of the inactivation curve of possible target cells (233, 438), but cell inactivation data favouring a similar interpretation in other cases is lacking. A discussion on this point will be found in paragraph 151.

143. In the majority of cases, the dose-effect relationship is of a complex type and shows an initial rise at increasing radiation doses, a peak or a plateau at some intermediate dose levels and in many cases, a final decline of incidence of the type as shown in figure I(f). The relationships for the induction of myeloid leukaemia and thymic lymphoma in RF (694, 671, 684, 692, 145, 107), C57BL (330) and LAF_1 mice (688) (figs. II and III), of ovarian tumours in LAF_1 (514, 688), SAS/4 (385), RF (145, 692, 107) (fig. VI) and BALB/C mice (750), of mammary carcinomas, fibromas and sarcomas in LAF_1 mice (688) and in Sprague-Dawley rats (614, 611, 712) (fig. VII), of kidney tumours in Wistar rats (422) (fig. VIII), of skin tumours in CBA (285) and Swiss mice (7) and in Sprague-Dawley (94) and CD rats (80) (fig. IX), of hepatomas in LAF_1 (688) and SAS/4 females (385), and of lung tumours in RFM (754) (fig. V) and in (C57BL X C3H)F_1 mice (135), conform to this general pattern. Systemic and non-systemic, benign and malignant neoplasms, mostly with rather low spontaneous incidences are included in this category. Although a large variability of this typical pattern is observed according to the various systems tested and to the quality of radiation, the doses at which the initial rise becomes detectable and the shape of this rise, the dose range where the peak incidence is observed and the height of the peak, and the presence and slope of the final negative part of the curve may usefully serve to characterize the various responses.

144. Regarding the shape of the incidence curves at low doses, myeloid leukaemia has been tested down to the level of 25 rad of x rays in the RF mouse; if one considers the observed points from that dose up to the peak incidence, the shape may be described as curvilinear (671) (possibly quadratic (233)) without excluding a linear component (685). There are however quite substantial variations in x ray inducibility between male and female RF mice (685), and neutron doses have not been tested below 50 rad in the female, which is less inducible (145), or below 130 rad in the male (692). Judging from these series, it would appear possible that the initial rise in incidence with dose may be more prompt after neutron irradiation than after x or gamma rays in both sexes. The dose-incidence curve for thymic lymphoma, up to the peak incidence, may be described as being of a curvilinear or possibly quasi-threshold type, but there appears to be considerable variation between strains, with a faster rise between 300 and 500 rad of x rays in the C57BL (330), a more gradual increase between 25 and 300 rad of low-LET radiation in the RF (694, 686, 692, 107) and a very slow rise up to 700 rad in LAF_1 mice (688). Where neutrons have been tested (688, 692, 145) (in these cases the observations do not extend below 50 rad) the curve might possibly be described as becoming more linear.

145. The incidence of ovarian tumours is greatly increased with respect to controls by a dose as low as 50 rad in RF mice, and for this reason it appears difficult to attribute any shape to the response curve at lower doses (692, 108). In the only instance where the effect of 25-rad gamma radiation was estimated, the point did not appear significantly different, although lower, than the control value (692) and a plateau was already apparent at 100 rad. Neutrons yielded conflicting results: 50 rad of 14-MeV neutrons produced a substantial increase in incidence, but a beam of 5-MeV neutrons seemed rather inefficient in producing ovarian tumours in the same strain of animals.

146. The only instance in which a linear dose-effect relationship has been reported in the interval of 17-250 rad is the early-appearing mammary neoplasia of the Sprague-Dawley rat (611) although, even in that case, some departure from linearity was apparent at the lowest doses (575). In the same system, but on late-appearing tumours, the hypothesis of linearity has been questioned (714) at least for neutron irradiation with doses as low as 5 rad. This observation does not exclude, however, linearity of the response below this limit, although it would indicate a much steeper rise of the induction curve upon neutron treatment. In the case of kidney, skin and lung tumours after local sparsely ionizing irradiation (422, 285, 80, 7, 754), the response at low doses would be termed in general to be of the curvilinear type, while alpha-particle irradiation data show less curvature than the electron irradiation curve in the same system (80).

147. To the extent that simple biophysical models could be applied to a biologically complex phenomenon like tumour induction, the above conclusions would appear to be in general agreement with the observations made for a variety of radiation effects on cellular and subcellular structures, according to which the dose-effect data at low doses (delivered at high dose rate) can be fitted by power functions of the dose, with lower exponents for high-LET radiation than for sparsely ionizing radiation (13). They are also in agreement with the arguments of Kellerer and Rossi (340), according to which the interplay of primary biophysical events produced by at least two low-LET particles is required to initiate biological effects, whilst one single densely ionizing particle might suffice to produce these effects. Such a hypothesis implies predominant quadratic kinetics as a function of dose in the case of low-LET radiation and linear kinetics in the case of high-LET radiation. Actually, an analysis of mammary tumour induction in the Sprague-Dawley rat (575)—the only case where a linear relationship has been claimed down to very low dose levels of low-LET radiation—suggests that linearity, although consistent with the data points, may be fortuitous and that more than one cell may be involved in the origination of these tumours.

148. In the most complete set of data reported for transformation of hamster cells *in vitro* by x rays (57), the power function which would best fit the

experimental points in the interval 1-10 rad would have an exponent of less than one, although a linear dependence of induction on dose would not fall outside one standard deviation of the data. Thus, even at this very simple level, the expected quadratic shape of the response to x rays cannot be confirmed, probably due to heterogeneity of the cell population to transformation (an inherent characteristic of the cell system used). Population heterogeneity might also explain the paradoxical results of dose fractionation in this same system (58), where dose splitting is shown to enhance rather than depress (hypothesis of a quadratic relationship) or leave unaltered (hypothesis of linearity) the transformation phenomenon. These data emphasize the difficulties in the interpretation of the transformation effect even at the rather simple level of *in vitro* cells and therefore indirectly point to the conclusion that similar analyses in *in vivo* systems may at present be unwarranted.

149. Concerning the doses at which the maximum incidences in the dose-effect relationships of reticular systemic tumours are found, the peak incidence for myeloid leukaemia is generally observed at doses of 200-300 rad with both high- and low-LET radiation in the RF mouse; at higher doses, a declining incidence is usually observed. For thymic lymphomas the peak appears at somewhat higher doses (300-700 rad) and a subsequent negative slope is rarely seen, probably because of the post-irradiation bone-marrow syndrome which can reduce substanstially the survival of the animals at these high doses (694). The peak incidence seems to occur generally at lower doses with densely ionizing radiation. This feature is compatible with the theory of dual radiation action and with the model of two competing processes discussed in paragraphs 50 to 66. Peak incidences of between 40 and 60 per cent at 100-200 rad have been reported for ovarian tumours in the most sensitive RF and BALB/c strains, and within each strain there appears to be no special tendency for the maximum to occur at lower doses with fast-neutrons or alpha particles than with x or gamma irradiation. This phenomenon seems, on the contrary, well documented for mammary and skin tumours in the rat, in spite of the great diversity of the doses at which the peak incidence occurs (400-500 rad and 3000 rad of low-LET radiation, respectively). Maximum incidences in the dose range of 1500-1700 rad are found for lung and kidney tumour induction by local x-ray treatment.

150. In conclusion, there appears to be no obviously identifiable correlation between the susceptibility to tumour induction and the character of the dose-effect relationships resulting from low- or high-LET irradiation; neutrons and alpha-particles have a tendency to produce peaks at lower doses than x or gamma rays in all systems. The height of the peak is also not clearly influenced by the radiation quality but may rather be regarded as an intrinsic biological characteristic of the particular system, having little correlation with radiation quality.

151. The declining trend in tumour incidence at high doses of radiation could be qualitatively explained by taking into account two concomitant dose-dependent phenomena: on the one hand, the effect of transformation tending to increase with increasing doses according to some linear or curvilinear function (see paragraphs 144-146; and, on the other hand, the inactivation of the reproductive integrity of potentially transformed cells, which also increases with dose following complex kinetics which in mammalian cells are usually described by a multi-target one-event type of equation (170).

152. A quantitative analysis of this hypothesis was carried out by Gray (233), who tested data on the incidence of myeloid leukaemia in RF mice (671) and more recently by Mole (459) and by Mayneord and Clarke (430). Gray found that at the low doses the induction of tumours would proceed in this system with the 2.28 power of the dose; the loss of reproductive integrity of the transformed cells at high doses could reasonably be described by a survival curve having an extrapolation number of 2 and a D_0 of 120 rad.

153. However, a similar model fitted to the skin tumour data of Hulse (285) by Hulse *et al.* (288) showed that a dose-squared function would adequately describe the initial rise, but the D_0 resulting for potentially tumorous cells from the declining portion of the curve would be 20 times greater than the 135 rad reported by Withers (741) as the sensitivity of the clonogenic cells in irradiated mouse skin. Fitting other linear or two-hit kinetics to the induction process did not essentially change the conclusions of the analysis, nor could the high D_0 be explained on the basis of cell migration from non-irradiated areas of the skin. Very similar arguments have also been developed by Barendsen (25) for his system of tumour induction in the skin and might also be easily applied to other results on kidney carcinogenesis (422). It might further be added that if the negative slope at high doses does in any way reflect the sensitivity to killing of the potentially transformed cells, one should expect a steeper decline after high-LET radiation than after x or gamma rays in the same system, which is by no means an obvious or a consistent finding in all the data reviewed.

154. Finally, the data of Borek and Hall (57) indicate that the plateau and the decline in incidence of the transformed clones with dose is independent of the killing of potentially transformed cells, since it is observed also after correcting for loss of reproductive integrity. This would imply, therefore, that transformed cells have a higher sensitivity to radiation with respect to normal cells in the same population. On the basis of these data (which are anyway of doubtful applicability *in vivo:* see paragraphs 147 to 148) the hypothesis of a balance between transformation and killing of potentially tumorous cells should therefore be considered under a different perspective. Granted that tumours must by definition arise from cells which have retained their reproductive ability, the peculiar shape of the induction curve would show that at the highest carcinogeneic doses an excessive amount of damage may render the transformed cells more sensitive than their normal counterparts to radiation-induced loss of mitotic integrity. In this respect, the plateau and the declining portion of the curve would not reflect the intrinsic sensitivity to killing of the transformed cells, but rather the differential sensitivity of these cells with respect to the normal clonogenic population.

C. RADIATION QUALITY AND THE EFFECTS OF DOSE RATE AND DOSE FRACTIONATION IN CARCINOGENESIS

1. The concept of RBE

155. In addition to absorbed dose, the quality of radiation, sometimes specified as the linear energy transfer (LET) of the charged particles (primary or secondary) in the medium of interest, is also an important physical factor in radiation carcinogenesis. This factor was discussed in the 1972 report of the Committee (670). In experimental work the concept of relative biological effectiveness (RBE) is commonly used to characterize the quantitative differences of effect brought about by different types and energies of radiation. For this purpose, the RBE of one kind of radiation compared to another is defined as the inverse ratio of the doses of the two kinds of radiation that produce the same biological effect (563), under the stipulations that *(a)* the basis for comparison should be the absorbed doses, and *(b)* other radiological or biological factors known, or suspected, to influence the response of the irradiated system should be the same.

156. It is clear however that since the nature of the biological effect, the nature and physiological conditions of the irradiated system, the dose level, the distribution of the dose in time and within the irradiated system affect the RBE estimates, the strict definition given above would imply a very detailed knowledge of the exposure conditions and of the system and effect under study before reference could be made to true RBE values. Short of this knowledge, an "equal-effect ratio" could be derived, defined as the ratio of two doses producing equal responses, when undetermined factors, other than the LET of the two radiations compared, would affect the biological response (563).

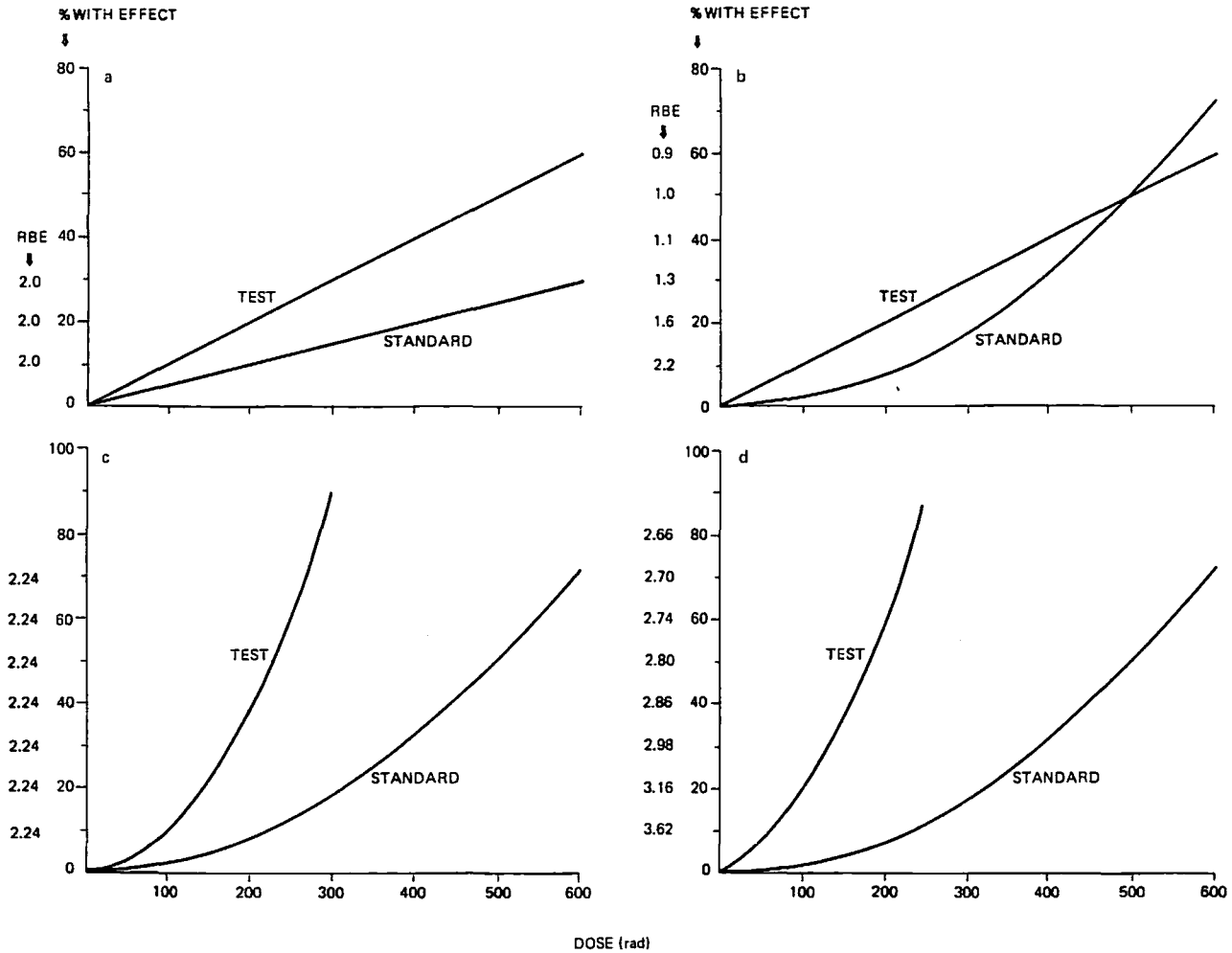
157. Actually, the vast majority of the so-called RBE values for tumour induction published in the literature and reviewed in the present report fall into this latter category of estimate, since only seldom have the physical parameters of exposure and the biological characteristics of tumour system studied been determined or reported with the necessary degree of precision. This observation refers especially to the use of inappropriate end-points or of uncorrected estimates of tumour incidence for the calculation of the dose ratios and to the lack of a systematic exploration of the dose-effect relationships within a large range of doses in most of the systems studied. All this might largely account for the scatter of the values reported. Chapter I of this Annex discussed the appropriate methodology for RBE studies. The influence of the shape of the dose-effect relationship on the RBE values, especially at the low doses of interest in radiation protection, was already discussed in the 1972 report of the Committee (670), where the rationale for the interpretation of the relevant RBE changes was reviewed. Although additional experimental data have since become available, these concepts have not been sufficiently considered in general terms (except in references 340 and 430) and need review and systematization in the light of the most recent theoretical acquisitions.

2. Dose-RBE relationships

158. Figure X, taken from the 1972 report of the Committee (670), illustrates schematically the influence of the shape of the dose-effect relationships on the change of RBE values with dose. It appears that when the effects brought about by the two radiations under comparison follow simple linear (case *a*) or second-order (quadratic) polynomial kinetics with different second-order coefficients (case *c*), there is no reason why the RBE should differ at different levels of dose and/or effect. However, when the effect of the standard radiation follows a curvilinear shape and the test radiation produces a linear dose-effect relationship (case *b*), the RBE will tend to increase at very low doses; at higher doses the RBE would gradually decrease and might in principle even become less than 1 above the intersection of the two curves. However, as was mentioned in paragraphs 91 to 103, simple polynomial approximations are only valid at the lower doses. A similar increase of RBE values at low doses, but without a tendency for inversion at high doses, will take place when the effect of the standard radiation follows a second-order polynomial relationship and the test radiation produces a dose-effect relationship with an appreciable first-order component in addition to the quadratic term (case *d*).

159. The most recent theoretical analysis of the concept of RBE has been carried out in the context of the theory of dual radiation action (340) which leads to rigorous mathematical formulations and, even for complex effects such as tumour induction, may account for the shape of the dose-RBE relationships. Concerning the RBE changes as a function of dose rate, it is customary to explain the experimental data on the assumption that high- and low-LET radiation can operate through single-track and multi-track mechanisms, with a very high probability of multi-track phenoma in the case of the low-LET radiation. As the dose rate decreases, the probability of simultaneous or near simultaneous multi-track events for sparsely ionizing radiation also decreases and only the single-track component remains effective. The RBE would then tend to a high limiting value which is the same as the limiting value of the ratio of the initial slopes of the dose-effect curves (563). The loss of efficiency at very low dose rate is comparatively smaller for the high-LET than for the low-LET radiation, and therefore the RBE increases towards a limiting value that would correspond to the RBE at low doses.

160. The mathematical formalism for the dependence of effect on dose and on RBE in the presence of inter-track phenomena, as a function of the irradiation time and of the recovery time of the irradiated system, has been recently worked out on the basis of the theory of dual radiation action (340). The relations holding for constant irradiation times and for constant dose rates are given, and the pitfalls in interpreting RBE values at constant low dose rates as being due exclusively to single-event mechanisms are also discussed. Data on RBE of different radiations in various tumour model systems are examined in the following paragraphs. The values of RBE pertaining to high and low dose rate will be considered separately for those systems where sufficient data are available.



(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 a (which in this case equals 0) and the second-order term cx^2, but with different second-order coefficients c

(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, and the first- and second-order terms, $y = a + bx + cx^2$

Figure X. Influence of character of dose-effect curves on RBE (670)

161. Concerning the induction of tumours of the reticular tissues, when myeloid leukaemia was induced in RF mice, the RBE of fast neutrons (1, 5 and 14 MeV) compared with x and gamma rays was shown to vary with dose and dose rate. For acute exposure in the dose range of 25-450 rad, the neutron RBE was estimated to be not appreciably different from 1 (145, 693, 692), while at low dose rates an unequivocal increased relative effectiveness of the neutron treatment (perhaps by a factor of 10) was reported, owing to the greatly reduced yield of tumours in the animal groups irradiated with sparsely ionizing radiations (692). Treatment of the same strain of mouse with 60-MeV protons appeared slightly less effective than irradiation with 300-kV x rays in the interval of 50-200 rad, but at higher doses the effectiveness of the two radiations was very similar (107).

162. Thymic lymphoma incidence was also examined in the course of the same experimental series (145, 692, 107). At the highest dose rates, the RBE of neutrons of all energies was not significantly greater than 1 at all doses tested, but 60-MeV protons tended to be less effective than x rays at doses of 300 and 400 rad. At low dose rates the efficiency of the low-LET radiation treatments decreased by two to three times and a corresponding increase of the neutron RBE was observed (692). As already pointed out (see paragraph 142), other reticular tissue neoplasms such as non-thymic lymphoma and reticulum cell sarcoma show an inverse relationship of incidence with dose, with x, gamma, neutron and proton irradiation. In view of the inhibitory effect of the radiation treatment and due to very pronounced variability introduced by biological factors (see paragraphs 80-82) the RBE calculation would be here of limited interest.

163. The different shape of the dose-incidence curves for the various classes of leukaemia seen in the rodent, the different times at which the leukaemic syndromes occur, the distortions introduced on the final incidence estimates of the late-appearing leukaemic syndromes by the early-appearing ones, and the frequent lack of appropriately corrected incidence data account for the

difficulties in generalizing meaningful RBE values for all leukaemias considered together. In cases where such comprehensive analyses have been attempted, 60-MeV protons appeared slightly but consistently less effective (0.80-0.65) than 300-kV x rays in the interval 100-400 rad, but microdosimetric and biological considerations could not account for this difference and would not permit in any case extrapolation of such data to larger animals (107).

164. Observations on the mortality and pathology at death were carried out on hybrid mice irradiated with 200-kVp x rays (0-200 rad) or with 400-MeV neutrons (0-84 rad) at comparable dose rates. No differences were observed in the longevity, which would suggest an upper limit to the RBE for life-span shortening of approximately 2.5. Similar conclusions were also drawn with respect to the induction of all types of leukaemias and of other solid tumours (136). Preliminary data on a large RBE experiment on C57BL mice have been published by Mewissen and Rust (442). The dose range was between 3.2 and 47.2 rad of reactor fast neutrons and between 18 and 141 rad of ^{60}Co gamma rays. A spontaneous spectrum of tumours including a major proportion of reticular tissue was established in control animals and modulation of this spectrum by the radiation treatment was observed, particularly in the reticular tumours. Dose-effect relationships for tumour appearance were non-linear and the radiation-induced changes in tumour spectra seemed to be related more to different intercompetitive processes, rather than to probabilistic random events. No numerical RBE factors were however provided. In conclusion therefore, as far as neutrons are concerned, their RBE appears to be about 1 in the range of a few tens to a few hundred rad at high dose rates; at low dose rates the tendency is towards an increase of the RBE by a factor of 2-10, according to the particular type of leukaemia and the particular dose rate examined.

165. In RF mice, the incidence of lung adenomas has a negative trend with dose which is not appreciably different in groups irradiated with 300-kVp x rays or 60-MeV protons (107); fast neutrons at various doses and dose rates caused a greater reduction in incidence of these neoplasms than gamma rays (692).

166. The RBE for the induction of ovarian tumours by neutrons in the RF strain cannot be established with certainty: in one series (145) 14-MeV neutrons appeared no less effective than x or gamma rays, whilst in other experiments (693) lower energy neutrons appeared to be very inefficient for the induction of ovarian neoplasia. In a more recent report by the same group of workers (692), RBE was studied as a function of dose and dose rate, and similar results were found, with the exception that tumours appeared in a significantly increased number after only 2 rad of neutron irradiation delivered at the dose rate of 0.004 rad/day. If this observation is a spurious one, then the RBE for neutron carcinogenesis of the ovary could be low; but if it were confirmed, it might imply that the absence of tumours at higher doses and dose rates (neutrons) could be due to excessive injury or life-span shortening due to the treatment. The latter would be then in favour of a very high RBE value for ovarian carcinogenesis by 1-MeV and 5-MeV neutrons. The RBE for x rays and fast protons for this same effect was rather similar at all doses tested, with a possible higher efficiency between 100 and 400 rad for protons. However, for both radiations the maximum incidence was seen already at 50 rad, suggesting that down to this dose level the efficiency of the two radiations under comparison is not appreciably different from unity.

167. The RBE for the induction of mammary neoplasia in the rat following acute irradiation has been the object of considerable attention. The 1972 report of the Committee (670), in examining the older RBE data for this tumour, commented on their technical heterogeneity. Actually, although the same animal strain was used in all the experiments, the most extensive results on low-LET irradiation were obtained in one laboratory on 40-day-old rats by scoring the neoplastic response at about one year post-irradiation (for a comprehensive analysis of the low–LET data see Shellabarger (611)). The neutron irradiations, on the other hand, were performed in another laboratory on animals 2-3 months old, with lifelong observations (708, 712). The differences in the scoring technique account for the fact that the background incidence of mammary neoplasia in non-irradiated rats is negligible in the first case and approaches 50 per cent in the other. In addition, the use of data uncorrected for competing risks, probably did not alter greatly the final estimates of tumour induction in the first case, since only 4 per cent of the rats had died at all doses within the observation time of one year (611), while in the neutron series it seems likely that the calculation of appropriate final incidence values might have changed the conclusions to some extent.

168. There is no doubt that if one considers the data produced by the ^{60}Co gamma treatment, which are reported as being linear in the interval of 16-250 rad (611), and the data of the fission neutron series (where a dose as low as 5 rad produced a near-maximum effect (714), and one calculates the ratio of doses producing the same neoplastic effect, one finds very high values of the RBE. However, comparing the results of 5 rad of fission neutrons and 100 or 300 rad of x rays by the same lifelong technique of scoring shows that at all times from irradiation to death the curve describing the percentage of rats bearing tumours for the neutron-irradiated group is intermediate between the curves following 100 and 300 rad of x rays (714). Thus, RBE values of between 20 and 60 could be applicable to the data.

169. The problem of RBE for breast tumour induction in the rat was discussed recently at the Symposium on Biological Effects of Neutron Irradiation (43), where the results of the two groups of scientists active in the field were updated and compared. Long-term observations on animals irradiated with neutron doses of about 2 rad were matched by the results of 100 rad of x rays, implying an RBE of about 50. A non-linear "step function" of the neutron dose-effect relationship between 2 and 20 rad was also reported, the explanation of which, except for the possibility of statistical fluctuations, seems rather obscure (709), especially since no such trend was found by the second group of workers in an experimental series extending down to 0.1 rad of neutrons (613).

170. These latter data were thoroughly analyzed by means of dose-effect relationships based on the time-integral of the tumour incidence rate *P(t)* (see paragraph 103) for the two radiations under comparison (0.43-MeV neutrons and 250-kVp x rays). In good agreement with previous analyses (575), the neutron dose-effect relationship showed an effect proportional to a dose power of less than 1, an observation interpreted to imply that the induction of neoplasia in this particular animal system might be due to the interaction of a number of cells, rather than to the transformation of an individual cell developing into a tumorous clone. The RBE approached values of 100 at the lowest neutron dose of 0.1 rad and of about 10 at the highest dose used, 6.4 rad. Thus, the earlier discrepancies found in the analysis of the breast tumour system by the two laboratories were apparently reconciled, at least to the extent that at the very low neutron doses the RBE would attain extremely high values, as the theory of dual radiation action (340) would predict.

171. However, the biological peculiarity of this tumour system should be emphasized, since radiation acts in this case essentially through an acceleration of tumour appearance, rather than by the induction of new neoplasms. There seems to be agreement about increasing values of the RBE with decreasing doses, but whether the above conclusions would also apply quantitatively to all other tumour systems remains to be established by new experimental evidence. An equal effect ratio of 1.5 between ^{60}Co gamma rays and 2.2-GeV protons for the induction of breast neoplasia has also been reported (620), following a pattern qualitatively similar to the induction of this tumour by other low-LET radiations and well within a range of RBE values reported for different cellular and functional end-points. Finally, the RBE of ^{3}H administered internally as compared to gamma rays from ^{137}Cs given externally at similar dose rates was found to be around 1.8 for the yield of mammary tumours in rats between 13 and 19 months after exposure (475).

172. No data are available for the breast tumour system on the changes of RBE as a function of the dose rate, except for the facts that after gamma irradiation at exposure rates of 10 R/min or of 0.03 R/min there is no sparing effect of the low dose rate in the incidence of mammary fibroadenoma, but a lower incidence of adeno-carcinoma. The total breast tumour response is however unaffected (612). Thus, since at the relatively high doses used the overall low-LET radiation effect is not changed, one should not expect consistent changes in the RBE because the predominantly linear component in the neutron dose-effect relationship would not be expected to change with dose protraction. Similarly, at the very low dose rates, for which, according to the theory (340), the inter-track interaction is negligible by comparison with the intra-track effects, one should not expect the RBE values to exceed those which apply for the acutely delivered very low doses.

173. Another tumour system where there appears to be enough data for some analysis of RBE is the skin tumour. Scattered information on the induction of this neoplasia by neutrons and x rays in the rat has been reported by Jones *et al.* (312) and in the mouse by Lippincott *et al.* (394) after proton and alpha-particle irradiation, but this information is unsuitable for deriving RBE values. A fairly complete dose series in the rat has, however, been reported (80) following irradiation with cyclotron-accelerated helium nuclei or with monoenergetic electrons, which allows some estimate of an RBE for skin tumour induction. If the RBE is calculated in this system (see figure IX) according to the displacement of the rising portion of the two curves, then a value of 2.9 is obtained. Since there is the suggestion that the initial slope of the alpha-particle curve is greater than that of the electrons, at very low tumour incidences of between 0.1 and 0.2 tumour/rat appreciably higher values (possibly about 5) might be calculated. The authors themselves point out, however, that the significance of the experimental points at these low levels of induction is questionable in view of the very low number of tumours involved. A range of RBE values dependent on dose and dose rate can be estimated from the data of Fry *et al.* (206) on harderian gland tumours. By comparing the irradiations with fission neutrons and ^{60}Co gamma rays, an RBE value of about 12 may be inferred.

174. A number of values have been obtained from other improperly called RBE studies in various animals and tumour systems, and they are reported here mainly for the sake of completeness. It should be pointed out, however, that in these cases the effectiveness ratio of the radiation is often obtained by dividing the level of effect induced by similar doses, instead of dividing the doses for equal effect. In addition, these data refer mainly to single acutely delivered doses in the range of some hundreds of rads and therefore they do not allow any generalization relating to the changes of RBE with dose and dose rate.

175. In the mouse, RBEs of between 2 and 3 were obtained between 250-kVp x rays and fission-spectrum neutrons for the induction of kidney tumours (118), gastro-intestinal carcinoma (514) and hepatomas (118). Mean after-survival and tumour incidence were the same for BAF_1 mice irradiated with acute whole-body doses of 250, 135 and 80-kVp x rays (229). In the rat, a comparison between fission neutrons and x rays yielded a ratio of about 2 for skin tumour induction (312). In the rabbit, 2.5-MeV gamma rays and 0.7-MeV neutrons gave a ratio of effectiveness of about 3 for the production osteosarcomas, fibrosarcomas and basal-cell carcinomas (286).

3. Conclusions

176. The number of tumour systems for which analyses of the RBE of different radiation can be performed with any degree of accuracy is still rather scanty, in spite of the repeatedly pointed out need for such data in radiation protection (563, 670, 564). From the fragmentary information available it appears that the efficiency of high-LET radiation is greater than that of low-LET radiation for the induction of tumours of various kinds. In those systems where complete dose-effect relationships for both types of radiation are available, the RBE appears to change with the dose, according to patterns dictated by the shapes of the dose-incidence curves. At high sublethal dose levels, RBE

values as low as 1 may be found, but for various tumours the pattern is that of an increasing RBE toward the lower doses. Values of up to 10 have been reported at doses of 25-100 rad, according to the various tumour systems studied.

177. When doses of the order of 0.1 rad of neutrons were tested in the rat breast-tumour system, RBE values approaching 100 were reported. Although such high values conform to the theory of dual radiation action (207) and have previously been reported for acute and delayed somatic effects in irradiated plants and animals, they remain unique in the field of tumour induction. Even though such high RBEs "cannot be used to predict the radiation induction of other tumours in other systems" (613) they certainly require further confirmatory work in other appropriately selected tumour-model systems.

178. An increase of the RBE is generally to be expected also at low dose rates, mainly due to a decreased efficiency of low-LET radiation. Data in this respect however are even more fragmentary and do not allow precise quantitative evaluation, except perhaps in the case of mouse leukaemia where chronic, as compared to acute, treatment could decrease the efficacy of the low-LET radiation by factors of 2-10, with a corresponding increase in the RBE of the high-LET radiation.

4. Effects of temporal distribution of irradiation

179. A physical variable of great relevance in radiation carcinogenesis is the dose rate. The most recent theoretical treatment of the dose-rate effect has been presented within the framework of the theory of dual radiation action (340, 574). According to the general foundations of this theory, a wide range of radiobiological effects in higher organisms (including the induction of tumours) may be visualized as the end-result of elementary lesions taking place in the cells at the subnuclear level.

180. The relationship of these effects with dose may be considered as the sum of two components, a linear and a quadratic one. The former predominates in the case of densely ionizing radiation and is essentially independent of the dose rate since it is associated with the interaction of the lesions produced by one single-particle track. The quadratic component is more clear for low-LET radiation: it is very dependent on the dose rate because it reflects the interaction of lesions produced by different charged particles. Lowering the dose rate in irradiation with sparsely ionizing particles causes a reduction of the inter-track effects because of the spontaneous recovery processes of the elementary lesions and consequently reduces the probability of effects resulting from the interaction of lesions produced by different tracks. In very general terms, the reduction of the inter-track effect will depend on the ratio between the characteristic recovery time of the system and the exposure time; therefore when the latter becomes long compared to the recovery time (i.e. at progressively lower dose rates) the final effect of a given dose will decrease through a reduction of the quadratic component. The case of dose fractionation may be analyzed in a manner which is qualitatively similar to that of continuous irradiation.

181. A further consequence of the postulated model is that correct dose-effect relationship determinations at different dose rates require the use of dose rates proportional to the total dose (constant irradiation time) in order that equal recovery apply at all dose levels. This technique appears to have been followed only rarely in the work reviewed, since the vast majority of the experiments have been performed at constant dose rates for different dose levels, a procedure which makes the analysis of the data very complicated, due to the need of applying to the effect reduction factors inversely proportional to the total dose.

182. It should be pointed out in addition that the preceding theoretical analysis, although valid in principle for any biological effect including carcinogenesis, is based essentially on arguments stemming from the theory of dual radiation action which are applicable only at the subnuclear level; the extrapolation of such formal treatments to the level of cell population, tissues or the whole animal is subject to the methodological difficulties discussed in chapter I and is further complicated by intercellular and physiological effects not easily amenable to generalization. Among these effects one should consider the kinetics of target-cell population for the induction of any particular tumour type (compartment size, cell turnover rates and intercompartment transit times), the phenomena of cellular inactivation, intracellular recovery and compartment repopulation induced by the radiation treatment (which have variable dependencies on the dose rate) and also the modifying factors discussed in chapter II and the biological variables to be considered in chapter IV.

183. All these factors have different relevance in the various tumour systems considered and, although included in the overall carcinogenic response of the system, make it impossible to derive a true quantitative analysis of the dose-rate effect. Hug (283) has analyzed several dose-effect relationships in several animals for tumour induction by external whole-body exposure and internal irradiation. He has attempted to link the effects of dose and dose rate on tumour induction with the incidence and latency time of the spontaneous neoplasms, with the purpose of extrapolating the estimates of malignancy induction to man.

5. Dose-rate effects

184. In agreement with the theoretical interpretation given previously, the reviewers who have considered at various times the effect of dose rate on tumour induction have all confirmed the reduction of the yield of tumours with decreasing dose rate and the relatively lower dependence on dose rate of the effect of densely, as compared to sparsely, ionizing radiation (671, 672, 676, 454, 230, 670). The evidence available up to the present on chronic and protracted exposures will be reconsidered in the following paragraphs in view of attempting general qualitative conclusions referring to all

tumour systems examined and of providing, when possible, quantitative parameters to the effect of dose rate. Experiments on fractionated and protracted exposures will also be considered. On the other hand, the cases of lifelong exposure and of split-dose irradiation will be discussed separately for their methodological and/or theoretical peculiarity.

185. Concerning the tumours of the haemo-lymphopoietic system (446, 325, 674, 675, 676, 678, 670), summaries of the state of knowledge have been published on various occasions. The changes of induction of myeloid leukaemia appear to have been studied mainly in the RF mouse. Dose rates of 0.01 rad/min and 0.004 rad/min of ^{60}Co gamma rays induce considerably less of the disease as compared to acute irradiation and also change the characteristic shape of the dose-effect relationship found with acute doses (which has a maximum at about 300 rad) into a flat dose-effect curve with a maximum incidence of about 5 per cent. The ratio of the peak incidences appears to be about 5. Irradiation by neutrons of about 5 MeV mean energy, at a dose rate of 0.0004-0.004 rad/min, compared to irradiation by cyclotron neutrons (mean energy about 1 MeV) at 100 rad/min, had somewhat less leukaemogenic efficiency, probably by a factor of 2-3, at the same peak incidence of 300 rad. If, alternatively, the reduction of the initial slope of the dose-effect relationship is taken as a measure of the reduced effectiveness at low dose rates, it may be estimated that in the case of low-LET radiation the efficiency is possibly reduced by a factor of 2 at the low dose rates. No difference in slope is seen in the case of neutrons (693).

186. In another series of experiments male RF mice were subjected to daily ^{60}Co gamma-ray exposures at 0.007-0.07 R/min and showed a peak incidence of myeloid leukaemia of about 12 per cent at doses of 250 rad, compared to an approximate incidence of 40 per cent after single high-intensity x or gamma ray exposure. A further reduction of the exposure rate from 0.008 to 0.004 R/min resulted in a still lower incidence of less than 5 per cent at the peak (685).

187. Finally, in an exhaustive report, the influence of dose and dose rate on the induction of myeloid leukaemia was tested in male and female RF mice whole-body exposed as young adults to neutrons of 1 and 5 MeV, or to ^{60}Co gamma rays or 250-kVp x rays at dose rates varying from 10^{-6} to 10^{2} rad/min (554, 691, 692). For a given total dose of neutrons, chronic irradiation was found to be as effective as acute irradiation, but with x or gamma rays the reduced dose rate led to a considerably decreased incidence of the disease, so that no leukaemogenic effect above the control level was observed at dose rates of 0.056 to 0.0038 rad/min for total doses of 200-300 rad, whereas the incidence was up to 40 per cent in animals irradiated at 80 rad/min. The loss of effectiveness induced by the low dose rate of gamma rays was about 1/20 and consequently the RBE values for neutrons at low dose rates might be estimated to be of the order of 10-20 (692). A reduced effectiveness of the low dose rate is therefore consistently found in the case of myeloid leukaemia induced by sparsely ionizing radiation. The magnitude of the reduction factor is difficult to evaluate in view of the changes introduced by the low-rate treatment in the character of the dose-effect relationships. Neutron induction appears to be less sensitive to the decrease of the dose rate.

188. The pattern of response of thymic lymphoma to low dose rates appears definitely less uniform. A graded sequence of whole-body x-ray doses in 2, 4, 8 equal fractions at intervals of 1, 4, 8 and 16 days given to C57BL mice of both sexes produced a gradual increase in lymphoma incidence as a function of dose. For a given total dose the induction of tumours did not seem to be affected by daily fractionation, but fractionation at intervals of 4 and 8 days resulted in a higher incidence of tumours appearing at shorter latency times. A further increase of the fractionation interval to 16 days resulted however in a decreased incidence (330). These results appear to be in contrast with those obtained for other immediate effects of irradiation and for the induction of many types of neoplasia, indicating that different pathogenetic mechanisms are involved in the induction of thymic lymphoma. According to Kaplan and Brown (330), the presence of optimal rythms of fractionation for lymphoma production is to be related to the optimal sequence of the pathogenetic mechanisms (bone-marrow injury, viremia, thymic regeneration, immunodepression) leading to the transformation of the thymic cells (see paragraphs 46 to 48).

189. An enhanced effect of dose-fractionation at intervals of 5 to 8 days has also been confirmed after neutron irradiation of the RF mouse (689). On the contrary, a change in the dose rate of ^{60}Co gamma rays from 7 to 0.004 rad/min results in a rather shallower slope of the induction curve, while the yield of neutron-induced lymphomas appears to be unchanged by the decreasing dose rate (693). These results were confirmed and enlarged in a subsequent series showing that with decreasing dose rate of neutrons no change in the induction of lymphoma takes place, while chronic daily exposure to gamma rays consistently reduces the effectiveness of the treatment to such an extent that there is no detectable tumourogenic effect on the thymus at dose rates of 0.0038 rad/min (692). In CF1 femal mice with doses of 60 rad of fission neutrons or 300 rads of gamma rays administered at the average rate of 1 rad/min in weekly irradiations given in 1, 3 or 6 equal fractions per week, the incidence of thymic lymphoma increased as the number of weekly fractions increased from 1 to 6, whilst at 3 fraction/week a decreased incidence was noted (688).

190. In conclusion, while a difference of behaviour among different strains cannot be excluded, it appears that dose-rate reduction by continuous or by fractionated exposure acts in the case of thymic lymphoma through quite different mechanisms. A decreased rate of exposure rate on a continuous treatment leads to a reduced tumour induction in the case of x or gamma rays but not in the case of neutron irradiation. Dose fractionation, on the contrary, tends to enhance the incidence of tumours and the optimum weekly fractionation schedules may be related to the pathogenetic mechanisms discussed in paragraphs 46 to 48.

191. The incidence of reticular tumours other than those previously discussed is also variable with the dose rate, reflecting probably the heterogeneity of the syndromes included in this class of malignancies. Mice of the CBA and C57BL strains given limited periods of daily x irradiation at an average dose rate of 81-1.3 rad/hour up to total doses of 900-1000 rad and then followed for the rest of their lives, showed that the degree of life-span shortening and of lymphoid leukaemia incidence (on which life-span shortening was primarily dependent in these strains) were markedly dose-rate dependent. The uncorrected incidence of leukaemia in the highest dose-rate group was found to be 39 per cent (average between the two strains) and fell to 5 per cent in continuously irradiated animals. These figures should be compared to a 2-per-cent incidence in control animals (448).

192. In contrast, fractionation of a dose of 690 rad of x rays into 2, 4 and 8 equal fractions given in 8 weeks resulted in an increased incidence of non-thymic lymphoma in LAF_1 mice, with respect to animals receiving a single dose of the same total magnitude (122). Fractionation of x irradiation has also been reported to increase the incidence of leukaemia in CAF_1 mice (115). Finally, it has been reported that in RF mice the incidence of reticular tumours other than myeloid leukaemia or thymic lymphoma has a negative trend with single doses of both neutrons and x rays (see paragraphs 117 and 118). With decreasing dose rates the inhibitory effect of the gamma rays decreases markedly, and at a dose rate of 5 rad/day, there is an actual increase of the incidence in males. Chronic irradiation with neutrons has different effects depending on the sex (since in females no change is found with respect of acute irradiation but in males a failure of the inhibitory effect is found), resembling in this respect the pattern seen with gamma rays (692).

193. In the RF mouse the induction of ovarian tumours by ^{60}Co gamma rays is decreased by a reduction of the dose rate from 7 to 0.04 rad/min. The dose-effect relationship obtained after acutely delivered single doses is also very different, the maximum incidence being obtained at higher total doses; this difference makes it very difficult to specify a numerical value for the reduction factor. In the case of neutrons a very shallow dose-effect relationship is seen at all doses with a very slight increase at low dose rates (about 5 per cent) over the spontaneous incidence (about 1 per cent). For comparison, the maximum incidence obtained in the range of 100 rad/min is of the order of 15 per cent (693).

194. In a more recent report the effectiveness of gamma-ray irradiation decreased with smaller dose rate, even though tumour induction was evident down to dose rates of 10^{-4}-10^{-5} rad/min. Neutrons at 0.004 rad/day significantly increased the induction of ovarian tumours after a total dose of only 2 rad, but no such effect was seen at higher dose-rates. This result clearly needs further confirmation to verify whether the low incidence at higher dose rates could be attributable to excess of damage (692). In sharp contrast with the above data, the incidence of ovarian adenoma was increased to 80 per cent after 618-1335 rad of ^{60}Co gamma rays at 1.45 rad/hour in the LAF_1 mouse (515) starting from a background incidence of about 6 per cent. Animals irradiated previously with comparable doses at 28-30 rad/min had shown an incidence of ovarian neoplasia of 35 per cent (514).

195. A detailed quantitative analysis of ovarian tumour induction in Balb/C mice as a function of dose rate has also been reported recently (750). Animals were exposed to graded doses of ^{137}Cs gamma rays in the range of 49-392 rad at dose rates from 1.75 to 112 rad/day, and it was shown that the incidence of neoplasms was a decreasing function of the exposure time. At variable dose rate, i.e. at constant exposure time, the incidence of ovarian turmours appeared to follow a square function of dose, and when the exposure time was variable, the incidence seemed to be inversely related to the 0.69 power of the exposure time. It was found, in addition, that about one third of this exposure-time factor could be accounted for by an age-related loss of sensitivity of the tumour system, while the rest was attributable to recovery phenomena at the intra- or intercellular level. In summary, therefore, the most complete studies available have confirmed on two different strains the presence of a significant dose-rate effect for the induction of ovarian tumours by x and gamma rays. The neutron data are, on the contrary, inconclusive.

196. Some experiments are available concerning the effect of dose rate and fractionation on the mammary tumour system of the Sprague-Dawley female rats. A dose of 500 rad given in one single exposure at 40 days of age, or divided into 4 equal fractions given over 2 weeks or 8 fractions in 4 weeks, or 16 or 32 fractions for a total treatment time of 8 or 16 weeks, respectively, did not appreciably change either the percentage of tumour-bearing rats or the total number of tumours observed over the entire life span. The susceptibility of the system to tumour induction by a single dose remained constant during the time the experiment was performed. As regards the histological type of tumours, a decreased yield of adenofibromas and a relatively increased yield of adeno-carcinomas was found in the irradiated animals: in this strain adeno-carcinoma is observed particularly in old age and appears to be shifted forward in time after all fractionation schedules (618).

197. The results of the change in dose rate were somewhat similar, in that an inversion of the time of appearance of the two histotypes seemed to be operating. Animals given ^{60}Co gamma irradiation at 0.03 rad/min or at 10 rad/min and followed for about one year had an overall tumour incidence of 37 per cent and 40 per cent after 88 rad given at the lower and higher dose rate, respectively. After 265 rad the total incidence of tumours was 57 per cent at 0.03 R/min and 60 per cent at 10 R/min. However, while the adeno-carcinomas showed a reduced incidence at low dose rate, the fibroadenomas were not reduced (612). Considering the peculiarity of the mammary tumour system, these results are not incompatible with the data obtained in many other tumour systems. In fact, the decrease in dose rate and the dose fractionation act by reducing the yield of the tumour type which is actually induced.

which is the adeno-carcinoma, and the effect is manifested through a relative increase of the induction time by comparison with the acute irradiation.

198. In the case of lung tumours the data on the effect of dose rate and fractionation are few and uncertain. It has been reported that in male LAF_1 mice, urethane alone in appropriate doses produces 16 per cent tumour incidence within 25-26 weeks, while a dose of 300 rad of x rays results in 12.5-per-cent incidence; the two treatments combined give 50 per cent animals with tumours. Fractionation of the x-ray dose into 6 equal fractions of 50 rad daily followed by urethane elicits a higher tumour response than observed in several appropriate groups of control animals (116). In RF mice whole-body irradiated with mid-lethal doses of radiation, the neoplastic response of the lung shows in general a decreased trend with dose, but, paradoxically, gamma rays at a low dose rate cause an increased incidence. To explain these data, it has been postulated that a tumourogenic effect on the lung may result at all dose rates, but may be masked at high dose rates by life-span shortening caused by other forms of injury. Neutrons, for any given dose, generally yield a greater reduction than gamma rays at all dose rates (692).

199. In the $B6CF_1$ mouse the incidence of mammary tumours is around 1 per cent and shows little increase with either single or fractionated exposures to ^{60}Co and fission neutrons (206). Ainsworth *et al.* (3) reported a greater life-span shortening in hybrid in $B6CF_1$ mice with fractionated doses than with single doses (80 or 240 rad of neutrons in a single dose or in 24 doses given over 23 weeks), associated in part with the appearance of pulmonary tumours. Less killing of potentially neoplastic cells because of fractionation, the possibility that acceleration rather than true induction could be operating and changes in age-dependent susceptibility during irradiation are explanations that have been invoked to account for these findings.

200. Some results are also available on dose-fractionation effects on skin tumour induction by beta particles. A sparing effect of fractionation has been reported in the rat by Henshaw *et al.* (262) and by Zackhaim *et al.* (755). CBA mice irradiated with 6 000 or 12 000 rad of ^{204}Tl beta particles in 4, 12 or 20 doses over a maximum fractionation time of three months showed little evidence of change in skin tumour incidence with respect to animals receiving single exposures to the same total doses. However, the yield of epidermal and dermal tumours after extreme fractionation and protraction (20 fractions in 25 days) was reduced to 50 per cent with respect to other groups receiving fractions of bigger size. It was noted that this relative insensitivity to fractionation is in sharp contrast with the great dependence of the acute and chronic skin damage on the fractionation regime, which would indicate that the induction of skin tumours has little correlation with acute skin damage (287, 25).

201. Vanderlaan *et al.* (696) reported a model to account for dose and dose-rate effects on skin carcinogenesis in rats. The model assumes that tumours can arise as a result of either one or two dose-dependent events and predicts that the one-step mode of tumour induction is very small, if at all present. For the two-step mechanism, the first step is visualized as reversible with a recovery time constant estimated to be of the order of 0.17 $hour^{-1}$.

202. In contrast with what would be predicted by the study of chromosomal damage in partially hepatectomized mice (142), an increased incidence of hepatoma (32 per cent) has been reported in LAF_1 mice irradiated with ^{60}Co at 1.45 rad/h (515) with respect to animals irradiated with x rays at 30 rad/min (2 per cent) (514). Control incidence of hepatoma in this strain is of the order of 6 per cent.

203. The incidence of gastro-intestinal carcinoma is also increased above control level in LAF_1 mice by whole-body irradiation with 690 rad of x rays. Fractionation of this dose into 2, 4 and 8 fractions over a total time of eight weeks resulted in a definitely reduced incidence. It has been pointed out that the effect is not dependent on life-span shortening since comparisons between the same age groups show a similar reduction (122). Scattered observations on the effect of dose rate, fractionation and protraction on miscellaneous tumours can also be found in Reincke *et al.* (558), Bustad *et al.* (85), Upton, Randolph and Conklin (692), Vesselinovitch *et al.* (706) and Ainsworth *et al.* (2).

204. Tumours of the thyroid have also been reported after chronic administrations of ^{131}I. Jorno and Zapolskaya (316) have treated mongrel rats with activities of 0.015-0.0015 μCi ^{131}I/day for cumulative thyroid doses up to 4500 rad for the highest dose group. The incidence of neoplasia in these animals was about 10 per cent in the two years after the treatment. No tumours were found in the low-dose group. In another paper (84) a significant increase of malignant (up to 20 per cent) and non-malignant (41-44 per cent) tumours of the thyroid was reported following chronic intake of ^{131}I in drinking water at 0.07 μCi/day for 180 days. However, short-term (10 days up to an activity of 0.1 μCi/rat) versus long-term (6 months up to 1.6 μCi/rat) administration of ^{131}I produced similar carcinogenic effects in the thyroid (15-18 per cent tumour incidence) and the yield of tumours was in both cases higher than in controls (8 per cent) (702). Morphological and ultrastructural data were also reported in the same publication in the thyroid of ^{131}I-treated animals.

6. Lifetime irradiation

205. A number of experiments have been reported on the effect of dose rate on animals irradiated continuously during their lifetimes. They should be considered separately as a rather uniform group, interpretation of which is very difficult, both conceptually and because of problems of technique. It has, in fact, been pointed out (445) that the radiation received during the last part of a duration-of-life exposure is less effective than that received earlier. The difference in efficiency per unit dose between a short-term and a lifelong exposure has been referred to as "wasted radiation" that is, radiation given in excess of that required to elicit the effect. In the present context,

the concept of wasted radiation applies to the dose in excess of that strictly required to induce a tumour, namely, the dose received during the tumour latency time plus that received between the clinical appearance of the tumour and the death of the animal. When dealing with an effect characterized by its late manifestation in time, not allowing for wasted radiation may lead to very important alterations of the determined dose-effect relationship.

206. Groups of LAF_1 mice of both sexes were submitted to lifelong ^{60}Co gamma irradiation starting at 100 days of age with daily exposures from $2\ 10^{-5}$ to 5 R. The survival data were analyzed in terms of accumulated lethality per unit daily dose, and four distinct phases of early lethality corresponding to different types of damage were thus identified. Coefficients of life-span shortening for after-survival in excess of 60 days were also worked out (582). The induction of tumours as a function of daily dose, age and sex at dose rates below 56 rad/day were reported in a subsequent publication (370), and tumour incidence data were obtained both after serial sacrifice and after lifelong observation.

207. Concerning thymic lymphoma, the slope of the cumulative incidence curves increased with daily dose up to 32 rad/day and remained constant thereafter. There was no evidence that lymphoma incidence was higher than control in the 5-rad/day group, but 12 rad/day gave rise to an abrupt increase in incidence in both sexes and to a marked shortening of the latency time. Pulmonary tumours were above control values only in females irradiated at 5 rad/day but otherwise declined with increasing dose in all other dose groups; above 12 rad/day there was a shift forward in the time of appearance of these neoplasms. Hepatomas were only found in the control and in the irradiated groups with long survival times; radiation had little effect on their incidence in both sexes. The incidence of ovarian tumours rose sharply in the irradiated groups but rapidly decreased above 12 rad/day, suggesting that the most effective carcinogenic dose for this organ is to be set at some dose rate below this limit.

208. Comparison of these data with the tumour incidences reported for the same strain with single terminated exposures led to the conclusion that the duration-of-life exposure is considerably less carcinogenic per unit of accumulated dose. The duration-of-life experiment was later extended to mice of six different genotypes. Evidence at dose rates below 6 rad/day, where life-span shortening is less than 15 per cent, indicated that all of this life-span shortening could be associated with neoplastic diseases (227, 228). The pattern of age-specific mortality rate for reticular tissue tumours indicated a maximum in the incidence-rate curve at daily doses from 6 to 43 rad/day, with total accumulated doses of about 3000 rad. Pulmonary tumours, hepatomas and ovarian tumours showed, on the contrary, a modest increase in incidence at 6 rad/day or less, followed by a sharp decline at higher daily dosages. A possible model accounting for the observed life-span shortening due to causes other than reticular tissue tumour has been also proposed (583). Lifetime periodic gamma-ray exposure experiments have also been reported in other mouse strains, with special regard to leukaemia and life-span shortening on five successive generations (735) and in the guinea-pig (581).

209. Yakovleva (744) reported data on tumour development in 150 dogs exposed for six years to chronic (21, 63 and 125 rad/year at dose rates of 0.06, 0.17 and 0.34 rad/day) or to combined chronic and acute gamma irradiation. Various types of benign and malignant tumours of various organs were seen at autopsy and the majority of them were seen in animals exposed chronically at the highest dose rate and at the highest total dose.

210. Of special interest is an experiment being performed on beagles irradiated continuously in a ^{60}Co field at daily doses varying from 5 to 300 rad, delivered over 22 hours (205). In this experiment the causes of death appear to be related to the dose rate and total accumulated doses; septicaemia, anaemia and myeloproliferative disorders usually under the form of myeloid leukaemia appear to be the haemopoietic syndromes most common in these animals (204, 203). At 35 rad/day or higher the dogs die with septicaemia, but not at 10 rad/day or less. At 17 rad/day all three syndromes appear; at 10 and 5 rad/day only anaemia and leukaemia are seen, the latter at longer exposure times. Two out of 13 animals dying at 17 rad/day developed leukaemia after 1038 days; 6 of 13 at 10 rad/day after 719 days, and 4 of 6 at 5 rad had leukaemia at an average time of 1063 days. Thus, lower dose rates produced leukaemia in equal or shorter exposure times, so that the optimum rate of exposure for leukaemia induction would appear to be around 10 rad/day, and higher rates might be inhibitory (205).

7. Split-dose irradiation

211. Attempts to utilize the split-dose methodology (170) to evaluate the time-course and the extent of recovery processes in the case of tumour induction have been reported. The data are extremely few and scattered so far, although our knowledge of the kinetics and of the nature of the recovery from late damage could be considerably expanded by the use of such methodology, which has proven to be very fruitful in the case of short-term radiation effects. Split doses of radiation given at various intervals from 4 to 48 hours have resulted in increased long-term mouse survival following a kinetics which is reminiscent of the recovery curves for the survival of single cells (628). The pathological observations performed on these animals were not very satisfactory but showed clear evidence of a decreased tumour incidence even at such short fractionation intervals (439).

212. Split-dose experiments with a 24-hour interval in the mouse lung-tumour system were reported by Yuhas (751), showing significant recovery when the total dose was well in the curvilinear part of the dose-effect relationship (1500 rad), while no recovery was apparent when the total dose fell on the linear portion of the induction curve (750 rad). The split-dose method applied to the mammary tumour system of the Sprague-Dawley rat yielded negative results (605). These latter findings might be explained on account of the linearity of the

dose-effect relationship in this particular experimental model. Recovery with respect to skin tumour induction in the rat was measured by split-dose methodology at a fixed 31-day fractionation interval after a conditioning dose of 750 rad (surface dose of fast electrons) (81). The difference in dose between the fractionated and the non-fractionated treatment to obtain the same level of skin tumour induction was found to be about 650 rad, in good agreement with the 600-rad value found for hair follicle atrophy. More recently the same group (82) reported on the tumour incidence and the lethality of hair follicles in rat skin following several single doses of fast electrons (1000-4000 rad) and split doses (1000 and 1000-4000 rad) with a 24-hour interval. The number of tumours per rat 70 weeks after single doses showed the usual peak at 2000 rad (fig. IX) followed by a decline at higher doses. With split radiation the peak was displaced by at least 70 per cent of the initial conditioning dose. Since the interval of 24 hours is too short for any significant cell repopulation, it was concluded that the effect could be best explained by a rapid process of recovery, similar to the intracellular recovery described by Elkind (170).

213. Split-dose data are, in conclusion, very incomplete and inadequate to resolve between the intracellular component of the recovery and the component due to cell repopulation; the approach seems, however, well founded and should be pursued in the future in view of the essential need for information on recovery from neoplastic damage. In this context, *in vitro* techniques of cell transformation could also be very valuable for the interpretation of experiments on *in vivo* systems. Experiments *in vitro* have already been reported at a 5-hour fractionation time (58) and they deserve further attention since they have shown an increased yield of transformed clones by fractionation, which would appear to be the exception, rather than the rule, in all the *in vivo* systems examined.

8. Conclusions

214. The following conclusions may be drawn from an analysis of the effects of dose rate and fractionation on the induction of tumours in various animal systems. When methodological and technical difficulties are conveniently accounted for, a decrease in the dose rate of low-LET irradiation results in general in a decrease of tumourogenic effect, following some inverse function of the exposure time. The form of the dose-effect relationship applicable to acute irradiation is often greatly altered by the change in the dose rate, and therefore precise values of the reduction factor have so far been estimated only for very few tumour-model systems. Reduction factors of 2-20 have been reported between the highest and the lowest dose rates tested (10^{2}-10^{-6} rad/min) and between single and extremely fractionated and protracted doses, for various systems and different end-points.

215. In the few cases where high-LET radiation has been tested for tumourogenic effects (essentially the haemo-lymphoreticular neoplasms of the rodent) the reduced effectiveness of the low dose rate appears to be quantitatively less important than that induced by a corresponding decrease of dose rate of x or gamma radiation, or it may even be absent. Departures from this very general pattern are found in special cases (the lymphoma, for example); rather than exceptions to the fundamental radiobiological mechanisms they may be regarded as special cases due to the pathogenetic mechanisms of these tumour systems. There are well founded theories accounting for the decrease in effect of low dose rate and fractionation, which may be conceptually ascribed to repair of the elementary biophysical lesions responsible for tumour induction. It seems reasonable to postulate, in addition, that intra- and intercellular mechanisms of recovery may be operating in this case as in the case of short-term radiobiological effects. But the kinetics and the nature of these repair phenomena are still essentially unknown and urgently require elucidation.

IV. CARCINOGENESIS BY INTERNAL EMITTERS

A. GENERAL

216. In reviewing the data on tumour induction by incorporated radionuclides each nuclide will be dealt with separately in this report, the specific distribution of a nuclide being by far the most significant variable. The general problems posed by internal irradiation are in principle the same as for external irradiation, though the presentation by nuclide requires a different format than that used in chapter III. One special aspect referred to in the 1972 report of the Committee (670) is the inhomogeneity of the dose in relation to space and time in the case of internally administered nuclides. The physical and chemical characteristics of the nuclides and the anatomo-physiological characteristics of the target tissues in different animal species give rise to widely different patterns of deposition, retention and excretion. The route and schedule of administration and also biological variables related to the genetic make-up, the sex, the age of the animals, add to the complexity of the main problem, which is the establishment of reliable dose estimates for evaluation of the neoplastic effects.

217. Any meaningful comparison of effects and risks between various animal species requires in fact that the dose delivered by the nuclides to the cells at risk be known with reasonable certainty. In spite of the efforts that have been made to refine the dose estimates (for reviews on dosimetry, see (634) and (635) for beta particles and (704) for alpha particles), there are still considerable uncertainties which render any comparison between nuclides and between species at best semi-quantitative. Data for interspecies comparisons may be found in a monograph edited by Moskalev (469). The criterion for comparison used in many studies of bone-seeking radionuclides, namely the "mean accumulated skeletal dose" is calculated differently by different authors, which increases the uncertainties of the comparisons. Since the object of the present report is to discuss specifically the neoplastic response, the reader is referred to more specialized publications for the above problems (431, 703). There are, however, some problems that must be dealt with and that appear to be

relevant for all nuclides; they refer specifically to the establishment of dose-effect relationships and to the concept of RBE in internal radiation carcinogenesis.

218. In regard to dose-effect relationships for internal irradiation, it should be realized that the effect of dose cannot be readily tested independently from the effect of the rate at which it is delivered, that the dose rate is changing in the course of the exposure period, and that internal irradiation is often extended until the death of the animal and therefore the concept of "wasted radiation" (445, 185, 46) is intrinsic to the analysis of the dose-effect relationships. It is possible to take this factor into account by computing the dose accumulated by the tissues at risk up to the time of first appearance of the tumour or to some such extrapolated time (185, 433, 434). Secondly, although in external radiation carcinogenesis the concept of RBE may be reasonably defined, at least operationally (see paragraphs 155-157, in the case of internal emitters it is difficult to compare nuclides which, in addition to LET differences, have very peculiar types of distribution, retention and translocation to various tissues. These concepts are mentioned in order to stress the need of extreme caution in interpreting statements abstracted from the context of the reviewed experiments.

219. It is customary to divide the bone-seeking nuclides into volume and surface seekers (426). The volume seekers include the alkaline earths, calcium, strontium and radium, the atoms of which can occupy the same sites in bone mineral. They are initially deposited in high concentrations on the surface of the mineral bone and slowly migrate into deeper sites by chemical exchange. This process plus the continuous apposition of newly formed bone mineral eventually buries most of the radioactivity within the mineralized structures of the skeleton. Other radionuclides like plutonium, thorium and americium are surface seekers and deposit on the periosteal and endosteal surfaces in the immediate vicinity of the capillary vessels, after which they may be removed by bone resorption or buried by the apposition of new bone. Added to the physical characteristics of their radioactive decay, this different behaviour has of course the most direct consequences on the distribution of dose to the target cells. Volume seekers with short half-lives (like, for example, ^{224}Ra having a half-life of 3.64 days) represent special cases since they decay almost entirely on the bone surfaces before being buried in the mineral part of the bone.

B. BONE-SEEKING BETA EMITTERS

1. Bone tumours

220. Strontium-90 has a half-life of 28 years: it decays to ^{90}Y by beta emission with maximum energy of 0.54 MeV. The ^{90}Y has in turn a half-life of 64 hours and decays to stable zirconium by beta emission with a maximum energy of 2.27 MeV. The range of soft tissues of the ^{90}Sr + ^{90}Y beta radiation is about 10 mm. Strontium-89 has a half-life of 51 days and a beta-particle maximum energy of 1.46 MeV with a 7-mm range in soft tissue. Strontium nuclides are volume seekers. The data available on single administration of ^{90}Sr are more of theoretical than of practical interest, but have been reported in a number of animal species. Small rodents are particularly suitable to this type of experimentation, since they may be treated in large numbers, thus providing better statistics. Their body size however is very small and therefore not particularly appropriate to mimic the geometrical conditions of exposure of man, without adequate corrections.

221. The data on the incidence of bone tumours obtained in CF1 female mice injected with ^{90}Sr at 70 days of age by Finkel and Biskis (183) (nine dose levels between 1.3 and 2200 μCi/kg), have been updated, re-evaluated and statistically analyzed by Mays and Lloyd (434). When the average skeletal doses, calculated up to the estimated start of tumour growth and ranging in this experiment between 0 and 12 000 rad, were plotted against the percentage incidence of osteosarcomas, the dose-effect relationship was found to be highly non-linear. Furthermore, a decrease in incidence from 91 per cent to 73 per cent was seen after an accumulated dose between 6630 and 12 000 rad. The incidences found at low doses appeared consistently less than those which would be predicted from an assumed linear dose response extrapolated to the control incidence value and fitting the data up to the peak incidence. Median life spans decreased rather regularly from the lowest (1.3 μCi/kg) to the highest (2200 μCi/kg) dose injected.

222. Dose-related data on radiostrontium intoxication of CBA X C57BL female mice injected at two levels (0.2 and 1.0 μCi/g) were also reported by Van Putten (699) and Van Putten and De Vries (700). Incidences of bone sarcoma of 19 per cent and 82 per cent were found respectively in the two groups, to be compared with a 0 per cent incidence of the control mice. In another series, two malignant bone tumours were found in 102 RF male animals injected once with 0.2 μCi/g and one in 75 animals receiving 0.04 μCi/g. No tumours occurred in controls or in animals given 0.51 μCi/g (128). In a more recent series of papers, Nilsson (497, 499, 502), reported dose-related data for CBA mice injected with ^{90}Sr at levels of 1.6, 0.8, 0.4 and 0.2 μCi/g. The spontaneous incidence of osteosarcoma was low in these mice. Bone tumours were found in all groups but the highest number (292 tumours in 120 mice) was observed in the 0.8 μCi/g group. A tendency to multiple tumours was also found, except in the 0.2 μCi/g group. The dose-effect relationship has been analyzed by Mays and Lloyd (434) and found to be non-linear. Latency time of bone sarcoma was shorter (from 485 days to 268 days) as the dose increased.

223. Single dose experiments with ^{90}Sr were carried out by Moskalev, Streltsova and Buldakov (470) on Wistar rats injected intraperitoneal (IP) at three months of age with activities ranging from 0.005 to 500 μCi/kg. The dose to the bone at 170 days before death were calculated by Mays and Lloyd (434) to range between 0.2 and 5760 rad. The incidence of osteosarcoma in these animals was up to 51 per cent in the two highest dose ranges and the average time from injection to death tended to lengthen as the dose decreased. The dose-effect relationship found did not appear to support a linear non-threshold hypothesis.

224. Brooks *et al.* (64) reported data on hamsters injected with ^{90}Sr (0.2 to 5.0 μCi/g, given IP). An activity-related shortening of life-span was observed. No animal survived within the first two weeks with 3.0 and 5.0 μCi/g. The 50 per cent survival times ranged from 90 days with 2.0 μCi/g to 1100 days at 0.2 μCi/g. With 1.0 μCi/g, an activity known to produce a high incidence of bone tumours in mice, only a few osteosarcomas were observed. Myeloproliferative diseases were, on the contrary, very common in the controls and in injected animals. ^{90}Sr was also injected into rabbits of various ages (from 2 days to 165 weeks). Osteosarcoma was found in animals receiving 500 μCi/kg at 6 weeks of age and occasional bone tumours were also found at 50-200 μCi/kg (705). Two bone sarcomas were observed in 15 miniature pigs with single injections of 64 μCi/kg (281).

225. The latest published data (April 1970) on the Utah experiment on beagle dogs given at 1.4 years of age single IP injections of 0.57 to 97 μCi ^{90}Sr/kg (corresponding to doses of 105-9100 rad at one year before death) were reported by Mays and Lloyd (434). Eight out of 14 (57 per cent) dogs that died at the highest dose level had bone sarcoma. Two of 12 dogs injected with 63.6 μCi/kg, which died, had osteoscarcoma. No bone tumours have yet been observed in the lower dose groups. Data are far from complete and no firm dose-effect relationship can yet be established, but the results so far would not support a linear response. Other interim data on ^{90}Sr toxicity in dogs (the Argonne Study), in relation to age effects and dose pattern, were reported by Finkel, Biskis, Greco *et al.* (188). Finally, acute inhalation studies with $^{90}SrCl_2$ were also performed and reported by Boecher *et al.* (49) and by McLellan *et al.* (414). Seventy-two dogs were exposed to aerosols which resulted in long-term body burdens of 1-120 μCi/kg. In the animals already dead, hemangiosarcomas, osteosarcomas and chondrosarcomas were observed.

226. Another volume seeker is ^{45}Ca, a beta emitter with a half-life of 165 days decaying to stable Sc. The radiation emitted is weaker than that of ^{90}Sr and has a maximum energy of 0.254 MeV and a maximum range in soft tissue of ~ 0.7 mm. A dose-effect relationship for single injections of ^{45}Ca in 70-day-old female CF1 mice has been reported by Finkel and Biskis (183), and these data have been reanalyzed by Mays and Lloyd (434). The activity range extended from 16 to 49 600 μCi/kg, corresponding to average skeletal doses from 63 to 111 000 rad. The highest incidence of bone sarcoma (96 per cent) occurred at 26 400 rad, after which a pronounced decrease in incidence was observed. Median survival time from injection to death decreased regularly with dose. Seven cases of bone sarcoma were observed in the dose interval 63-4700 rad, while a linear model would have predicted 26 cases. The chance that the linear extrapolation would actually be valid in the low dose region, appears to be less than one in 10^5. Kuzma and Zander (361) have also carried out a comparison of the neoplastic effects of ^{89}Sr and ^{45}Ca in rats and have established that the carcinogenic effect of calcium per unit activity administered is lower. A number of benign osteomas were found after its administration. Histologic and histochemical studies were also reported on ^{45}Ca-induced autochtonous and transplanted osteosarcomas in Donryu rats (257).

227. A single treatment with ^{90}Sr results in an uneven distribution of the dose both as a function of time and within the bone. The dose rate is bound to be very high at the time of injection, after which dose will accumulate at a progressively slower rate. In addition, the nuclide will be deposited initially only in those bone zones which are actively laying down bone mineral at the time of treatment, thus producing a non-uniform irradiation of the osteogenic and haemopoietic tissues. Repeated administration, on the contrary, is likely to result in a more even distribution of the dose within the bone tissue. Also, by injecting the nuclide in different fractions or by continuous administration, it is possible to deliver the same dose at various average dose rates, which may give indications about the role of the temporal distribution of dose in internal irradiation. Following this idea (185), experiments on fractional and on continuous exposure to ^{90}Sr have been carried out in various animal species.

228. Seventy-day-old female mice of the CF1 strain were injected with three different activities of ^{90}Sr (250, 500 and 1000 μCi/kg), once or five times in 5 weeks or 20 times in 4 weeks. It was found that for the same total dose the tumourogenic response (both as tumour incidence or as tumour expectancy) was highest when the nuclide was delivered in one injection and lowest when the dose was divided into twenty fractions. This experiment shows that the distribution in time of the same dose reduces its carcinogenic effect and that immediate high dose rate is more important for bone tumour production than the dose from the isotope retained in the skeleton (194). Similar data with ^{45}Ca gave a maximum yield of tumours at five injections in five weeks and lower responses at 1 or 20 injections. The data were explained on the basis of the lower energy and of the non-uniformity of deposition of ^{45}Ca with respect to ^{90}Sr (185).

229. ^{90}Sr was also incorporated into food, and female CF1 mice were kept on this contaminated diet from three days before mating until death, together with their offspring. A ^{90}Sr level of 15 μCi/g of stable calcium produced bone tumours in adult females, but at lower levels the tumour expectancy was within control limits. Females on ^{90}Sr diet since conception had osteogenic tumours at dietary levels of ^{90}Sr from 15 to 5 μCi/g of calcium, but not at lower levels. Males, on the other hand, developed three times fewer tumours than the female siblings. A careful analysis of body burdens in these animals and comparisons with the results of single injections, suggested that the activity accumulated in the skeleton was a valid indicator of the absorbed radiation responsible for oncogenesis (185). Preliminary data on the dose-rate effect following continuous ingestion of ^{89}Sr in Balb/C, C57BL and RFM mice have been reported for both haemopoietic and osteogenic tumours (742). It has also been shown that the incidence of ^{90}Sr-induced malignancies in CBA mice decreased after gestation and lactation, by comparison with unmated controls (495), and that this effect results from a decreased dose rate to the bones of the lactating females owing to a higher excretion rate of the nuclide (503).

230. In the rat, data on short-term administration (from 10 to 30 days) of ^{90}Sr in the drinking water were reported by Casarett *et al.* (93) and reanalyzed by Sundaram (746). Myeloid leukaemias, angiosarcomas and osteosarcomas were observed at total activities of ^{90}Sr of 330-464 μCi. There was an indication that at low dose levels the primary effect might be leukaemia and that at high levels osteosarcoma might be prevailing. 718 miniature swine representing three generations were kept on a continuous ^{90}Sr diet at levels from 1 to 3100 μCi/day; some animals were also sacrificed for dosimetric and histological studies. The experiments are still in progress and the data have been reviewed in various reports (280, 110, 281, 278, 109). Tumours of the bone (giant cell tumours, osteosarcomas) have been found at bone doses of 6300 rad (434), corresponding to an intake of 125 μCi/day of the nuclide. The chance that a linear non-threshold model for bone-tumour induction may correctly apply to these data has been estimated to be about 16 per cent (434). However, the high competing risk of leukaemia and other proliferative disorders and the non-completion of the study render these calculations very uncertain.

231. A study on chronic feeding of ^{90}Sr has been set up at the Davis campus of the University of California on several hundred **beagle dogs** treated from mid-gestation (onset of foetal ossification) up to 1.5 years of age with the purpose of labelling uniformly the skeleton of these animals. Average levels of ingestion range from 0.03 to 12 μCi/day. Metabolic and dosimetric parameters are evaluated in parallel experiments (217, 218) as well as non-neoplastic skeletal changes like endosteal or periosteal sclerosis, fractures, osteolytic lesions and trabecular coarsening (462). Up to 1972, osteosarcomas and other tumours were seen at the highest intakes of 12 and 4 μCi/day, after accumulated doses to the skeleton of 8000-11 000 rad (166, 543, 87). In a most recent report of these experiments (463), the delay period between exposure and bone sarcoma incidence was estimated to be 1.5, 5.1 and 9.4 years with activities of 36, 12, and 4 μCi respectively, starting from birth. The interplay of dose, dose rate and age were analyzed in this experiment in order to attempt extrapolation to low doses. Other data on dogs given fractional injections of ^{90}Sr during one year have been reported by Finkel, Biskis and Greco (188). Malignant bone tumours occurred in this case at 150 μCi/kg but none was seen after 10-100 μCi/kg.

232. Chronic feeding studies with ^{90}Sr in dogs were also reported by Burykina (83) at levels of 0.2 to 0.0004 μCi/kg per day, yielding average skeletal dose rates from 0.4 to 0.004 rad/day. Treatment lasted from 2 to 4 years. The tumours observed were mainly in the soft tissues (16 cases out of 51 dogs in all treatment groups) but 1 out of 15 and 2 out of 15 dogs at the highest dose levels developed osteosarcoma and leukaemia, respectively. The latency period of all tumours decreased with increasing dose. The data show that marrow and soft-tissue neoplasms are more readily induced than tumours of the bone for chronic irradiation.

233. A detailed statistical analysis of the dose-effect relationship for bone sarcoma induction, in ^{90}Sr and ^{45}Ca treated animals of various species, has been made by Mays and Lloyd (434), and it seems relevant here to report the main conclusions. They have normalized the data analyzed to a common quantity, the "average skeletal dose" (i.e., the dose from the time of treatment initiation to the time of initial tumour growth), which has been estimated differently in the various animal species. They have found that in all analysed cases the number of bone tumours appearing at low doses is considerably lower than the number that would be predicted from a linear model of the dose-induction relationship. The probability that a linear dose-induction relationship might adequately fit the data, ranges from 10^{-13} in the case of ^{90}Sr-injected rats (470) to $1.6\,10^{-1}$ in the case of continuously treated swine (281). In their opinion, the data at low doses would strongly support a "practical threshold" model with extremely low incidences below a few hundred to 1000 rad spread over the lifetime. At very low doses this model would not be distinguishable from a "sigmoid" model where the dose-incidence curve would first be very shallow, then would rise steeply and eventually would reach the plateau or bend down at extremely high doses. Mays and Lloyd have ascribed the sigmoid trend of the data to the efficient recovery from low-LET radiation damage at sufficiently low dose rates.

234. Extrapolating from the analysed data, the authors have inferred estimates for the 50-year risk from ^{90}Sr-induced bone sarcoma in man, which are (1 ± 1) 10^{-6} tumour per man rad for average skeletal doses below 1000 rad, according to a linear model, and (4 ± 4) 10^{-10} tumour per man rad^2 for average doses below 1000 rad according to the dose-squared model. These figures should be compared with the natural incidence of bone tumours, which is of the order of $5\,10^{-4}$. Vaughan (703) has however pointed out some of the difficulties in accepting these conclusions, which extrapolate single-injection and continous-treatment data between species, while it is clear (see paragraphs 236 to 240) that different types of neoplasia may be relevant under the two exposure conditions. In addition, the dose estimates should be treated with caution in view of the differences in bone structure in various species.

235. It is of some interest to report, for comparative purposes, that the lowest estimated average skeletal doses proven to induce bone sarcomas in various animal species after intravenous (IV), IP and oral administration of ^{90}Sr range, according to Mays and Lloyd (434), from 2500 to 6300 rad. Concerning the effect of dose rate, the data available suggest a reduction of bone sarcoma incidence at low dose rates. Dynamic studies of the growth of osteosarcomas produced in beagle dogs by various IV-injectod nuclides have been reported (662) together with comparative studies on the skeletal location of naturally occurring or radiation-induced tumours in the dog and in man (544, 663).

2. Myeloproliferative diseases and other tumours

236. Tumours of the bone are not the only form of neoplasia found after radiostrontium intoxication. Another important neoplastic disease is leukaemia. The general problems concerning the induction of this

disease in animals and in man after ^{90}Sr contamination have been discussed by Loutit (404), especially in relation to the risk of osteosarcoma. Concerning the experience with laboratory animals, a high incidence of reticular tumours by comparison with the controls was noted by Finkel (182) in the mouse (CF1) given ^{90}Sr in a single injection or in fractionated administration. In another report, an activity of 0.2 μCi/g in intact or splenectomized RF male animals increased the incidence of thymic lymphoma; other forms of leukaemia and non-thymic lyphoma also increased in number and occurred earlier (128).

237. Continuing reported experiments on the effects of various levels of ^{90}Sr on the haemopoietic system (marrow, spleen, thymus) of four groups of mice at the 0.2-1.6 μCi/g level (498), Nilsson reported more recently (501) on a complete series in which 1430 CBA mice were administered graded activities of ^{90}Sr (0.2-1.2 μCi/g), in order to investigate the site of origin, the development and the dose-effect relationship of leukaemia induction. The significance of the bone marrow in the thoracic vertebrae as the site of origin of the leukaemia and the relations among marrow, spleen and thymus in leukaemogenesis were also studied. The highest frequency of leukaemia developed among animals in the 0.2-μCi/g group and the incidence of the disease decreased with activities of the nuclide. The latency time did not vary greatly among the different groups. In a comparative study of the leukaemogenic action of x rays and ^{90}Sr in mice it was found that 680 rad of fractionated x rays produced 77.3 per cent of mostly thymic leukaemia, while 1.0 μCi/g of ^{90}Sr gave 61.8 per cent of lymphoblastic, reticulum cell or stem cell leukaemia. Thymectomy inhibited the development of the x-ray-induced but not of the ^{90}Sr-induced disease (298).

238. In a recent and yet incomplete study, CBA mice of a low-tumour strain were given from 6.7 to 20.0 μCi per mouse. The predominant tumours found were not osteosarcomas but haemangial and lymphoreticular sarcomas, presumably arising in the bone marrow. In this case also, the highest incidence was more likely to be at the lowest dose (405). The effect of ^{90}Sr (0.4 or 0.8 μCi/g) and of combined ^{90}Sr (0.2 μCi/g) and fractionated x irradiation on the thymus and other haemopoietic tissues of CBA mice were also studied by Järplid (305, 306) with serial sacrifice and long-term studies. Following the ^{90}Sr irradiation changes of the weight and cellularity of the thymus, spleen and marrow were reported. In the case of combined irradiation, the administration of ^{90}Sr delays the haemopoietic regeneration that takes place after an x irradiation, resulting in an increased incidence of thymic lymphoma. The induction of non-thymic lymphomas by ^{90}Sr was also enhanced by small doses of external x rays.

239. In the rat, myeloid leukaemias were reported after chronic administration of ^{90}Sr in drinking water, suggesting that at low dose levels the primary effect might be leukaemia and not bone tumours (93, 646). An incidence of 6.1 per cent of leukaemia (reticulosis, haemocytoblastosis and myeloid) was noted in 82 rats given 10 μCi/kg, corresponding to a marrow dose of 530 rad. These data should be compared with a spontaneous incidence in the controls of 1.7 per cent (470). Marrow changes, but no leukaemia, were also reported in rabbits given 600 μCi of ^{90}Sr per kg (703). In miniature swine fed on a ^{90}Sr diet (1 to 3100 μCi/day) for three generations a large number of myeloproliferative disorders were described, including myeloid, lymphoid and stem cell leukaemia, the incidence of which seemed to be in general relationship with dose and to have latent periods shorter than those of bone sarcoma (280, 110, 277, 278, 109, 551).

240. Haemopoietic changes (leukocyte depression, erythrokinetic disturbance, formation of ectopic haemopoietic centers) were described in beagle dogs chronically fed ^{90}Sr at dose levels of 12 and 4 μCi/kg (86). At later times, myeloproliferative disorders became apparent (166, 218, 165, 543). In these animals there was a continuous spectrum of diseases ranging from myeloid metaplasia to neoplastic proliferation of the granulocytic series. The main feature of these lesions consisted of an infiltration of the haemopoietic sites by mixtures of stem cells and granulocytes in various stages of development, rather than an increased blood leucocytosis. Infiltrations of the subendothelial and perivascular spaces of various organs (liver, lung, etc.) were also found. Finally, lymphosarcomas, myeloid leukaemias and reticulum cell sarcomas were also observed in the Argonne dog experiment (188). Other tumour types found in various mammalian species with single or continuous treatment with ^{90}Sr included haemangioendoteliomas and angiosarcomas of the bone marrow (195, 431, 49, 498, 499, 405), carcinomas of the mucous membranes of the head (496, 652), squamous cell carcinomas of the external ear or of the skin (705, 500, 502, 474), epidermoid carcinomas of the oral cavity (195, 652) and tumours of the mammary gland (474). In most of these cases (including leukaemia) the observations were too few to allow the derivation of complete dose-effect relationships.

3. Conclusions

241. The general picture drawn from the reviewed data cannot yet be very detailed and systematic, but appears in any case sufficient to support some inferences. It will have of course to be refined in the future by other data, either becoming already available or in progress, concerning the deposition, excretion and dosimetry of ^{90}Sr in the many species tested, for the various routes and schedules of administration. A detailed discussion of all these problems is clearly not within the scope of the present report and more specialized publications have dealt with them extensively (703).

242. Even if qualified by the uncertainties mentioned above, some important conclusions seem to emerge from the reviewed data. Firstly, the incidence of bone tumours, especially osteosarcoma, increases with dose in all the experiments examined, the form of the dose-effect relationship is probably sigmoid, and a dose-rate effect can be found if adequately looked for. Secondly, in most animal species tumours of the haemopoietic tissues are also found, sometimes in fairly high numbers. Thirdly, bone tumours predominate at high total doses and dose rates, while the incidence of

haemopoietic neoplasms follows in general gross haematological disturbances and is particularly high at low doses or with continuous exposure (415, 703). Fourthly, it seems possible that the neoplastic syndrome that will kill the animal may be determined by the different latency periods of the various forms of leukaemia and of bone tumours which are species-specific, and which depend on the dose and dose rate delivered by the nuclide. These variables, however, have not yet been incorporated into a comprehensive model. Finally, vascular and epithelial tumours may appear in some cases.

C. BONE-SEEKING ALPHA EMITTERS

1. Radium isotopes

243. Radium-226 has a half-life of 1620 years and decays to ^{222}Rn with the emission of alpha particles of 4.6 MeV having ranges in soft tissue of 31-70 μm. Radon-222 is in turn, as are several of its decay products, an alpha emitter, with a half-life of 3.82 days. Since radon is an inert gas, it does not become fixed in tissues and tends to escape at a rate that is different in different species and depends on the tissue characteristics. Radium-226 follows the metabolism of calcium and is therefore a volume-seeking isotope. Since information on ^{226}Ra is available in man (578), it is regarded as the standard bone-seeking nuclide and a basis for deriving estimates of risks for other bone-seeking nuclides in man by comparing radium and these other nuclides in the experimental animal (185). Earlier animal studies with ^{226}Ra have been summarized by Chiacchierini *et al.* (101).

244. In a report comprising 3210 femal CF1 mice (191), 70-day-old animals were injected singly with 14 different amounts of the nuclide, ranging from 0.05 to 120 μCi/kg. In these experiments, bone sarcoma was found to be the most sensitive indicator of damage, since it was induced even at dose levels where histological evidence of damage was not apparent. When the average tumour expectancy (the number of tumours still to appear divided by the number of animals still alive) was plotted against dose, the effect was shown to increase linearly between the control and the 2.5-μCi/kg level. At higher activities, up to 20 μCi/kg, another linear response having a lower slope was obtained; still higher activities produced no further increase in tumour response. According to the authors, the change in slope at around 20 μCi/kg would reflect severe damage and possibly the interplay of several carcinogenic factors, the relative importance of which would change at that turning point. Tumour expectancy is an unusual end-point in carcinogenesis and one rarely to be found in the analysis of dose-effect relationships; the above data are therefore not directly comparable with other experimental series.

245. Actually, when a more conventional end-point such as the (uncorrected) percentage incidence of tumours was employed, a different dose-effect relationship could be generated (433), and the incidence of radiation-induced bone tumours was shown to increase linearly with the average skeletal dose up to about 1000 rad. In the low-dose region (below 300 rad), the cases of bone sarcoma observed were in good agreement with those predicted by a linear dose-effect relationship. Other tumours, such as osteomas, hemangioendoteliomas and reticular tissue neoplasms, were also observed, in no obvious relation with dose (191). Radium-226-induced osteosarcomas were also reported in H strain mice (511) and (648).

246. Two still incomplete experiments on dogs injected with ^{226}Ra are also available. In the Utah study (163) beagles were given single injections of the nuclide at 9 levels from 0.0074 to 10.4 μCi/kg, corresponding to cumulative average skeletal doses at one year before death of up to 10 900 rad. Osteosarcomas were found (433) down to the 0.166-μCi/kg level (458 rad). At the three highest dose levels (1.07-10.4 μCi/kg), 32 of 35 animals died with osteosarcoma. At 0.339 μCi/kg and at 0.166 μCi/kg respectively, 5 out of 13 and 1 out of 9 of the dogs that died had osteosarcoma. No bone tumours were found in 13 out of 22 animals dead at the lower levels or in the 12 out of 22 animals dead in the control group. A progressive decrease of the survival time of the animals who died with bone tumours was noticeable with increasing dose. Some more recent data from this experiment were analyzed in terms of dose effect by Mays and Lloyd (433), and it was observed that a linear relationship fitted through the data would predict 0.7 sarcoma cases at a dose level of 147 rad, while up to that time no case had been observed. It was also noticed that the slope of the linear dose-effect relationship (0.043 per cent incidence per rad) is remarkably similar to the slope found for the previously considered experiment on mice (191).

247. In the Davis study (218), ^{226}Ra was administered to beagles in 8 injections at 14-day intervals. Retention and distribution studies were carefully performed (461). The data on late effects are still incomplete, but osteosarcomas have appeared, the number being roughly related to dose. Acute haemopoietic effects (leukopenia and ensuing anaemia) have been described in these animals, but no myleoproliferative disorder has yet been found. Eye melanomas were also reported in the dog (651). A comparison of the toxicity of ^{90}Sr and ^{226}Ra, on the basis of injected activities causing bone cancer in equal times, has been performed by Blair (47) showing that the ratio of ^{226}Ra to ^{90}Sr is about 40 to 1.

248. Radium-228 is a beta emitter that decays (half-life 5.7 years) to radiothorium or ^{228}Th, an alpha emitter (energy 5.4-8.8 MeV, particle tissue range 39-88 μm) with a half-life of 1.9 years. Thorium-228 concentrates on the endosteal surfaces and is therefore to be considered a surface seeker. With this nuclide, experiments have been carried out on dogs given a single IV injection (163). It appears from the results (433), that at 8.49 μCi/kg, 1 of 4 dogs had died with bone tumours; at the 2.62-μCi/kg level, 4 of 5 dogs; and at the 0.973-μCi/kg level, 3 of 9 dogs had developed osteosarcomas. There appeared to be a shorter induction period at increasing doses. A relative carcinogenic potency of about 2.5 for ^{228}Ra compared to ^{226}Ra has been computed for the average skeletal doses accumulated to the mean time of death with bone tumours. This high figure has been ascribed to the longer alpha-particle

range of the ^{228}Th daughter and to the redeposition of ^{228}Ra, ^{228}Th and ^{224}Ra (163). The dose-effect relationship up to the peak incidence (corresponding to an average skeletal dose of 485 rad calculated at one year before death), has been reanalysed by Mays and Lloyd (433), and it appears that many functions could be fitted to such data. However, a linear function passing through the origin would predict at least one case of bone sarcoma among the four dogs that had died already at an average skeletal dose of 226 rad. Six dogs at that dose level were still alive and it cannot be excluded that bone sarcomas might develop among them. Until the conclusion of the experiments, therefore, no firm statement can be made.

249. Radium-224 (thorium X) has a half-life of 3.64 days. The decay scheme of the isotope is complex, but essentially it is an alpha emitter with energies of 5.4-8.8 MeV. Radium-224 is not a surface seeker, but its short half-life results in its decaying almost entirely on the bone surface. When IP-injected into Neuherberg mice of both sexes 20-30 days old in single administrations of 5-200 μCi/kg at weekly intervals, it induced bone tumours very efficiently (284). Even at 5 μCi/kg, about 13 per cent of the females developed osteosarcoma and a further increase up to 50 μCi/kg did not result in a higher incidence. At still higher levels, the incidence decreases owing to a high acute-mortality. Differences in induction between males and females were conspicuous. The monthly tumour rates and the integral of tumour rates in males increased with increasing doses up to 100 μCi/kg. Tumours of other tissues and organs were also observed but, with one exception, not in higher incidences than controls. The microscopic distribution of the ^{224}Ra and its relationship to tumour induction in various bones were reported on by Hendringer and Gössner (261).

250. The observations on sarcoma induction in these animals were also reported by Gössner *et al.* (222) and, supplemented by further data, provided the basis of an analysis of the dose-effect relationship for the induction of osteogenic tumours at low doses, carried out by Mays and Lloyd (433). In the female, a mean skeletal dose of 150 rad (5 μCi/kg) already produced a peak incidence of 17 per cent; in the male, 1500 rad (50 μCi/kg) were needed for an incidence of 7.6 per cent. Spontaneous incidence was zero in 259 males and 1.3 per cent among 460 females. The experimental points agreed better with the hypothesis of linearity than with the threshold model. On a "per rad" basis, females would appear to be 15-20 times more sensitive to the induction of bone sarcoma than males. Whether this phenomenon is related to the higher spontaneous incidence of bone tumours in females or to other reasons, such as more active bone remodelling by oestrogen stimulation in the female (507), it would, in the opinion of Mays and Lloyd (433), give cause to question the hypothesis of Mole (456) that radiosensitivity to tumour induction by alpha and beta emitters is the same in all species.

251. In more recent work, single injections of ^{224}Ra (1-100 μCi/kg, corresponding to skeletal doses of 70-3000 rad) produced incidences of osteosarcomas from 7 per cent to 22 per cent in female mice. In contrast with other data with beta emitters (185), dose protraction by fractionation (twice weekly up to 36 weeks) resulted in increasing incidence (up to 90 per cent) of osteosarcoma with protraction time and total dose. This phenomenon might be related to cell kinetics or disturbed cell turnover (478, 479, 223). Similar experiments in rats (5-40 μCi/kg) produced an incidence of osteosarcoma of about 19 per cent. The radionuclide appeared to be slightly more effective than in mice, for the same activity injected. A comparison between ^{226}Ra and ^{224}Ra data in mice on a μCi-to-μCi basis showed that ^{224}Ra might be 10 times less effective in the low and medium dose range, taking the life-span shortening effect of the two nuclides as the basis for comparison (284).

2. Thorium isotopes

252. Another series of beagles was injected in the Utah experiment with ^{228}Th in single IV injections of a monomeric solution (163). From the latest published data it would appear that the peak incidence (83 per cent of animals with bone sarcoma) occurs already at the 0.0302-μCi/kg level (corresponding to an average skeletal dose of 249 rad accumulated until one year before death). There is, as in other cases, a good inverse relationship between the dose and the time to death with osteosarcoma. At lower levels some departure from linearity is observed, in that one case of sarcoma would have been predicted by a linear model among the six dogs dead without tumours at doses of 16 and 47 rad. However, the experiment is not yet complete and more than 20 animals are still alive at the lowest doses. Thorium-228 was evaluated to be 9 times more carcinogenic than ^{226}Ra on the basis of the average time to death with osteosarcoma (163). On the basis of incidence per unit dose (433) the efficiency would seem to be 6-7 times that of ^{226}Ra.

253. Thorium-232 has received attention because colloidal thorium dioxide has been used as a contrast medium in radiological practice. The content of ^{232}Th in Thorotrast (the commercial name of the medium) is about 25 nCi/ml. Thorium-232 has a half-life of $1.4\ 10^{10}$ years and emits alpha particles with an energy of about 4 MeV. Upon IV injection it is taken up by the reticulo-endothelial cells and becomes encapsulated in fibrotic lesions of the liver and spleen, from where some daughter products, ^{224}Ra, ^{228}Ra and ^{228}Th, may escape to reach bone. However, the characteristic lesions of Thorotrast in the human are liver tumours and myeloproliferative diseases. Information on the distribution, retention and late effects of Thorotrast is to be found in 151 and an up-to-date collection of papers, mainly on human Thorotrast cases, has recently become available (549). Studies in animals are relatively few. Guimaraes and Lamerton (240) found concentration of Thorotrast in the liver, spleen and lung of injected mice. Bensted (31) described late-occurring vascular spleen tumours, anaemias and a high incidence of leukaemias in mice injected with Thorotrast, but questioned its carcinogenic activity as being due to the radioactivity of the injected compound. Nodular adenomatous hyperplasia, adenomas and parenchymal cell carcinomas of the liver have been observed, and a dose-effect curve for lung tumour induction in the rat has been obtained (231,

232). Spindle cell sarcoma of the cheek pouch and liver cholangiosarcomas were also reported in Syrian hamsters (465).

254. Thorium-227 has a half-life of 18.7 days, decaying to a relatively long-lived nuclide (^{223}Ra) that can enter mineral bone. Dose-effect curves for the induction of bone sarcoma in mice were reported for single administrations of this nuclide (410, 411, 223) in the range 0.1-50 μCi/kg, corresponding to average skeletal doses of 20-10 000 rad. A peak incidence of osteosarcomas (60 per cent) was observed with 5 μCi/kg, with a median time for appearance of these tumours of about 17 months. Some differences in the anatomical location of the tumours with low and high activities of the nuclide and with similar activities of ^{227}Th and ^{224}Ra were also reported. Metabolic and dosimetric studies were performed by Muller *et al.* (480) with rats inhaling solutions of ^{227}Th in nitrate form. These authors showed that an initial deposition of 100 nCi in the lung resulted in alpha-ray doses of 150 rad in this organ, 76 rad in bone, 2 rad in the kidney and 0.1 rad in the liver.

3. Plutonium

255. Although there are many isotopes of plutonium, ^{238}Pu and ^{239}Pu are the most widely used in radiobiological research. They are both alpha emitters, with half-lives of 87.8 and 24 390 years, respectively. Plutonium may exist in many valency states, but tetravalent Pu is the most important for biology. Plutonium tends to form complexes very easily and its deposition and toxicology are greatly influenced by the chemical form in which it is injected: monomeric plutonium is taken up preferentially by the skeleton, polymeric plutonium by the liver. Long-term exchanges between liver, skeleton and other deposition sites take place. Uptake through wounds and by inhalation are the most frequent routes of contamination in occupationally exposed workers. Animal experiments (292) suggest that bone and lung tumours are likely to be the most important risks of uptake by these routes. In the skeleton, Pu concentrates characteristically on the endosteal surfaces; it may however be found in the marrow, especially when administered in the polymeric form.

256. A thorough comparative discussion of the distribution, excretion and effects of Pu as a bone seeker has been published by Vaughan *et al.* (704). Updated reviews on the uptake, clearance, translocation and excretion of inhaled Pu can be found in Sanders (585) and Bair *et al.* (21). The deposition, retention and metabolism in the liver of various animal species has been reviewed by Lindenbaum and Rosenthal (381). The concentration of plutonium in gonads of five mammalian species and man was investigated by Richmond and Thomas (565). References and details on the radiation biology and radiotoxicology of Pu and other transuranium elements can be found in the extensive reviews by Stover and Jee (645), Hodge *et al.* (269), Medical Research Council (436), Bair (20) and Thompson (661). A review of experimental data obtained by investigators in the Union of Soviet Socialist Republics in 1971-1975 on the carcinogenic action of radiation and dealing mainly with plutonium and other actinides was also obtained by the Committee (477). Additional data will also be found in a chapter by Buldakov *et al.* in (72).

257. The available experimental studies concerning the induction of bone and bone-marrow tumours show that CF1 female mice of about 70 days of age given a single IV injection of (probably) polymeric ^{239}Pu in the range 0.04-15.6 μCi/kg developed a number of osteosarcomas (184, 185). As in other cases reported by the same authors, the carcinogenic effect was analyzed in terms of tumour expectancy, and it was found that this variable was reasonably linear with dose. A reanalysis of these data by Mays and Lloyd (433) shows that the highest percentage incidence of bone tumours (77 per cent) occurs at 3.1 μCi/kg, corresponding to an average skeletal dose of 560 rad at 140 days before death. No bone tumours were found in 195 mice injected with 0.04 and 0.08 μCi/kg, while a linear relationship of percentage incidence to dose including all points up to the peak would have predicted about 3 Pu-induced tumours in this range, in addition to about 2 spontaneous tumours. The probability of observing no tumour against the predicted 5 would be about 0.5. In these same mice, the low-dose groups had an incidence of lung tumours up to 68 per cent, and the decreased incidence at higher doses was attributed to life-span shortening. The frequency of tumours of the reticular tissues was highest at 0.16 μCi/kg and decreased thereafter, probably owing to the same cause. Liver changes (mainly degeneration and a few hepatomas) were also noted in a number of cases, but their significance could not be attributed with certainty to the nuclide, in view of the poor state of health of the colony (184). Monomeric ^{239}Pu (0.0058-0.025 μCi) and polymeric ^{239}Pu (0.0087 and 0.015 μCi) in solution was injected intravenously into other CF1 female mice. When the induction of bone sarcoma was compared on the basis of equal amounts of the nuclide in bone, mice given the monomeric solution appeared to develop twice as many tumours with a shorter induction time. The higher concentration of the monomeric nuclide on bone surfaces was primarily responsible for the difference (572).

258. In a small study of the toxicity of ^{239}Pu (2.95 μCi/kg) injected into (Marshall X August)F_1 rats 6-8 weeks old, Bensted *et al.* (33) reported the occurrence of osteogenic tumours and myelogenous leukaemia. Fractionation of the radionuclide into 5 injections given at two-week intervals seemed to increase the leukaemia incidence. In the same strain of rats, fractionation of the administration did not significantly alter the incidence of bone tumours but shortened the latency interval (177). Plutonium-239 citrate administered intraperitoneally to three-month-old rats (in the range 0.65-5.0 μCi/kg corresponding to an estimated accumulated bone dose of 700-4300 rad) (460) produced a high incidence of bone tumours; the time from injection to tumour death decreased with increasing doses. The incidence data were said to be inconsistent with a linear non-threshold hypothesis. As reported in the same publication, ^{239}Pu was also administered orally in daily fractions that gave an estimated dose to the bone of 33-57 rad. Osteosarcomas, leukaemia and other soft-tissue tumours appeared in a relatively high percentage of rats.

259. Buldakov and Lubchansky (73) studied the induction of bone tumours in Wistar-derived rats by ^{239}Pu administered in various chemical forms (citrate, nitrate, ammonium pentacarbonate), various routes of administration (inhalation, intratracheal, oral, intracutaneous, subcutaneous, intraperitoneal) and at various concentrations. All these data were analysed by Mays and Lloyd (381) by plotting computed (non-corrected) average skeletal doses against the percentage tumour incidence. Within the large scatter of the experimental points (to be expected from such a heterogeneous set of data) a linear function was fitted, corresponding to an induction rate of 0.06 per cent per rad. This value might increase to 0.1 per cent per rad if dose corrections for wasted radiation were applied.

260. Chronic oral administration of ^{239}Pu citrate in activities of 0.1 to 1.0 μCi per rat (average skeletal dose of 1-10 rad) also resulted in an increased incidence of osteosarcoma, leukaemia and marrow aplasia. Life-span changes were minimal in the treated animals (74). Malignant and non-malignant tumours of the skin and of subcutaneous tissues were also described by Buldakov *et al.* (75) after intracutaneous and subcutaneous injection of ^{239}Pu in various chemical forms. Finally, albino rats injected IP with 2.8 μCi submicron-sized $^{239}PuO_2$ particles developed mesotheliomas and sarcomas of the omentum in great number (591). Other data on ^{239}Pu-induced sarcomas of the skeleton in rats were given by James (300) and by Pesternikov and Bukhtoyarova (531).

261. The Utah study on beagle dogs injected intravenously at 1.4 years of age with monomeric ^{239}Pu citrate has been summarized by Mays and Lloyd in 1972 (433, 432), and more definitive data on the completed injection groups were recently presented by Stover (644) and by Jee *et al.* (308). Plutonium-239 levels ranged from 0.016 to 2.9 μCi/kg. The dose-effect relationship for bone sarcoma induction up to the peak level of 69 per cent at 0.048 μCi/kg (corresponding to an estimated average skeletal dose of 191 rad at one year before death) was analysed in one of the papers (433). The two low-dose points (0.0157 and 0.0477 μCi/kg) and the control point fitted a straight line reasonably well. Five further injection levels (between 0.00064 and 0.016 μCi/kg) were added to this experiment in 1973 but no data are yet available. In terms of injected activity the carcinogeneic potency of ^{239}Pu in dogs was evaluated by Hems and Mole (260) to be 10-20 times that of ^{226}Ra. The efficiency of ^{239}Pu relative to ^{226}Ra for life-span shortening was estimated to be 6:1 (163). On a "per rad" basis of average skeletal dose, and for the induction of bone tumours in beagles, this ratio would appear to be of the order of 9:1 (433). It has however been pointed out (397) that the relative toxicity of ^{239}Pu to ^{226}Ra in adult man may be expected to be higher than in dogs.

4. Other actinides

262. Some data on the distribution and carcinogenic effects of other actinides have also been reported. An indexed bibliography of works up to July 1976 includes most of this information (661). In the present context only the most significant data on tumour induction will be briefly reviewed for each nuclide tested.

263. *Neptunium-237* (alpha emitter; half-life, 2.14 10^6 years). This nuclide was injected IV as nitrate and oxalate into rats in doses ranging from 0.017 to 2.0 μCi/kg. Osteosarcomas were produced with incidences ranging from 9 to 58 per cent after average skeletal doses from 5 to 520 rad, respectively (373). In other experiments (371) ^{237}Np oxalate was given IV in activities of 0.00083 to 0.0021 μCi/kg, yielding corresponding bone doses of 110 and 270 rad. Osteosarcomas were seen in 23 per cent of the animals receiving the highest dose. Activities of 0.0001-0.005 μCi/g (100-3100 rad average skeletal dose) of ^{237}Np citrate were also injected into rats by the same route. Tumour incidence was highest in the animals receiving the highest doses, but results were not considered statistically significant when compared with control tumour incidence (472). At injected activities resulting in average skeletal doses higher than 100 rad a more frequent occurrence of soft-tissue tumours has been reported, together with an accelerated ageing. Leukaemia and malignant tumours of the liver and kidney are also consequences of single and chronic administration (372).

264. *Americium-241* (alpha emitter; half-life, 458 years). The distribution and retention of this nuclide were studied in adult mice by autoradiography after a single IV injection of 1 μCi of the nitrate compound (242), and in the developing teeth of rats after IP injection of the same activity (243). The isotope accumulates mainly in the bone and liver tissues. In rats, 30 μCi/kg of monomeric ^{241}Am citrate injected IV produced some impairment of the metaphyseal bone resorption, manifested as abnormal trabeculation (538). In experiments by Filippova *et al.* (181) on rats, the IP administration of ^{241}Am nitrate in doses of 26-13 330 μCi/kg (7-2099 rad to the skeleton) the incidence of osteosarcoma was increased with a maximum (9.3 per cent) at the average skeletal dose of 376 rad. A somewhat different picture with a maximum (24.5 per cent) at doses around 1660 rad was obtained with the citrate of the same isotope (493). Renal and liver tumours were also reported by Moskalev *et al.* (473) in rats injected with ^{241}Am.

265. The liver and the skeleton were confirmed to be the principal deposition sites also in beagle dogs injected IV with 0.00179-4.49 μCi/kg of the citrate. Some concentration of the nuclide in the thyroid gland and in kidney glomeruli was also noted (398). In the skeleton, americium deposits on bone surfaces more uniformly than plutonium. The endosteal and trabecular deposits of the isotope are 1.5-2 times greater than the periosteal deposits, while for plutonium this ratio varies from 2 to 4 (402). At the University of Utah the carcinogenic effects of ^{241}Am in beagles are being studied with eight activity levels ranging from 0.0018 to 2.8 μCi/kg. Two dogs at the 2.8-μCi/kg level have died with extreme liver degeneration after estimated doses of 5500 and 7600 rad in the organ. At 0.19 μCi/kg, 6 of 10 animals that died had developed osteosarcomas and had damage of the liver, kidney and thyroid. Osteosarcomas have been

observed with activities down to 0.096 μCi/kg, but more definite results are not expected to be available for many years (644). Americium-241 chloride injected IV in dogs at 1 μCi/kg (corresponding to an average skeletal dose of 1660 rad) was reported to induce osteosarcoma in 50 per cent of the treated animals (476).

266. *Curium-244 and 243* (alpha emitters with half-lives of 17.9 and 28 years, respectively). Only data on excretion, retention and distribution of injected curium citrate have been reported, showing that although the liver and skeleton are the major deposition sites, other tissues, particularly thyroid, have significant concentrations of the nuclide (400).

267. *Californium-249 and 252* (alpha emitters with half-lives of 352 and 2.63 years respectively). In the rat the distribution and biological effects of ^{252}Cf nitrate were studied with eight administered activities from 0.0005 to 0.064 μCi/g. One to two days after IV injection, about 70 per cent of the nuclide was found in the liver and about 30 per cent in the skeleton. The $LD_{50/15}$ was estimated to be 0.032 μCi/g, and the $LD_{50/30}$ 0.012 μCi/g. With acute doses the animals developed an agranulocytic syndrome. On the basis of the LD_{50}, ^{252}Cf was shown to be 5 times more toxic than ^{241}Am and 9 times more toxic than ^{244}Cm (757). In the beagle, the excretion and retention of ^{249}Cf and ^{252}Cf citrate were followed during 160 days after IV injection. After one week about 20 per cent of the injected californium was in the liver and about 60 per cent in other tissues, mainly in the skeleton (399).

268. *Einsteinium-253* (alpha emitter; half-life, 20.5 days). A study in beagles covered the early retention, excretion and distribution of ^{253}Es over 8 weeks following IV injections of the citrate. The isotope closely resembled californium in its behaviour and localized mainly in the skeleton, liver and thyroid (401).

5. Conclusions

269. The reviewed information on the incidence of bone sarcoma by alpha-emitting nuclides should be evaluated with great caution since the experimental data available are in general fragmentary and heterogeneous and, in particular, the series on large animal species are still incomplete. The relevant variables on which dose estimates should be based have not yet been identified and measured with any confidence (644); until such data are available, any conclusion could well be regarded as open to doubt. Moreover, even if accurate estimates of the dose and dose rate to osteogenic tissues could be made, the lack of knowledge on the variability among species and on the kinetics of normal and malignant cell populations would still make any projection of the risk to man (301) quite doubtful.

270. However, if some conclusion is to be drawn at the present time, the one arrived at by Mays and Lloyd (300) should probably be offered. Analysing the dose-effect relationships for the induction of bone sarcoma in 10 experimental series performed in man, dog, rat and mouse for a number of nuclides such as ^{224}Ra, ^{226}Ra, ^{228}Ra, ^{228}Th and ^{239}Pu injected by various routes and in various amounts, they observed linear responses with dose in some cases and threshold or sigmoid relationships in others. These conclusions are in sharp contrast with the results of parallel studies with beta emitters (434), where the relationship appears to be in all cases non-linear. The higher probability of linearity in the case of the alpha emitters has been ascribed to lower efficiency, or even the lack of repair processes after high-LET irradiation. An alternative explanation is provided by the theory of dual radiation action. Under the assumption of linearity it would of course be impossible to identify the lowest dose for which osteosarcoma can be demonstrated, as is the case with the "practical threshold" models of the beta emitters.

271. Comparisons of efficiencies among alpha emitters could be justified, and if one accepts at face value the dose estimates (433), it might be concluded from the slope of the fitted relationships that ^{239}Pu and ^{228}Th based on the mean skeletal dose might be about 10 times more carcinogenic to bone than ^{226}Ra, and that ^{226}Ra may be equally carcinogenic in mouse and dog, but an order of magnitude less effective in man. Finally, regarding the effect of dose rate, no clear demonstration of a sparing effect of low dose rate has been provided, and the best-documented case would even give indications in the opposite direction. Information on other types of tumours induced by alpha emitters is definitely too fragmentary for any generalization.

D. INHALED ALPHA EMITTERS

272. In regard to the effects of inhaled alpha emitters, important contributions in the field of lung pathology and oncology are found in the books edited by Hanna *et al.* (244) and Nettesheim *et al.* (409). A detailed account of all toxicological effects of inhaled plutonium is given by Bair *et al.* (21). In regard to the induction of tumours, particularly of the lung, there are a number of studies in various species of animals. Mice (BAF_1 female) were injected intratracheally with 0.003-0.16 μCi $^{239}PuO_2$ (doses estimated at 115-4000 rad to the lung) and developed pulmonary fibrosarcomas and carcinomas with a maximum incidence of 12 per cent at 0.06 μCi (657, 656).

273. Carcinomas and bronchio-alveolar adenocarcinomas were also reported, with a maximum incidence of 25 per cent in three groups of female Sprague-Dawley rats inhaling 0.005-0.207 μCi of $^{238}PuO_2$ (9-375 rad to the lung). Lower incidences were found at lower intakes down to 0.005 μCi deposited in the lung. Tumours of other sites were also found in a significantly higher percentage in Pu-treated animals (586). An increased incidence of mammary tumours in rats injected with $^{239}PuO_2$ was reported, although, in general, the deposition of less than 1 μCi/kg of Pu did not result in an increased incidence of tumours of the breast, irrespective of the method of Pu administration or of the solubility of the compounds (588). The uptake in the lung and the effects of $^{239}PuO_2$ particles injected intraperitoneally (589) or transthoracically in the lung (592) were also reported. Preliminary data on pulmonary carcinogenesis in Wistar rats after inhalation of various transuranic compounds are also available, and

they show an influence of dose and dose distribution on the type and the incidence of neoplasms (590). An experimental study of the effects of inhaled alpha emitters (^{238}Pu, ^{239}Pu and ^{241}Am given as oxide and nitrate) was reported recently (468). The accumulated doses varied between 1 and 10 000 rad, and the spatial and temporal dose distributions depended on the different physico-chemical forms used. Survival times and tumour latency times and tumour frequencies, locations and histotypes were analyzed as a function of dose rate and dose distribution. On the basis of these data a model relating dose and the acceleration of tumour appearance was developed.

274. Two large-scale studies in the USSR are also available in this field. Yerokhin *et al.* (745) carried out an extensive study on 1097 male and female Wistar rats administered intratracheally with 0.00042-1.0 μCi of ^{239}Pu nitrate or 1 μCi plutonyl acetate. The range of doses to the lung in the first study was 3-5855 rad, and in the second the pulmonary dose was 1870 rad. The percentage tumour incidence varied rather regularly from 2.5 per cent in the lowest intake group to 33 per cent at 0.42 μCi. A decrease to 24 per cent was noticed at 1 μCi, while this same activity of plutonyl acetate gave rise to about 40 per cent lung tumours. The histological types observed were squamous cell carcinomas, adeno-carcinomas and hemangiosarcomas. Koshurnikova *et al.* (358) observed up to 27 per cent of pulmonary tumours in rats inhaling ^{239}Pu citrate (0.008-1.030 μCi/g of pulmonary tissue) and up to 48 per cent of tumours after ammonium ^{239}Pu pentacarbonate (0.004-1.46 μCi/g of lung). Squamous cell carcinomas, adeno-carcinomas and hemangio-sarcomas were the most common pathological forms found. In the same study, ammonium ^{239}Pu pentacarbonate and ^{239}Pu nitrate in various amounts produced up to 20 per cent malignant tumours in the rabbit. The induction of lung tumours in rabbits administered intratracheally ^{144}Ce (25 μCi per animal, corresponding to 24 000 rad to the lung) was also described by Ivanov and Kurschakova (299). Comparison of these data with other data on ^{239}Pu (358) would give an RBE of ^{239}Pu as compared to ^{144}Ce of about 12 at this dose level. Data on interspecies comparisons of the efficiency with which tumours are induced by intratracheally administered plutonium in soluble form are reported by Moskalev *et al.* (471).

275. In the dog, Park and Bair (22) produced nearly 90 per cent of bronchio-alveolar carcinomas after inhalation of 0.6 μCi of ^{239}Pu, corresponding to a lung dose of 2922 rad. At higher doses up to 4094 rad, the incidence of tumours and survival time of the dogs decreased. The acute and chronic toxicity of inhaled plutonium in dogs was also described by Park (522), Park *et al.* (523, 525) and Clarke *et al.* (111). In experiments by Moskalev *et al.* (473) the inhalation of ^{241}Am nitrate in dogs (0.14-1.39 μCi/kg, or 344-3320 rad to the skeleton) induced the appearance of osteosarcomas in all cases, while there was no incidence of this tumour in control animals at all. Park *et al.* (524), Levdik *et al.* (373) and Koshurnikova *et al.* (357) reported co-carcinogenic studies on Pu-induced pulmonary neoplasias, and Filippova and Nifatov (180) published data on lung sclerosis and carcinogenesis following intratracheal administration of ^{237}Np and ^{241}Am, respectively. A quantitative assay was recently developed by Nolibé *et al.* (510) for the transplantation of lung fragments from Pu-contaminated rats into immunodepressed mice or genetically compatible rats. In the host animals transplantation of lung tissue from old normal donors resulted in differentiation resembling a tumorous condition. Lung from contaminated rats showed an increased frequency of these lesions with a complex dose-effect relationship.

276. An analysis of the dose-effect relationship for lung cancer induction, derived from some of these experiments, was attempted by Bair *et al.* (22). The plot of the data showed that in the rat, an accumulated dose to the lung of as low as 10 rad might be carcinogenic. The peak incidence in mice and rats probably occurs between 200 and 1000 rad and the few available results in dogs would show an even higher incidence. Special consideration was given in this paper to the problem of tissue distribution of plutonium, and it was concluded that the non-uniformity of the dose distribution does not produce a higher hazard by the nuclide but that on the contrary, a more homogeneous dispersion in the lung can be more hazardous. A similar conclusion was reached by Little *et al.* (396), by Snipes and Brooks (631) and in a recent report (487) by the National Council on Radiation Protection (NCRP).

277. In another review, Baily concludes (155) that radiation from either alpha or beta radioactive materials is usually, but not invariably, more effective than external irradiation for lung tumour induction. The difference in effectiveness is not sufficiently large to abandon the presently accepted concept of average lung dose in evaluating the hazards from radioactive particles in the lung. Lower efficiency for lung cancer induction of inhaled beta-gamma emitters, by a factor of about 10, would confirm the higher RBE of the alpha irradiation by about the same factor (22).

V. BIOLOGICAL VARIABLES IN RADIATION CARCINOGENESIS

A. GENERAL

278. The object of the present chapter is to examine the role of various biological factors in the induction of tumours by ionizing radiation. The most common variables known to alter the neoplastic response of irradiated animals, such as genetic constitution, sex and age, will be reviewed, and additionally a problem of great relevance for radiation protection will be considered, namely the question of the cells and tissues at risk. This question will be considered with the aim of identifying in the tissues susceptible to carcinogenesis, the cellular compartments where tumours originally arise; this identification might allow the quantification of induction phenomena on a cellular basis, and would thus establish a link between information and work *in vitro* and *in vivo*.

B. GENETIC VARIABLES

1. Species

279. Few systematic comparative studies have been made on the influence of the species on the neoplastic response in mammals, and most of the data available have been obtained in the rodent. This problem has been discussed on the basis of the limited available information in previous reports of the Committee (669, 670) and also by various reviews (69, 672, 675, 678). It should be emphasized that the question of species susceptibility to radiation-induced neoplasia has far reaching implications, both theoretical and practical. In fact, it relates not only to the obvious need of extrapolating from one species to another, not only the carcinogenic effect, but also the relationships between latency time and life-span of the species (69). It is also relevant to the relationships between the spontaneous incidence of certain tumour types in certain species *versus* the radiation susceptibility of these animals to the same tumours.

280. Concerning tumours arising after external irradiation, it has often been pointed out (69, 670) that the variation between species appears to be considerable and that in any case, it seems larger than that observed after internal irradiation (456). Although it is true that virtually any type of tumour can be induced in any species by the appropriate doses and administration schedules (670), some species may develop certain tumours after rather low doses, or with relatively shorter latency times than others, so that the spectrum of malignancies found after irradiation in different species is extremely variable.

281. There are numerous examples of such differential effects. By comparison with other species, the mouse ovary is an example of an exceptionally high sensitivity to tumour induction. The rat is reputed to be considerably more susceptible to kidney tumour induction by 500 rad whole-body x irradiation than other species, in particular the mouse (36), but the apparent resistance of the mouse may be attributed to the particularly long latency of these tumours or to different pathogenetic mechanisms operating in the two species (422). Doses of 300-500 rad are definitely carcinogenic for many species, but the burro after single and total multiple doses of 320-545 rad develops an important dose-related shortening of life, without evidence of tumours (67). Lung cancer after 3000 or 4000 rad in the chest occurs in 43 per cent of rats but only in 2 per cent of hamsters (239), and this observation is confirmed by continuous irradiation experiments (734). Rats may develop leukaemia after irradiation, but in a less consistent pattern than mice (683), and so do guinea-pigs (581); Chinese hamsters, on the other hand, appear to be strikingly resistant (450). Data on the incidence of myeloproliferative disorders in animals other than rodents have been reviewed by Nielsen (491).

282. When five different species of rodents were continuously exposed to ^{60}Co radiation, more bone and, especially, lung tumours appeared in rats than in hamsters; other differences in inducibility of lung and oesophageal cancer were also shown to exist between various mouse strains (734). The differences between species found in this latter irradiation experiment appeared, on the whole, to be smaller than the differences in spontaneous tumours. This fact has been interpreted as evidence that radiation is so effectively carcinogenic as to override minor variations in susceptibility (734). Data are still insufficient to draw a comprehensive picture, and it may be concluded that the genetic character of the species is probably the main factor in these variations, to which other physiological and environmental components could add secondary, but by no means unimportant, contributions.

2. Strain

283. The genetic variation of the susceptibility to long-term effects of radiation has been explored, particularly in inbred strains of mouse, and discussed, for example, by Grahn (226, 225) and Grahn *et al.* (227). Data on the spontaneous incidence of various forms of leukaemia in several strains of mice and on their susceptibility to radiation induction have been repeatedly mentioned in this annex (see particularly paragraphs 45 to 49) and will not be examined again. The conclusions drawn by Upton and Cosgrove (683) and Upton (678) are still applicable since, in general, strains having low spontaneous incidence of a particular disease are prone to develop an increased incidence after irradiation, while high-leukaemic strains are not as susceptible. The presence of a viral agent and its vertical transmission may be seen, for some forms of leukaemia, as a necessary condition for interspecies variations of the disease, although the condition is not sufficient since it may be modified to a large extent by the immunological, hormonal and ambient factors discussed in chapter II of this Annex.

284. The analysis of chronic-radiation lethality data from many different mouse strains suggests that all genotypes respond to radiation according to a single primary-injury parameter that can be expressed as life-span shortening. Strain or genotype specific sensitivities to tumour induction are of a secondary genetic nature and may be separated from the basic injury under special conditions of exposure (224). Daily irradiation experiments have indicated, for example, that life-span shortening at doses below 6 rad/day can be associated with specific neoplastic disease, but at higher dose rates a non-specific component of the damage is detectable (227). Such observations agree with the general view that at sufficiently high doses genetic differences tend to disappear (670). Information concerning sex differences in tumour induction by external irradiation, can be found in paragraphs 68 and 73.

3. Internal irradiation

285. Although it is commonly held that the neoplastic response of different animal species is more uniform after internal than after external irradiation (69, 456, 670), differences in the tumour susceptibility in the former case are also quite apparent. For internal exposures, in addition to the genetic factors discussed.

anatomical and physiological factors could modify the neoplastic response through modifications of the dose received by the relevant cells. For example, differences with species and age of the trabeculation pattern of bones are quite substantial (544, 18), and they influence the dose to the osteogenic or haemopoietic target cells in the case of bone-seeking radionuclides. Metabolic differences in the retention and excretion of radionuclides between different animals have also been shown, even for closely related chemical substances, and when operating over a long time they will result in appreciable differences of the accumulated dose in the target tissues (680). Thus, extrapolation to man of metabolic patterns and of the ensuing neoplastic effects only appears possible after careful consideration of several animal species with different life spans. Evaluation of the relative species sensitivity should therefore be made after appropriate corrections for all the factors mentioned above, and on the common basis of the estimated dose to the target cells.

286. Attempts to express sensitivity in terms of tumour induction have been made in the case of certain alpha-emitting radionuclides (433), and it has been concluded, for example, that the dog and the mouse are very similar in their response to ^{226}Ra, but that man appears to be less susceptible by an order of magnitude. After appropriate corrections, mice and dogs seem also to be equally sensitive to the oncogenic effects of ^{90}Sr (188) or ^{226}Ra (219) and, on the basis of the lowest dose of ^{90}Sr proven to be carcinogenic for bone, mice, rats and dogs, would also appear to be very similar in their susceptibilities (434), while the hamster would be more resistant (64). The cat, on the other hand, has been reported as particularly sensitive to ^{89}Sr induction of osteosarcoma (489).

287. Systematic comparisons between species and strains are, however, rather few. In one of them, 70-day-old CF1 and CBA mice were given the same activity of ^{90}Sr and examined every week radiographically for bone tumours. CF1 animals developed the first bone sarcoma at 98 days, and from then on tumour appearance followed a normal distribution with the mode at 27 weeks. The average time from the first scoring of tumours to death was 39 days. In CBA mice, on the other hand, tumours started to appear later and the peak incidence was at 35 weeks. The presence of inhibiting host factors, the higher spontaneous incidence of osteosarcoma in CF1 animals and the different rates of tumour growth in the two strains might account for these effects (185). More recently, four inbred strains of hamster treated with multiple intratracheal administrations of ^{210}Po absorbed onto hematite particles were found to have very different tolerances to the treatment and induction times of the lung tumours. However, the final incidence of the tumours was very similar in the four strains, varying between 33 per cent and 50 per cent (395).

288. Species differences in the response of dogs, rabbits and rats to subcutaneous injections of ^{210}Po were also reported (490). An important difference in susceptibility to osteosarcoma induction by ^{224}Ra between male and female mice of the NMRI strain (284) has already been discussed (paras. 250-252); this observation appears to be in contradiction with what is found in humans (636). Chameaud *et al.* (98) have recently compared the susceptibility to lung tumour induction by radon and its daughters in man and in rat. They have shown that the tumour incidence plotted against the accumulated exposure in working level months (WLM) is similar in experimental studies with animals and in epidemiological surveys in man. They concluded that the rat could be a good model system for analyzing this type of neoplasia. In conclusion, until further progress in the specification of anatomo-physiological characteristics of the various species is made, and until assessments of the dose to the relevant tissues may be carried out with better confidence, the scanty available data appear to be unsuitable for meaningful generalizations.

C. AGE EFFECTS

1. Post-natal irradiation

289. The relationship between age and susceptibility to the induction of tumours has been explored by irradiating animals of different post-natal ages or, in other cases, by comparing animals irradiated *in utero* or after birth. The two cases will be considered separately. It has long been known that life-span shortening in mice and rats after single acutely delivered doses of radiation is frequently associated with tumour induction, even at relatively low doses. Life-span shortening changes considerably with the age at irradiation: it is maximum in juvenile animals, then decreases with increasing age and can rise again in very old animals (383, 384, 385, 386, 387, 451, 349, 313, 130, 682). These variations have been attributed in part to the long latency in the expression of the life-span shortening effect (682) and in part to an intrinsic age-dependent change of the animals' susceptibility (313, 385).

290. Concerning specifically the induction of tumours, only fragmentary data on age-dependent differences in response are available. Mice of the RF strain given whole-body doses of 100-300 rad at several ages from birth to 180 days, showed that their susceptibility to granulocytic leukaemia is minimal shortly after birth, reaches a maximum at about 70 days of age and then slowly declines thereafter. This trend occurs in both sexes, although in the male peak incidence reaches 54 per cent after 300 rad of x rays, while in the female the incidence after the same dose at the same age is only 26 per cent (690). Susceptibility to the induction of thymic lymphoma in the same strain is maximal shortly after birth and declines later in life with natural thymic involution (690). These observations are in good agreement with data on strain A mice, where maximal susceptibility to induction of lymphoid tumours after 1000 rad of x rays (given in 12 days) occurs at the age of 1 month or earlier, with a sharp decrease at 2 months and later (319). They are also in agreement with data on the C57BL mouse given fractionated daily doses of 50 rad of x rays for 12 consecutive days, where the increased incidence in early life is also associated with a shorter mean induction-time (320), and with data on SAS/4 animals, where leukaemia incidence tends to decrease with increasing age at exposure (386).

291. Sensitivity to the induction of ovarian tumours in RF females appears to be high (61 per cent after

300 rad) between 1 and 9 days of age and to decrease progressively up to 70 days (26 per cent for the same dose) (573). A very definite age variation is also found in SAS/4 mice where a dose of 650 rad of 15-MeV x rays produces about a 30 per cent incidence of ovarian tumours at 10-20 weeks of age, whereas in younger and older ages the incidence is smaller and may even be less than the 15-per-cent spontaneous incidence observed in the non-irradiated control mice (386). In another report, the spontaneous incidence of this neoplasia appeared to be different in three different mouse strains (IC, XLII and C3He/A), but a whole-body dose of 300 rad of x rays produced in all strains a higher tumour incidence in mice irradiated at an age of 4-6 weeks than in mice irradiated at an age of 4-6 months (566). In LAF_1 mice the induction of ovarian tumours was likewise lower after irradiation at 1 year than after irradiation at 10 weeks of age (130), but no differences with age, between 5 months and 2 years, were found in CAF_1 mice (349). In Wistar rats, the induction of ovarian tumours was significantly larger when x irradiation was performed at 13 days of age with a single dose of 270 rad (560).

292. A lack of dependence of **mammary tumour** development on age at the time of irradiation, between 40 and 160 days, was observed in Sprague-Dawley females exposed to 500 R of ^{60}Co gamma radiation (610). **Pulmonary tumour** induction tended to increase with age in SAS/4 mice (386), but was unaffected in LAF_1 mice between 10 weeks and 1 year of age (130) and in CAF_1 mice between 5 months and 1 year (349). In the rat the induction of these tumours was significantly higher at 3 months than at 1 or 21 months (95). **Kidney tumours** were found more frequently in mice given 690 rad of x rays at birth than in animals irradiated at 3 months of age (123). Other data on the incidence of miscellaneous tumours as a function of the age at exposure may also be found in Kohn and Guttman (349), Reincke *et al.* (560), Jones, Osborn and Kimeldorf (315), Jones (311) and Castanera, Jones and Kimeldorf (95).

293. It may be concluded that there are quite definite age-dependent changes in the susceptibility to the induction of various types of tumours by external irradiation. The best-documented case is that of leukaemia (both thymic and granulocytic) where data on four different strains of mouse have confirmed the presence of a low susceptibility at birth, followed by a peak incidence in the young mouse and a final decrease of induction with age. The sensitivity of the ovarian tissue tends in general to decrease with post-natal age, while the susceptibility to pulmonary tumours appears to be variable in the different animals examined. Data on other neoplasms are insufficient to allow any conclusion.

2. Pre-natal irradiation

294. Data on the relative susceptibility to tumour induction in animals irradiated before or after birth are relatively scarce compared to the data on pre-natal irradiation in humans. Up-to-date lists of references on this subject have been published (562, 458).

295. When RF mice were irradiated *in utero* 1-3 days before birth with 300 rad of x rays, it was found that the incidence of granulocytic leukaemia was nil, but it increased substantially when irradiation was performed after birth to reach an incidence of 30-50 per cent at 70 days of age. Thymic lymphoma was similarly not induced by irradiation *in utero* but was readily induced after birth. Ovarian tumours were significantly less common in mice irradiated *in utero* than post-natally. There are no data at lower doses, but it could be assumed that 300 rad is too large a dose for effective induction of these tumours, because at doses of this magnitude the dose-effect relationship observed in the adult could be already in the declining portion (see paragraphs 151 to 154) (690). In a study carried out in RF mice irradiated at various pre- and post-natal ages, life-span shortening was found to be minimal in animals exposed pre-natally except for males exposed to 300 rad at 14½ days of gestation, where survival time was very short. Mice exposed pre-natally showed stunting of body growth, microcephaly and premature glomerulosclerosis but no increases in incidence of leukaemia or solid tumours were noted (682). These data appear to be generally in agreement with data on CF1 mice with doses of 100 rad of x rays, where the evidence for any increment in neoplasia following embryonic or foetal irradiation was equivocal. There was, however, much evidence of reduced growth and permanent stunting (580). It may thus be concluded from all these data that the long-term effects of pre-natal irradiation relate more clearly to growth disturbances than to tumourogenesis.

296. From the available data in the rat (560), it would appear that animals irradiated *in utero* with a single dose of 270 rad of x rays had a considerably higher short-term mortality, and the survivors showed growth retardation, microcephaly and micro-opthalmia. Genital tumours in the female increased significantly only after post-natal irradiation, and their relatively low incidence in pre-natally irradiated rats was attributed to hypoplasia of the genital organs. Other data on Wistar rats, irradiated on the 18th day of gestation, have been reported by Piontovski and Kalashnikova (535). The beagle dog foetus responds to continuous irradiation *in utero* in a manner similar to that of the adult dog, but no effects on tumour induction were reported. At a dose rate of 17 rad/day or less of ^{60}Co gamma rays, beagle bitches irradiated continuously from conception delivered apparently normal litters. At 5 rad/day, all female offspring were sterile, and at 10 rad/day, all male pups were sterile (512).

297. From the fragmentary data available, which do not cover specific tumour types in many different strains and species, it could be concluded that pre-natal irradiation affects the growth and differentiation of mammalian systems, rather than their malignant transformation. There is no evidence that irradiation *in utero* of mice and rats may be more carcinogenic than irradiation of young or adult animals.

3. Internal emitters

298. Age-related differences in the susceptibility to the induction of tumours by internal emitters have at times been reported. In the case of radiostrontium intoxica-

tion, the mouse (3-20 weeks) (701), the rat (6-60 weeks) (646) and the dog (new-born to adult) (188) were apparently more sensitive to bone sarcoma induction in youth than in old age. However, when appropriate dosimetric corrections to account for body size and higher retention in the young animals were made, these differences disappeared, showing that there is no major age variation in the intrinsic susceptibility of the cells at risk. Similarly, a larger susceptibility to bone tumours was noted after injection of ^{144}Ce (but not after treatment with ^{239}Pu) in weanling rats than in adults (417).

299. Comparisons of tumour induction between pre- and post-natal ages have been made by Finkel and her group using foetal and infant beagle dogs exposed to ^{89}Sr. At the level of 1.33 μCi/kg *in utero*, ^{89}Sr was not acutely lethal, nor did it produce haematologic disorders and bone sarcoma, however, extremely abnormal skeletal growth was found (186). In a later report (188) on ^{90}Sr, some tumours were seen at higher levels of contamination. Differences in retention were held responsible for differences in tumour induction with respect to post-natal exposures, but it was concluded, on the whole, that pre-natal exposure was not more carcinogenic than post-natal exposures at comparable levels of dose. In the pig, exposure of the foetus to ^{90}Sr ingested by the mother, plays an important role in the development of leukaemia (517). It has been reported that the administration of ^{32}P to pregnant mice produces a significant increase of the incidence of leukaemia in female offspring (272). Finally, the age dependence of metabolism and effects of ^{239}Pu has been studied in the rat by Sikov and Mahlum (626).

300. The relative sensitivity of the thyroid gland to the induction of tumours by ^{131}I was investigated by Walinder and Sjoden (729) in mice exposed *in utero* or at the age of 3 months. They found 3 benign and 4 malignant neoplasms in 109 mice irradiated *in utero* to 7800 rad but no tumours at all after irradiation of 91 animals 3 months old to approximately similar doses. It was therefore concluded that the foetal thyroid gland is more susceptible than the adult thyroid. In analysing other evidence (160, 627), Pochin (537) concluded, however, that the numbers involved are probably too small for any conclusive statement about a higher sensitivity of the foetal thyroid.

D. TISSUES AT RISK

1. General

301. As pointed out in a publication (291) of the International Commission on Radiological Protection (ICRP), no general criteria are available at present to make reasonable predictions of the susceptibility of various tissues to tumour induction by radiation on the basis of known properties of the tissues themselves. Tumour susceptibility is therefore an empirical concept derived from the observed frequencies of cancer in different tissues or organs, following a given radiation dose. In man such a relative scale of sensitivity to tumour induction has been derived, with possible use in establishing dose limits to individual parts of the body (291). An empirical procedure is perfectly adequate for practical purposes such as setting dose limits, but fails to identify and explain biologically the reasons why some tissues or organs are more prone to neoplastic transformation than others, in a manner which is obviously quite independent of the number of cells they contain or of the renewal rate of these cells.

302. In considering this problem, it has to be kept in mind that although the natural occurrence of tumours is a rather common phenomenon in animal populations, the probability that a neoplastic clone would be induced in cells exposed to radiation is quite low. Induced neoplastic transformation may therefore be regarded as a rare phenomenon (70, 429, 459). There are general hypotheses compatible with this fact and also with the extreme variability of cell susceptibility to tumour induction; they have been discussed at some length in chapter II of this Annex. Other basic questions have not yet been discussed in detail, such as whether all the cells in any one tissue or organ, irrespective of their state of differentiation, are susceptible to the induction of neoplasia or only some of them can be transformed, or whether it is possible to identify the cells in a population having a higher risk of neoplastic transformation by radiation. These questions have already been considered in the 1972 report of the Committee (670) with special regard to bone and skin tumours.

303. In a recent publication (430), Mayneord and Clarke have discussed the relevance and importance of the number of cells at risk in studies of radiation carcinogenesis and have developed some biomathematical concepts to relate the transformation of these cells to radiation dose under various conditions of irradiation. Although the authors themselves recognize the limitations of such an approach in view of the complex reality of the biological mechanisms, the formulations proposed and the general consequences to be drawn provide a stimulus for a better definition of the relevant problems. In the following paragraphs the question of the cells at risk will be considered systematically in the light of available information, in an attempt to elucidate the problem of the differential susceptibility of cells to tumour induction and also to provide a rational basis for possible extrapolation of data between species.

304. *Leukaemia.* The comparative aspects of radiation-induced leukaemia in animals have been considered by Upton (678) and Kaplan (328). It is quite apparent that the histological type, the time of onset and the organ distribution of the reticular tissue disorders developing in the experimental animals are extremely variable. In the mouse, which is the species most extensively studied, the inducibility of leukaemia by external or internal irradiation and its type depend primarily on the strain and then on sex, age at irradiation, environmental factors, radiation dose and type of fractionation. All these factors have been considered at some length in this Annex. In this species the tumours of the reticular tissue may frequently take the form of a lymphoma (in the C57BL strain typically) which appears to arise early in life in the thymus and then to spread in some cases to the thoracic lymph nodes or to other lymphatic and haemopoietic districts (326). Alternatively (and more

rarely) a myelogenous granulocytic leukaemia may occur, particularly in the RF strain, involving primarily the marrow, spleen and liver and producing peripheral blood leucocytosis (685).

305. In the mouse another form of non-thymic reticular tumour of complex and still uncertain classification has also been observed, which generally arises late in life, involving primarily the reticular cells of the spleen and of the abdominal lymph node and which may then extend to other organs where reticular tissue is present (683). In addition to anatomo-pathological and epidemiological evidence, there are also radiobiological reasons to keep these tumours separate from the others since radiation appears to depress, rather than enhance, the incidence of the diseases (see paragraphs 117 and 119). In the rat the development of radiation-induced leukaemia is less well documented as to form and induction time and rate, but myeloid leukaemia, leucosarcoma and reticular diseases have been reported (683, 161). In guinea-pigs, leukaemias of a chronic lymphatic type (683) or lymphosarcomas (581) have been described. Swine irradiated chronically with ^{90}Sr develop high incidences of myeloproliferative disorders, including myeloid, lymphatic and stem cell leukaemias (278), while beagle dogs submitted to chronic irradiation by external sources (205) or by ^{90}Sr feeding (166) show highly proliferative infiltrating forms of myeloid leukaemia.

306. In view of the diversity of these syndromes and in the absence of any indication as to whether and to what extent any of them might be akin to the human leukaemias, attempts to identify the nature and the number of the cells at risk on the basis of our present knowledge may only be regarded as an "academic pursuit" (459). For all practical purposes, in fact, reliance must be placed mainly on the few observations made in the cases of human leukaemia (562). The virus-induced thymic lymphoma of the mouse, the complex pathogenesis of which has been sufficiently well documented, may be a good example of the difficulties involved in assessing the cells at risk.

307. As already discussed in paragraphs 46 to 48, anatomo-pathological observations and the effects of thymectomy and thymus reimplantation have shown that thymus is the target organ for the action of the virus. Further experimental evidence has identified the immature lymphoid cells of the thymus as the target cells in this tumour system. However, irradiation of the target organ is not sufficient, as such, to induce lymphoma without irradiation of the haemopoietic system and, in addition, other micro-environmental, humoral, immunological and consitutional factors are essential requirements for the expression of the disease. The relative abundance and the susceptibility of the target cells to the virus are very dependent on their state of differentiation and on the age and constitution of the animal (326, 327). It is clear, however, that since a viral agent is present at the origin of the disease, the problem is primarily one of investigating quantitatively *in vivo* the interactions between target cells and virus, since radiation acts primarily through a change in the host-virus relationships. The evidence on this point has been reviewed by Kaplan (327).

308. The same approach should probably be followed in the case of myeloid leukaemia, although definitely fewer data are available. The anatomo-pathological evidence concerning the site, origin and histological type of the disease, and the fact that it occurs after localized irradiation of the skeleton by bone-seeking nuclides (particularly high-energy beta emitters) point to the bone marrow as the target tissue and, among the great variety of cells of the marrow, to the more immature myeloproliferative elements as the target cells. Since it is now possible to titrate progenitor haemopoietic cells by *in vivo* and *in vitro* assays (629), it should also be possible to study cell-virus interaction in the case of myelogenous leukaemia.

309. Special consideration should be given to the haematological neoplasms occurring in animals (swine and dogs) submitted to chronic external irradiation or to internal irradiation by beta-emitting bone seekers. The character of these diseases is rather heterogenous when compared to other forms of leukaemia in the rodent. They are often preceded by profound disturbances of haemopoiesis, including all the differentiative lines of the marrow. Considerable differences in the invasiveness of the diseases in different species are noticeable. Although they are frequently referred to as myelogenous leukaemias, morphologically all cell types, from the more differentiated ot the "stem cell", are often described. It seems reasonable, therefore, to conclude that the identification of one type of progenitor haemopoietic cell as a possible target and the assumption of a common induction mechanism are probably not justifiable, in view of pathological, epidemiological and clinical variety.

310. For other non-thymic lymphomas, for which there is as yet no definite proof of a viral origin, preliminary data on the relationships between dose and probability of cell transformation have been obtained *in vivo*, in a model system where heavily irradiated animals have been repopulated with a known number of isogenetic bone-marrow cells, intact or irradiated (135, 437). A dose-related excess of leukaemia has been documented in the animals given irradiated marrow and, correcting for radiation cell-killing, some estimates of the probability of leukaemic transformation of the injected bone-marrow stem cells have been obtained. Quite aside from the absolute value of these estimates, which may or may not be relevant, it was shown that the rate of induction per unit dose of leukaemia per surviving cell was higher at 400 than at 200 rad; this would be compatible with the fact that the probability of transformation in this system is not linear (concave) up to the doses tested.

311. It appears, in conclusion, that in order to investigate the relationships between dose and probability of neoplastic transformation of target cells, in cases where radiation is not simply directly acting on the target tissue but through indirect or systemic mechanisms, highly sophisticated techniques of quantitative radiation biology and cellular virology must be developed and applied *in vivo*. Nevertheless, if the data on radiation-induced cell transformation *in vitro* (paras. 53 to 58) should at some stage be applicable to *in*

vivo systems and be useful not only for investigations of mechanisms but also for practical applications (564), suitable *in vivo* models ought to be developed to fill the gap. These models should have under better control the number and the functional characteristics of the cells that appear to be the likely candidates for neoplastic transformation.

312. *Ovary.* Irradiation of the ovary leads in general to a precocious reduction of the number of oocytes and ovarian follicles (14). With the exception of these cells, practically all the other cells forming the organ (lutein and granulosa cells, mesothelial and endothelial cells) appear susceptible to neoplastic transformation by radiation (675). Ovarian tumours are particularly frequent in the mouse, where doses as low as 50-100 rad of low-LET radiation may produce peak incidences of tumours (107). They appear to be responsive to hormonal mediation by the pituitary gonadotropins or by the controlateral non-irradiated ovary, in the case of partial-body irradiation (211). No special cell may be identified as being characteristically at risk in the case of ovarian carcinogenesis.

313. *Lung.* The pulmonary tissue is very complex, both morphologically (633) and functionally (623). A considerable spectrum of tumour types occur spontaneously (492) or are induced in domestic animals after pulmonary deposition of radionuclides. Bronchio-alveolar carcinomas have been reported in dogs (111), squamous cell carcinoma, adeno-carcinoma and hemangiosarcoma in the rat (358, 741) and fibrosarcoma, squamous cell carcinoma and bronchiolar carcinoma in the mouse (657). It is apparent, therefore, that all cells of endodermal origin composing the lung may give rise to neoplasia. With succeeding degrees of anaplasia, the cells may express any of the characteristics of the embryonic pulmonary endoderm (633). Connective and vascular tissues are also capable of neoplastic transformation. The role of non-specific fibrosis of the lung, preceding or accompanying the lung neoplasia, has been discussed (111) and it has been concluded that it may be an important contributing factor when a specific carcinogen is present. Bronchiolar and alveolar proliferation into scarred areas of the lung gives rise to proliferative and metaplastic cells, which are often the primary changes of the lung in the case of inhaled compounds (490). Pulmonary adenomas are frequently found in mice both spontaneously and following whole-body and partial-body irradiation (see paragraphs 119 and 120). They are frequently of alveolar origin, with a variety of histological patterns (641, 642, 65).

314. *Mammary gland.* Most of the studies on the mammary gland are confined to breast tumours of the Sprague-Dawley rat. In this system, irradiation of other tissues except the target tissue is not required to elicit the neoplastic effect (52, 616, 617, 606). The intact function of the ovary is however required for maximum expression of the neoplastic effect (138). By histological and biological criteria, the tumours produced are described as mammary adeno-carcinomas, adeno-fibromas or fibroadenomas, according to the relative abundance of fibrous and adenomatous tissue (611). No information is available on which are the possible cells at risk, although this system, which has good characteristics for oncological studies (614), would appear to be open to quantitative developments on a cellular basis. It is of interest to note that very recently an experimental technique to quantify radiation effects on rat mammary tissue has indeed been developed by Clifton *et al.* (112).

315. *Kidney.* In the Sprague-Dawley and the FAF1 rat, radiation-induced kidney tumours appear to be tubular in origin, while in mice they seem to arise from the glomerular capsule with secondary tubule involvement. Nephrosclerosis and arteriosclerotic changes would appear to play a major role in their pathogenesis (36). In a thorough study of the histogenesis of kidney tumours in rodents (422), Maldague has confirmed that in the absence of radiolesions, leading to renal atrophy and nephrosclerosis, no tumours are found in Wistar rats and in mice of the strain XVII. Concerning the tumour types found in the rat, cortical adenomas originating from cells of the convoluted tubules, carcinomas with various degrees of anaplasia and a few sarcomas were described. In animals locally irradiated in the kidney and then uninephrectomized controlaterally, it was found that focal localized proliferation of the epithelial cells at the junction between cortex and medulla (which are probably the induced cells transformed to malignancy) give rise very frequently to the neoplastic nodules. Cortical adenoma, cortical carcinoma and transitional cell carcinoma were also described in rats (569). In the mouse, tubular adenomas and clear cell carcinomas, similar to the tumours found in rats, were also seen (422). It may therefore be concluded that the available evidence points particularly to the tubular cells as the cells susceptible to neoplastic transformation, but that tumours arise in other degenerative and sclerotic lesions. The role of these pathological components is still unclear.

316. *Skin.* The histopathogenesis of skin tumours after irradiation with low-energy beta particles of the CBA/H mouse has been described by Hulse (421). Epidermal (papilloma and squamous carcinomas), dermal (mainly fibrosarcomas, but also fibromas and hemangioendotheliomas) and subdermal (fibrosarcomas) tumours were found. In spite of the fact that early and late effects on skin and skin annexes were carefully followed and described, it was not possible to find any correlation between the degree of non-neoplastic skin damage (depigmentation, ulceration, scars) and the likelihood of tumour development. It was definitely stated however that, contrary to other reported results, tumours seemed to arise as a direct effect on irradiated cells and in areas of the skin which did not appear to have suffered gross radiation damage. In a later report on dose fractionation, the lack of correlation between skin damage and tumour formation was confirmed and the relative independence of skin tumour production on the mode of exposure to radiation suggested, in the opinion of the authors, the existence of a mechanism of tumour induction of a permanent and cumulative type, such as a somatic mutation (287). It was further argued that the sensitivity of the transformed cells to radiation killing might be exceptionally low compared to the values commonly found in mammalian radiation biology (288). Other results in the mouse are particularly interesting for a discussion of the cells at risk (369). By skin irradiation with helium ions of different energies it was found that

the number of tumours increased with increasing penetration of the beam, in agreement with other data relating to the rat to be discussed below. The dependence of tumour formation on acute skin damage was in this case partially confirmed.

317. The situation in respect to skin tumour induction in the rat appears to be quite different, in the sense that in the skin of this rodent there is an association between hair follicle damage and the magnitude of tumour response. The incidence of atrophic follicles reaches a peak at about the same dose at which maximum tumour yield is found, and also there is good correspondence between the shape of the dose-effect relationships for the two types of damage (6). In a study performed with electrons of several energies it was established that, when the dose delivered with all energies is normalized at a depth of 0.27 mm, the dose-incidence curves coincide, indicating that the cells located at this depth from the surface (identified as the cells at the bottom of the resting hair follicle) are to be considered as the cells at risk for this type of tumour in the rat. In recent experiments (7), a comparison of the skin tumour response of mice and rats showed that the markedly lower susceptibility of the mouse was due to the failure to develop adnexal tumours, which are the predominant type of neoplasia in the rat. Marked differences in hair follicle injury in the two species were noted. In particular, the mouse develops relatively little follicular atrophy, and hair follicles appear to be either intact or destroyed; in addition, the mouse hair follicle appears to be more sensitive by a factor of about 2. The susceptibility to the induction of connective-tissue tumours, on the contrary, is roughly similar in the two species.

318. *Bone.* Detailed descriptions of the histopathological changes observed in bone after irradiation by bone-seeking nuclides have been provided by Nilsson (499, 509, 647, 494) and Vaughan (703). It is doubtful, however (459), whether the described microscopic damages have any relation with tumour induction since the occurrence of tumours has been shown to be the most sensitive parameter and indicator of radiation damage to the bone (185, 703). Histopathological evidence points to the following cells as the most important cells at risk in the case of internal irradiation by bone-seeking nuclides: the osteogenic tissues of the bone surfaces giving rise to osteogenic and chondrogenic sarcomas; the bone marrow for all haemopoietic, lymphopoietic and myelopoietic disturbances, and the epithelial cells in close contact with the bone, giving rise to epithelial tumours of the mucous membranes of the head. The case of the marrow has already been discussed in connection with leukaemia (paras. 304 to 311), and it should be pointed out that in rare cases other cells than the haemopoietic elements might be susceptible to neoplastic transformation, as for example in the case of haemangial tumours.

319. Concerning osteogenic tissue tumours, chromosome-marker experiments on chimerized CBA mice have definitely proven that osteosarcomas developing after ^{90}Sr treatment derive from the osteoprogenitive tissues of bone and not from the pluripotent cells of marrow (26, 48). The cells at risk are therefore to be found among the progenitor cells of the bone-forming tissue, namely the pre-osteoblasts and pre-osteoclasts. These cells lie within 10 μm of the endosteal and periosteal surfaces (703) and therefore are at risk in cases of irradiation by both alpha and beta emitters of all energies deposited in bone. These cells are the ones becoming malignant due to an abnormal proliferation following irradiation while maintaining the functional activity of the original progenitors (499, 4). The particular location of these cells explains the observation that bone tumours are more frequently of endosteal than of periosteal origin, on account of the fact that endosteal surfaces are far larger than periosteal. It also accounts for the observation that surface seekers are more effective than volume seekers for bone tumour induction, since the dose delivered to the target cells is higher in the first case.

2. Conclusions

320. It may be concluded that further refinements of our knowledge about cells at risk for neoplastic transformation are of extreme importance, both for elucidation of mechanisms and for better systematization of data. The problem has been tackled so far (and in some cases qualitatively solved) only in those tumour systems where indirect mechanisms of induction and promotion are relatively less important, and for which the direct action of radiation on the tissue at risk appears to be the determining factor for tumour induction. A more quantitative approach seems now required, as well as the development of investigation techniques aiming at the establishment of links between observations *in vivo* and model systems of cell transformation *in vitro*.

VI. SUMMARY AND CONCLUSIONS

A. GENERAL

321. A selective review of experimental radiation carcinogenesis has been carried out in order to set the old information and the newest acquisitions in the more general framework of cancer induction as a biological phenomenon, and with the ultimate aim of identifying mechanisms or regularities which might facilitate the interpretation of human data. The reviewed information is both qualitatively and quantitatively inadequate for numerical prediction of tumour induction rates in man, even though projections between species may be considered as the main objective of animal experimentation. The experimental data are, however, invaluable for understanding mechanisms, for the formulation of useful generalizations applicable to all species, and for the development of models to test specific hypotheses of tumour induction.

B. METHODOLOGY

322. Several methodological approaches have been followed in the past, ranging from the large-scale epidemiological-actuarial analysis to the morphological

and pathological approach, and from biochemical and molecular experimentation to the more recent analysis of model systems of carcinogenesis. All of these have advantages for specific purposes, but each of them appears inadequate for comprehensive solutions of general validity. The long-term nature of the work *in vivo* is such that it requires a careful choice of experimental animals, high standards of animal husbandry and maintenance, advance planning of the size of the experiment, selection of appropriate biological end-points, quantitative observations on the relation of dose and time parameters with the carcinogenic effect, and careful statistical evaluation of the age-specific tumour induction rates. Although continuous improvements on these points are evident in the work reviewed, much could still be done in order to refine the technical requirements for reliable investigations and to standardize the working conditions on an international basis to permit a wider applicability of the individual observations.

C. MECHANISMS

323. The probability of radiation-induced changes in individual cells leading to the appearance of tumours is very low. Neoplastic transformation is presently visualized as the end-result of a complex chain of etiological and pathogenetic events that confer upon the tumorous cell an irreversible and unlimited capacity for proliferation outside the normal control mechanisms. Unlike some chemical carcinogens, radiation can both initiate and promote neoplasia; it may also interact with other physical, chemical or biological carcinogenic agents with variable results under different circumstances.

324. The genetic foundation is common to the currently accepted hypotheses of radiation carcinogenesis, and the recent advances in molecular genetics and virology are gradually closing the gap between the classical "theories" of the "somatic mutation" and "viral" induction of cancer. Vertically transmitted RNA oncoviruses have definitely been shown to be at the origin of some radiation-induced murine tumours, and in the very few cases where the analysis of mechanisms has been carried to a sufficient depth radiation has been found to act through a modification of the host-virus relationships, in a complex interplay of physical, genetic, micro-environmental, hormonal and immunological actions. Attempts to study cell transformation by radiation on cultured cells have been initiated and should be pursued to investigate the mechanisms of cancer induction in the absence of other interactions operating at the whole-body level.

325. There are data to show that a transient non-specific immunosuppression caused by fairly high doses of radiation may have a promoting role in the development of radiation-induced tumours. Moreover, the viral infection *per se*, acting through very specific cellular mechanisms, can cause a depression of the immune reaction in cases where tumour viruses are implicated. Although these effects would only appear to have a secondary role, the questions as to their actual importance and their relevance at low doses and dose rates remain unsolved. Similarly, no definite answer can be given about the role and the mechanisms through which hormones could alter the susceptibility of certain radiation-induced tumour systems *in vivo*, although the animal's hormonal balance may affect the carcinogenic response of some systems. Cellular proliferation is implicit in the notion of a promoting action and is certainly required for tumour progression. Cell division is however a non-specific type of tissue reaction to radiation-induced cell depletion, and it is very difficult to attribute to such an action a primary or a secondary role in tumour induction. Other environmental conditions concerning the host microflora, physical conditions, chemical substances and biological treatments may affect to various extent the neoplastic response to radiation.

326. In conclusion, a variety of biological mechanisms through which radiation can induce tumours have been identified and, in some cases, analysed. The evidence shows that mechanisms that appear very important for a particular tumour system may, under a given set of experimental conditions, be less important or even not relevant for the induction of other neoplasms. Our present knowledge of mechanisms therefore provides partial answers, but it is still insufficient for conclusions of general validity.

D. DOSE, DOSE RATE AND RBE

327. Among the physical parameters affecting tumour induction, the dose, dose rate and quality of radiation have been considered. Concerning the dose, three major patterns of tumour response can be identified. The first refers to those tumours which do not seem to be effectively induced in the usual range of low to midlethal doses but may however be induced at higher doses. The second refers to those tumours for which the dose-effect relationship has a negative trend. The third, and probably the most common pattern, is more complex, showing an initial rise at increasing doses, a peak or a plateau at some intermediate level and, in many cases, a final decline of incidence at sufficiently high doses.

328. The peculiarities of each tumour-model system which have been pointed out repeatedly in this Annex are such as to prevent undue generalizations, particularly when they might apply to all systems. There are also difficulties in interpreting tumour induction curves in the animal on the basis of simple mechanisms of action, in view of the complex interplay of primary and secondary factors, also discussed at length in this Annex. With few exceptions, the existing data come from observations at doses above 50 rad, since lower doses have generally failed to cause an increased tumour incidence large enough to be quanitified in experiments of the usual size involving no more than 100 animals per dose-group. Even in those instances where the incidence of a particular neoplasm has been observed to increase with dose, the data usually do not suffice to define the dose-effect relationship unambiguously in the low- to intermediate-dose region.

329. With one exception, namely the rat mammary tumour, the dose-incidence curves obtained at high dose rates with low-LET radiation generally increase in slope

with increasing dose in the range from 50 to a few hundred rad. The data are not incompatible therefore with the notion that an appreciable dose-squared component might be present in these curves, which would imply that linear interpolation or extrapolation from the observed data would tend to overestimate the risks to be expected at low doses (less than 5 rad) and at low dose rates (less than 10^{-3} rad/min). With high-LET radiation, on the other hand, the dose-effect relationships are more often compatible with a linear non-threshold response, and their slopes vary relatively little with dose and dose rate. Those instances where the tumour induction curves are seen to decrease in slope at high doses and dose rates may be interpreted to result from two independent dose-related phenomena: neoplastic transformation of the susceptible cells, the probability of which increases with increasing dose, and survival of the transformed cells, the probability of which decreases as a function of dose.

330. Detailed analyses of the dependence of the RBE of different ionizing radiations on dose and dose rate are only possible at present for very few experimental tumours. It appears that the efficiency of high-LET radiations for tumour induction is higher than that of low-LET radiations, and the efficiency often changes at different dose ranges. At doses of 100 rad or more the RBE is often about 1, and it shows a rather general tendency to increase at low doses and dose rates, owing probably to the form of the dose-induction relationships, where the linear component prevails in the case of densely ionizing particles, while the quadratic component might prevail, at least at high doses and dose rates, in the case of low-LET radiation. A noteworthy example of this type of effect is seen in the acceleration of breast-tumour development of the Sprague-Dawley female rat, where effects of fast neutrons are detectable at doses of 0.1 rad, with corresponding high values of the RBE.

331. A spreading in time of the delivered dose through a decrease in the rate or through fractionation of the dose results in general in a decrease of the oncogenic effect of radiation, following some inverse function of the exposure time. It is however difficult to assign precise values to this sparing effect, since the shape of the dose-induction relationships is often altered by the change of dose rate. The magnitude of the reduction of carcinogenic effect at low dose rates is often found to be smaller with high-LET radiation. Departures from this general pattern have been documented in some tumour systems but are attributed to the pathogenetic mechanisms of the particular system and not regarded as exceptions to some fundamental radiobiological mechanisms. Recovery processes are responsible for the sparing effect of fractionation and exposure rate; their nature and kinetics in the case of neoplastic induction remain largely unknown.

E. INTERNAL EMITTERS

332. Carcinogenesis by internal emitters has been considered as a special case since, in addition to the general problems of radiation carcinogenesis, it poses other problems related to the inhomogeneity of the dose distribution in time, and also to the concentration of the radionuclides in some organs or tissues. In addition, the comparison of effects of various nuclides is often made uncertain by the difficulties of assessing the dose to the target tissues, because of the peculiar behaviour of nuclides having different physical and chemical characteristics and, therefore, different rates of uptake, retention and tissue localization. The cases considered in detail cover the induction of bone tumours and myeloproliferative diseases by beta- and alpha-emitting bone-seeking radionuclides and the induction of lung tumours following inhalation of alpha emitters in various animal species where data are available. A discussion of the probable form of the dose-induction relationship for the various types of neoplasms has also been included.

333. When the special factors mentioned above are taken into proper account, it appears that the qualitative picture emerging from these data is compatible with the concepts developed from the analysis of the effects of external radiation. The general form of the dose-induction relationships, the fact that at low doses beta emitters tend to produce curvilinear responses and alpha emitters linear ones, the higher efficiency of the alpha emitters, and the sparing effect of low dose rates of sparsely ionizing radiations, are all phenomena that can be documented in the case of internal irradiation. This strongly suggests that, with appropriate corrections, the general knowledge on tumour induction may safely be applied to both irradiation conditions.

F. BIOLOGICAL VARIABLES

334. Among the biological variables influencing radiation carcinogenesis, the effects of species, strain, sex and age at time of irradiation have been reviewed. Even with the lack of systematic data, it is possible to conclude that the genetic character of the species and, within species, of a particular strain, represents a major determinant of the carcinogenic response, to which other physical, physiological and environmental parameters may contribute as secondary variables. Genetic differences in susceptibility to tumour induction by radiation are especially manifest at low doses; with increasing doses and dose rates they tend to be cancelled. There are also quite definite changes in the susceptibility to the induction of various types of tumours as a function of the post-natal age at which animals are irradiated. Irradiation of experimental animals *in utero* would not appear, on the whole, to be more carcinogenic than irradiation during post-natal life.

335. Finally, the existing data on the problem of the tissue and cells at risk for the induction of various tumours have been reviewed. It appears that this subject may have important implications for the elucidation of mechanisms and for possible practical applications. Existing data relate, however, only to those tumour systems where the direct action of radiation on target cells appears to be the determining factor for tumour induction. A better quantitative definition of these problems by development of more sophisticated techniques of analysis at the cellular level is desirable.

VII. NEEDS FOR FURTHER RESEARCH

336. The previous report of the Committee (670), as well as other publications (563, 291, 564, 419), have indicated some topics of special interest for future research. Adequate selection of research topics is particularly necessary in carcinogenesis studies because of their long-term nature and of the major organizational and financial efforts they require. The Committee calls attention to the role of the experiments on animals for the eventual elucidation of the mechanisms involved and therefore for the extrapolation of data to man. Considerably more data would be required to extrapolate the few available data in humans to different conditions of exposure. A systematic analysis of the effects of the main radiobiological variables in experimental systems could make possible the refinement of the risk estimates in man by a considerable factor within the next decade (564).

337. Concerning the strategy of future experiments, special emphasis should be placed on the development and analysis of models of the carcinogenic action, rather than on large-scale experiments. It seems likely that some elucidation of the many factors interacting in carcinogenesis could be obtained through the study in depth of conceptually simplified experiments. A multidisciplinary effort of a quantitative, rather than a descriptive, nature seems to be called for. For example, our present knowledge of some tumour systems *in vivo* makes it possible to select as an indicator the induction of tumours in a definite cell line at risk, rather than the gross appearance of any type of tumours in a population of animals. The use of more relevant end-points may provide a rational basis for possible extrapolations from one species to another.

338. It is generally recognized that the area of greatest applied interest is, and will continue to be, that of the effects of low doses and dose rates. It follows that the experimental efforts should be concentrated in that area. It should also be emphasized that experiments on tumour induction as a function of dose and dose rate in selected animal model systems appear at present to be the type of studies that might best contribute to further advancement. Careful planning and design of the experiments, refined statistical analysis of the data, and also a better standardization of the techniques used in different laboratories would strengthen the validity of the observations.

339. The following are some specialized topics requiring further elucidation, and for which currently available techniques would justify increased efforts with reasonable hope of progress. The topics are given in the same order as they have been discussed in the main text of the report, without any indication of priority.

(a) The somatic mutation hypothesis of tumour induction and its possible relations with the viral hypothesis could be investigated by means of studies of the damage and repair to DNA and genetic structures in transformed cells following irradiation or viral infection. An attempt should be made to clarify the relationships between neoplastic transformation of the cell and its capacity for further reproduction and other possible damage to important cell structures.

(b) On the basis of the data reviewed, it seems that different radiation-induced tumour systems do not have the same etiopathogenetic mechanisms; on the contrary, it seems that the relative importance of each mechanism is different in different systems. By testing this relative importance, better elucidation of the role and relevance of the various inductive and promotive factors in different experimental situations could reasonably be expected. Further experiments of the role of various co-carcinogenic factors with particular relevance to the presence of potentiating effects in regard to tumour induction would also be desirable.

(c) Since viral agents are implicated in the induction of at least some radiation-induced tumours, attempts to demonstrate the viral origin of other tumours should continue together with studies on virus activation and on the immunological mechanisms interacting in such cases.

(d) The development of models of cell transformation *in vitro* should actively be pursued to clarify the kinetics of cell transformation and its relationship to cell inactivation. Several possible models have already been identified (564), and it is not unreasonable to expect that some of the classical radiation-induced tumour systems *in vivo* could also be subjected to more quantitative *in vitro* analysis.

(e) For *in vivo* studies, the identification of the cells at risk would greatly help in identifying the mechanisms and unifying the observations. Quantitative analysis of the capacity for division and differentiation of these cells, in relation to the transformation events, would provide important links between *in vivo* and *in vitro* studies. Furthermore, the period elapsing between the initial transformation of the cell and the clinical manifestation of the tumour should be studied, together with the influence of immunological, hormonal and other promotive factors.

(f) More experimental data are required to establish with precision the dose-effect relationship below 10 rad for many tumour systems. Studies of the relative importance of the linear *versus* quadratic components in dose-induction curves would be very valuable in this context. Better knowledge of the nature of such relationships would considerably improve the confidence in the estimation of the risks of tumour induction in man at low doses and dose rates (see Annex G). The development of model systems *in vitro* and the analysis of the data by means of refined theoretical models could help identify the relevant trends. It should be pointed out, however, that any conclusion will have to be confirmed by data *in vivo*, which are extremely difficult to obtain, particularly in the less susceptible species.

(g) The mechanisms involved in the determination of the nature of the dose-effect relationships at medium to high doses are uncertain. It seems reasonable to assume that the identification of such mechanisms might indirectly help establish the possible shape at very low doses.

(h) There are few studies of RBE for tumour induction. More effort is needed in this direction, particularly with the most sensitive systems which could allow an assessment of the RBE at low doses and dose rates, for which information is definitely insufficient.

(i) The lower efficiency with which irradiation at low dose rates induces tumours, which has been qualitatively described for some systems *in vivo*, should now be explored in other tumour systems and evaluated quantitatively.

(j) Although it seems reasonable to postulate that repair phenomena with various time constants are operating at various levels of the biological organization, the nature and kinetics of such repair mechanisms in the case of low dose-rate irradiation are still essentially unknown and require elucidation.

(k) Further comparative studies of tumour induction in different species and strains would increase our confidence in interspecies extrapolations. In this respect it would be desirable to test in other animals the conclusions reached in rodent experiments about the effect of the main physical and biological variables. However, no large-scale studies should be undertaken without sufficient scientific justification, which could be based on the relevance of the information to be gained for human assessments.

(l) The importance of systematic studies of tumour induction in various animal species and in animals of different size and age should be recognized. These studies should attempt to correlate the induction of neoplasia with the number and functional state of the target cells at risk of malignant transformation in any particular tissue.

(m) The conclusion that irradiation *in utero* is not more carcinogenic than in the young or in the adult animal appears to be based on rather scanty data. A more systematic search covering various tumour types in different strains and species and relating tumour induction with the rate of maturation of the relevant organs would considerably strengthen that preliminary conclusion.

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