IONIZING RADIATION: SOURCES AND BIOLOGICAL EFFECTS

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NOTE

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ANNEX K

Radiation-induced life shortening

CONTENTS

Introduction

1. Since the 1958 and the 1962 reports of UNSCEAR [U1, U2] the Committee has not presented a review of the cumulative evidence in the field of non-neoplastic long-term effects of whole-body irradiation. The scope of this Annex is to consider the data available in order to ascertain:

(a) The existence and extent of life-span shortening in irradiated animals and man and the relationships of life shortening to the physical and biological variables which may influence this effect of radiation;
(b) The extent and ranges of the physical and biological components of this effect which might be attributed by careful pathological analysis to either real non-tumorous conditions or to specific neoplastic diseases;
(c) The range of doses within which a non-specific radiation effect may be identified and measured;
(d) Whether such a non-specific shortening of life may be similar to the normal biological aging process.

Although answers to some of the above questions may be difficult in the light of the present biological and radiobiological knowledge, the Committee believes that a review of the field may be of value as a selective collation of the existing information. All data in the human species have been grouped for convenience in chapter IV. Causes of death due to non-stochastic effects are dealt with in Annex J.

2. Due to its coherence and wide acceptance, the international system (SI) of units of measurements has been employed wherever possible. The use of SI has resulted in the replacement of the former unit of absorbed dose, the rad, by joule/kilogram and in a special name of the unit, the gray (Gy), with one Gy being equal to 1 J/kg and to 100 rad. Similarly, the unit of exposure, the roentgen (R), has been replaced by C/kg, where one C/kg is equal to about 3876 R. Furthermore, the unit of activity, the curie (Ci), has been replaced by the reciprocal second and its special name, the becquerel (Bq), where 1 Bq is ($1/3.7\ 10^{10}$) Ci.

3. The use of the SI units poses problems in the presentation of results, except those obtained in the recent past. Due to the simple relation between the rad and the gray and that between the curie and the becquerel it is possible to easily perform these conversions. This has been done throughout this Annex. For the quantity exposure, however, it has been decided to employ the units provided by the authors.

4. The relation between exposure and absorbed dose and the recent tendency to use the latter in quantifying irradiations presents another difficulty. As an example, for soft tissues exposure to 1 R of low-LET radiation results in an absorbed dose of about 0.009 ± 0.0005 Gy, when the quantum energy is more than about 25 keV and electron equilibrium exists. However, the variation in absorbed dose can be far greater for other tissues (e.g., bone). Other uncertainties arise when animals larger than the mouse are irradiated. In these cases the conversion depends on whether the exposure quoted is that in free air or the mean exposure in the animal. In the more usual case of free air exposure, there is a complex relation between exposure and absorbed dose, depending on the size of the animal, irradiation geometry and radiation energy. For these reasons no attempt has been made to replace quoted exposures by corresponding absorbed doses.

A. HISTORICAL BACKGROUND

5. Radiation-induced life-span shortening was described first in the rat by Russ and Scott [R1] and in the mouse by Henshaw [H1]. They reported that irradiated animals had a shorter life span and appeared to age more rapidly than their non-irradiated controls. These and other observations led quite naturally to the establishment of a conceptual link between the life-shortening action of radiation and natural senescence. In 1952 Brues and Sacher [B1] discussed the problem of radiation-induced long-term radiation lethality. These authors recognized that single acute exposures to radiation tended to displace the Gompertz age-mortality function upward, while chronic exposure throughout life increased the slope of this function. Other techniques of analysis by the cumulative or the impulse lethality functions were also proposed as quasi-empirical actuarial and kinematic descriptive approaches. A comparative review of radiation lethality in various mammalian species, particularly under conditions of chronic treatment for the entire duration of life was presented by Sacher in 1955 [S1].

6. Although the treatment of this subject had proceeded quite far by 1958, there was little coverage of it in the 1958 report of the Committee [U1]. At that time the analysis of the biological end-point was not very sophisticated. It had been established that the pathogenesis of early death was due to the failure of self-renewing systems in the body, but that the precocious extinction of an animal population as revealed by actuarial analysis, was due to different mechanisms. However, there seemed to have been poor discrimination of the two mechanisms. In particular, no attention was given to the actuarial approach which had already been advocated by Sacher [S2] and Brues and Sacher [B1].

7. Although the review presented by Mole at the First International Congress of Radiation Research [M1] criticized the idea that radiation-induced life shortening might be equivalent to natural aging, this notion gained acceptance as a result of some observations on animals surviving doses in the lethal range made by Henshaw [H1] and later by Alexander [A1]. The "equivalence" idea was first based on actuarial observations of an increase in mortality rate from all causes of death, with an apparent shift of diseases characteristic of older age to younger age groups. The occurrence of phenomena typical of the old age in survivors (greying of the fur, cataracts, loss of reproductive capacity, etc.) tended to support the hypothesis of "equivalence". However, Upton in his 1957 [U3] and 1960 [U4] reviews warned against the attempt to establish a close relationship between certain effects of irradiation and aging, because not all age-dependent changes were affected similarly by radiation and the incidence and severity of the various diseases differed in control and irradiated animals.

8. Comfort [C1] discussed similarities and differences between natural aging and radiation-induced life shortening. His review is an important effort to define basic concepts and to differentiate between the various biological effects observed but his analysis of data according to dose and time is less elaborate than elsewhere. Storer and Grahn [S3] presented an accurate review of information available. This paper is still of interest for reference purposes. Neary [N1, N2] regarded theories of aging as belonging to one of two main groups: those interpreting aging as due to random

events in a population of supposedly uniform individuals; and those examining the individual and its component cells. Neary proposed his own theory, based on the analysis of original data on irradiated mice. According to his formulation aging proceeds in two successive stages, induction and development, each characterized by appropriate parameters. Although no attempt was made at the time to identify these stages, experiments reported later from the Soviet Union [V8, V9, V11, V12] tend to show that induction consists of the spontaneous occurrence of lesions in cellular DNA and development (promotion) in the activation of endogenous viral genomes by chemical carcinogens or radiation.

9. Another interesting contribution was provided by Casarett [C2]. By a critical comparison of natural aging and of late radiation effects, he proposed that radiological aging can be ascribed to the damage of endothelial cells of the fine vasculature, leading to fibrotic changes of the arterioles and of the interstitial collagenous substance. These mechanisms would be followed by loss of parenchymal cells, replacement fibrosis of the organs, loss of the functional reserve capacity and, eventually, by an increased susceptibility to trauma, stress and disease.

10. In recent years research tended to be more experimental than theoretical, except perhaps for the work of Sacher and Grahn [S4], Grahn and Sacher [G1] and Sacher [S5] who further elaborated previous ideas in an attempt to derive, from a refined analysis of the data, a basis for a comprehensive theory of a natural and radiation-induced aging. Attempts towards a better systematization of the experimental data were also carried out in contributions from scientists of the Soviet Union [A11, K26].

11. A recent report of Walburg [W1] was essentially a critique of the concept of non-specific life shortening, especially at the low doses of practical interest. Walburg came to the conclusion that life-shortening effects after irradiation may principally be explained by the induction or acceleration of neoplastic diseases. This conclusion was supported by Storer [S6]. These and other [K26] authors recognized that at higher doses other mechanisms of death prevailed.

B. METHODOLOGY

12. Life shortening can only be assessed on the basis of death, an end-point that can be defined rather precisely in time. However, it is usually more informative to know also the reasons why an animal dies. To ascertain the cause of death is often difficult and, in some cases, impossible as death is often the result of a variety of causes all acting jointly. This is particularly true as animals grow older [D1, A2, D2] because aging animals of all species (but particularly of the long-lived ones) die with multiple lesions, contrary to early death where there is often a single pathological cause. In old animals the number of possible causes of death increases and the primary or precipitating cause is difficult to diagnose. Most irradiated animals die of diseases which are unrelated to radiation exposure and this complicates the identification of the terminal pathological syndromes. Thus, multiple disease conditions, and interactions between diseases in the same animals should be correlated with parameters such as age and dose to provide a meaningful interpretation of the pathology at death.

13. The first difficulty with much of the work reviewed, particularly with the earlier contributions, is the lack of careful pathological observations on the animals at death, or a refined multifactorial analysis. Many experimental series are therefore difficult to interpret, as the representation of the life-span shortening, which may be accurate with respect to time, masks the complexity of the biological end-points. Another difficulty is that even when good pathology is available, information is usually collected at death. Under these conditions it is impossible to assess the contribution of each specific cause to life shortening, since there is no reason to presume that all causes are equally accelerated by radiation. Serial sacrifice experiments could, in principle, provide such information, but these require considerable time and effort and such reports are therefore not common in the literature [K1, C3, A3].

14. Apart from the difficulties in defining and describing a complex effect such as life shortening, quantification can create problems by giving implicit support to one or another possible interpretation. Interesting comments have been made by Mole in this respect [M2, M3]. He points out that it is not immaterial to think of the effect as a differential between the life span of the control population (t_0) and the life span of the irradiated animals. If it is postulated that survival after a given dose (t_D) is a function of that dose, it is implicitly ignored that animals may die of some unrelated pathology, and there is no implication that the effect of radiation may persist up to the end of life. If, on the other hand, the postulate is that the differential life time ($t_0 - t_D$) is a function of the dose, then the implication is that the effect of radiation may be equivalent to natural aging. No problems arise for single acute exposures given at young ages or for duration-of-life experiments, because under these conditions the two postulates are compatible. However, when experiments with various t_0 are involved, that is, when groups of animals are started on a course of irradiation at variable ages, one could come to quite different conclusions from the same experimental data simply by accepting one or the other postulate.

15. By definition, life shortening is an effect that must be estimated statistically by comparing irradiated and non-irradiated animal populations. The different ways of describing and expressing the effect quantitatively include the mean or median life span, the per cent cumulative mortality or the age-specific mortality rate. All these may be regarded as compounded expressions of specific and non-specific causes, acting within each individual to decrease fitness and ultimately to cause death.

16. Life shortening is expressed in days of life lost and since the time to death has a statistical variability, life shortening may be represented by one of the following statistics: shortening of mean or median age at death, shortening of mean or median survival time. In these cases the effect is given in units of time. Alternatively, the effect can be given as a percentage of control values and in such cases the per cent shortening of the mean or median age at death or the per cent shortening of the mean or median survival time would be the relevant parameters. It should be noted that the percentage effect as measured by the shortening of the mean or median age at death is not equivalent in most cases to that measured as per cent shortening of the mean or median survival. Although it would have been desirable to use the same method of expressing the effect

throughout this Annex, it was impossible to do so due to the lack of suitable data in the documents reviewed.

17. Mean and median life span are the average duration of life experienced by the animal population and the time required for 50 per cent of the animals to die, respectively. These statistics do not offer any indication of the variability of the phenomenon with time: they are therefore, as such, unsatisfactory parameters for any statistical analysis. The curve describing the extinction of the population in time is more informative as it shows the time when this process begins and ends and whether it has taken place regularly. Irregularities of the curve may sometimes be attributed to specific causes or set of causes. Both the mean and the median life span can be easily calculated and the per cent cumulative mortality as a function of time can be readily plotted.

18. The age-specific mortality rate is a more elaborate parameter. It expresses the instantaneous rate of mortality of the animals at risk as a function of age. The change over time is the main disadvantage in using this parameter. The main advantage lies in its sensitivity in measuring the changes in the distribution of times at death. It should be recalled that the displacement of the age-specific mortality rate curve for irradiated animals above the curve for non-irradiated controls does not measure days of life lost, but the increased rate of dying at a given age. The trend of this parameter in time and any irregularity in it are extremely useful to identify possible specific causes of death.

19. In estimating mortality rates it is desirable that assessments be independent of the proportion of animals that have died by any given time, i.e., that the estimate should be truly non-parametric with respect to survival. To this end, different formulas for its calculation have been proposed and may be utilized in radiation experiments [U5]. Upton, Kastenbaum and Conklin [U6], in an analysis of the age-specific death rates in irradiated LAF1 and RF mice pointed out that beyond a certain age this parameter tends to assume an exponential trend and that death rate curves specific for certain diseases vary in shape and slope. These observations emphasize the complexity of the relationships between dose and disease incidence. Therefore, the generalized notion that irradiation may advance the onset of old-age diseases is an oversimplification in the light of the variability observed with respect to specific injuries.

20. Other refinements in the analysis of life-shortening data may be introduced in order to account for the effect of competing diseases. It has long been known that the estimates of final incidence of diseases occurring late in life may be affected by the rate of mortality at times preceding the onset of these diseases [M4, F9]. Hoel and Walburg [H2] have compared various interval techniques of analysis with a non-interval technique by Kaplan and Meyer and have come to the conclusion that the latter may be used with advantage when the age at death of the animals is known. This technique has been employed for analysing the significance of the difference between treatment groups with respect to their cumulative mortality. There are also techniques to adjust the comparisons of mean ages at death, according to the presence of competing, lethal and non-lethal, diseases. Using these techniques Walburg [W1] has analysed some existing data on life-span shortening in experimental animals and has convincingly shown the usefulness of such methods in discriminating between specific, i.e., neoplastic, and non-specific life shortening.

21. Risk estimates for long-term somatic effects of radiation exposure have mainly been based on the incidence of fatal tumours. In principle, an improvement in these estimates could come from consideration, in addition to cancer incidence, of the mean ages at death. Sato et al. [S52] proposed an index which takes into account the contribution of each cause of death to life shortening. This index is the sum of three terms. The first reflects the tumour incidence, the second the changes in mean age at death from each cause of death and the third is an interaction factor for the preceding two terms. If radiation exposure increases the incidence of a given death cause and shortens the respective mean age at death, the index gives a large positive value. On the other hand, an increase in incidence of a late occurring cause of death gives a small positive or even a negative value for the index. The paper has a numerical example based on animal data.

C. THEORETICAL FOUNDATIONS

22. Although it is the primary object of this Annex to review and discuss experimental data on life-span shortening, it is impossible to do so without some background information on the hypotheses of aging. Such information is given in the next few paragraphs in a very simple form and is limited to those hypotheses that were proposed in the field of radiation research. More comprehensive discussions of the various theories of aging are, for example, in Strehler [S7], Walburg [W1], Vilenchik [V8], Nikitin [N13].

23. Gompertz in 1825 found that the age-specific mortality rate in man as a function of age increased exponentially over a considerable portion of life and assumed that this phenomenon reflected an exponential decline with age of some vital system. In the field of radiation research Brues and Sacher [B1] first introduced a mathematical approach to long-term mortality based on the observation of Gompertz and this was followed later as a basis for the analysis of experimental data and for many theoretical formulations. According to this approach, the survival characteristics of a group of individuals may be described by actuarial functions. One of the most widely used is the Gompertz function.

24. The Gompertz function $\ln \Omega(t)$ is the logarithm of the age-specific rate of mortality which is defined as [S16]

$$\Omega(t) = -\frac{1}{N}\frac{dN}{dt} \qquad (1)$$

where $\Omega(t)$ is the age-specific mortality and N is the number of animals surviving up to the time t. Linearity of the Gompertz function with time implies that

$$\Omega(t) = P_0 e^{P_1 t} \qquad (2)$$

where P_0 and P_1 are positive constants. Experience shows that a single acute dose of radiation is followed (after a period of latency) by an upward displacement of the Gompertz function without change in slope and that the amount of displacement with respect to the control is a function of dose. In other words, acute irradiation changes the constant P_0 in equation (2),

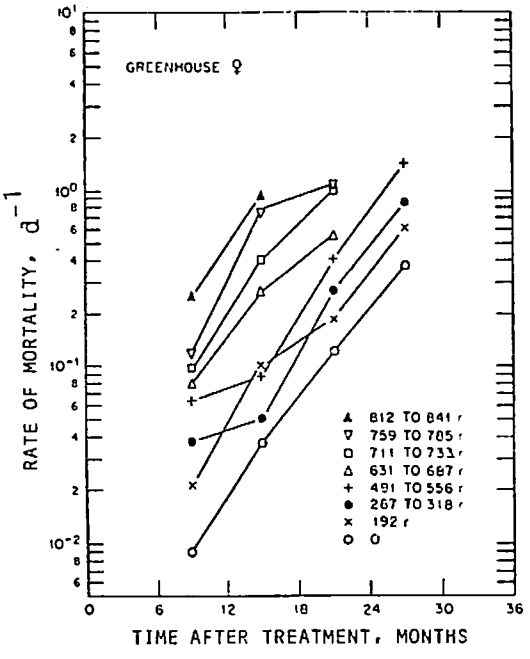
without affecting P_1. If single exposures would affect median survival, t_{med}, linearly with dose D, then

$$t_{med}(D) = a - bD \quad (3)$$

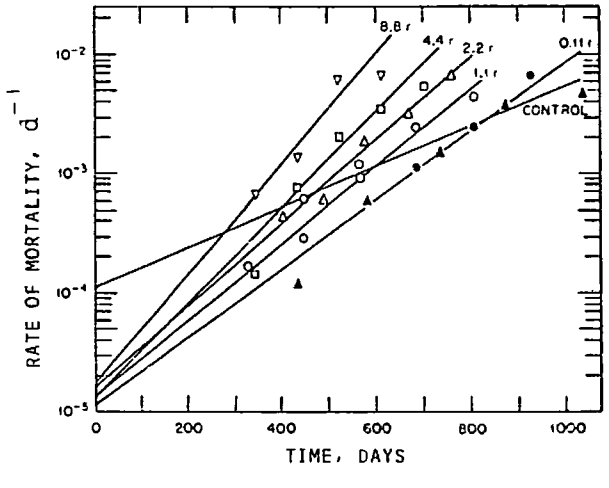
where a is the median survival time of the control group and b a dose-dependent constant. Chronic irradiation, on the other hand, characteristically increases the slope of the Gompertz function proportionally to intensity of irradiation, so that

$$t_{med}(I) = a\, e^{-cI} \quad (4)$$

where $t_{med}(I)$ is the survival time following duration-of-life exposure at dose rate I and c is a dose rate-dependent constant. These basic trends of the rate of mortality in irradiated mammalian populations are shown in Figure I.



A. Gompertz plots for LAF1 mice (females) after single acute exposures to gamma radiation. Data from Furth et al. [F2] *plotted by Sacher* [S2]



B. Gompertz plots for LAF1 mice (both sexes) under daily exposure to gamma radiation. Data from Lorenz et al. [L6] *plotted by Sacher* [S2].

Figure I. Basic trends of actuarial parameters in irradiated mammalian populations. In the mouse exposure to 1 R will result in an absorbed dose of approximately 0.009 Gy

25. The assumptions underlying such interpretations are that the Gompertz function is a measure of the amount of aging injury present at any given time. Acute exposure increases this amount of injury initially and for the rest of life. However, if a new induced injury adds to the residual present injury at any given time or to the underlying aging injury, one should expect a change in slope produced by chronic irradiation, with a divergence from the control slope proportional to the amount of daily dose administered. It should be clear that such characteristics of the actuarial functions are not necessarily related to the form of the dose-effect relationships, which may themselves be linear or not, as discussed in the next chapter.

26. In 1952 [B2, B3] and again later in a more complete form [B4, B5] Blair formulated a model of the relationships between radiation dose and life shortening. This model postulates that total injury is linearly proportional to dose and that such injury is only in part reparable. Recovery from reparable injury proceeds exponentially at a rate proportional to its magnitude; while, on the contrary, the irreparable portion of injury would accumulate linearly with dose. Finally, reparable and irreparable injuries add and death occurs when the effect of their sum is proportional to the remaining life expectancy. Starting from these premises, Blair developed simple equations relating dose and injury under different conditions of exposure and showed that some of them conformed to the then available data. Blair's formulation stimulated much research to ascertain the amount of reparable injury and the kinetics of repair under a variety of experimental conditions but was recognized later as an oversimplification leading to incorrect estimates and as such inadequate to account for the form of the dose-injury functions.

27. Mewissen et al. [M5] developed a complex equation relating life shortening to chronic whole-body irradiation and applied this formula to the irradiation of the burro. The formula is based on an analysis of the injury, which is also assumed to consist of a reparable and an irreparable fraction. Wasted radiation is accounted for by the transformation of a latent into an actual injury at a given measurable rate. The numerical parameters of the equation may be computed from experimental results in cases of chronic and acute irradiation. Weekly exposure to gamma radiation of burros, between 175 and 2800 R, with corresponding mean survival times of 9 weeks to 1 week, were the time-dose conditions in which the above formula was found to apply. They are clearly of little value to the present discussion referring to low dose rates and to extended survival times. Storer [S8, S9] in a review of data on recovery rates and their possible relationships to life shortening showed that the mean rate at which mice recovered from radiation exposures, which if acute would result in acute death, could be related to the number of fractions delivered daily, rather than to the size of the exposure. This and other observations suggested modifications of the original formulation of Blair.

28. Krebs, Brauer and Kalbach [K3] measured the kinetics of non-recoverable injury by exposing C3H female mice to conditioning irradiations (600 to 1500 R) and then estimating at different times (4 to 20 weeks) the injury remaining. This estimate was obtained indirectly by taking the $LD_{50/30}$ values on the preirradiated mice. A proportionality between conditioning dose and reduction in tolerance to x rays, as measured by a reduction of $LD_{50/30}$, was found; however, the

injury parameter did not account for the observed mortality when animals were chronically irradiated. Further work [K4, K5] suggested that different recovery components with different half-times could be shown to apply to acute and chronic radiation exposure conditions.

29. Complete disappearance of residual damage was seen by Alexander and Connell [A4] three weeks after conditioning exposures of 600 to 1100 R prior to $LD_{50/30}$ determinations. Spalding et al. [S10] gave conditioning fractionated doses of gamma rays (2.4 to 12 Gy) or of fission neutrons (0.9 to 4.5 Gy) to RF female mice and, after a repair period of 3 months, exposed them for the rest of their lives to a dose rate of 0.5 Gy d^{-1}. They found that radiation-induced damage had a permanent and irreversible component, that at least a part of this damage was proportional to the dose and measurable in terms of reduction of survival time, and that fission neutrons produced about five times as much irreversible injury as gamma rays. Always with the same animals, an investigation of the two-component theory of Blair [B4, B5] under the assumption that the half-time of the reparable component was 7 days and that the irreparable injury would be equivalent to 5% of any given dose, showed that such a formulation was only useful under a limited range of exposure conditions.

30. The above limited discussion of the results of a vast amount of literature shows that short-, medium- and long-term mortality are produced from different pathogenetic mechanisms. There is probably more than one single formula to account for the variety of mechanisms. Further, no single recovery time or residual injury value can define all of the conditions of protracted exposure. The constants applicable to acute injury may to some extent predict the results of exposures to within about 100 days and 15 Gy in the mouse, but for longer times and low doses a new set of relations between injury and recovery must be established [G1].

31. Neary [N1, N2] also proposed a model, based on the observation that the great majority of animals in a population die during the last part of the life span. The preceding period of life, in which deaths are relatively few, is called "induction" by Neary, who defines it as a state of intracellular changes and intercellular reactions proceeding insidiously and without marked functional impairment. When a certain level of this type of change is reached, the second stage sets in quite abruptly. This stage, called "development" involves a different level of organization and is sustained by physiological interactions proceeding autonomously and autocatalytically and culminating in death. The most interesting feature of this model is that once development sets in further inductive change is superfluous and therefore irradiation during development has comparatively little effect. This point was emphasized conceptually by Mole [M6] and by Mole and Thomas [M7] in the notion of "wasted radiation". Neary suggested that small radiation doses would essentially act by shortening induction without affecting development, and also showed that there was a good correlation between the results of experiments on mice [N3] and the formal requirements of the model. Kohn and Guttman [K6] pointed out, however, that the model, derived from results of duration-of-life exposure was difficult to apply to results derived from acute irradiation experiments. Experimental evidence has more recently been reported [V8, V12] in support of a two-stage model of aging.

32. In a paper published in 1956 Sacher [S2] proposed a model in which all individuals in a population were assumed to be initially identical. However, with time, due to fluctuations in the physiological state of the animals and to external stresses, there was a progressive change and a dispersion in the physiological state of the population. In this model, when a fluctuation of large amplitude in the homeostasis of an animal takes place, death ensues. By a mathematical description of a physiologic fluctuation process, it is possible to derive an approximate relationship between the rate of mortality and the mean physiologic state of the population. The relationship has the form of a linear function of the logarithm of the mortality rate with respect to the mean physiologic state of the population at any given age.

33. A more analytical presentation of this theory and of the derived functions can also be found in other papers [S4, S12]. In a later contribution [S13] attempts were made to interpret lethality in terms of very simple cell population kinetics, without building into the models known parameters of cell kinetics such as maturation time or feed-back control of self-renewing systems. Other features of cell kinetics, with special regard to lengthening of the generation cycle upon continuous irradiation, were discussed in another paper [S5] as possible causes for a cumulative lesion related to the life-shortening effect. Cytogenetic injury due to rearrangements of chromosomes has also been considered to account for radiation-induced life-span shortening [S14].

34. A critical comparison between the model of Blair and that of Sacher is contained in Sacher and Grahn [S4]. The latter model assumes linearity and additivity functions formally equivalent to those contained in the former, although Blair postulated the existence of only one component of recovery from injury, which operated soon after exposure and caused the injury to fade away exponentially. When the equations derived by Blair were fitted to the cumulant lethality function of Sacher the fit failed, owing to significant systematic deviations. In addition, the mean recovery time estimated from Sacher's data was 4 to 10 times longer than the recovery value of 5 days accepted by Blair on the basis of fractionation experiments. For these reasons Sacher and Grahn [S4] rejected the central assumption of Blair referring to the single linear component of recoverable injury. All the remaining assumptions of Blair are included in the more generalized formulations of Sacher. The assumptions are that radiation injury is proportional to dose and to dose rate; the recovery rate from this injury is proportional to the amount of injury present and is independent of age; death occurs when the sum of all injuries reaches a given value, called the lethal bound; radiation injury is additive to the injury accumulating due to age; and that age-cumulative injury is linear with age.

35. Stover and Eyring [S15] and Eyring and Stover [E1] developed a steady-state theory of mutation rates and applied it to the survival data of beagle dogs injected with ^{239}Pu and ^{226}Ra. The fits of the experimental data obtained by the use of this model were good and allowed the identification of various mechanisms of death caused by the two nuclides. The formalisms developed in this series of papers adequately describe the experimental data and may be of use in further interpretations.

36. Sato, Nakamura and Eto [S16] performed calculations of the life-shortening effects of radiation as a function of dose and dose rate under the assumption of linearity of the Gompertz function for both acute and continuous exposure. They showed that within the range of doses usually employed with mice the values of percentage life shortening are not appreciably changed if the survival time is measured as mean, median or mode.

37. Iberall [I3] examined the various models of radiation lethality in great detail and attempted a unitary description of the various modes of death, from those due to very high acute doses to those due to low chronic treatments, through an analysis of much experimental data. In so doing he illustrated the level of complexity required for a careful mathematical description of the actuarial properties of a population. This description pointed towards the isolation of five or six possible conditions affecting lethality as a result of the various irradiation regimes. The paper supplemented the studies of Sacher and Grahn [S4] with a widespread examination of the entire problem from a mathematical point of view.

38. Another model for life shortening by late effects of ionizing radiation was developed by Scott and Ainsworth [S47]. It applies to data in the mouse and it is specific for doses much below the $LD_{50/30}$. It focuses on the number of individuals with life-shortening injury and variations due to dose, dose rate and quality of radiation. For these individuals the survival time distribution differs and shows earlier times to death as compared to other members of the population without life-shortening injury. The results of the model's analysis are consistent with available data at comparatively low doses, including the convex upward life-shortening responses. The model predicts enhancement of effects after fractionated exposure to ^{60}Co gamma rays and an approximately linear response in most cases of acute exposure to low-LET radiation. The model also provides a means of extrapolating between mouse strains or age groups, an extrapolation which can be achieved by changing a single parameter [S48].

39. Finally, other publications should be cited for completeness, where the problem of long-term chronic exposure to carcinogenic agents in general (or specifically to radiation) was addressed, in an attempt to account for both the increased incidence and the early displacement of the tumours induced which, in turn, cause shortening of life span. In this context the papers of Blum [B27], Druckerei [D11], Albert and Altschuler [A15], Hug [H20] and Mayneord and Clarke [M32] should be recalled as valuable contributions. However, these papers refer to tumour induction and not to life shortening in general and have therefore a narrower approach to the problem under discussion here than many of the papers cited previously. They should be kept in mind mainly in view of the general conclusions to be arrived at in this Annex.

D. LIFE SHORTENING AND AGING

1. Specific and non-specific life shortening

40. There is considerable discussion in many of the papers reviewed about the specificity or non-specificity of the life shortening observed in a variety of experimental situations. Semantic considerations as well as important reasons of substance have complicated this issue. It should first be recognized that speculations about specificity often conceal the lack of good pathological analysis. Life shortening must be due, if properly assessed, to some specific cause. However, the word specific has been taken to mean that the irradiated animals die earlier than their controls with a characteristic spectrum of diseases or causes of death different from the spectrum seen in the non-irradiated controls.

41. Since it is well known that not all diseases are readily induced by radiation, to expect that radiation acts non-specifically in shortening the average life of an animal population would be to reject all radiobiological experience. Recently the discussion has been more reasonably centered on whether or not radiation may produce life shortening by induction of tumours and how much of the observed shortening can be accounted for by neoplastic diseases. Though never defined clearly, the words specific and non-specific have therefore been taken to indicate neoplastic and non-neoplastic contributions to life shortening. Under these conditions, the question of specificity of the life-shortening action is legitimate and of great practical significance.

42. In discussing the problem of specificity, ICRP publication 14 [I1] and Mole [M2, M3] point out that in order to detect a general non-specific deleterious effect of radiation, long-term survival data should first be corrected for diseases known to be specifically induced by radiation. The concept of life shortening is ambiguous as it may be regarded either as an overall measure of deleterious effects or as a measure of the effects remaining after allowance for the induction of tumours and other defined diseases. Non-specific life shortening, if it exists, must have some basis in damage to biological structures and functions. Actually, some damage, anatomical or functional, may be shown for some tissues [C4, D3, C5], but not for all. Under these conditions an increase of causes of death related to damage in those particular tissues may be expected. The resulting effect should be a change in the spectrum of diseases induced in irradiated animals. On the other hand, one could envisage that damage to body components such as the blood vessels or the connective tissue, which are uniformly distributed in the body, could be the cause of non-specific life shortening at high doses. However, it appears unlikely that damage to blood vessels in skin, muscle and fat tissue results in changes ultimately affecting the vital capacity of an individual, whereas damage to blood vessels of the kidney, the brain, the heart can be expected to result in important changes affecting the capacity for survival. Thus, if the determining factor is the anatomical location of the damaged blood vessels, again a change in the spectrum of diseases compared to the spectrum of diseases of unexposed animals would be expected in irradiated animals.

43. In conclusion, the notion of non-specific life shortening is compatible with that of aging (advanced or accelerated) induced by radiation. The two concepts are inevitably linked with the demonstration of the principle that radiation, although advancing the instant of death, does not modify the spectrum of normally occurring diseases. This demonstration is difficult in practice and probably impossible to visualize as the mechanisms that may be hypothesized for non-specific effects will also change the spectrum of diseases appearing in irradiated animals. Such change is incompatible with the notion of aging or of non-specific life shortening.

2. The phenomenon of aging

44. Attempts to show that irradiation may non-specifically age animals were begun with observations that radiation did produce life shortening and that irradiated animals showed phenomena similar to those observed in old age (greying of the fur, appearance of cataract, loss of fertility). Although it should have been clear that the resemblance was only superficial [M3], the hypothesis of radiation-induced aging gained momentum and stimulated much work. The interested reader may refer to the following reviews – which are some of the many available – for more detailed evaluations of data obtained in experimental animals [A1, A11, U4, C2, C32, H3, C6, C7] and in man [A4, A6, F1, B6].

45. Difficulties in experimental work on aging are related to its definition, to the lack of any direct measure of senescence other than in terms of life span, and to the impossibility of deciding whether pathological processes in old animals are the causes of aging, the effects of aging or indeed aging itself. The only acceptable generalization is that in mammals the age-specific death rate increases as a function of time in a roughly exponential manner by a constant factor for each year of the adult life. That is, that the probability of death per unit time increases with age (see control curves in Figure I). However, to accept this generalization as a measure of aging requires the assumption that aging of each individual is paralleled by the average changes of the population to which the individual belongs. In addition, there are uncertainties in sorting out, both for the individual and for the population, intrinsic and environmental factors, primary and secondary effects, specific and non-specific phenomena.

46. Radiation is by no means the only agent producing life shortening. Other treatments have often been reported to produce similar effects in conjunction with radiation experiments. These life-shortening agents include various types of toxins and non-specific toxic substances [C8, C9] or cytotoxic drugs [C10, A4, U6, C11, D4] in various combinations and dosages. It appears from all the data that the effect of these agents is in general less readily induced than the effect from radiation and that the diseases leading to precocious death are specific for each drug.

47. In the context of the hypothesis of radiation-induced aging, the concept of differences between advanced or precocious aging on the one hand, and accelerated aging, on the other has been discussed repeatedly (see, for example, [C2] and [C7]). The two notions can be formally visualized in terms of the theory of radiation injury of Blair [B2, B3, B4, B5]. If one assumes that aging in an individual is determined by the sum of deleterious irreparable injuries accumulating in time; that radiation causes irreparable injuries which may add to the aging injuries; that beyond a given level of injury death of the animals occurs; that such processses within each animal may also be reflected by the Gompertz curve; then a displacement upward of this curve without change of its slope would be interpreted as precocious aging, whereas an increase of the slope would be formally equivalent to accelerated aging (Figure I). However, such definitions may hold formally but are difficult to verify experimentally.

3. Mechanisms of aging and life shortening

48. In spite of the above important considerations of principle, attempts were often made to identify a possible effect of life shortening with some non-specific, diffuse, subclinical deterioration of tissues that might advance the onset of all old-age diseases to roughly the same degree. There are a great variety of non-tumorous degenerative changes in irradiated tissue [U4, C7]. Some of these superficially resemble senescent changes, although on closer inspection there are profound dissimilarities between radiation-accelerated and senescent lesions [W1, M3]. Among the least equivocal mentioned by van Cleave are [V7] the following: involution of the cartilage discs, involution of the thymus and all lymphatic tissues, lymphocytopenia, marrow hypoplasia, atrophy of the iris, atrophy and dysplasia of skin and degeneration of the skin collagen, degeneration of the elastic walls of the arteries, nephrosclerosis with glomerulosclerosis, dysplasia of the lens epithelium, vacuolization and degranulation of endocrine glands, involution of testis and ovary, generalized progressive fibrosis of the arteriocapillaries and generalized increase in fibrillar density of the interstitial connective tissue.

49. Casarett [C7] proposed a "histopathological theory" of natural and radiation-induced premature aging. It rests on the notion that the most generalized deleterious change in aging mammals is an increase of the histohematic barrier, the layer of connective tissue between blood and parenchymal cells, with an increase of arteriocapillary fibrosis. Functionally, a loss of selectivity of the barrier to nutrients and to wastes and a decreased efficiency of circulation are the consequences of such changes. Under these conditions a decrease of parenchymal cells and functions follows with more fibrosis and loss of vasculature becoming progessively more serious with time and leading to increased susceptibility to infection, stress, degenerative and neoplastic conditions and eventually to death.

50. Irradiation advances such an increase of the histohematic barrier and ensuing consequences, to various degrees in various tissues, depending on the sensitivity of the constituent parenchymal cells. Non-specific damage to the endothelium of the fine vasculature directly or indirectly caused by radiation would be the primary cause. The consequent morphological (interstitial oedema, increased fibrillar density) and functional changes (loss of reserve capacity of single organs reflecting gradually and progressively on other parts or on dependent organs) would tend to perpetuate and to increase themselves by circular reactions where the natural and radiation-induced aging would not be separable any longer.

51. The basic notions of Casarett's model [C7] appear to be well founded, as it is known that radiation may cause an interstitial fibrillar density and capillary fibrosis. The mechanisms of these phenomena have recently been discussed by Streltsova [S58], by Gerber [G1] who has examined the possible pathways responsible for fibrosis and by Hopewell [H16] who has particularly addressed vascular changes. But whether the initial endothelial and connective changes operating in natural and in radiation-induced aging may be the same, remains to be demonstrated as do the further steps of Casarett's hypothesis, which should be set on firmer ground [W1]. In addition, more recent information on the radiosensitivity of the endothelial cells [R11] seems to cast considerable doubt on the applica-

bility of the hypothesis to very low doses and dose rates and to confine its applicability to the region of the intermediate to high doses.

52. The hypothesis that late effects of radiation on the duration of life may be brought about via alterations of the immune system can also be entertained. In this respect two possible mechanisms of action can be envisaged. The first implies that auto-immune diseases are possible causes of a diffuse deleterious action. Alternatively, life shortening can be viewed as the result of an earlier appearance and a higher incidence of tumours, elicited in turn by radiation-induced immune disturbances. In no case does the effect of life shortening have a truly non-specific character, because an acceleration or an advancement in time of old-age diseases without changes in their spectrum could hardly be expected as a result of such mechanisms.

53. In 1972 the Committee extensively reviewed the effects of radiation on the immune response and considered the general question of radiation as it may relate to auto-immunity and possibly to aging [U15]. At the time there were few results on irradiated animals consistent with the hypothesis of a breakdown in the balance of self-tolerance leading to auto-immune conditions. On the whole the data were thought to be inconclusive as far as positively showing any such effect.

54. Studies of the late effects of radiation on the immune system are relatively few and their results vary according to the test system and radiation doses [S46]. In general, intact animals examined individually many months after exposure to moderate doses (1.5 to 6 Gy) of x or gamma rays showed little if any changes of their immunologic competence [S45, S46]. On the other hand, lymphoid cells derived from these animals and examined for various immunologic functions frequently show significant delayed effects [see S46 for a review]. However, this reduced immunologic competence could be due to an artifact resulting from a dilution of the lymphocytes or from suppression of lymphocyte functions by an excess of non-lymphoid elements in the test cell preparations. Reduced immunologic competence may or may not be compensated by a change in the total number of lymphoid cells in the whole animal. The radiation dose, the age at exposure, genetic and environmental factors (particularly the microbiological flora) could affect the expression of late immunological affects and, hence, the life span of the exposed animals, if radiation-induced shortening of life is indeed related to a dysfunction of the immune system.

55. A life span study performed with Biozzi mice specifically selected for a high or a low antibody response has some relevance to the present discussion. It was shown in that study [C30] that mice with a low antibody response had a higher incidence of spontaneous malignancies and a shorter life span than others of the same genetic background having a high antibody response. On the other hand, it is known that total lymphoid irradiation performed on NZB/NZW mice with a high incidence of an auto-immune disease reversed the expression of this condition and thus produced a prolongation of survival [K22].

56. In a comprehensive review of the immunological action of radiation Anderson and Warner [A10] discussed three general hypotheses for the possible induction or acceleration of auto-immune processes. The first one suggests that radiation can alter tissue constituents to create new auto-antigens or to release previously inaccessible components. The second possibility is action via somatic mutations thus leading to the emergence of auto-reactive clones. The third is action through the imbalance of natural mechanisms of regulation controlling the potential auto-immune expression. Several studies are in favour of the third mechanism but at the present time few definitive statements are warranted. The first statement is that the interplay of regulatory mechanisms in the immune system is so complex and variable that radiation effects are hardly predictable and at present cannot be extrapolated with any confidence from one experimental situation to another. Secondly, although immunological mechanisms may actually operate at high radiation exposures and cause extensive tissue damage, their possible relevance at the low doses of interest for radiation protection can only be viewed with great reservations given the present state of knowledge.

57. The Committee has reviewed in its 1977 report [U14] the role of the immune system in the pathogenesis of radiation-induced tumours. The conclusions pointed to a secondary role of immune reactions in the development of neoplastic conditions, particularly at low doses and dose rates. No new information has appeared since then that might change this general proposition. A most recent review of the subject [S46] confirms the above conclusion and therefore indirectly supports the view that, whatever the role of tumours in radiation-induced life-span shortening, there is as yet no clear evidence that the role is mediated through immunological mechanisms.

58. There are other hypotheses of aging that have been considered either alone or in conjunction with radiation and for which some experimental evidence has been claimed. The older theories were discussed by Walburg [W1] and their applicability to a possible effect of premature aging was criticized as mortality data and causes of death in irradiated animals indicate a life-shortening action essentially related to tumour induction. According to that analysis, exposure of mammals to life-shortening doses of radiation almost uniformly fails to accelerate lesions characteristic of senescence.

59. Recently other hypotheses related to molecular changes have been considered. Cutler [C31] reviewed the concept of primary aging processes. This term covers causes which can underlie many different specific disease processes at the organismic level and many age-related losses of function resulting in a progressive decline of general health. At the molecular level, cross-linkage between biologically important molecules effected by various agents (free radicals and their derivatives, aldehydes) may be postulated to be at the origin of natural senescence and of possible radiation-induced changes. This hypothesis has received little experimental support when applied to cellular and extra-cellular constituents such as collagen, age pigments, etc. It can, however, be more attractive when applied to information transfer molecules such as DNA or to structures such as chromatine. For these cellular constituents a more systematic approach might be envisaged.

60. Work by Vilenchik [V8, V9, V10] and others [L20] was directed to illustrate the similarities between the changes in the DNA induced by aging and by radiation, showing that spontaneous DNA lesions

result from thermal degradation of DNA at normal body temperatures and lesions may also be induced by free radicals such as $OH^{\cdot}$, which are known to be responsible for radiation-induced damage. Accumulation in this molecule of various lesions (alkali-labile sites, DNA-protein bonds, changes in the circular dichroism spectra) as a function of age has been taken as valid confirmatory evidence of a hypothesis of age-related multistage DNA damage advanced in the past [V8]. For a review of the free-radical theory of the aging process see [H21].

61. DNA damage is, however, only the initial step in reactions of this kind, as it is well known that this damage can be repaired. Hart [H17] discussed the most recent data concerning another complementary working hypothesis. This envisages the aging process as a sequence of events involving the induction of the DNA damage and its subsequent manifestation at the physiological level. The ability of the system to repair DNA damage and the redundancy of the genetic information for vital functions within the system are the factors controlling the manifestation of such damage. Alterations in one or both of these mechanisms are expected to modify life expectancy. Since it is known that DNA damage and repair is also involved in radiation carcinogenesis, the hypothesis has been entertained [V8, V10] that physiological aging and carcinogenesis (both spontaneous [V8, V10] and induced [V9]) may be inhibited by error-free repair systems. Although interesting and often supported by some indirect evidence, all the above hypotheses have not yet been sufficiently formalized and their general applicability has not been extensively tested to warrant more than the present mention.

4. Conclusions

62. In summary, although at some stage research on aging was advocated on the ground that radiation might represent a unique tool for the study of senescence [C7] resulting efforts have been rather unproductive. Data in animals and man lend no support to the view that radiation may cause premature aging or that the carcinogenic effect observed is only part of a more general effect of acceleration of aging [B6]. Attempts to identify a possible life-shortening action with non-specific diffuse changes in tissues, particularly of the connective and vascular structures have been difficult and are probably inapplicable at low doses and dose rates. Information about a possible role of the immune system via an increased incidence of autoimmune conditions or a favouring influence on tumour acceleration or induction are few and contradictory. In any case, such mechanisms are not expected to yield non-specific life shortening without changes in the spectrum of old-age diseases.

63. Therefore, in view of the difficulties of defining aging, of the lack of reliable parameters of senescence, of the impossibility of distinguishing between specific and non-specific causes of aging and between genetic and ambient factors, of the generally negative conclusions to be drawn from the available data, the Committee decided to limit the present analysis to the only effect of radiation that has been shown convincingly, namely the shortening of life span. It would in fact be unreasonable under the extremely undefined conditions discussed above, to carry out an analysis of the physical and biological variables affecting such an ill-defined effect as aging. Pending clarification of the points reviewed previously, the relationships between radiation-induced life shortening and aging (if indeed the latter effect exists to justify such relationships) will not be taken up again for discussion in the rest of this Annex.

I. THE EFFECTS OF PHYSICAL VARIABLES

64. Establishing a relationship between the degree of life shortening and the characteristics of the acute or chronic exposure to radiation is important in determining criteria and levels for human exposure. Such a relationship may also be useful in order to indirectly validate hypotheses and models of the nature of aging and on the similarity between natural and radiation-induced senescence. Experiments on single acutely-delivered doses are the simplest of all possible models. Single-dose irradiations are not interesting for radiation protection purposes, but represent the most efficient means of exposure, as under these conditions the action of any repair system is minimal. On the other hand, there are experimental treatments such as the duration-of-life exposure which may more closely resemble the situations of interest in practice. These yield, dose for dose, less effect than the acute exposures. Between these two extremes there is a whole range of exposures where any given amount of effect can be obtained by infinite combinations of many interrelated variables. These include the number and size of the dose fractions, the radiation-free time interval between fractions, the time over which a given radiation treatment extends, the total accumulated dose, the instantaneous dose rate, etc. All these variables interact for any given radiation treatment to produce the final effect on survival and it is in practice extremely difficult to design experiments allowing their separate analysis. It should also be added that each experimental system has its own biological, physiological and pathological characteristics (to be examined in chapter II) and that an end-point such as life shortening may be the result of an infinite number and type of underlying biological effects.

65. Having thus recalled the complexity of the problem at hand, the following irradiation conditions will be considered in turn; single acutely-delivered exposures; continuous life-time irradiation; the effect of dose rate; the effect of fractionation; protracted exposures; and the effects of different types of radiation. The various effects will be examined in the sections thought to be most relevant. However, a certain amount of overlapping and repetition is unavoidable in comparing the various conditions of irradiation. The problem of partial-body exposure will be dealt with in chapter III.

A. THE EFFECTS OF ACUTE SINGLE DOSES

66. In the following section the effect on long-term survival of acutely-delivered single doses of radiation is examined. The data are reviewed with the criterion of considering together all information pertaining to a given species. The data are arranged according to the time of publication to give some historical perspective. As it was often found that data on low- or high-LET radiation were included in the same paper, the review will consider the information pertaining to different types of radiation together. A summary of the numerical values to be derived from the documents reviewed is given in Tables 1 and 2, where low- and high-LET data are tabulated separately.

1. Mouse

67. The earliest data of Gowen and Stadler [G2], Grahn and Sacher [G3], Furth et al. [F2], Kallman and Kohn [K7], Storer and Sanders [S17], Storer et al. [S18], Boone [B8, B9] and Nowell and Cole [N4] will only be mentioned in this context. The essential information in these reports may be derived from Tables 1 and 2.

68. In 1960 Upton et al. [U5] reported on a very extensive series of data (the Greenhouse experiment) on late effects including life shortening in LAF1 mice (6 to 12 weeks old) exposed at a nuclear test site. Nineteen groups of 220 mice each were exposed to gamma rays from 1.79 to 7.82 Gy. Neutron doses in eight groups ranged from 0.28 to 2.5 Gy. Mean survival times were obtained for each exposure group and tested for linearity versus dose. In both sexes, for the gamma as well as for the neutron data, significant departures from linearity were observed and the best interpolation to these data was a curvilinear quadratic relationship fitted empirically. The authors felt that the shape of the curve should be taken with some reservation, particularly since later tests with more refined dosimetric methods (which in this particular instance left something to be desired) gave more nearly linear dose-effect relationships.

69. In the Greenhouse series [U5] the Gompertz plot of irradiated mice showed a displacement upwards and to the left of the control curves for both sexes. Life-span shortening was reported to be due to premature onset of all diseases observed in normal aging mice. The onset of old-age diseases was advanced to essentially the same extent by any one dose, an exception was thymic lymphoma whose incidence was greatly increased in both sexes. There was no consistent relationship between frequency of neoplasia and dose, because the incidence of some tumours (thymic lymphoma, granulocytic leukaemia, tumours of the ovary) increased but that of others (reticulum cell sarcoma, mammary sarcoma) decreased with increasing doses within the dose range studied. Thus, no overall clear-cut relationship could be established between life-span shortening and tumour incidence. It should be pointed out that the classification of lymphoreticular tumours in the mouse is a controversial issue and that these diseases are different in many respects with regard to similar conditions seen in man.

70. Some of the data from the Greenhouse experiment (male and female animals receiving up to 2.67 Gy) were analysed again by Walburg [W1] on the basis of the original pathology data and with appropriate corrections for competing probabilities of death [H2, H4]. A significant life-shortening effect was observed when all causes of death were considered together; but when only non-neoplastic deaths were taken into account there was no advancement in time of mortality due to these diseases. Walburg therefore concluded that evidence of life shortening due to non-neoplastic causes was lacking, although these experiments are often cited as an example of non-specific life shortening.

71. Using data from work on six mouse strains irradiated with single doses of x rays around the $LD_{50/30}$, Grahn [G4] reported a curvilinear type of relationship with dose. By appropriate correction for animals dying of leukaemia and ovarian tumours, he was able to eliminate much of the variability between strains and sexes and to analyse the whole process culminating in life shortening to produce a basic injury parameter (0.28 d of life lost/R or 19% life lost for irradiation at the $LD_{50/30}$) applying to all strains and sexes. Other factors, specific for life shortening due to leukaemia and ovarian tumours, could be superimposed on this basic parameter to give predictable amounts of effect at any dose and for any strain and sex. Other data by Vogel, Frigerio and Jordan [V1] are summarized in Table 2.

72. Lindop and Rotblat [L1, L2] reported on experiments with SAS/4 inbred mice exposed to single whole-body irradiation (50–780 R, 15 MeV x rays). When the percentage of survivors was plotted against age for each dose group, the life-shortening effect for the pooled sexes had a good fit to a linear relationship with dose without apparent threshold. The data suggested that life shortening was the result of a loss of early life and not of a contraction of the time scale. Lindop and Rotblat [L2] established the cause of death of these animals and came to the conclusion that life shortening was not due to induction of specific diseases but to the forward displacement in time of all causes of death. In this respect radiation could thus be considered as a cause of aging, although not identical to natural aging, as the relative ages of onset of the various diseases were different in irradiated and control animals.

73. Storer's [S19] data on RF/J mice were limited to a single exposure of 400 R of 250 kVp x rays administered at the age of 90 days. They are summarized in Table 1. Storer also performed other experiments [S20] on DBF1/J female mice treated at three months of age with graded exposures (100, 300, 500 R) of 250 kVp x rays. Under these conditions shortening of median survival followed a linear non-threshold function of dose. Autopsies performed on large samples of the animals showed that tumour incidence was not increased by radiation exposure, although tumours tended to occur earlier. The time interval between irradiation and the occurrence of a significantly increased death rate was inversely related to the size of dose, as though low doses required longer times for the injury to become manifest. On this basis Storer postulated that in experiments where animals are sufficiently long-lived (or the latent period is sufficiently short) so that the elevation of the death rate may show over the time interval in which essentially the whole population is dying out, life shortening will be proportional to radiation dose. But with low doses or short-lived animals a curvilinear relationship may apply.

74. Upton and collaborators [U7, U9] performed an exhaustive series of experiments on RF/Un mice irradiated with various doses and dose rates of 1 and 5 MeV neutrons, 250 kVp x rays and ^{60}Co gamma rays. At high dose rate (about 0.1 Gy/min or higher) both with x rays and with 1 MeV fast neutrons, the shape of the curves appeared distinctly non-linear (convex upwards). With x rays within the 3 to 30% range of life shortening the days lost per Gy at the various doses varied between 56 and 2 at progressively higher doses, with differences between male and female animals. With fast neutrons between about 20 and 50% of life shortening, the days lost per Gy were between 21 and 3, again with differences between the two sexes. In these animals death was characteristically associated with neoplastic and degenerative diseases common to the natural aging, except for animals treated with high doses in which death was attributed to necrosis and aplasia of the lymphatic and haemopoietic tissues. The shape of the dose-survival curve (for both neutrons and

x rays) may conceivably be explained by differences in the effects responsible for life shortening, as not all effects which may contribute to earlier death are identical in dose-response relationships. Leukaemia and other neoplasms could not entirely account for life shortening in this series of experiments.

75. Data on induction of neoplasia in the experiments described above were reported in a paper by Upton, Randolph and Conklin et al. [U9]. There is no specific discussion in this paper about the relationships with life-span shortening but some of the data (^{60}Co irradiation at high dose rates for single doses of 1 and 3 Gy) were analysed again by Walburg [W1], on the basis of rather careful macroscopic examination of the animals at death. There was no significant difference between control and irradiated animals when all causes of death other than neoplasia were considered. But when all causes of death including tumours were analysed together the difference between control and irradiated mice became very significant. It may thus be concluded that there was no significant residual life shortening when only the non-neoplastic causes of death were considered. This conclusion which is partly at variance with the conclusions of the authors themselves is to be attributed, in Walburg's view [W1], to the use of a more refined analysis of the lethality data.

76. Darden et al. [D1] also reported data on RF/Un female mice exposed to graded doses of 14 MeV neutrons (dose rate 0.01–0.02 Gy/min). The mean age at death of animals surviving beyond 30 days decreased with increasing dose, with a maximum difference between control and irradiated animals being observed in the 4 Gy group and amounting to 151 days or 27% of the control life span. Life shortening per unit absorbed dose was an approximately constant or slowly decreasing function of dose up to about 2 Gy, but at higher doses the efficiency/Gy tended to decrease, as in the series by Upton [U7]. Tumour induction could not entirely explain the life shortening observed, although thymic and myeloid leukaemia could account for most of the increase in mortality in irradiated groups.

77. By the use of a radioprotective agent (WR-2721 or S-2(3-aminopropylamino) ethylphosphorothioic acid) which protects against acute mortality more efficiently than it does against the life-shortening effects of radiation, Yuhas [Y1] expanded the range of doses studied. The shapes of the dose-response relationships were consistently different for the two strains studied. In the A/J strain the curve was linear non-threshold at low doses and came to a plateau in the high dose range. In the C57BL/6J life shortening was curvilinear over the entire range of doses. It is impossible to assess whether the radioprotective treatment altered the actual shape of the dose-response relationship in ways and amounts different for the two strains used. Actually, if one considers the dose relations obtained at doses below the $LD_{50/30}$ without the use of the WR-2721, a certain amount of curvature can be seen in both sets of data, perhaps more pronounced in the C57BL/6J.

78. In a more recent experiment Grahn, Fry and Lea [G5] gave LAF1 hybrid mice of both sexes single exposures of ^{60}Co gamma rays in the range of 390 to 900 R. Mean after-survival showed a curvilinear trend with dose. The principal life-shortening effect was attributable to excess tumour mortality up to 390 R, while at higher exposures the loss of life expectancy was not paralleled by a further increase of tumour incidence. Walburg [W1] commented on these data and interpreted them to show that when the life-shortening effect is 15% or less of the control the increased mortality is entirely attributable to induction or acceleration of tumours.

79. Clapp et al. [C12] reported on a large-scale experiment on life shortening and disease incidence in RF/Un mice irradiated with 300 kVp x rays (0.5–4 Gy) and with 60 MeV protons (0.47–3.72 Gy). The data indicated a flattening of the dose-response curve at doses in excess of 2 Gy and a reasonably straight trend at the lower doses. When animals dying from thymic lymphoma and myeloid leukaemia (which were induced in up to about 40 and 25%, respectively, of the mice) were removed from the calculations, the mean survival time of the remaining animals still showed a decrease as a function of dose. Gompertz's analysis confirmed that removing the leukaemic animals did bring the death rate curve nearer and more parallel to the control line. The curves, however, did not superimpose except at doses below 1 Gy. Thus, not all of the observed life shortening, particularly at doses above the $LD_{50/30}$, can be explained by the induction of leukaemia, as in male RF animals. A possibility does remain (but was not examined in a more recent publication, [C15]) that ovarian tumours occurring in 50% or more of the animals might account for the extra life shortening remaining after subtraction of leukaemia.

80. In his 1975 review Walburg [W1] refers to data in the male RFM mouse exposed when 5–6 weeks old to a single acute treatment of 300 R of 300 kVp x rays. Routine histopathology allowed the assessment of causes of death with reasonable accuracy and the data were corrected for competing probabilities of death. The cumulative mortality curves for all causes showed significant life shortening; when deaths attributable to leukaemia were excluded the cumulative mortality curves of the control and of the irradiated mice became superimposable, suggesting that radiation did not significantly induce or accelerate under these conditions other non-specific causes of death.

81. Ainsworth et al. [A7] irradiated male and female B6CF1 mice with single doses of gamma rays (0.9 to 7.88 Gy) and found that life shortening had a reasonably linear dose-response. In the case of fission neutron irradiation, however, the shape of the dose-response curve (0.2–2.4 Gy) appeared to be convex upward. Possible explanations for this shape of the relationship were suggested. They will, however, remain unclear until the causes of death will be completely worked out. A paper updating these experiments confirmed essentially the above conclusions [T4].

82. Data of life-span shortening induced by single acute exposures of 250 kVp x rays (100 to 900 R) were obtained by Maisin et al. [M8] in the course of experiments on the effects of chemical protectors. Data refer to male BALB/c mice (4–12 weeks old) and to male C57B1 mice (1 to 3 months old, 350 and 650 R). In spite of the dose-square form of the relationships for tumour induction an essentially linear decrease of the life span with dose was found for the two sets of data: the numerical values are given in Table 1. Pathological observations in these experiments were evaluated by the method of competing risks [M10] with a classification of the causes of death comprising various forms of leukaemia and solid tumours, glomerulosclerosis, non-neoplastic lung lesions and others. In the non-irradiated BALB/c animals tumours were mainly responsible for deaths, while in the normal C57Bl mice

other non-neoplastic causes were observed in the majority of cases. An increased and advanced incidence of specific diseases, mainly thymic lymphoma, was associated with radiation-induced life shortening in the low-to-medium range of exposures. For higher doses in excess of the LD_{50} life shortening was instead characteristically associated with glomerulosclerosis.

83. Very extensive data on RFM and BALB/c mice were presented by Ullrich and Storer [A8] and Storer et al. [S44]. The effects of dose, dose rate and radiation quality on life shortening and carcinogenesis were examined. Caesium-137 gamma rays at 0.4–0.45 Gy/min and 0.083 Gy/day (0.1 to 4 Gy total doses) and fission neutrons at 0.05–0.25 Gy/min or 0.01 Gy/day (0.05 to 1.88 Gy total doses) were used. Dose-effect relationships for life shortening at high dose rates will be examined here. In the RFM females a dose-squared or linear-dose-squared model described the data adequately between zero and 0.5 Gy, with the dose-squared component predominating after about 0.04 Gy. The curve for RFM male animals was thought to be linear. High dose rate neutron curves in both RFM and BALB/c females were linear in the range of zero to 0.47 Gy, with an ensuing decrease of effectiveness which gave rise to an upward convex trend up to 2 Gy. No specific discussion was given of the contribution of particular diseases to life shortening.

84. Metalli et al. [M9] irradiated hybrid male mice of the $(C57BLxC3H)F_1$ strain (100 d old, 250 kVp x rays, 1 to 7 Gy). A dose of 9 Gy with bone marrow infusion from isogeneic donors or with shielding of one leg in order to overcome the early effects of radiation on survival was also used. These procedures did not appear to appreciably alter the long-term survival of the animals. The mean after-survival of the mice as a function of dose could be reasonably fitted by a linear function. These animals had a spontaneous incidence of about 55 to 60% of reticulum cell sarcoma. The incidence of this disease was still quite high at 4 Gy but fell gradually at higher doses to about 5 % at 9 Gy. On the contrary, the incidence of glomerulosclerosis (which is very low in normal animals) increased to about 70% after 9 Gy. Since life-span shortening versus dose could be fitted by a linear regression, in spite of such profound changes in the spectrum of induced diseases, linearity should probably be regarded as a fortuitous event. The data are in no way reconcilable with theories which postulate a non-specific aging effect.

85. Some data have also been reported about a very extensive study designed by Spalding et al. [S22] to investigate in the same experimental series the effect of dose, dose rate, age at exposure and genetic background for a variety of late effects, including life shortening, by ^{60}Co gamma rays in mice. Preliminary data on C57Bl/6J mice [S54] indicate that in this strain, which has normally a very low incidence of neoplastic diseases at death, radiation-induced life shortening is not statistically significant at all combinations of doses, dose rates and age tested.

2. Other species

86. There are a few data of single-dose irradiation of rats. Hursh et al. [H5] irradiated Wistar male and female animals with 250 kVp x rays in the range of 150 to 600 R. A decrease of the survival time roughly proportional to exposure was found. The per cent reduction of life span/100 R was between 4.2 and 4.9 for male and between 2.8 and 4.0 for female animals. Inspection of the data shows an approximate linearity of the experimental points, although the error is fairly large, as the various dose groups included a maximum of 24 animals each.

87. Wistar females surviving an acute whole-body exposure to hypoxic irradiation (250 kVp x rays, 1000 R) showed some life shortening compared to controls. Tumours appeared sooner in the irradiated animals but their final incidence was not increased. This early onset of neoplasia was best explained as one aspect of the accelerated aging process, although other diseases prevalent in old rats (cataract, acute inflammations, epilation, skin ulcerations) were also accelerated to a comparable degree [L3]. Nephrosclerosis in 46% of these animals and increased blood pressure (the two conditions being rather unrelated) were reported as pathological findings in another paper by the same group [L5]. Also in the rat (female Long-Evans-Wistar hybrid) life-span shortening was observed after acute whole-body x ray exposures (250 kVp at 55 R/min) of 120, 240 and 480 R. Under these conditions the efficiency of the treatment per unit dose was found to vary from 0.60 to 0.76 to 0.52, respectively, at the above-mentioned exposures [L4].

88. In experiments by Kimeldorf, Phillips and Jones [K8, K9] young adult male guinea-pigs from an SPF Hartley colony were exposed to a simulated fission spectrum of fast neutrons. The median life span of the controls was 828 days; of the 1 Gy-exposed animals, 730 days (12% reduction); of the survivors in the lethal dose range (1.2–1.6 Gy), 698 days (16% reduction). Both values of the median life span were significantly lower than control survival. In a related study [K9] young adult male rats (94 to 110 d of age) were treated with 2.15 to 2.3 Gy from the same neutron source. Although this dose was sublethal to the animals at 30 d, the median life span was reduced by about 22%. It was concluded that the dose range producing acute mortality in the guinea-pig is less effective in reducing life span than a sublethal dose in the rat. The reduction in median life span per unit dose is, however, comparable for the two species.

89. There are a few data obtained by Kohn and Guttman [K11] on the Chinese hamster. Although this animal is more resistant to the acute effects of irradiation than other rodents under similar conditions, the late effects tend to be more severe, at least judging from the life-span shortening. In fact, 5.5 Gy of x-ray whole-body exposure caused a loss of 32 weeks (corresponding to about 30%) of the life span remaining at the age of 230 days. At higher doses, for each increment of 1 Gy above 5.5 Gy and up to 9.5 Gy there is an additional approximately linear loss of life span of 20 weeks up to a per cent life-span reduction of 93%.

90. Hulse [H18] reported recently some data on rabbits exposed acutely to 4.4–14.1 Gy of gamma rays or to 1.8–5.5 Gy of fission neutrons. Although the irradiated animals died earlier than the non-irradiated controls, the difference was statistically significant only after the highest neutron doses. The earlier deaths could be accounted for by an increased incidence of tumours, of which a large spectrum was observed, while other phenomena associated with natural aging (particularly nephrosclerosis and teeth degeneration) were not changed or were even decreased after irradiation.

91. An experiment on the life span of 360 normal and irradiated female beagle dogs has been reported by Andersen and Rosenblatt [A2]. At 10–12 months of age the dogs were given single or fractionated 250 kVp x-ray treatments to a total of 100 or 300 R. All irradiated beagles had a shorter life span than controls. For single-dose treatments the life-span shortening relative to controls amounted to 9.5% and 20.7% in the 100 and 300 R groups, respectively. The average life-span shortening per 100 R amounted to 6.7%. Mortality rates were calculated for the last 6 years of life and the Gompertz slopes were found to be similar for all control and treated groups, except that the irradiated dogs attained higher rates of mortality earlier in life than controls. Major causes of death were tumours and chronic diseases (nephrosclerosis, heart failure, pancreatitis) with no obvious qualitative differences between control and irradiated animals. However, malignant neoplasms developed at an earlier age in irradiated dogs, thus accounting in large part for the life-span shortening.

92. The above data were reanalysed by Walburg [W1] by the method of Kaplan-Meier [K2] for competing causes of death, the analysis being limited to controls and to dogs exposed to 100 R, where sufficient numbers were available. For ages at death beyond 3000 days (an epidemic of canine distemper or a vitamin-E deficiency altered the pattern of early deaths to some extent) there was a significantly increased rate of mortality in the irradiated dogs with respect to normal animals. However, this increase disappeared when the neoplastic deaths were excluded from the comparison. Thus, in Walburg's opinion, the data are in accordance with the view that all the radiation-induced shortening of life seen at relatively low doses can be explained by induction or acceleration of neoplasia.

93. Experiments on life-span shortening in large animals were also carried out. In the burro irradiations with single and fractionated doses of gamma rays and with single doses of neutron-gamma radiation from the detonation of a nuclear weapon have been performed [B10]. Results on this series are not sufficiently advanced for any definite conclusion. In the cow, single and fractionated doses of gamma rays were also administered in April 1960 for a life-span study [N5] but the experiment was terminated in 1973. The relevant data are of no use for life-span shortening since more than half of the animals were still alive when the experiment was ended.

3. Data analysis

94. Most of the data pertaining to the effects of single acute doses of x and gamma rays in the mouse are summarized in Table 1 and are plotted together in Figure II which shows the percentage of life-span shortening as a function of dose. The data in the Figure refer to about 35 experimental series performed on about 20 strains of inbred, outbred of hybrid mice of both sexes and various ages, performed in various laboratories around the world since 1956. A large scatter of the experimental points would not be unexpected under such conditions and in fact the agreement among such very heterogeneous data appears rather surprising. The variability about each experimental point (which is available in many of the experiments, although not in all) has not been plotted as it would be expected to be accounted for in the variability between series and could not in any case be used to weigh the points in the analysis to follow. In order to avoid including animals dying from early radiation effects, mice surviving less than 60 days were excluded. The analysis was limited to doses of up to 900 rad and to corresponding maximum effects of about 60%. In order to standardize the abscissa dose scale a conversion factor of 1 R = 0.0095 Gy was used. The ordinate scale is the percentage of life-span shortening (calculated from mean or median values as they were available) by comparison with the life span of non-irradiated mice, irrespective of the duration of life of the normal animals or of the pathology at death.

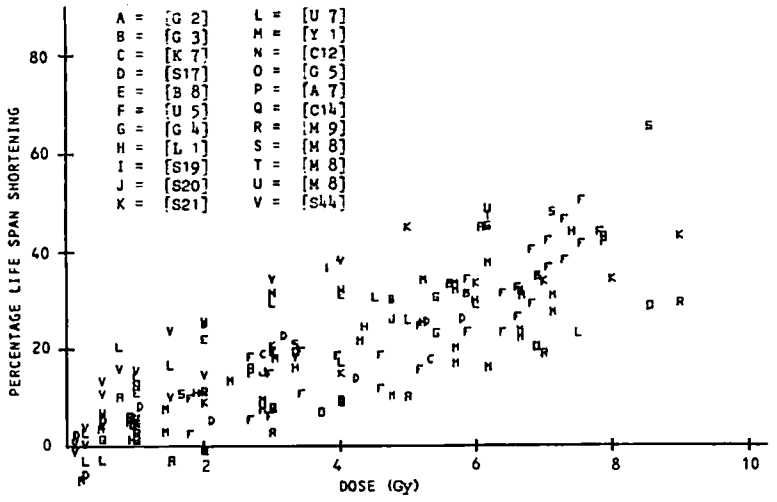


Figure II. Dose-effect relationship for life shortening in the male and female mouse following single acute exposure to x and gamma rays. Various experiments

95. The nature of the plot in Figure II is such that for very high doses a saturation of the effect must become manifest, although it may reasonably be assumed that within 50–60% no saturation might distort the plot. In the absence of any information as to the possible form of the dose-effect relationship a non-weighted linear regression was first interpolated to the data, according to the formula

$$y = a + b D \qquad (5)$$

where y is the percentage of life shortening, D is the dose and a and b are the coefficients of the regression.

The calculated least-square solution to the above equation was

$$y = (1.524 \pm 1.873) + (4.806 \pm 0.264)\, D \qquad (6)$$

and it gave an R^2 value of 0.747 implying a moderately good correlation. Although at inspection of the data a higher-order component was not clearly apparent, its existence could not be excluded and therefore the following relationship was also fitted

$$y = a + b\, D + c\, D^2 \qquad (7)$$

which yielded the following solution

$$y = (0.853 \pm 1.989) + (5.639 \pm 0.120)\, D - \\ - (0.115 \pm 0.020)\, D^2 \qquad (8)$$

The R^2 of this fit was 0.749.

96. The data obtained in the mouse by neutron irradiation (see Table 2) were similarly plotted on a common graph as in Figure III which includes doses up to about

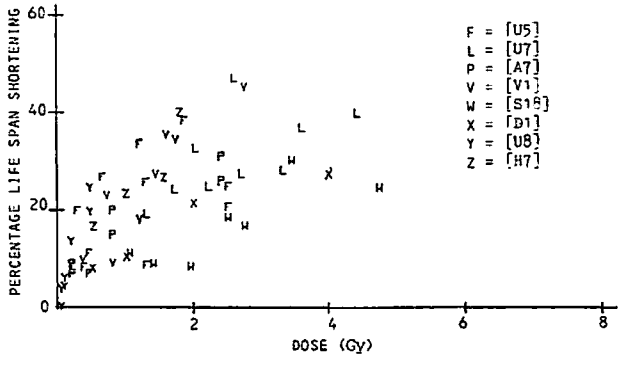


Figure III. Dose-effect relationship for life shortening in the male and female mouse following single acute exposure to fast neutrons. Various experiments

5 Gy and life-span-shortening effects up to about 50% of normal. Only the results with monoenergetic-, fission- and weapon-neutrons delivered acutely were included, for a total of 14 series and 4 different strains of mice. Inspection of the data makes it immediately apparent that the nature of the dose-relationship is in this case quite different from that observed with x and gamma rays. This impression is confirmed when the following equations are fitted to the data with the following results

$$y = a + bD \qquad y = (6.896 \pm 3.082) + (8.107 \pm 0.200)\, D \\ (R^2 = 0.565) \qquad (9)$$

$$y = a + bD + cD^2 \qquad y = (3.044 \pm 2.799) + \\ + (17.885 \pm 0.521)\, D - (2.731 \pm 0.202)\, D^2 \\ (R^2 = 0.683) \qquad (10)$$

Clearly, none of these two relationships provides a satisfactory interpolation to the neutron data, because the first fails to show the initial steep rise and the second shows a maximum of effect between 3 and 4 Gy and bends down rapidly towards lower values. This effect is difficult to interpret. The following relationship was also fitted [K10]

$$y = a + b\sqrt{D} \qquad (11)$$

and it yielded the following solution

$$y = (1.289 \pm 3.022) + (17.140 \pm 0.204)\sqrt{D} \\ (R^2 = 0.694) \qquad (12)$$

The square-root relationship seems to fit the data fairly well as it adequately describes the increase of effect seen at very low doses of neutrons and the ensuing levelling-off of the data for doses up to 5 Gy, along a slope roughly parallel to the slope of the low-LET radiation dose relationship.

4. Conclusions

97. In conclusion, data are not available in the mouse for x or gamma rays below 0.1 Gy and the scatter of the experimental points is such that for doses below about 1 Gy apparent life lengthening (rather than life shortening) may be found, depending on the variability of the control and irradiated groups of animals. Although errors affecting the above numerical constants must be fairly large under the conditions of the analysis performed, the life-shortening data for the mouse may follow a linear non-threshold relationship as a function of the x- and gamma-ray acute dose, indicating a life-shortening efficiency of about 5% per Gy down to the smallest doses. The data may, however, also be fitted by a linear-quadratic function, where the quadratic term is negligible and thus does not give rise to an appreciably different relationship within the errors of such an analysis or give rise to substantially different quantitative conclusions.

98. Analysis of the data in the various experimental series and an inspection of Table 1 makes it quite obvious that in any given instance the dose-effect relationship for life shortening may be linear or curvilinear (with upper concavity or convexity). The actual shape of any such curve depends on the interplay of the biological variables (strain, sex, age) with dose, which results in a different spectrum of life-shortening diseases or pathological conditions at the various doses. The observation that the combination of a variety of experiments produces a linear relationship cannot therefore be considered to depend on any particular biophysical law, at this stage of the analysis. It may simply reflect the fact that when all experimental conditions and all the resulting life-shortening effects are averaged over a number of different series, they combine by chance to produce an approximate linear relationship with dose. Therefore, taken as such, this observation may have no special meaning in the interpretation of the life-shortening action, but may be regarded as a very interesting observation in practice. It shows, in fact, that in a highly non-homogeneous mammalian population where all ages, sexes and strains are represented, the use of a linear function to describe the dose-effect relationship for acute exposures to x and gamma rays is not unreasonable.

99. Under the conditions of the present analysis, the neutron data at the energies available are best described by a relationship having a convex upward trend with dose, such that the efficiency of low neutron doses is higher than that of higher doses. The numerical value of this higher efficiency will be discussed in section II.D. It should be again stressed that there is no fundamental biophysical reason why the shape of the neutron curve is of the form roughly described by the above equations, as the same observations pointed out before for the x- and gamma-ray data can be expected to apply to the neutrons as well. However, the form of the neutron relationship is curvilinear (convex upward)

within a range of effects where a linear function applies to low-LET relationships. As saturation phenomena with respect to the expression of the biological damage may not be expected under such conditions, the only way to interpret the neutron data is to assume that the shape of the relationship reflects some primary biophysical difference in the mode of action of low- and high-LET radiation, particularly at the low doses.

100. The effects of single acute exposures of low-LET radiation on animals other than the mouse are summarized in Figure IV, in comparison with all the

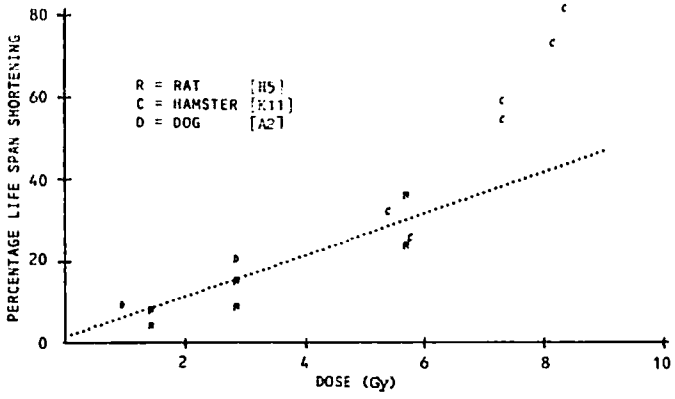


Figure IV. Dose-effect data for life shortening in various mammalian species following acute single exposure to x and gamma rays, compared with the response of the mouse. The dotted line is the best fit to the data for the mouse in Figure II, as in equation (6). Various experiments

mouse data. On inspection, no large differences may be traced from the small series reported in the literature. This is particularly true for the data for the rat, that are well superimposable up to 5 Gy with the mouse response. The effect on the dog has only been examined at relatively low doses and the data are perhaps on the high side of the data for the mouse. The Chinese hamster, on the contrary, has only been examined at doses in excess of 5 Gy and the data are suggestive of a concave upward trend. Among the species tested, however, the variability of the response is apparently rather small.

B. THE EFFECT OF CONTINUOUS LIFE-TIME IRRADIATION

101. The "duration-of-life" exposure condition has been used since the very beginning and is documented in the early papers of Henshaw [H1], Evans [E2], Lorenz et al. [L6] and Boche [B11]. It has been widely utilized in the experimental series of Sacher and Grahn [S4] who have largely contributed to the interpretation of this type of data and is still in use [N6, N7]. In case of internal irradiation from radionuclides of long half-life it is the only possible irradiation condition. Exposure for the entire life represents a base-line condition of irradiation useful for comparison with other exposure types such as the acute single-dose. In this respect it has the advantage of mimicking an exposure pattern which is of most practical interest. Research workers [G1, G6] have pointed out other advantages, such as the linearity of the relationship between the log mean after-survival of the animals and the daily exposure level. That property may facilitate the description of the effect and justify comparisons between various animal species or various types of radiation.

102. On the contrary, others believe that the terminated exposure technique, rather than the exposure to death may be more apt to give unbiased answers. Based on evidence from irradiated DBA mice, Mole [M6] examined the concept of what he called "wasted radiation" for exposure to death, that is, the amount of radiation administered in excess of that strictly required to kill the animals. Mole showed that under some conditions of exposure the wasted radiation amounted to over one-half of the mean accumulated dose. This implied that the duration-of-life exposure condition was unsuitable to establish precise dose-time relationships for life shortening. Actually, the mean accumulated dose would have been overestimated on account of the wasted radiation and the mean survival time would have been put in doubt by the fact that each specific biological response to radiation might have taken a different and characteristic time to develop. According to Mole [M6], for these reasons it is preferable to use terminated exposure conditions.

103. The concept of wasted radiation was used by many research workers, although often without much experimental basis, to account for data that could not otherwise be explained. The concept stems from the notion that each specific disease or pathologic condition has a latency time between induction and clinical manifestation; there is also more time intervening between the appearance of the disease and its development to a lethal condition. The biological arguments underlying the concept of wasted radiation are well founded but there are different views as to the practical importance of this concept as the amount of wasted radiation appears to be either negligible [L7] or very substantial [M6] under different experimental conditions. Sacher and Grahn [S4], Grahn and Sacher [G1] and Sacher [S23] have repeatedly criticized the concept of wasted radiation pointing out that it does not lend itself to any easily testable implications. In their opinion, there are changes in the effectiveness of a given dose with an increase of the protraction time (see section I.C.) and under appropriate circumstances these changes may at least in part be interpreted as being due to an effect of wasted radiation. According to Grahn and Sacher [G1] this concept is contradicted for rather high doses and short survival times (the concept was actually derived from experiments at 200 to 25 R per day and on the $LD_{50/30}$ end-point); but for long protraction periods the idea would be unjustified as no amount of radiation may be considered as truly wasted.

104. In continuous exposure until death, time and dose cannot be experimentally separated from each other. Thus, it becomes difficult to isolate the dose that would have been given in excess of the minimum required to kill the animal within a given time from an end-point such as the life-span shortening, which is measured in units of time. An additional difficulty lies in the nature of the biological event of death which is a final end-point in survival experiments, whereas in experiments on tumour induction, for example, it is possible to account in part for the wasted radiation by computing the dose absorbed at the tissue of interest up to the time of the first appearance of the tumour or to some such extrapolated time [F3, M11, M12].

105. It is natural therefore that, in spite of its wide acceptance, specific work to experimentally test the concept of wasted radiation has not been very extensive. In fact, this concept has a shortcoming in the difficulty of its experimental analysis and in the precise evaluation of its importance under each specified experimental condition. There appears to be little hope that these problems will be settled in the near future. Any conclusion concerning the relevance of this notion in the interpretation of radiobiological experiments in animals or, more so, in human radiation biology must remain open for the time being.

106. The available evidence of the biological effects of chronic radiation exposure for the whole life of the animals is reviewed in the following. This field has been reassessed at various times, among others, by UNSCEAR [U1], by Sacher and Grahn [S4], Grahn and Sacher [G1], Grahn [G6], Sacher [S14]. The reader is referred to those contributions for more extensive coverage of the subject. The life-shortening effects of incorporated radioisotopes are considered in a separate subsection.

1. Mouse

107. All known experiments on irradiation for the duration of life [H1, H6, H7, E2, B11, L6, L8, S2, N3] were reviewed by Mole in 1957 [M13] and his paper was made a part of the 1958 report of the Committee [U1]. Only 5 of 11 known reports (see [M13] for a complete list of references) contained sufficient details for the reconstruction of a curve showing the decrease of the mean survival time versus the dose per week. Fast-neutron as well as gamma-ray data were plotted together with the dose scales in the ratio of 1 to 13 (see Figure XIV). The agreement of the experimental series was, at least for the mouse, surprisingly good and exposure levels of 10 R per week or higher of gamma rays shortened the mouse life in a reproducible manner. There were eight experimental estimates at weekly exposures of less than 10 R (or its neutron equivalent) and in none of them the duration of life was significantly different from the respective control value. Taken at face value, these data suggested therefore an apparent threshold at dose rates below 10 R per week or its neutron equivalents.

108. Moos et al. [M14] and Yusken et al. [Y2] carried out experiments on CFW mice of both sexes, individually caged and irradiated with 400 kVp x rays at daily exposures of 2 to 512 R. The survival time of the mice decreased as the daily dose increased but the decline was not very rapid up to 8 R per day. Exposure of up to 4 R per day allowed the animals to accumulate 600 to 1400 R before one-half of the mice died. About 2900 R of accumulated radiation was given at 16 or 32 R per day. In a subsequent paper Moos [M15] tested the possible existence of a threshold in the same mice. He showed that variability of the control population and of the animals receiving 2 R per day was the same or could not be resolved statistically and concluded for a continuous effect of life-span reduction down to the smallest dose rates tested.

109. Of particular interest to the problem of life-time irradiation are the data by Sacher and Grahn [S4] on more than 5000 LAF1 male and female mice given ^{60}Co gamma-ray exposure starting from the age of 100 days. These data represent up to the present the most complete and exhaustive experimental series on this subject. The exposure levels used were 36, ranging from 5 to 200 000 R per day and corresponding mean survival times from about 500 days to 6 hours. The daily exposures between 5 and 2500 R (giving mean after survival times of 5 or more days) were delivered during 12 or 15 hours per day; higher daily doses were given almost continuously. Dosimetry was particularly accurate and fully discussed.

110. Survival data were analysed by an empirical function of survival time and dose rate, the cumulant lethality function, C_L, defined as

$$C_L(t^*) = \frac{1}{I}\left(1 - \frac{t^*}{t_o}\right) \qquad (13)$$

where I is the daily exposure in R, t^* is the mean after-survival at dose rate I and t_o the mean after-survival of controls. The first derivative of this function, called the impulse lethality function, S_L, allowed the identification of four distinct phases of injury with peaks at 0.5, 5, 13 and 40 days and these times could be related to different modes of injury to the nervous system, the intestinal epithelium, the leukopoietic and the erythropoietic marrow, respectively (see Figure V). A plot of the log mean after-survival versus the daily dose was found to be very nearly linear for mean after-survivals in excess of 60 days. This procedure allowed the assessment of life-shortening coefficients with small uncertainties. The paper by Sacher and Grahn [S4] contains a full discussion of the mathematical formalism underlying the cumulative lethality functions. This represents an advancement in the identification of the phenomenology of radiation injury and lethality.

111. Lesher et al. [L9] reported on the pathology of these animals, in an attempt to establish the cause of death. The daily exposures of 5 and 12 R per day were considerably more carcinogenic than higher exposure rates, and the lower carcinogenic efficiency of the higher dose rates was tentatively attributed either to the earlier death of the more heavily irradiated animals or perhaps to a "therapeutic" effect on the potentially transformed cells as the dose rate increased. It was found, in general, that the duration-of-life exposure yielded fewer tumours per R of accumulated exposure than single or terminated irradiation regimes. Tumours of the genital tract and a higher incidence of lymphoma were responsible for the much higher tumour incidence in female mice. Furthermore, some diseases were accelerated in the irradiated mice and some were not.

112. Sacher and Trucco [S13] analysed a model for mammalian radiation lethality and recovery, which was essentially based on the kinetic characteristics of self-renewing cell populations. The model assumes that

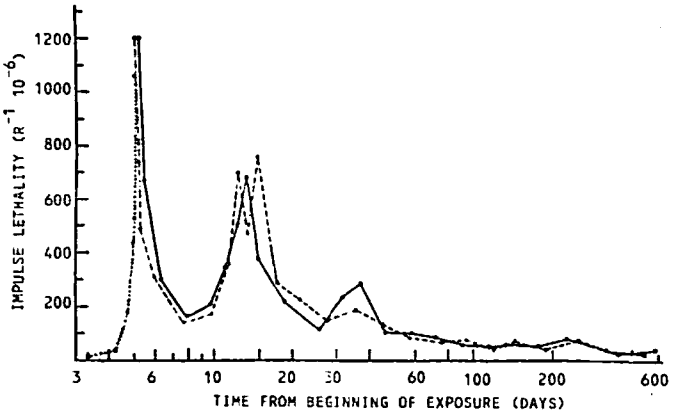


Figure V. A plot of the impulse lethality function versus time from the beginning of exposure in duration-of-life experiments. The data are for LAF1 male (solid line) and female (broken line) mice exposed to cobalt-60 gamma radiation at exposures from 5 to 200 000 R d^{-1}. Data from Sacher and Grahn [S4]

population growth proceeds at a rate proportional to cell number but that growth is constrained, so that each cell population attains a given stationary size. The rate of growth is therefore the product of two terms, one of which is a monotonic function of the size of the population and the other is a function of the difference between actual size and limiting size at any given time. Based on these simple assumptions Sacher and Trucco produced a complex phenomenological theory which was applied to radiation data on survival after split doses, multiple fractionation and protracted continuous exposure and showed some qualitative agreement between the curves obtained experimentally and those predicted by the model. However, the formulation of this theory is not sufficiently developed and may be regarded as a first attempt towards a more comprehensive treatment.

113. In another paper Sacher, Grahn, Fry et al. [S5] examined the late consequences of gamma-radiation with respect to two major categories of effects: the incidence of tumours of the reticular tissue and the life shortening induced by all causes other than the reticular tumours. The data were obtained from male and female mice of four different genotypes exposed in duration-of-life experiments (^{60}Co gamma rays, 0.3 to 56 R per day). In agreement with that observed on the LAF1 mouse [S4] the data showed that the log mean after-survival plotted as a function of the daily dose followed a very nearly straight line.

114. The Gompertz transforms of these data (see Figure VI) for all causes of death were slightly convex upward and formed a fan of lines of increasing slope with increasing dose rate with small differences between genotypes. When the cumulative incidence of four tumour types (reticular, pulmonary, hepatomas, ovarian), summed over the four genotypes was plotted as a function of daily dose, three tumours showed a modest increase in incidence with a peak at 6 R per day or less followed by a sharp decline. Reticular tumours, on the contrary, rose to a peak between 24 and 32 R per day and then showed a sharp decline at higher daily dosages. This phenomenon was explained in terms of the hypothesis put forward by Gray [G7] which postulates two phenomena (induction and cell killing) acting together but with different dose dependencies in the relevant target cell populations.

115. In the experiments under discussion [S5] the log mortality rate data for all causes except leukaemia plotted as a function of age indicated in the BCF1 mouse a linear rise at all daily dose levels. The slopes of these lines increased with increasing dose levels to form a fan of lines intersecting with the control slope at 100 days, at which time exposure began (see Figure VII A). These slopes plotted on a semi-logarithmic scale as a function of the exposure rate (R per day) gave linear

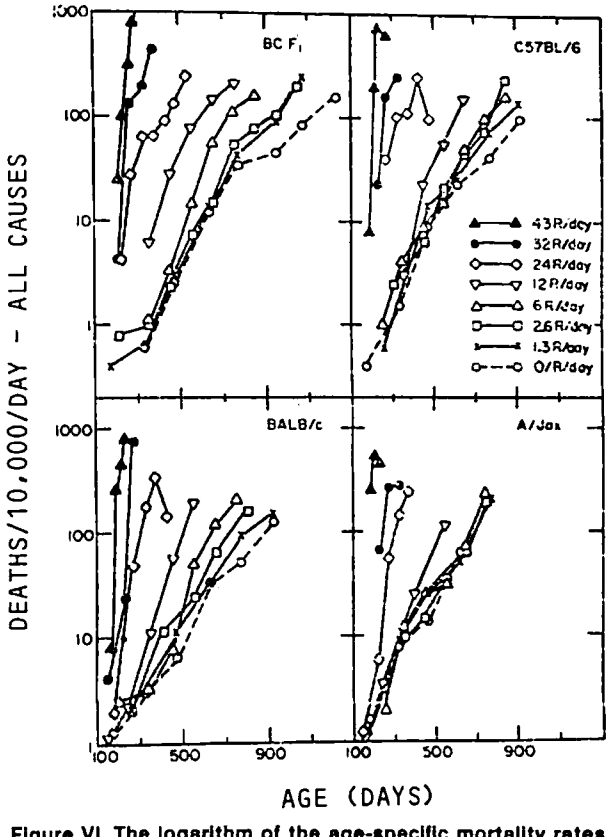
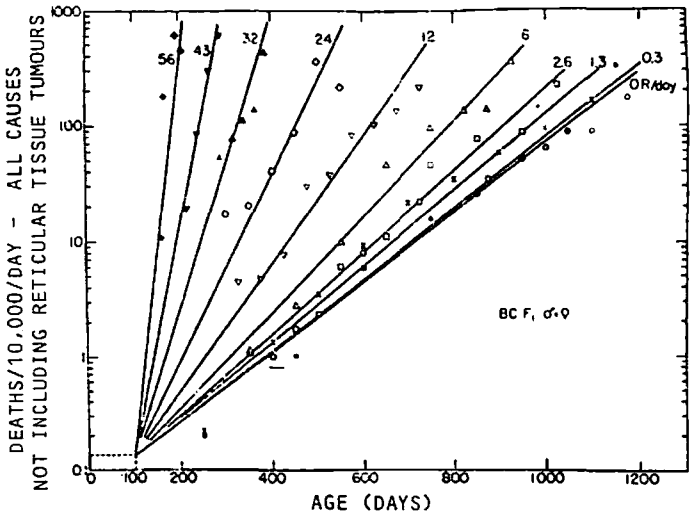


Figure VI. The logarithm of the age-specific mortality rates for all causes of death (Gompertz transform) in mice of four different genotypes (BCF1, C57BL/6, BALB/c, A/Jax) plotted as a function of age. Mice were irradiated in duration-of-life experiments at the exposure rates shown. Data from Sacher, Grahn, Fry et al. [S5]

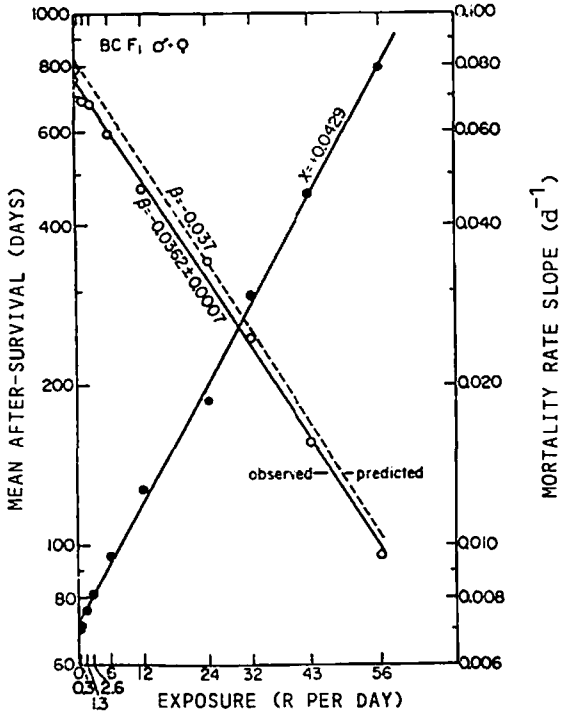
relationships and thus justified the conclusion that the slope of the Gompertz lines increases exponentially with daily dose (see Figure VII B). Finally, this paper [S5] has interesting aspects concerning the cellular mechanisms of life shortening because it provides some link between phenomena at the whole-body level and at the cell population level.

PANEL A



The logarithm of the age-specific mortality rate (Gompertz transform) for all causes of death except leukaemia in BCF1 mice of both sexes irradiated in duration-of-life experiments at the exposure rates shown. Straight lines were fitted by least squares through the control incidence at 100 days of age when the exposure began.

PANEL B



Plots of the Mean After Survival (MAS, open circles) and of the slope of the Gompertz transform (closed circles) versus exposure level. Data are for BCF1 mice of both sexes, as in panel A. The dashed line is that predicted by MAS from the estimated Gompertz slopes in order to show the consistency of the relationships. The lines were fitted by least squares analysis.

Figure VII. Changes of the Gompertz transform as a function of exposure rate in duration-of-life experiments [S5]

116. Another paper by Grahn, Fry and Lea [G5] summarized a number of studies on various strains of young adult mice exposed to various levels of ^{60}Co gamma radiation ranging from 0.3 to over 30 R per day and discussed the problem of a "non-specific" life-shortening effect as opposed to a "specific" effect, that is the induction of neoplasia. Data from mouse strains BALB/c, C57BL/6 and their F_1 hybrid show a steady increment of mortality associated with neoplastic disease upon irradiation as the age increases and the daily exposure increases up to a few R per day. An excess mortality from non-neoplastic conditions with respect to controls was seen only at 6 R per day and above. Thus, the risk of early or excess death from radiation exposure at intensities of the order of 100 or 200 times the background is related entirely to the

increase in incidence and to the shift in the time of appearance of the neoplastic diseases.

117. Sacher [S14] pointed out that when the slope of the Gompertz curves obtained at various daily doses is plotted as a function of the daily dose on a double logarithmic scale for two mouse strains, the LAF1 [S4] and BCF1 [S5], the resulting relationship can be resolved into two straight lines (Figure VIII). At

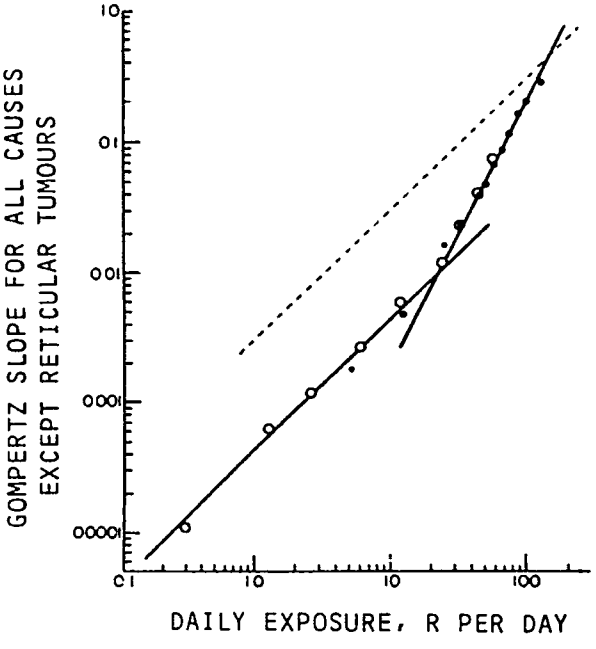


Figure VIII. A plot of life shortening to daily exposure for mice treated with life-time gamma-ray exposure. Life shortening is measured by the increase of slope of the Gompertz function in irradiated as compared to control populations. Open circles refer to BCF1 and closed circles to LAF1 mice. The dashed line corresponds to the inferred relationship for single exposures with constant effectiveness per roentgen of $0.003\,R^{-1}$. Data from Sacher [S14]

exposure rates below 24 R per day the data lie close to a first-power trend while above this value they conform closely to a second-power trend. At about 24 R per day the contribution of the two terms is equal.

118. New data were recently reported [T5] on the life shortening in $B6CF_1$ mice given weekly exposures to ^{60}Co gamma rays (0.07, 0.174 or 0.319 Gy per weekly fraction) or to 0.85 MeV fission neutrons (0.0067, 0.0167 or 0.0267 Gy per weekly fraction) either for 60 exposures or for the duration of life. The amount of life shortening produced by the life-long or by the terminated exposure regimes was essentially identical, so that the two series were analysed as a single experiment. The data are generally in good agreement with those reported from other laboratories.

2. Other species

119. One hundred day-old male and female guinea-pigs were started on a fractionated course of radiation (^{60}Co gamma rays) for the entire duration of life [R2]. Together with a number of control animals, groups receiving 1.35 R, once or four times a week; 2.6 R, 5 times a week; 6.0 R, 4 times a week; 24 R, once a week; 6 R, 6 times a week; were included for a total of 344 animals. The relationship of the log mean after-survival time against the weekly exposure in R was approximately linear and the life-shortening coefficient came to about 0.06 days/R, in close agreement with the data of Lorenz et al. [L6]. At 5.4 R per week a paradoxical early decrease of mortality was noted in males for which no explanation could be given. Fatty degeneration of the liver, chronic kidney diseases, spleen amyloidosis and various tumours were noted in the animals in no obvious correlation with life-span shortening.

120. The survival of goats was followed by Hupp et al. [H8] and by Hupp [H9] for groups of 11–12 animals for each sex submitted to chronic ^{60}Co gamma-ray exposure (3, 7, 15, 30 and 40 R/20 hour day). Great individual variability was observed in the survival time at all except the highest exposure level. The lethality pattern observed was quite different from that of mice and rats. Females exhibited little exposure rate response in the range of 7–40 R per day, while males accumulated the maximum exposure at 7 R per day. Rats and mice, on the contrary, accumulate maximum exposures at 30–50 R per day [G6].

121. Casarett [C16] reported briefly on the survival data of dogs (1000 kVp x rays, 5 days per week at daily exposures of 0.06, 0.12 and 0.6 R per day beginning at 21 months of age). The accumulated exposures at death in these three groups varied between 122 and 257 R; between 243 and 465 R; and between 1088 and 2198 R, respectively. Average ages at death were 13.8, 13.2 and 12.3 years, respectively, the control age being 13.0 years. Median death age was 13.1 years in the control and 14.1, 13.8 and 12.7 years in the irradiation groups, respectively. In addition to these groups, a similar fractionation scheme was applied in other groups, giving 3 R per day in 10 minutes for 5 days per week for a total of 25, 32 and 42 weeks. Two other groups received 300 and 375 R whole-body at rates of 10 and 64 R per minute, respectively. For these latter groups no survival data were reported. More recent data for the dog are also to be found in [N7] (see subsection II.A.1).

3. Data analysis

122. The effect of life shortening induced by continuous exposure may be analysed as a function of the dose rate of the treatment or against the total dose received (at the various dose rates) from the beginning of exposure to death. There is enough data for the mouse to examine both types of dependencies and to attempt some descriptive analysis.

123. Figure IX shows the percentage life shortening induced at various dose rates. All data available for various strains and sexes have been grouped, separately for the cases of neutron and of low-LET radiations. The graph therefore includes all the variability expressed in these experiments. The data by Moos et al. [M14, M15], although qualitatively following a similar trend, have quite different quantitative relationships and cannot be considered with the other series. The x- and gamma-ray data include seven different series performed on five strains of male and female mice; the neutron data include seven series on four strains and both sexes.

124. The nature of the plot in Figure IX is such that the low dose rate end of the abscissa is greatly expanded. Sigmoid relationships of the type

$$y = 100\,(1 - e^{-\alpha A}) \qquad (14)$$

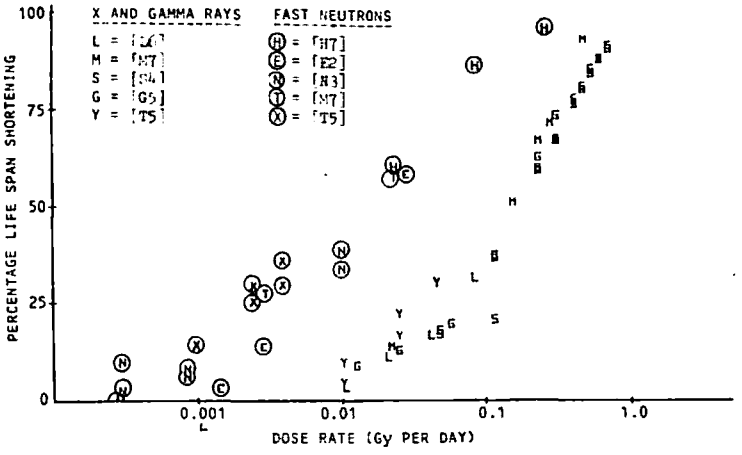


Figure IX. The relationships between dose rate and the life-shortening effect following duration-of-life exposures to fast neutrons and low-LET radiation in the male and female mouse. Various experiments

where A is the dose rate in Gy per day, may reasonably be fitted to the data. When a non-weighted curve was fitted to the data by a least-square method, the solutions were, in case of the low-LET radiation

$$y = 100\,(1 - e^{-3.89\,A}) \qquad (15)$$

and in the case of neutron irradiation

$$y = 100\,(1 - e^{-44.14\,A}) \qquad (16)$$

By inspection, the above relationships interpolate the low-LET data quite adequately, but fail to properly follow the fairly high effect seen at the very low doses of neutrons and the tendency of the x-ray and neutron data to merge in the high dose region of the graph. The relationship

$$y = 100\,(1 - e^{-a\sqrt{A}}) \qquad (17)$$

which fits the neutron data with the following values

$$y = 100\,(1 - e^{-5.078\sqrt{A}}) \qquad (18)$$

seemed more adequate for that purpose.

125. Another analysis is one where the percentage life shortening is plotted versus the dose accumulated at the various dose rates under duration-of-life exposure. Data obtained in the experimental series shown in Figure IX are plotted separately for the x and gamma ray and for the neutron series in Figure X. For

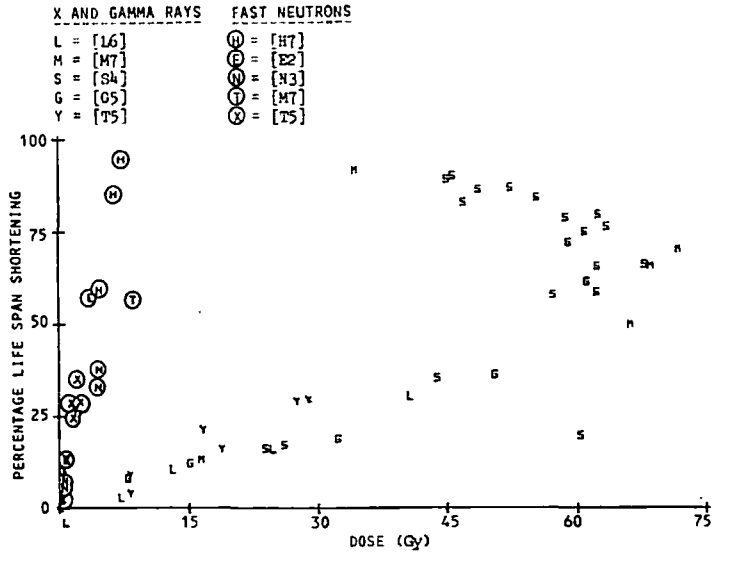


Figure X. Relationship between the total accumulated doses of fast neutrons and low-LET radiation in the male and female mouse, following exposure for the duration of life. Various experiments

increasing doses the life-shortening effect of low-LET radiation also increases in an apparently linear fashion at low doses and then with a progressively accentuated upper concavity to doses of about 60 Gy administered for the duration of life at dose rates of about 0.2 Gy per day.

126. At higher dose rates the life shortening continues to increase but, owing to the progressive reduction of life span, the accumulated dose decreases and the curve bends backwards towards the origin. Such an effect was previously described by Lorenz et al. [L6] and may be predicted by the theories of Blair [B5] and Sacher [S1]. Although this observation is not immediately apparent from Figure X, all along the curve the data obtained at approximately similar dose rates are reasonably well clustered together. This immediately points to a relationship between the three quantities under study in the graph: dose, dose rate and life-shortening effect.

127. In order to describe the data with a maximum of precision, an attempt was made to fit a curve where the three quantities cited would all contribute to determine the final shape of the relationship. The following

equation was assumed to reasonably interpolate the data

$$y = b\,D\,e^{cA} \qquad (19)$$

where y is the percentage of life-span shortening; D the dose and A the dose rate; b and c are proportionality constants. Such a relationship cannot be adequately fitted in the absence of some function relating dose and dose rate. In order to find such a function the simplifying assumption of an exponential decrease of the life span with increasing dose rate was made for any given total absorbed dose

$$T = T_0\,e^{-A/A_0} \qquad (20)$$

Since the total absorbed dose is the product of the duration of life and the dose rate

$$D = A\,T \qquad (21)$$

it follows that

$$D = A\,T_0\,e^{-A/A_0} \qquad (22)$$

A plot of total absorbed dose versus dose rate for data belonging to the same experiments in Figure IX was found to agree reasonably well with an expression of the above type. Therefore, the previous relationship was fitted to the experimental data, yielding

$$D = 698.81\,A\,e^{-3.687\,A} \qquad (R^2 = 0.97) \qquad (23)$$

128. By the use of the above relationship a fit of the experimental data was then attempted with optimization of the various parameters to achieve the minimum square deviations. The experimental points from the fitted curve gave the following solution

$$y = 0.7253\,D\,e^{1.469\,A} \qquad (24)$$

in which the functional relationship between A and D is given by the above expression (equation 23). Figure XI

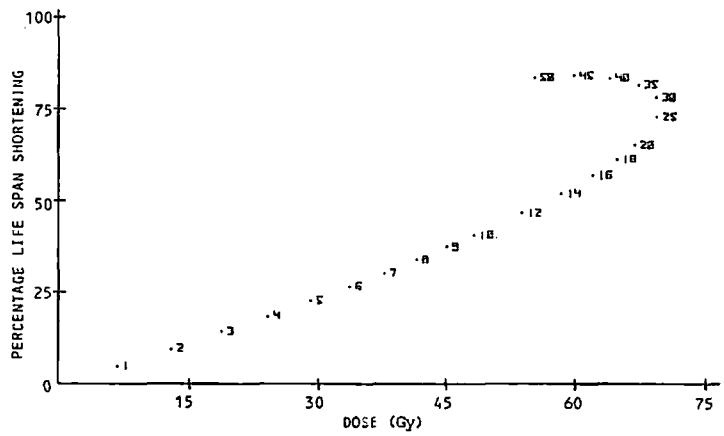


Figure XI. Best fit of the low-LET radiation data in Figure X. The numbers in the body of the graph are the dose rates (10^{-2} Gy per day) at which the doses specified in the abscissa are cumulated during the entire life of the animals

represents the best fit to the experimental data in Figure X and provides for each dose (in the abscissa) the percentage of life shortening to be expected (on the ordinate) at the dose rates (in Gy^{-2} per day) specified at the various points along the fitted curve in the body of the graph.

129. The neutron data in Figure X deserve separate mention because for them the very characteristic trend of the x- and gamma-ray data in duration-of-life experiments has not been verified. On the contrary, the data available may point to a continuously increasing effect of life-span shortening without any inflection in the trend. The data are too few and too scattered to establish with certainty such a difference in shape. It may be speculated that the effectiveness of the neutron treatment in duration-of-life experiments is so high compared with x and gamma ray that the bending of the curve is not possible in view of the short life of the irradiated animals. But it should also be noted that the experimental points in excess of about 60% of life shortening (where the curvature becomes apparent with the low-LET radiation) are only two of the same series and therefore insufficient to confirm a difference of shape. In any case, the point is of little practical significance because the doses involved are extremely high.

4. Conclusions

130. In duration-of-life experiments the variables "time" and "dose" are linked and difficult to resolve experimentally. Data in the mouse were analysed by the Committee as a function of the dose rate and showed an increasing life-shortening effect following an exponential function of the dose rate, up to a maximum of 1 Gy per day. Neutrons appeared to be more effective in causing life shortening, particularly at dose rates of 0.001 Gy per day or less.

131. When analysed as a function of total cumulated dose, life shortening appeared to be induced according to a linear trend up to doses of 30 Gy of x or gamma rays. The percentage life shortening then followed a curve with a progressively accentuated upper concavity up to 60 Gy administered for the whole life at dose rates of about 0.2 Gy per day. At still higher dose rates life shortening continues to increase. However, as the animals have a shorter life, the dose accumulated decreases and the dose-effect relationship bends towards the origin. The same trend for the neutrons cannot be precisely established for lack of data.

132. It is of great interest to examine the change of effectiveness observed in the mouse between the single acute and the extremely low dose rate data. If the linear term with dose of the single acute exposure (about 5% life lost for 1 Gy) is divided by the slope of the curve for duration-of-life exposure obtained at, for example, a dose rate of 0.01 Gy per day (total dose about 7 Gy) the efficiency is lower by a factor of about 7. In the case of neutrons the experimental results show in some cases increased life shortening after increasing the exposure

time. But until further work clarifies the situation a precise comparison of acute and low dose rate data is not justified.

133. The guinea-pig, the goat and dog were also exposed for the duration of life and revealed differences from the mouse. The differences are related to the sensitivity of the various species to haemopoietic death or, more precisely, to the dose rate level at which the susceptibility of the bone-marrow becomes the main cause of life shortening. The guinea-pig was consistently more sensitive in two experimental series; goats showed differences between the two sexes and an increased response with respect to the mouse. There was evidence that the bending point of the curve as a function of dose (see Figures X and XI) may occur at dose rates consistently lower than in the mouse, so that the maximum dose that this animal may accumulate in duration-of-life experiments occurs at less than 10 R per day, as compared to the 20–40 R per day applying to the mouse. The qualitative response of the dog might be similar to that of the mouse, since the dependencies on the dose of the life-shortening effect change when haemopoietic or non-haemopoietic mechanisms influence survival. Quantitatively, the primary mechanisms of death might be neoplastic non-haemopoietic or possibly degenerative at dose rates below about 0.035 Gy per day, while in the mouse the relevant figure would be in the region of 0.2 Gy per day.

5. Internal irradiation

134. Irradiation by injected, ingested or inhaled radionuclides is a special form of localized chronic treatment which is worth considering in relation to its effects on the life span of contaminated animals and to the existence of any non-neoplastic life-shortening effect. Finkel, Biskis and Schribner [F5] examined the effect of ^{90}Sr in CF1 female mice injected at 70 days of age with nine acute doses between 1.3 and 8.1 Bq/kg. The same data with a more extended range of doses were also reported by Finkel and Biskis [F3] and made the object of a comparative analysis of life-span shortening and incidence of neoplasms. When plotted against dose, life-span shortening and bone sarcoma induction were not linear over the whole dose range observed. Life-span shortening and tumour induction appeared to be equally sensitive indicators of radiation damage. There was a good correspondence between life shortening and tumour induction up to a dose of 3.3 10^7 Bq/kg but at still higher doses, in spite of a decreased incidence of the bone tumours, life span further decreased.

135. Finkel's [F5] data were further analysed by Mays and Lloyd [M11]. Mice dying with bone sarcoma had a median life span from injection to death which decreased rather regularly with increasing average skeletal dose, owing to a shorter latency time of the bone sarcoma incidence at higher doses. An effect of life shortening induced by single injections of ^{90}Sr (3.7 10^4 or 7.4 10^3 Bq/g) was also described by Van Putten and De Vries [V2] on (CBAxC57BL)F1 hybrid female mice and these data plotted as the percentage of the control life span were rather close to those of Finkel et al. [F5].

136. Similar observations can be made regarding the data on rats by Moskalev, Streltsova and Buldakov [M16] as re-analysed by Mays and Lloyd [M11], since the average time from injection to death tended to increase as the dose decreased from 1.9 10^7 to 1.9 10^2 Bq kg^{-1}. A dose-related life-span shortening was reported by Brooks et al. [B12] in hamster injected with ^{90}Sr (7.4 to 185 10^3 Bq). The 50% survival times ranged from 90 days with 7.4 10^4 Bq g^{-1} to 1100 days at 7.4 10^3 Bq g^{-1}. In this species, however, myeloproliferative diseases rather than osteosarcoma were the most common pathological conditions observed.

137. Another bone seeker, ^{45}Ca, was studied in single injections by Finkel et al. [F5], and their data were analysed again by Mays and Lloyd [M11]. They were able to show that median survival time from injection to death in mice dying with bone sarcoma declined with increasing dose owing to a progressively early appearance of the bone tumours.

138. Sarcoma incidence in the bone tissue and life-span shortening were evaluated as a function of dose, dose rate and time in beagle dogs fed from mid-gestation to 1.5 years of age a diet containing ^{90}Sr [M17]. Under these conditions the observed life-span shortening was attributed mostly to radiation-induced tumours. Also, in the same paper a reduction of the delay time in the appearance of bone sarcoma with increasing activities administered was reported in dogs. The same observation was true for the same species in the experiments of Burikina [B13], thus confirming that a shortening of the induction period for tumours (giving rise to a shorter life span of the tumour-bearing animals) holds true also in the case of chronic uptake of the nuclide.

139. There is some information regarding bone-seeking alpha-emitters. In a further analysis by Mays and Lloyd [M12] of data on single injections of ^{239}Pu in CF1 female mice by Finkel and Biskis [F3, F6] a progressive decrease of the average survival from injection to death (for mice living beyond 200 days post-injection) was seen at increasing skeletal dose, even when the incidence of bone tumours at doses in excess of 11.5 10^4 Bq kg^{-1} decreased, rather than increased. At these very high doses there may of course be some question about how much a non-specific life-span shortening might have contributed to the observed decrease of the percentage tumour incidence.

140. Shortening of the latency interval of tumours induced by ^{239}Pu injection in rats was also shown by Bensted et al. [B14]. But in the same species chronic administration of ^{239}Pu—in spite of an increased incidence of osteosarcoma, leukaemia and marrow aplasia—was reported to produce minimal changes in the life span of the treated animals [B15].

141. The life shortening observed in dogs carrying osteosarcomas induced by various injected bone-seeking radionuclides (^{239}Pu, ^{228}Th, ^{228}Ra, ^{226}Ra, ^{90}Sr) were calculated by Dougherty and Mays [D5]. The accumulated skeletal doses up to one year before death were computed and used as the independent variable. In all tumour-bearing animal groups and for all nuclides tested the log of the time from injection to death was a linear function of the log average skeletal dose. Thus, not only was the average life span reduced by the appearance of bone tumours (whose incidence is a function of dose) but a further reduction of the life span was seen in tumour-bearing animals by the earlier appearance of tumours at higher doses. Based on life-span shortening, the approximate efficiency of the various nuclides relative to ^{226}Ra (taken equal to one) was $^{239}Pu = 6$; $^{228}Th = 8$; $^{228}Ra = 2.5$; $^{90}Sr = 0.07$ to

0.24. These differences could best be interpreted by taking account of the local site of energy absorption and of the type of radiation. The surface-seeking alpha emitters are substantially more effective than the volume-seekers.

142. In 1970 Eyring and Stover [E1] examined the life-span shortening from internal irradiation by ^{239}Pu and ^{226}Ra reported for beagle dog experiments [M18, S24, J1] making use of the steady-state theory of mutation rates [S15, S51]. They fitted cumulative survival curves as a function of the average skeletal dose accumulated by groups of dogs injected when young adults with various doses. There was a high correlation between the mean survival time and tumour induction with the average skeletal dose. The log of the dose was proportional to the 50% survival time and the experimental data followed two quite unrelated slopes at low and at high doses of injected ^{226}Ra. In the case of ^{239}Pu, on the contrary, the 50% survival times followed a linear function of dose at the low doses.

143. The analysis of life shortening was also extended to ^{228}Ra, ^{228}Th and ^{90}Sr in subsequent publications [S25, S26]. When the percentage of osteosarcoma induction was plotted against the percentage of the life shortening produced by each dose level of each nuclide, a life shortening of 60% was obtained when the tumour incidence reached 100%. At high dose levels the degree of life shortening was similar for all five nuclides but this similarity was not maintained at the lower dose levels. In the case of ^{239}Pu the incidence of osteosarcoma greatly exceeded the control incidence even at the lowest dose level where no life shortening relative to controls was apparent. In the case of ^{226}Ra progressive life shortening was seen at skeletal doses in excess of 21.2 Gy, where the occurrence of osteosarcoma was between 92 and 100% but practically no life shortening was found at skeletal doses between about 3.7 and 9.5 Gy, although sarcoma incidence in these groups was 10 to 20% and 42%, respectively.

144. From an analysis of data on young beagles injected with single intravenous doses of ^{252}Cf, ^{249}Cf, ^{241}Am, ^{238}Pu, ^{228}Th, ^{228}Ra, ^{226}Ra and ^{90}Sr Mays and Dougherty [M18] concluded that all or virtually all of the life-shortening effect observed at medium and at low doses of the nuclides is attributable to radiation-induced bone sarcoma. Thus, the thesis that the induction of neoplasia is responsible for all of the life shortening observed in the low-dose range of the experiments available was also confirmed for the case of a medium size mammal injected with a variety of bone-seeking radionuclides.

145. In the field of inhaled alpha emitters an experimental study in rats treated with ^{238}Pu, ^{239}Pu and ^{241}Am given as oxides or nitrates was reported [M19]. Survival time of the animals and latency time, frequency, location and histotype of the tumours were analysed as a function of the dose rate and of the dose distribution. An acceleration of tumour induction time (and therefore of after-survival time) with increasing dose and the existence of a non-neoplastic life shortening at high doses were also apparent. Similar findings were also obtained in dogs inhaling ^{239}Pu by Bair [B16] and by Park [P1].

146. In conclusion, a large variety of injected, ingested or inhaled radionuclides have been studied for their capacity to induce life shortening. The largest body of experimental evidence is for bone-seeking beta emitters (^{90}Sr and ^{45}Ca) or alpha emitters (^{226}Ra, ^{228}Ra, ^{228}Th, ^{238}Pu, ^{239}Pu, ^{241}Am, ^{249}Cf and ^{252}Cf) administered to different animal species under a variety of routes, doses and dosages. Very good correlations were generally found between life shortening and induction of bone tumours, thus justifying the conclusion that whatever reduction of life is apparent from the experiment it may entirely or almost entirely be explained by tumour induction or acceleration, except at extremely high doses where aspecific mechanisms of death may produce short-term mortality. This conclusion is very clear-cut and not surprising, as selective partial-body exposure is the mechanism operating in case of internal irradiation and, under these conditions, non-specific damage to the whole body cannot be expected. The data are therefore not strictly comparable to those from whole-body irradiation and the above conclusions carry little weight in respect to the problem of life-shortening specificity.

6. Uncommon findings

147. In some experiments involving life-time irradiation [L6] low doses of radiation led to an increase, rather than to a decrease, of the expectation of life. Here mice were exposed to 0.11 R of gamma rays daily. Although the increase was not statistically significant, it was confirmed in a subsequent test where differences between groups concerning the air conditioning and the temperature of the animal quarters made comparisons difficult. Sacher and Grahn (reported by [S3]) also noted no harmful affect of 5 R per day in three different strains of mice, following cumulative exposure to about 2500 R. Yuhas [Y3] reported life-span lengthening when old mice (15, 18 and 24 months of age) were exposed to 10 fractions of 140 R given over 12 days, whereas the same amount of radiation administered to 4 and 9 month old animals produced some life shortening. Similar observations were made repeatedly after relatively low single doses [G2, U7, S17, E3], as may be deduced from Figure II.

148. In addition to the above cases, life prolongation has also been reported following the interaction of suboptimal ambient temperatures and low radiation doses. Carlson et al. [C21] exposed male Sprague-Dawley rats at 25°C and 5°C to ^{60}Co gamma-irradiation for 8 hours per day during one year. The animals were caged individually and a parallel control group was run at each temperature. The dosimetry was such that the animals in the room at 25°C received from 38 to 96 mR per 24 hour-day and the exposed ones 895–931 mR per 8 hour-day. In the room at 5°C the respective dose rates were: control, 42–149; irradiated, 897–966. Oxygen consumption, food consumption, body weight and metabolism were checked routinely. The irradiated animals at both 5°C and 25°C lived over 20% longer than their respective non-irradiated controls, the half-lives observed were: at 5°C, control 240 days, irradiated 305 days; at 25°C, control 460 days, irradiated 600 days. No explanation was offered for this observation, except the suggestion that a mild injury might result in apparently beneficial effect by stimulation of cell and tissue repair and repopulation processes.

149. Trujillo et al. [T1] reported that RF/Un female mice showed a linear decrease with increasing age in their ability to withstand a standard cold stress (6°C to 7°C for 14 days). Mice exposed to protracted ^{60}Co gamma-ray exposure at 0.5 Gy per day and then

allowed to recover for 90 days showed a similar linear decrease with increasing radiation exposure in their ability to withstand the same cold stress. This radiation-induced effect was considered similar to life shortening by natural aging and was equivalent to 9.3 days per Gy.

150. In a rather more elaborate set-up Carlson and Jackson [C22] studied the interaction among radiation and high temperature. The animals were divided into 8 groups of 22 rats each, individually caged. Four of them were kept at 28°C and exposed to 0.29, 0.64, 2.60 and 4.18 R per day over a period from 4 to 16 months of age. The other four groups were kept at 35°C for the same length of time and exposed to 0.28, 0.60, 2.57 and 3.96 R per day. The age at which 50% of the irradiated animals died increased with increasing dose at all dose levels tested, with good statistical significance of the data, except for two points. It was suggested that ionizing radiation may have interacted with the environment in increasing longevity by stimulation of the repair processes. These experiments [C21, C22] are noteworthy, not only because they show an interaction between radiation and ambient temperature, but also for the finding that radiation in the region of 4 R per day or lower has (at all temperatures tested) increased, rather than decreased, survival. As to the first point, the observation has so far remained without confirmation; concerning the second one, it should be mentioned that Bustad et al. [B17] working on individually caged mice within the same exposure range but at normal ambient temperature could not confirm the data of Carlson. The problem therefore remains unsolved, as the different species or environmental conditions might have been responsible for the negative observations of Bustad.

151. Following the formulation of a theory on the statistical nature of mortality by Sacher [S2] and by Sacher and Trucco [S12] in which the death of an organism is viewed as a random event arising from the fluctuating nature of its physiological performance, these authors proposed [S32] a modification of the theory that makes it possible to account for the paradoxical observations described. Radiation (particularly at low doses) induces a decreased fluctuation of the signalling and control systems of physiological processes. As a result, the probability of a large fluctuation leading to an irreversible change is decreased. In essence, the decreased variability among the exposed compared to among the control animals, is the main effect of the irradiation and the improved survival at relatively low doses results from it as an occasional consequence.

152. The above model may provide a phenomenological explanation of life-lengthening effects in actuarial terms, but the intimate mechanisms through which such effects may be brought about are still unknown. Data showing stimulation of antibody formation [D10, L19], increase in phagocytic activity and lysosome content [T3] and activation of reparative enzymes by relatively low radiation doses [K24, V8] can, in principle, be cited in this respect, but their general applicability cannot be decided at present.

153. Biological variability of the control and experimental animal groups and long-term changes of the baseline reference values may have been responsible for at least some of the above observations and these cases should probably be viewed separately from the others in which interplay of environmental factors led to the phenomena under discussion. Kuzin [K24] considered that an increased resistance of the animals brought about by unfavourable environmental conditions may have been responsible for life span prolongation.

C. DOSE RATE, DOSE FRACTIONATION, PROTRACTED EXPOSURES

154. Results of other experiments are available in which radiations of different types were given at various dose rates in chronic terminated or in fractionated exposures to animals of various species. The experiments were sometimes made to examine the effect of a given regime of chronic terminated exposure. In other instances, the experiments were carried out to study changes in the dose rate; and in other cases in order to compare the effects of splitting a single dose into fractions separated by various time intervals. In all of these experiments the interplay of dose-time parameters is extremely variable and the final effect may be expected to be intermediate between the two extremes of the single or of the duration-of-life exposure. It is difficult and somewhat arbitrary to separate all this work into various chapters: however, the following will separately consider the effect of dose rate, of dose fractionation and of protracted exposure, in an attempt to draw more systematic conclusions about the different radiobiological variables. The effect on life span of the distribution in time of low-LET radiation has been discussed in [N14].

1. Dose rate

155. The papers where dose rate was examined as a separate variable in acute exposures or in the course of chronic terminated experiments are very few and all on mice. Vogel, Frigerio and Jordan [V1] reported that between 10 and 44 mGy min^{-1} of fission neutrons the effect on life span was independent of dose rate, although there was dependence for gamma rays in the range of 10 to 130 mGy min^{-1}. The efficiency of the treatment was lower at low dose rate. The experiments were performed on CF1 female mice irradiated with 13 brief daily exposures. In another series the mice were irradiated with single neutron exposures at 80 mGy min^{-1} or 2 mGy min^{-1} (0.36–1.74 Gy total dose). Survival did not differ within the above dose rates.

156. Vogel and Jordan [V3, V4] irradiated the same mice with fission neutrons and gamma rays (10 to 350 mGy min^{-1}). Four weekly doses of 2 Gy per week of ^{60}Co gamma or 1 Gy per week of neutrons were employed, delivered at variable dose rates. For both radiations, the lower the dose rate, the longer the life span of the animals. Lindop and Rotblat [L10] reported on the changes in effectiveness (expressed in weeks of life shortening per Gy) as a function of the dose rate at the extremely high intensities of 0.77 to 1580 Gy min^{-1}. They showed that the maximum effectiveness (5.7 to 6.2 weeks Gy^{-1}) was at around 10 Gy min^{-1}, but could not explain the loss of effectiveness at still higher dose rates. Oxygen depletion induced by these high intensities could not have been responsible for such an effect, as it was also seen in mice made artificially hypoxic.

157. Upton, Randolph and Conklin [U7] and Upton, Randolph and Darden [U10] used variable dose rates of gamma rays (0.8–0.01 Gy d^{-1}) or of fast neutrons (110 to 0.04 mGy d^{-1}) to induce life shortening on RF/Un male and female mice (total doses of 100 and 10 Gy,

respectively). In females, a consistent reduction of the gamma-ray effectiveness was seen at the lowest intensities, amounting to about a factor of 3, by comparison with acutely-delivered (0.067 or 0.8 Gy min^{-1}) doses. A further reduction to a factor of 6 was observed if continuous irradiation was carried out to the time of death of about 50% of the animals. For neutrons, loss of efficiency of continuous against acute administration was 0.9 and decreased further to 0.7 for exposures protracted to death of 50% of the mice. In male animals, the loss of efficiency of the gamma rays was even higher, amounting to 0.1 upon continuous administration and to 0.04 for irradiation protracted up to 50% survival.

158. Spalding et al. [S21] performed experiments on RF female mice irradiated with gamma rays (0.025 to 2.5 Gy h^{-1}, 1 to 12 Gy total dose). Within a given total dose the mean after-survival was changed more or less randomly with the dose rate. Biological and environmental factors such as individual variations in radiosensitivity and cage effects rather than any identifiable physical parameter were held responsible for these observations. Dose rate studies (gamma rays, 1 to 1000 Gy min^{-1}, 1 to 3 Gy weekly exposure for a substantial duration of the life span) were also reported by Willhoit and Wiggins [W5]. Some decreased effect at the lower dose rates was noted, but it was impossible to attribute the effect to any specific disease, owing to the lack of pathology.

159. In the experiments of Ullrich and Storer [U8] and Storer et al. [S44] on RF and BALB/c female mice lowering the dose rate of gamma rays led to a modification of the shape of the dose-effect relationship in the range 0.5 to 4 Gy from a very complex pattern at 0.45 Gy min^{-1} to a nearly linear shape at 0.083 Gy d^{-1}. The large difference in effectiveness was related to an upward displacement of the regression line in the 0 to 0.5 Gy range in the high dose rate groups. BALB/c females showed a similar trend, in that the 0.5 Gy dose point was displaced upward in the high intensity curve, suggesting a dose rate dependent injury component which saturated at high dose rates at about 0.5 Gy, similar to the one identified by Sacher [S2] in female mice given 2 Gy or more. The response to neutron irradiation of high (0.25 Gy min^{-1}) or intermediate (0.01 mGy d^{-1}) dose rate was somewhat different. In RFM mice the low dose rate was less effective at 0.24 Gy but more effective at 1.88 Gy than the high dose rate. In BALB/c mice little dose rate dependence was seen at low doses but at 1.88 Gy the low intensity was more effective. The results are somewhat less clear at lower doses.

2. Dose fractionation

160. The experiments reported in this subsection were performed by splitting a given dose or a series of doses into two or more fractions, irrespective of the time over which the total dose was administered. The dose per fraction, the fractionation interval and the total time to complete the course of irradiation are variables that interact to produce the final effect. They cannot be separated from each other under most of the experimental conditions used. Often the comparison is therefore between a dose given in a single treatment and the same dose over a very protracted course of fractionation. Only seldom is the accuracy of the data such that numerical protraction factors can be derived with the necessary degree of precision.

161. Sacher [S2] performed experiments on the life-shortening effect in the mouse of 400, 800 and 1200 R given in equal fractions 5 day/week over 2 or 8 weeks. The life shortening of mice dying from causes other than lymphoma decreased with increasing number of fractions, even though the effect of leukaemia induction increased by fractionation, as reported for the C57BL mouse by Kaplan and Brown [K12]. The dose fractionation experiments performed by Curtis and Gebhard in 1958 [C17] with fission spectrum neutrons and 250 kVp x rays in CF1 female mice did not show any change in effectiveness upon fractionation but the authors recognized the peculiarity of this finding and attributed it to the use of fairly large doses. In their opinion, the recovery rate from such doses would be essentially different in the x-ray and neutron groups, as compared to the recovery from small fractional doses.

162. Survival and leukaemia incidence were studied in RF male mice irradiated with 250 kVp x rays by Upton, Wolff, Furth et al. [U11]. After 150 R given in a single exposure the life span was 15.6 months and it increased to 16.3 and 16.5 months when this same exposure was split into two 75 R fractions and given 2 and 6 days apart, respectively. Similarly, 450 R given in a single treatment or in 3 equal fractions at 2 or 5 days interval changed survival from 10.3 to 10.8 to 11.1 months, respectively. These changes are small and of dubious significance, in spite of the relatively high number of mice per group. They could be attributed to changes in the incidence of reticular tissue tumours which are by far the largest part of the causes of death in this strain, particularly after irradiation.

163. Mole [M1, M20, M21] reported that when 1000 R of x rays were delivered in 10 daily fractions of 100 R the mean survival time was shortened by 10% with respect to controls. When the same total exposure was delivered in 100 fractions of 10 R each the mean survival time was shortened by 37%. Thus, spreading a given dose over a longer time would apparently increase the amount of damage. The same result was obtained on CBA mice when 750 R were given in a single dose or spread out over several weeks. In this case fractionation induced a change in the shape of the age-mortality curve and of the age-specific mortality rates owing to the appearance of more leukaemia deaths after the protracted than after the single exposure. It seems possible therefore that the important factor in this case might have been a change in the spectrum of the induced diseases rather than the fractionation per se.

164. Cole et al. [C18] examined in the LAF1 mouse the influence of 250 kVp x-ray fractionation. The incidence of leukaemia was increased significantly when 690 R were subdivided into 2, 4 or 8 equal fractions separated by 8 weeks, 19 days or 8 days, respectively. Irradiation shortened survival time in all groups, but the largest decrement was seen in mice receiving 8 exposures of 85 R, an effect which would be contrary to expectation if leukaemia had not specifically shortened survival in this case. In contrast, observations on nephrosclerosis showed a decreased incidence of this disease with fractionation from more than 50% in the mice receiving the single exposure to less than 10% in the group receiving eight fractions. Therefore, in these experiments nephrosclerosis was regarded as being mainly responsible for early death after the single dose, whereas malignancies specifically accounted for more than half of the deaths in the fractionation groups.

165. According to Vogel, Frigerio and Jordan [V1] fractionating 2.75 Gy of neutrons into 3, 4 or 10 separate daily exposures did not result in any significant difference of the mean survival time of CF1 female mice. Kohn and Guttman [K6] studied the effect of 520 R of 250 kVp x rays given as a single exposure or in two fractions administered 8 days apart on male and female CAF1 mice. Specifically with respect to the effect of fractionation, here again the results were unclear in showing any significant improvement in survival.

166. Vogel and Jordan [V5] examined on CF1 female mice the effect of fractionating a weekly dose (3 Gy of ^{60}Co gamma rays or 0.6 Gy of fission neutrons) into 1, 3 or 6 equal dose fractions per week. Both radiations were delivered at approximately 0.01 mGy min^{-1} and the treatments were continued for a total of 13 consecutive weeks, so that the mice were exposed to almost 40 Gy of gamma rays or 7.8 Gy of neutrons. The mean survival times of the gamma-irradiated mice were not significantly different whether they were exposed 1 or 3 times per week. There was some indication that a further dilution of the dose to 6 fractions per week might increase survival but the significance of the data could be questioned. No indication of a sparing effect of fractionation was, however, found in the neutron-irradiated mice.

167. Silini and Metalli [S27] showed in a small experimental series that survival time could be increased by a schedule of fractionation where a conditioning dose of 1.5 Gy was followed by 3.5 Gy given at 7 time intervals between zero and 48 hours. A positive regression of the data amounting to an 8% increase in survival time was detected. The kinetics of the phenomenon followed a pattern reminiscent of the short-term intracellular type of recovery described in cultured cells by Elkind and collaborators [E4].

168. Grahn and Sacher [G1] tested the effects of 450 and 750 R of ^{60}Co gamma-radiation delivered as single exposures or in two equal fractions separated by increasing time intervals from 3 hours to 28 days. The regression of survival time versus fractionation interval was negative in 3 out of 4 cases (2 doses x 2 sexes) but none of the regressions were significantly different from zero. The incidence of leukaemia was not consistently modified by fractionation and this disease was not specifically associated with life shortening, in contrast to results of other studies [G4, U11].

169. Ainsworth et al. [A7] reported that fractionation of a gamma dose of 8.38 Gy into 24 doses of 0.35 Gy administered over 23 weeks produced a "sparing effect" by approximately three-fold. On the contrary, a similar regime of fractionation with fission spectrum neutrons increased life shortening. This is a rather unusual observation in fractionation experiments, but it is in agreement with the theoretical expectation when the single-dose curve is, as in the case at hand, convex upward [R13]. Histopathological observations on pulmonary tumours could not explain all of the increased mortality resulting from neutron dose fractionation. Tentative explanations were offered, based on the differential acceleration of the lung tumour appearance or on the differential killing of potentially transformed cells in the lung. A more recent report [T4] confirmed the same conclusions in regard to the actuarial analysis but did not provide pathological data useful for their interpretation.

170. Storer et al. [S44] exposed RFM and BALB/c mice to 7 weekly doses of fission neutrons of 0.067 Gy (total 0.47 Gy) or to 0.235 Gy once every 4 weeks for 28 weeks (total 1.88 Gy). Animals exposed to a fractionated dose of 0.47 Gy had a life span not different from those given single high dose rate exposures or exposures at 0.01 mGy d^{-1}. BALB/c animals receiving 1.88 Gy had a survival time significantly shorter than that following a single exposure. RFM animals given fractionated treatment up to 1.88 Gy experienced the same survival as after single exposure and a significantly longer survival than following exposure at 0.01 Gy d^{-1}. It was concluded that the cause of death may critically determine the effectiveness of the fractionated exposure, although the authors were unable to provide an explanation for their observations.

171. Data on the effect of dose fractionation on life shortening were described by Hursh et al. [H5] in the Wistar male rat irradiated with x rays. Information on x-ray dose fractionation was also reported in the same animal species by Lamson, Billings and Gambino [L4, L11]. Increasing the number of fractions from 1 to 3 to 6 for the same total exposures of 120, 240, 480 R caused an increase of life span, compared to the same exposure in one fraction. The effect was dose-dependent in that it could be seen at the two higher exposures. Spacing of the fractions at intervals of 3, 5, 7 or 14 days did not influence longevity. It was concluded that fractionation after exposure in the 1 to 6 fraction range led to 30–46% of the sparing effect obtained by halving the total exposure in the 0 to 446 R exposure range.

172. In the Wistar rat Reincke et al. [R3] examined the effects on tumour frequency and life-span shortening of two different fractionation regimes of whole-body x-irradiation (300 R in 3 exposures over 2 months or 10 R in 90 exposures at daily intervals) and compared these regimes between themselves and with control non-irradiated rats. No significant differences in the overall incidence of tumours or on tumour types were observed. The average survival times were 20 and 25 months, respectively. Tumour induction rates and death rates were not different between the two groups, but some differences became apparent when age-specific rates due to neoplastic and non-neoplastic causes were compared. In general, all radiation effects were more pronounced in the group receiving 300 R x 3. There was no complete summation of the effects of the single doses and recovery processes were more effective after small daily exposures than after greater radiation exposures given at longer intervals.

173. Various schedules of fractionation as well as single exposures to 250 kV x rays were given to female beagle dogs by Andersen and Rosenblatt [A2]. For total exposures of 100 or 300 R, 4 equal fractions or 2 equal fractions given at 7, 14 and 28 days interval were administered. In general, differences between subgroups receiving fractionated exposures were apparent only in groups totalling 300 R. In these animals life shortening was increased when the total treatment time increased from 7 to 84 days. It was estimated that the decrease in life shortening produced by 300 R would be reduced from 23 to 10% as treatment time increased from 7 to 84 days.

3. Protracted exposures

174. The papers discussed in this subsection pertain to chronic exposures carried out with different radiations

on various animals. The heterogeneity of this work does not detract from the quality of some of the contributions in which many important conditions such as the protraction of dose administration or the duration of exposure (and therefore the cumulated total doses) are the variables under examination. The common feature is that in all cases exposures were terminated before a substantial part of the animals died, thus allowing estimates of the survival parameters under conditions in which the "wasted radiation" component was not effective.

175. The early contributions of Evans [E2] and Lorenz et al. [L6] are only cited here for completeness. The paper of Mole and Thomas [M7] is a systematic investigation of life shortening in CBA mice by changing the duration of exposure to daily irradiation of ^{60}Co gamma rays or of fast neutrons (mean energy 0.7 MeV). In the case of gamma irradiation, weekly exposures of 350, 210, 110 and 16 R for progressively longer times (4 to 30 weeks) and for the duration of life were tested. For neutrons, 0.16 or 0.02 Gy per week for 5 to 60 weeks or for the duration of life were the conditions tested. For both radiations, as the duration of exposure to a given daily dose (and therefore the total dose) increased, the mean survival time decreased. However, beyond a given point a further increase of exposure time and total dose produced no further effect. The lower the daily dose, the more survival time became independent of the total dose or of exposure time. The minimum dose or exposure time required to produce a maximum life-shortening effect could only be approximated. The shape of the cumulative mortality curves depended systematically on the particular level of daily dose and on the duration of the exposure, except possibly at the lowest daily doses. A summary of these data is given in Figure XII.

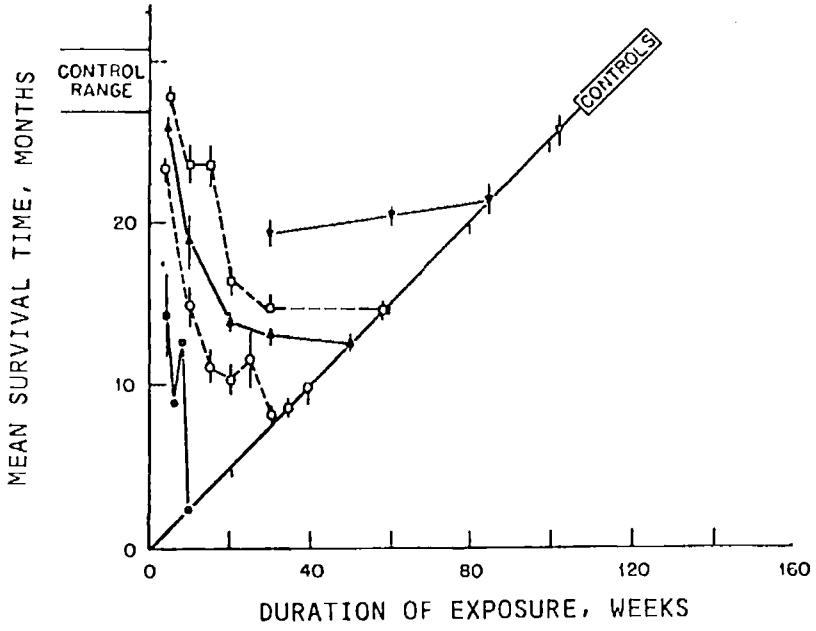


Figure XII. Mean survival times of female CBA mice after chronic terminated and duration-of-life exposures to gamma rays and fast neutrons. The nominal weekly exposures are: gamma rays, ● 350 R, O 210 R, □ 110 R, ▽ 16 R; fast neutrons, ▲ 0.16 Gy, ▼ 0.02 Gy. In duration-of-life experiments the mean survival time equals the mean length of exposure and therefore all points for such exposures must lie on the diagonal slope 1, as shown. Vertical bars show the range of mean survival time in various groups of control mice. Data from Mole and Thomas [M7]

176. Mole's paper [M7] contains, in addition to valuable experimental observations, a number of interesting points for discussion. Some pertain to the concepts of reparable and irreparable injury. Other points concern the problem of controlling and assessing biological variability in long-term experiments and here data are given for a discussion of the secular changes of the life span of the controls. Another observation relates to the presence of discontinuities in the response to chronic irradiation generated by biologically different modes of death. Data on the effect of acute versus chronic irradiation were also reported in the mouse by Curtis, Tilley and Crowley [C19] and are discussed elsewhere.

177. In the series by Bustad et al. [B17] hybrid (C57BLx101) mice were exposed for 8 hours daily from the age of 6 to the age of 58 weeks (that is for one year) to 0.1 R h^{-1} or 0.2 R h^{-1} of ^{60}Co gamma radiation. The cumulated total exposures were 290 and 480 R, respectively, after which the animals were taken out of the radiation field and followed for the rest of their life. Although the treatment did produce some differences in the average pattern of growth and longevity, in most instances these differences were found to be small relative to the variability of the normal samples.

178. Grahn, Fry and Lea [G5] also discussed the effect of protraction on mortality, showing that the risk of death from all and from specific causes is quite different if compared to acute exposure. Their data on LAF1 mice show that leukaemia death rate is reduced by a factor of 5 or more for daily exposure levels below 20–30 R d^{-1}. Data on all causes of death other than leukaemia show also a protraction factor which takes up different values (from 2 to 5) as the exposure rate decreases from 40 to 50 R d^{-1} to 12 or less R d^{-1}.

179. Spalding et al. [S28] exposed 13 groups of adult female RF mice to ^{60}Co gamma rays at about 0.028 Gy h^{-1} until a predetermined dose (from 4.57 to about 0.03 Gy) had been accumulated. As doses increased, there

was no accompanying increase of life shortening because any dose had about the same effect, amounting to an average of 83 days reduction of life. Assuming a linear relationship with dose in the range 0 to 0.47 Gy, the effect would be about 18 days per Gy, a value which is on the low side of those usually found for low-LET radiation (see Table 1).

180. The contribution of Russ and Scott [R1] on the rat should only be mentioned for historical reasons. Boche [B11] refers to some experiments in which rabbits received one year of treatment at daily exposures of 0.1, 0.5, 1.0 and 10.0 R. Life shortening was shown in various ways. Similar treatments were also given to a few dogs and when the experiments were conducted with irradiation for only a fraction of the life time at dosages below 1 R d^{-1} no effect on survival was noted. This was also true for monkeys.

181. The paper by Fritz et al. [F7] on the beagle dog is an attempt to clarify time-dose relationships after terminated chronic exposure to ^{60}Co gamma rays. Four exposure rates (5, 10, 17, 35 R d^{-1}) were used and the dogs (354 in total) were removed and allowed to die of natural death after total exposures of 600, 1400, 2000 and 4000 R. The experiment is still in progress but the provisional data are sufficient for a few tentative conclusions, as follows. The LD_{50} increased from 2.58 Gy delivered at 15 R min^{-1} to about 30 Gy at 10 R d^{-1}. Over this range of exposures the leading cause of death was haemopoietic damage. At 5 R d^{-1} or lower no definite LD_{50} could be determined: the haemopoietic function continued at a nearly normal rate and survival was sustained. The relatively high number of malignancies other than leukaemia observed among the few animals dead up to the time of the report suggested that tumours of the soft tissues in irradiated animals were significantly increased with respect to controls. It is yet too early to see whether a non-specific component in the life-span shortening may become apparent at the lowest dose rates.

4. Conclusions

182. On the whole, the modifications of the life span induced by changing the dose rate are rather variable. For single acute doses of low-LET beams, changing the dose rate from 0.004 to 0.4 Gy min^{-1} did not significantly alter the effect [S21]. When the dose rate varied between about 0.8 and about 1580 Gy min^{-1} [L10] the effectiveness of the treatments differed as a maximum by a factor of 1.6. Thus, acute treatments show little dependence on the dose rate down to 0.004 Gy min^{-1}. At lower dose rates, down to about 0.01 Gy d^{-1}, it becomes difficult to resolve changes due to the dose rate as such or to dose protraction over a time which allows adaptation of the animal to the treatment. Under conditions implying irradiations for weeks or months, the efficiency of the treatment with respect to acute doses may drop by a factor of 10 or even of 25 for extremely low dose rates and long irradiation times with accumulated doses involving less than 50% survival of the irradiated animals [U7]. With such extremely protracted irradiations the form of the dose-effect relationship may also change with various reduction factors for different total doses [U7, U8]. Modifications of the form of the dose-effect relationships are not surprising, as changes of the damage, repair and repopulation at the various doses would superimpose to changes of the biological system itself during physiological adaptation to irradiation. All these variables would be expected to change profoundly as a function of time and dose. There has been experience in changing the dose rate in the course of brief repeated exposures at daily or weekly intervals. For daily exposures, a dose rate dependence of ^{60}Co gamma radiation amounting to a factor of 2 has been found, but not for fast neutrons. Weekly fractions with higher doses and within a higher range of dose rates did, however, show some reduction of effectiveness even for neutrons [V3, V4].

183. In the case of neutrons, changing the dose rate between 0.08 and 0.002 Gy min^{-1} does not result in an appreciable loss of effectiveness [V1]. The data available at lower dose rates (250 to 0.04 mGy d^{-1}) given in protracted exposures [U7, U8] may be interpreted to show that the reduction of effect at the low intensities is modest, probably lower than a factor of 1.5. There may be question as to the significance of changes in the form of the curve within such a small range of variation. Thus, the dependence of life shortening on dose rate is modest for low-LET radiation and doubtful for neutrons, when treatments last a few hours to a few days. Only when extremely low dose rates and correspondingly long irradiation times are involved, do x and gamma rays (but not neutrons) show consistent reduction of effectiveness, of the order of a factor of 10 or 20.

184. Experiments performed by splitting a given dose into two or more fractions separated by a few hours to a few weeks [G1, S27] have yielded little increase in survival by the split dose. When fractionation intervals of progressively longer duration were tested with a given scheme, a tendency to a longer life span with an increasing interval between doses has sometimes been found, but the variations observed even for very long fractionation times are too small to make these observations clearly significant [G1, A2, S27].

185. It is very difficult to see an overall trend for more complex fractionation patterns. In some cases [S2, A2, A7, H5, L4, R3] dividing the dose into smaller and smaller fractions does lead to an increased survival time following x- or gamma-irradiation. So does the increase in the total treatment time for the same number and size of fractions. But in other cases [M1, K6, M20, C18] a paradoxical effect is observed, i.e., an increase of the life shortening upon dose fractionation. A changing spectrum of the various diseases contributing to life shortening with more leukaemia induced at longer fractionation times has been invoked to explain the observations. Neutron dose fractionation experiments have also been reported on mice with unclear results.

186. In spite of the absence of a component of wasted radiation that has been claimed to confound the analysis, the effects of chronic terminated exposures are more difficult to evaluate than the experiments involving duration-of-life exposure. In principle, for any given type of radiation, the effect to be expected should lie between the dose-effect relationships obtained for high dose rate acute exposures (see Figures II and III) and those operating under duration-of-life conditions (see Figure X). However, the most striking finding in these series is the modification of the dose-effect relationships taking place at progressively variable dose rates. These modifications, depending on the characteristics of the species and strains, determine the final outcome of any given course of irradiation. There are not enough data on any single species to analyse such a broad statement into any coherent

model as published data have essentially been obtained on two mouse strains [M7, U7] and other series [S11, S21, L6] have contributed relatively less information.

187. These data, involving x-, gamma-ray and neutron irradiations were analysed by Grahn and Sacher [G1] and their conclusions may be provisionally accepted. Apparently (see Figure XIII) the curve describing life shortening as a function of total dose accumulated for doses of 15 Gy or less or for protraction periods of 50 days or less shows an abrupt slope transition from an initial portion where the effectiveness of the treatment

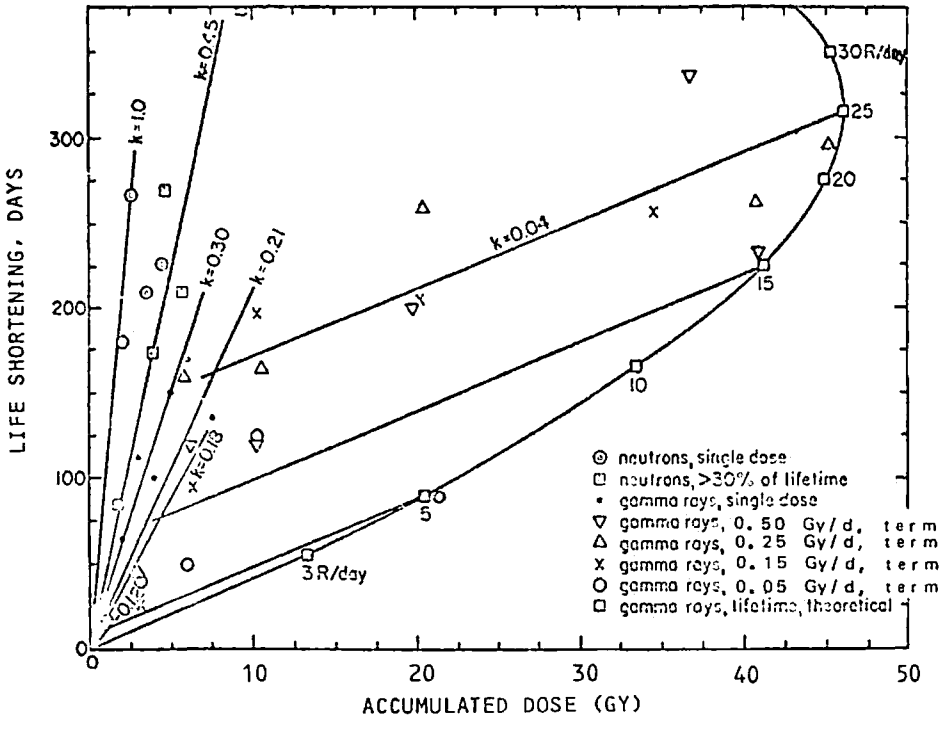


Figure XIII. Life shortening as a function of mean accumulated dose in RF female mice given various patterns of exposure (single, chronic terminated, duration-of-life) to gamma rays and neutrons. Data from Upton et al. [U7] as plotted by Grahn and Sacher [G1]

is of the order of 20–30 days of life shortening per Gy to a final slow-rising portion having an effectiveness of 4–5 days per Gy. This final slope applies to all protraction periods, including exposure for the duration of life; however, the point of transition between the fast-rising and the slow-rising segments of the curve is clear at 0.5 to 1 Gy d^{-1} but less so at intensities of 0.1 to 0.15 Gy d^{-1}. This flattening of response noted by Mole [M1] and by Sacher [S1] may be related to the establishment of an equilibrium between radiation injury and recovery mechanisms, which would depend on the kinetic modifications of the tissues that are important for long-term survival [S5, L13, L14, L15].

188. It may therefore be reasonably expected that the breaking point or transition in the dose-effect relationships depends also on the kinetic characteristics of the relevant cell lines, which are known to be species-specific. Such an analysis makes it also quite clear that conditions of protracted exposure may not be defined with respect to their life-shortening effectiveness by a single recovery constant or residual injury value valid for all conditions of protraction and all animal species. The neutron data would be such [G1] that when the transition from the fast- to the slow-rising portion of the curve is operative, the RBE would change from 2–3 to 5–15, as a result of the change in life-shortening effectiveness.

D. RADIATION OF DIFFERENT TYPES AND ENERGIES

1. Data

189. The action of different radiation is manifested through a change of effectiveness for the same amount of energy absorbed by the irradiated animal. The spatial distribution of the primary physical events that are responsible for the final biological effect is at the origin of these changes. Radiobiologically, the effect of densely-ionizing radiation becomes evident through an increased efficiency of the dose, by comparison with a sparsely-ionizing radiation. Under well specified irradiation conditions, when a given effect may be followed for a whole range of doses, the above phenomenon is expressed by the "Relative Biological Effectiveness" (RBE), a factor specifying the efficiency of the test treatment against a low-LET treatment assumed as the standard. X rays of around 250 kVp or ^{60}Co gamma rays may be used for this purpose: they are themselves of different effectiveness, the hard gamma rays being about 0.8 times as effective as the x rays. This Annex does not discuss the theoretical foundations of these concepts which are reviewed elsewhere [K10, R4] and are also discussed in Annex J. It considers only evidence regarding life shortening, according to the order of publication.

190. The early experiments on fission neutron RBE by Henshaw [H6], Evans [E2], Gowen [G8] and Neary et al. [N3] will only be cited. These experiments were analysed in the 1958 report of the Committee [U1] which discussed all data for the chronically irradiated rodent and summarized these in one graph [M13] (see Figure XIV). The percentage mean survival time was plotted versus the gamma-ray or the fast neutron

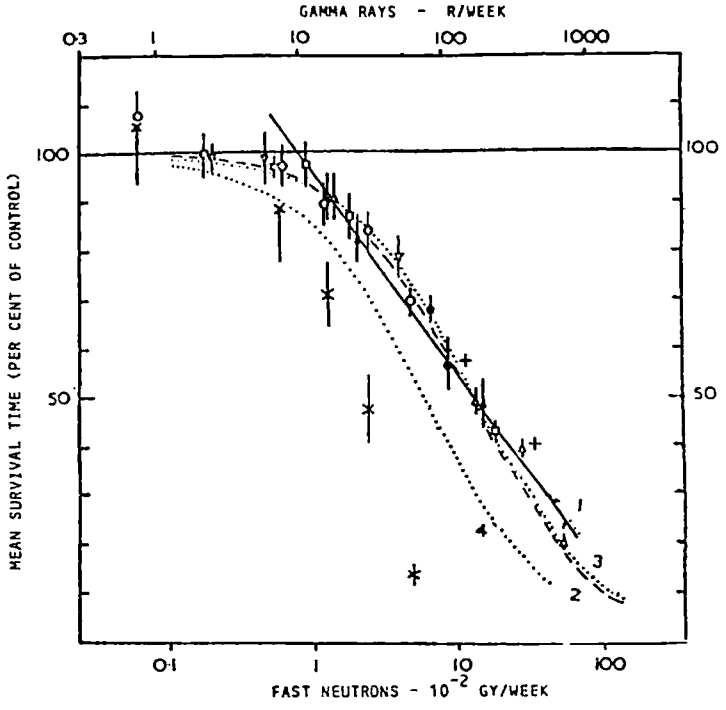


Figure XIV. Mean survival time expressed as percentage of the control survival, as a function of the weekly dose or exposure to fast neutrons or gamma rays. The gamma and neutron scales are in the ratio of 1 : 13. The symbols refer to different sets of data obtained on mice, rats and guinea-pigs by various authors, plotted by Mole [M13] and included in the UNSCEAR 1958 report [U1], as follows; Δ and ▽ [H7]; O and x, [L6]; □ [E3]; ■ [N3]; ▲ and ●, Neary et al., unpublished observations, + J. F. Thompson et al., Am. J. Roentgenol. 69 : 830-835 (1953)

exposure or dose rate. The data appear to be superimposable when the gamma- and neutron-scales were in the ratio of 1:13. From this it was deduced (in spite of some uncertainties in the comparison of data from different laboratories) that the RBE between fission neutrons and gamma rays applicable to life shortening in the rodent for chronic exposure was about 13. A study of x rays (250 kVp, 1.85 Gy min^{-1}) and of fast neutrons (fission spectrum, 2.7 10^8 neutrons cm^{-2} s^{-1}) was performed in CF1 female mice by Curtis and Gebhard [C17] following single or fractionated irradiations. The RBE for life shortening was estimated at 1.7. These results are difficult to interpret not only for the lack of an increase of RBE with fractionation, but also for the low RBE value of the acute exposures.

191. When straight lines were fitted to the data of Upton et al. [U5] on LAF1 mice irradiated with gamma rays or fast neutrons from a nuclear explosion, very similar RBE values of 2.1 and 2.3 were obtained in male and female animals, respectively. Mole and Thomas [M7] estimated the RBE of fission neutrons against ^{60}Co gamma with the same source of radiation and the same animals as reported previously [N1, N3, M13]. The life-shortening effects of about 0.16 Gy per week of fast neutrons or of 210 and 110 R per week of gamma rays were found to be equivalent both for terminated and for duration-of-life exposures. For all levels of response the neutron data were intermediate between the effects of these two intensities of gamma rays and nearer to those of the 110 R per week. The RBE was therefore estimated to be between 13 and 7, but nearer to the latter figure.

192. In a subsequent paper by the same group [N8] the RBE value was discussed for CBA mice chronically irradiated with fast neutrons as described in [N3]. The dose rates of the 0.7 MeV neutrons were 0.02 Gy d^{-1} or 0.003 Gy d^{-1}. Gamma irradiations were run at 0.16 or 0.023 Gy d^{-1}. Complete life-table data and cumulative survival curves were obtained in replicate experiments and several forms of dose-response curves were postulated to fit the data. RBE values around 10 were found, with a range of estimates between 8.6 and 15.0, according to the assumptions made. The data were thought to be inadequate to establish whether or not the RBE depended on the level of daily exposure.

193. The RBE of thermal column radiation, composed of thermal neutrons and hard gamma rays, was tested against 250 kVp x rays in experiments by Storer and Sanders [S17] performed on Swiss white mice. Since the neutron and the x-ray data could be fitted by a common linear non-threshold regression of per cent life shortening versus dose, the RBE had a value of unity. In another series, Storer et al. [S18] exposed CF1 female mice to neutrons or to mixtures of neutrons and gamma rays from an atomic weapon. The relative effectiveness of the neutrons was calculated to be 2.6 ± 0.9. In both series the RBE values for life shortening were in close agreement with those obtained for the production of acute effects.

194. In experiments by Vogel, Frigerio and Jordan [V1] CF1 female mice were exposed to daily doses of fission neutrons or gamma rays at dose rates of about 0.044 and 0.13 Gy min^{-1}, respectively. Groups of animals were given 13 brief exposures, each corresponding to 0.022 to 0.7 Gy d^{-1} of neutrons and 0.065 to 2.08 Gy d^{-1} of gamma rays. The neutron RBE was not increased over the figure of 2.8 previously obtained for acute single doses. Other experiments performed with 13 brief exposures of the two radiations given at 0.1 Gy min^{-1} indicated an RBE for median survival time of 2–3, in fairly good analogy with the figure of 2.8 for the $LD_{50/30}$ after single exposures.

195. Curtis, Tilley and Crowley [C19] reviewed the literature data on life shortening due to acute or chronic irradiation of mice with x rays or neutrons. They concluded that acute gamma doses could be up to 4 times as effective as chronic doses. For neutrons equal efficiency by acute and chronic exposures was the most common finding. Accordingly, the neutron RBE of about 2 for life shortening by acute doses may increase to about 8 for chronic treatments. Chromosome damage in the liver of animals was shown to behave similarly and these data were thought to provide some cellular basis for the differential action of low- and high-LET radiations. The data on chromosomes were also interpreted to indirectly support the hypothesis that mutations in somatic cells may be at the origin of natural and radiation-induced aging.

196. Sixteen-week-old female CF1 mice received 1 Gy per week of fission neutrons for 4 weeks at dose rates of 0.01, 0.03, 0.06, 0.35 Gy min^{-1}; or 2 Gy per week of ^{60}Co gamma rays at the same dose rates [V3, V4]. In all groups thymic lymphoma was the main cause of death and its incidence was not significantly affected by the dose rate. On the basis of mean survival time or of mortality curves, life time was reduced by about 65% by neutrons and by about 50% by gamma rays. The neutron efficiency was therefore higher than that of the gamma by more than a factor of 2. The mean survival times of both neutron- and gamma-irradiated animals were significantly shorter with 0.35 than with 0.01 Gy min^{-1}.

197. Vogel and Jordan [V5, V6] compared the lethality of fission neutrons produced by a CP-5 reactor to that of ^{60}Co gamma rays, both radiations being delivered at about 0.01 Gy min^{-1}. CF1 female mice were exposed according to a complex pattern of fractionation in which 13 weekly doses of 3 Gy of gamma rays were delivered as 1, 3 or 6 equal fractions per week. Since the arbitrary RBE value chosen was 5, the corresponding total weekly dose of neutrons was 0.6 Gy, delivered into 1, 3 or 6 fractions per week. The data showed that the postulated RBE of 5 was too high. Upton, Randolph and Darden [U10] reported that with fast neutrons the life expectancy of RF female mice was shortened by 80 days per Gy, irrespective of dose rate, whereas the life-shortening efficiency of the gamma rays decreased from about 30 days per Gy at 0.07 Gy min^{-1} to about 15 days per Gy at 0.05 Gy d^{-1}. The RBE increased therefore with decreasing dose rate from about 2.7 to 5.4.

198. In the experiments of Upton, Randolph and Conklin [U7] variable dose rates of x and gamma rays (0.80 to 0.01 Gy d^{-1}) and of fast neutrons (0.11 to $4\ 10^{-5}$ Gy d^{-1}) were administered to RF mice. There were also groups treated at about 1 Gy min^{-1} of both radiations. Gamma rays at the low dose rates were invariably and consistently less effective than at the high dose rates. Neutron effects, however, showed less dependence on the dose rate. The RBE evaluated on the basis of the average life-shortening effect (days/unit dose) was about 3 at high dose rates and it increased to about 8 for terminated chronic irradiation. When exposure continued until mortality reached about 50% of the mice, a further increase of the effectiveness to about 14 took place. Without knowledge of the dose rate to RBE relationships it was impossible to foresee whether higher RBEs might be found at even lower dose rates. Similarly, it was impossible to predict any trend at different neutron energies. However, since 5 MeV neutrons (from a Po-Be source) were essentially as effective as the 1 MeV cyclotron-generated neutrons in spite of the much lower dose rate ($3\ 10^{-8}$ to $1\ 10^{-4}$ Gy min^{-1} as opposed to 0.85 Gy min^{-1}) it was felt that neutrons of still higher energy might prove less effective.

199. Clapp et al. [C12] published an experiment in which the effects of acute doses of 300 kVp x rays (0.5 to 4 Gy) were compared with those of 60 MeV protons (0.47 to 3.72 Gy). Irradiation conditions were such that comparable LET values were obtained. The proton mean LET was estimated to be approximately 1.5 keV/μm within the animal's body. As expected on the basis of LET considerations, the protons RBE was 0.63 for life shortening and slightly less than 1 for all parameters, excluding the induction of ovarian tumours. Thymic lymphoma, myeloid leukaemia and ovarian tumours were increased significantly by radiation, while other alterations in the incidence and severity of diseases were minimal by comparison with non-irradiated mice. An RBE of 1.0 or slightly less would thus be applicable for most pathological parameters examined.

200. The experiments of Ainsworth et al. [A7] showed differences in the shape of the dose-response relationships which were linear with gamma rays and convex upwards with fission neutrons. The RBE was therefore dose-dependent. On the basis of more recent data from the same series [T4] the RBE for both single and fractionated exposures varied inversely with the square root of the neutron dose over the range of doses covered by the experiments. It was predicted that, depending on the method of calculation, the RBE at 0.01 Gy of neutrons would be 28–33 in male and 40–44 in female animals, for single exposures. For fractionated treatments the extrapolated RBE values would be 62–91 in males and 41–79 in females. Experiments are presently in progress to test the validity of these predictions. For duration-of-life or long-term fractionation exposures the RBE might be between 60 and 120 at 0.0005 Gy of neutrons per week, varying inversely with the –0.4 power of the neutron dose [T5].

201. The RBE of fission neutrons for life shortening, relative to ^{137}Cs gamma rays varied in the experiments of Ullrich and Storer [U8, S44] according to dose level. In the RFM female mice treated at high dose rates the two-component nature of the gamma-ray relationship produced RBE values increasing for progressively lower doses as the inverse of the square root of the dose in the dose range below 0.5 Gy. Such a trend would be predicted by the dual radiation action theory of Kellerer and Rossi [K10]. At doses above 0.5 Gy the RBE estimate (based on the ratio of the slopes of the linear regressions fitted to the gamma-ray and neutron experimental points) was 2.9. This value was similar to that observed within the same range of doses on the

BALB/c mice (3.0). In the experiments of Hulse [H18] on rabbits the RBE of fission neutrons was assessed at 3.5–4.0 for longevity.

2. Conclusions

202. The RBE experience on life shortening refers essentially to neutron irradiations in the mouse. For acute doses in the region of a few tenths to a few Gy of x and gamma rays (and equivalent doses of neutrons) RBE figures of 2 to 3 have generally been found. The evidence reviewed shows some increase of the RBE upon short fractionation courses and with decreasing dose rate down to hundredths of Gy of neutrons per day to figures of about 5–6. More consistent changes are found for extremely long courses of irradiation where RBE values of between 9 and 15 are quoted.

203. From the Committee's analysis of the mouse data in Figures II and III the RBE values that can be obtained for acute single doses of neutrons by pooling all available experience would differ at different doses. For acute doses of neutrons in the region of 0.01 Gy the RBE cannot be determined precisely from the data reviewed. The predicted values might be about 10, but values as high as 50 might be possible, depending on the assumed shapes of the dose-response curves.

204. The average RBE values applicable to exposures for the duration of life may be obtained from a comparison of the curves as a function of the dose rate shown in Figure IX. At 50% life shortening the neutron dose rate that would give the same effect as the x and gamma rays would be about 10 times smaller than that of the gamma rays. At dose rates corresponding to 0.01 Gy d^{-1} of low-LET radiation (and proportionately lower neutron dose rates) the effectiveness of the neutron treatment would increase to about 40. Alternatively, the RBE as a function of total accumulated dose might be calculated from the curves in Figure X where the RBE values applying to different levels of effect would be, between 10 and 20. It may be concluded that the RBE values derived in the mouse by the independent and comprehensive review of the Committee are in fair agreement with those that may be derived from the analysis of the single experimental series discussed in the preceding paragraphs.

E. SPECIFICITY OF LIFE SHORTENING

205. After the overall quantitative analysis in the preceding paragraphs, it is appropriate to review the problem of the specificity or non-specificity of the effect. Such a discussion presupposes the availability of experimental series with careful pathology of the animals at death or serial sacrifices to investigate the development of the pathology of aging. Experiments reported of this kind are very few and even when pathology is reasonable, any direct comparison with survival is made impossible by the presentation of the data. Therefore, the present section will be essentially qualitative. It will be based on the conclusions of the authors themselves which are often unsatisfactory owing to inadequate pathology (mostly macroscopic) or to insufficient statistical analysis. In other cases the conclusions of the experiments were biased by the models of action assumed in the interpretation of the data. However, in the absence of the original data, no better treatment of the subject matter is possible.

206. It was mentioned in the introduction on methodology that the usefulness and precision of the life-shortening data is often limited by the fact that increased risk from one life-shortening disease may be offset by the decreased risk for another. Unless efforts are made to establish the causes of death, information concerning the relative importance of disease states will not be obtained and the existence of mechanisms of death over and above those attributable to the diseases normally occurring in a given species or strain will not be proven. Identification of disease states at death or by serial sacrifice is in itself a difficult task, but it is preliminary to an appreciation of the relative significance of disease states. The relevant problems, particularly in rodents and in relation to life span studies, have recently been reviewed [H19].

207. It is easily appreciated that the quality of the pathology and its capacity for resolving different diseases will to a great extent condition the share of the non-diagnosed causes of death in a given experiment. In order to achieve good resolution, the pathologist should have experience of the animals used. Without going into details, it is well known that each species and strain of experimental animals dies with a characteristic set of pathological conditions. Data referring to the most common species of laboratory mouse [G19], rat [F10, W6, B26], rabbit [W7], dog [A14] and other animals [B25] may be found in reference publications. The variety of pathological conditions is very wide and their incidence extremely variable in each case. Most of the experience available on life shortening is in the mouse, where the variability of diseases between species is by now well documented. From an intercomparison of results in animal strains having different pathological characteristics an insight may be gained into the more general aspects of the life-shortening action.

208. Although the diagnosis of a given disease (or combination of diseases) in an animal is founded on objective criteria, the assessment of its significance to life shortening is to a large degree subjective, in that it requires an evaluation on the part of the pathologist as to the capacity by a given disease to produce death in that particular case. In principle one can think of a number of chemical and clinical examinations performed before death to aid in the diagnosis, but in small animals such as the mouse these cannot be carried out. Therefore, even under the best conditions of macro- and micro-scopic analysis, 20 to 30% of these animals die without an apparent cause. For them it may be assumed (but, of course, not proven) that death is due to true aging or physiological senescence [H19].

209. Once the pathological analysis has been performed, the actuarial data must be interpreted in the light of its results. In theory, correlation of the time at death with the occurrence of any specific disease makes it possible to assess in a given population the contribution of each nosographic entity to life shortening. Specificity or non-specificity of the life-shortening effect is essentially judged on these criteria. In practice, however, it should be emphasized that the occurrence of multiple disease conditions, particularly in old animals, and the problem of competing causes of death make this exercise difficult. It may not in fact be expected that the precision of the combined pathological and actuarial analyses may be higher than the resolution attaching to any of the two methodologies.

210. It is commonly reported [G4, S19, C12, L9] that correction of the data for animals dying of leukaemia

and of ovarian tumours, which are very common causes of death in the mouse, leads to a reduction of the large variability of the effect between strains and sexes and to a reduction of the life-shortening efficiency of the radiation treatment. This indicates that at least part of the reduction of life after irradiation must be attributed to tumour induction.

211. The first large experimental series where pathology was of such a quality to allow analysis of specific death causes was that of Upton et al. [U5]. The authors could establish no clear-cut relationship between shortening of life and incidence of tumours as the dose relationships for tumour induction had variable forms; some neoplasms increased and some decreased with increasing dose. These data gave impulse to the idea that radiation may cause non-specific aging by advancing all diseases by about the same degree for each given dose. However, a more recent re-evaluation by Walburg [W1], by a statistical method allowing for competing probabilities of death, justified the conclusion that life shortening, which was clearly apparent when all death causes were considered together, disappeared when tumours were excluded from the analysis.

212. Another set of data that was held to support the notion of non-specific life-span shortening was that by Lindop and Rotblat [L2]. The main conclusion of these investigations was that life shortening was due to advancing of all causes of death with respect to time, without change in the relative probability of each cause. It would be of interest to reconsider these data with a more refined statistical test [H2] in order to assess the reliability of the conclusion. This is particularly true as the pathology and the statistics of this experiment have been criticized [W1]. The authors did recognize differences in the relative times of onset of the diseases between control and irradiated animals. One may wonder therefore how these data may have been interpreted, as they were then and later, to support the existence of a non-specific effect of aging.

213. Storer in his 1965 [S20] series noted in the range of between 100 and 500 R of x rays a tendency of the neoplastic diseases to occur earlier in irradiated than in control mice. In the large series of Upton et al. [U7] and Upton, Randolph and Conklin [U9] microscopic pathology was not performed as a rule, but the quality of the macroscopic examination of the animals at death was quite good. The authors felt that the death of irradiated animals was characteristically associated with tumours and degenerative diseases of old age, but that neoplastic conditions could not entirely account for the reduction of life. When some of these data were reassessed by Walburg [W1] with more refined statistics, the life shortening in the irradiated mice was negligible if the tumour deaths were excluded, at least in the dose range of 1 to 3 Gy of gamma rays. This indicates that tumours did contribute substantially to life shortening. Similarly, Darden et al. [D1] and Walburg [W1] ascribed to thymic and myeloid leukaemia most of the mortality increase observed in RF mice irradiated, respectively, with neutrons and with x rays.

214. Grahn, Fry and Lea [G5] ascribed to excess tumour mortality the life shortening observed up to about 4 Gy, while at higher doses the decreased life expectancy was not accompanied by a parallel increase of tumour incidence. Maisin et al. [M10] on BALB/c and C57BL mice attributed life shortening at doses below the $LD_{50/30}$ essentially to thymic lymphoma and, at higher doses, to glomerulosclerosis. Similarly, malignant tumours at the low doses and glomerulosclerosis at high doses were identified by Metalli et al. [M9] as the main causes of premature death in irradiated mice. In the experiments of Lamson, Billings and Meek [L3] and Lamson, Billings, Ewell and Bennett [L5] acceleration of tumour appearance and nephrosclerosis were associated with life shortening in the rat; and the same was true for the dog in the series of Andersen and Rosenblatt [A2], according to the re-analysis of Walburg [W1].

215. Concerning duration-of-life exposure, the paper by Grahn, Fry and Lea [G5] contains a comprehensive discussion of the problem of specificity, based on data from different mouse strains. According to this analysis, the increment in long-term mortality at exposure rates up to a few R per day is associated with an increment of the neoplastic deaths which can entirely account (both as increased incidence and as accelerated appearance) for the relevant reduction of life. At exposure rates above 6 R per day an excess mortality from non-tumorous conditions becomes apparent. It should be added that data up to the present from the Argonne series on the life time irradiation of dogs are in agreement with the above conclusion.

216. Thus, the vast majority of data on rodent and non-rodent mammals, irradiated with sparsely- and densely-ionizing radiation and with acute or chronic doses, when properly analysed, appear to be consistent with the following conclusions. The life-shortening action observed on animals surviving the acute effects of irradiation, that is, after low-to-medium doses up to about the $LD_{50/30}$, may be essentially accounted for by an acceleration or an increased incidence of neoplastic conditions resulting in the premature death of some animals. From doses around the $LD_{50/30}$—but progressively more so at higher doses—other pathological conditions may also advance or accelerate death and among them the vascular changes leading to organ fibrosis, particularly of the kidney, have been described on irradiated animals. At these dose levels deaths from other non-stochastic effects described in Annex J would be expected. The hypothesis of a general deleterious action of radiation formally analogous to aging could, in principle, be entertained and, if so, it could not be disproved. However, if non-specific life shortening is viewed as an advancement in time of diseases normally associated with senescence without apparent changes in the spectrum of these diseases, no data are found to support such a concept. The notion of non-specific aging, based only on actuarial analogies and on superficial resemblances between irradiated and aging animals, cannot be substantiated by accurate pathology. Particularly at the low doses and dose rates of interest in radiation protection there appears to be no need to invoke any general non-specific noxious effect, because all the experience on animals does not require to postulate any other effect than tumour induction or acceleration to explain the reduced life expectancy observed after irradiation.

II. THE EFFECTS OF BIOLOGICAL VARIABLES

217. In this chapter the biological variables affecting the life-shortening response to irradiation are reviewed. The data refer to the genetic constitution of the animal species or strain, a major determinant of the response;

to the effects of age at irradiation, both in the intra- and in the extra-uterine life; and to the differential effect on male and female animals, because special physiological conditions or the expression of peculiar diseases in the two sexes may result in a variable amount of life shortening induced by a given dose. The effect of partial versus whole-body irradiation is considered in Section III.D. with other modifying biological conditions.

A. GENETIC BACKGROUND

218. Among the genetic variables, the inter-species and intra-species differences should be considered separately. In the first case, the object of the analysis is to establish a scale of sensitivity with respect to life shortening between various mammals, analogous to that repeatedly attempted for short-term survival (for an extensive discussion of these problems in relation to the acute radiation syndromes, see [B18]). In this connection the problem of data extrapolation to other species may be discussed. In the case of intra-species comparisons, the problem is that of analysing the character and the amount of life shortening in genetically different strains of the same species, in order to correlate the degree of radiation effect with some vital characteristics of the strain, such as longevity, age-specific rate of death and spectrum of spontaneous diseases. These experiments have been carried out so far in the mouse for the availability of inbred animals in large numbers and the relative ease of obtaining crosses of inbred genotypes.

1. Inter-species differences

219. It is well known that a large variability exists among various animal species in respect to life span and tumour incidence [B25]. The finding of a correlation between these two variables across various species might in principle be of help to put generalizations in the field of radiation-induced life shortening on a firmer basis. However, in view of the disease spectrum peculiar to each species, it can also be argued that generalizations not accounting for specific pathological characteristics would have heuristic significance but little practical value.

220. Attempts at inter-species comparisons in relation to life shortening with the objective of a projection to man, were discussed and proposed repeatedly. An approach based on the actuarial Gompertzian analysis of survival parameters was first put forward as a working hypothesis by Brues and Sacher [B1]. They envisaged that if the linear dependence of the log mortality rate on age (see Figure I) may hold for mammalian species of different life span, a common origin for the curves and a time-scaling factor may be chosen in such a way that actuarial functions belonging to various species may be made identical. Calculations of this kind using empirical constants obtained on mice and dogs indicated that in the absence of any recovery function the exposure of man to a continuously accumulated tolerance dose in use at that time (0.3 R per week) may decrease the human expectation of life by 10%.

221. On the basis of experiments by Henshaw [H1], Boche [B11] identified in the parameter α (the excess death rate per week divided by the exposure level in R per week for chronic irradiation experiments) the quantity that would be invariant for each species and might therefore allow inter-species comparison, because it expressed the susceptibility of that species to chronic radiation action. Based on the value of such a constant, Boche attributed about equal sensitivity to the rat, the dog and the mouse, a higher resistance to the rabbit and a higher susceptibility to the monkey.

222. Lorenz [L7] summarized the effects of long-continued whole-body irradiation of mice, guinea-pigs and rabbits. He accepted essentially the radiosusceptibility scale of Boche [B11] and discussed the problem of extrapolating the findings to man. He concluded that man should be considered to be as sensitive as the most sensitive animal found experimentally and on this basis proposed that an acceptable whole-body exposure might be 0.1 R per 8-hour day. Such an approach was criticized by Mole [M13] who pointed out the relativity of the criterion and the fact that extrapolation from animals to man required sufficient evidence of the similarity between man and other animals, to give confidence to the process of filling the gaps in our knowledge of human effects with experience on other mammals. Mole considered that in the absence of a satisfactory theory, efforts to define a relationship between daily dose and life span for survival times of the order of 95% or higher of the control values were hardly justifiable. On the other hand, it is only in this region of effects that extrapolation is of any interest.

223. In 1955 Sacher [S1] examined the evidence available on seven animal species (rabbit, rat, mouse, monkey, dog, burro, guinea-pig) treated with various acute or chronic doses and deduced for each species a cumulant lethality function (see section I.B.) describing the course of injury according to a given set of reasonable hypotheses. Regarding short-term lethality, the conclusion was that the most and least sensitive species investigated differed by a factor of about 10 in the steady-state or plateau values of their cumulant functions, while intra-species differences were within a factor of 4. However, the evidence available for long-term mortality showed considerably less species variation.

224. Blair [B4] and with him the 1958 UNSCEAR report [U1] by plotting together rat and mouse life-span-shortening data after acute irradiation and showing their good agreement on the basis of units of $LD_{50/30}$, implicitly recognized the existence of some relationship between acute and chronic survival response in these two species and the close similarity of their susceptibility to the long-term lethal action of chronic irradiation.

225. Boche's hypothesis [B11] that a given dose might produce the same proportional life shortening in different species has represented the basis of many attempts to derive life shortening per unit dose in man from laboratory animal data. The values proposed varied from 1 to 5 d R^{-1} [N1]. In Neary's model [N1] if the percentage life shortening per unit dose equivalent is taken to be the same for man as for the mouse, the absolute life shortening for the two species would be calculated at 8 d Sv^{-1} of chronic radiation. Thus, a person accumulating what was at the time a maximum permissible life-time dose of 2 Sv would suffer a life shortening of 16 days, instead of the figures of up to one year calculated on Boche's [B11] assumptions.

226. Spalding et al. [S21] attempted extrapolation of data obtained from mice that had been exposed to acute ^{60}Co gamma doses (1.1 to 12 Gy). They found

that if a mouse-to-man relationship of 1 day to 1 month may be assumed, similar conditions of exposure in man may be expected to cause a reduction of the mean after survival time of 900 to 1000 days per Gy of gamma-ray exposure.

227. Grahn and Sacher [G1] based their extrapolations on the linearity of the log mean after-survival in days as a function of daily radiation in rad or R, for mean after-survival of 25% or more of the control values. This linear trend of the mean after-survival was previously shown to hold for the mouse [S4] (see Figure XV). The coefficient of this regression is a species

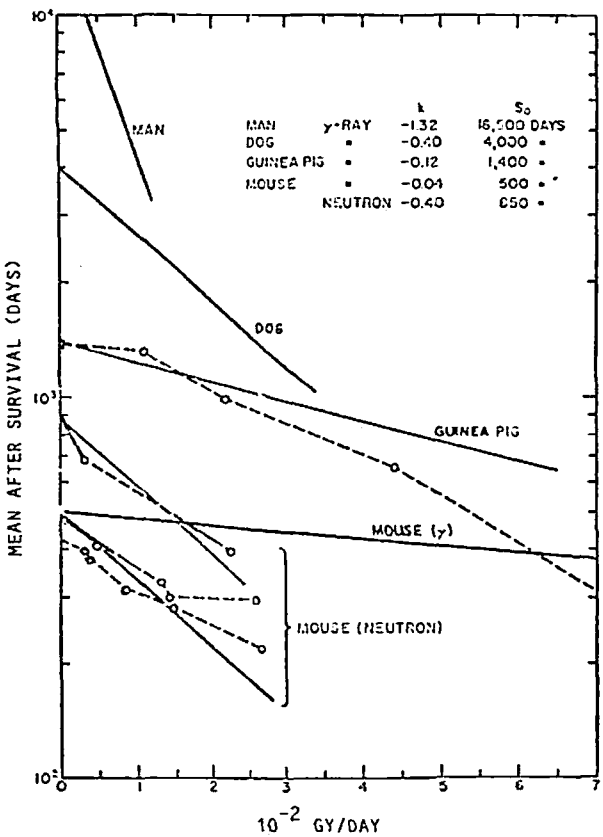


Figure XV. A plot of log mean after-survival as a function of daily exposure according to equation $S_I = S_0 e^{-kD}$ where S_0 is the survival and S_I the survival at dose rate I. The values of k and S_0 are shown for mammalian species. Data from Grahn and Sacher [G1]

constant [G9] and is related to the days of life lost per unit dose or the fraction of life lost per day. It may therefore allow one, when two points referring to a given species are known, to define the slope of the curve applying to that species. The ratios of the coefficients of regression would then be related to the ratios of life expectancies for non-irradiated populations or to the ratios of the age-specific mortality rate slopes. A radiosusceptibility scale may thus be constructed for man, dog, guinea-pig and mouse, on the basis of the slopes being in the ratio of 33:10:3:1 for life expectancies of 16 500, 4000, 1400 and 500 days, respectively. It may therefore be deduced that the relative sensitivity of the various species (expressed in per cent life shortening for unit exposure) was approximately the same for all species and in the ratio of: mouse = 1; guinea-pig = 1.8; dog = 1.25; and man = 1. Similar conclusions were also drawn by Sacher [S23, S14].

228. Grahn [G6] explored the problem of inter-species comparison further, starting from the notion of the exponential decline of mean after-survival with daily dose, which has been mentioned repeatedly (Figure XV). By comparing the vital statistics of two selected populations of male men and mice, he established that the ratio of time scale to equate the two populations is 10 mouse days = 1 man year, or 1 mouse day = 36.5 man days, a factor slightly higher than he previously used (33:1) [G1] and much higher than that used by Failla et al. (20:1) [F4]. In consideration of these other estimates Grahn selected a ratio of 1:30 for his calculations and established that the daily exposure to induce a 50% reduction of life expectancy in man was 0.65 R d^{-1}, compared with a 19.4 R d^{-1} in the mouse. Calculations for man and for other species showed that the guinea-pig was a relatively sensitive species in a framework defined by the mouse, dog and man. It should be pointed out that the life span and radiosensitivity values used for these calculations are very much at variance with those in the 1968 paper by the same authors [G1] and therefore the relative sensitivity scales in the two papers do not correspond.

229. Mole [M2] discussed in general terms the problem of extrapolation between species. He noted that experimental investigations are of value when they lead to quantitative generalizations that must include within themselves some allowance for any species difference. Mole mentioned three possibilities in this respect: the opacification of the lens of the eye, which may be inversely related to the body size or to the size of the eyeball; the susceptibility to the induction of bone tumours, which may be equal in all mammals; and the radiation sensitivity of mammalian oocytes, which may be inversely related to the metabolic activity or to the degree of lampbrush configuration of the chromosomes. Generalizations of such specific biological phenomena, rather than extrapolation of abstract matters such as mortality or life shortening should particularly be pursued. He further expanded these concepts [M3] and pointed out that in principle life-span shortening may be considered to be a meaningful parameter only when the spectrum of diseases in different animal populations receiving various doses is the same. In the absence of this condition, life shortening becomes simply a compounded but imprecise way of expressing differences in the incidence of pathological conditions that might be more adequately expressed otherwise.

230. An inter-species comparison of response in mice [S4, G6] and dogs continuously exposed to ^{60}Co gamma rays was reported by Norris, Tyler and Sacher [N7]. It was found in both species that plotting the log of the radiation-specific death rate (i.e., the difference of the reciprocals of survival times for the exposed and the control animals [S14, S29], see also Figure VIII) against the log of the dose rate gave rise to a dose-response with a slope of 2, indicating that the excess mortality increased with the square of the dose rate (Figure XVI). The phenomenon was seen over the whole range of dose rates in which damage to the haemopoietic tissues is the primary cause of death, that is above 0.2 Gy d^{-1} in the mouse. At lower dose rates in this species the slope was 1, indicating that injury was only a function of the total dose accumulated and independent of the rate at which it was given. Data available in the dog would suggest a similar inflection taking place below 0.035 Gy d^{-1}, but this suggestion will have to be proven by appropriate experimentation. The only point available for dogs below 0.01 Gy d^{-1} [C16] lies quite close to the curve for the mouse having slope of 1, which would be in favour of a roughly similar sensitivity of the two

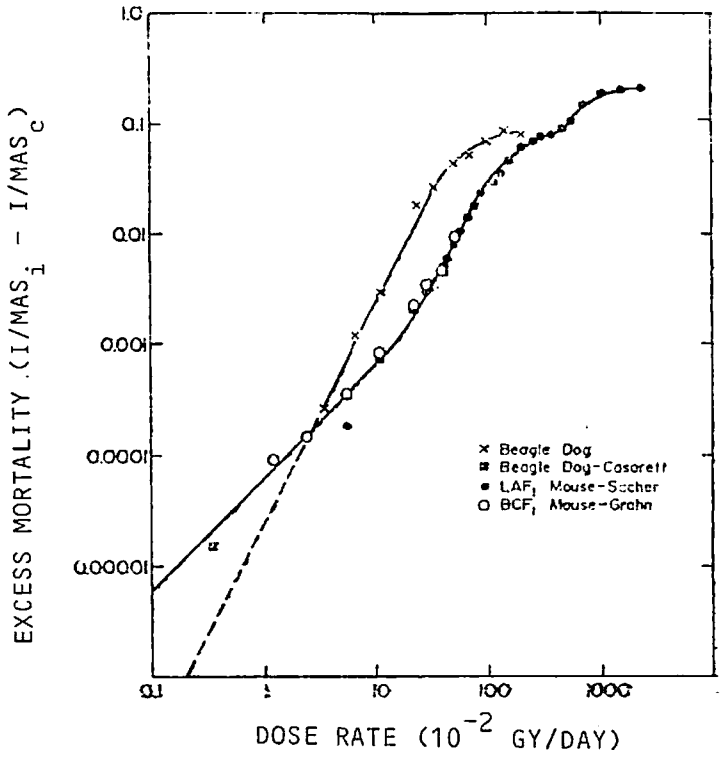


Figure XVI. A comparison of radiation-specific death rate in dogs and mice under duration-of-life exposure, as a function of the daily dose rate. Data from Norris et al. [N7]

species at the level where injury becomes independent of dose rate.

231. Grahn, Sacher, Lea et al. [G16] returned again to the problem of extrapolation from mouse to man on the assumptions [G6] that: the Gompertz slopes for mouse and man are in the inverse ratio of their susceptibility; the previously-mentioned ratio of 30:1 for mouse:man applies; and the ratio of slopes or the slope displacement has an identical relationship to the reduction of life expectancy in both species. They thus calculated that 2.5 Sv (i.e., 0.05 Sv a^{-1} which is the present limit of dose equivalent for workers x 50 years of working life) given chronically over a very long time would produce 15 days of life shortening for an average 100 day-old mouse and about 15 months for the average 20 year-old man.

232. At the same time Sacher, Tyler and Trucco [S50] extended their observations to 15 species of mammals from the orders of Carnivora, Arctiodactyla and Rodentia, exposed for the duration of life to gamma rays. The survival data analysed in terms of the radiation-specific death rate showed that for all species (with the exception of the black rat) the death rate increased as the square of the dose rate up to a break point above which death rate increased linearly with dose rate. A log-log plot of the co-ordinates of the breaking points showed a linear relationship, indicating that the species variation to chronic irradiation is due to a single parameter. A mathematical model based on the induction of cytogenetic damage was compatible with the findings and suggested that species susceptibility to continuous exposure could be related to an accumulation time for damage leading to chromosome breaks. At this level of analysis the actuarial parameters could be linked with the study of molecular lesions as discussed in "Mechanisms of ageing and life shortening" although filling the gap between the two approaches requires clearly much confirmatory work.

2. Intra-species differences

233. It is important to realize that a very large variability exists between different strains of the same species with respect to longevity and the incidence of leukaemia and tumours. Systematic data are available on rodents on differences in the life span and tumour incidence between inbred and hybrid strains. Life span in female mice may differ between strains by nearly a factor of three and in males by more than a factor of two [S56]. In 7 inbred strains the incidence of total tumours ranged from 7.3 to 44% in males and from 25 to 55% in females. Variability with regard to specific tumour types may be even higher, some strains not showing some tumour types at all [S55]. In rats very similar conclusions apply [A12, M30]. This extreme variability points, on the one hand, to the difficulty of generalizing findings in a given strain. On the other hand, the variability makes a given conclusion very significant if it holds in spite of strain differences.

234. The oldest contribution to the problem of strain differences in the response of mice to long-term radiation effects is that of Gowen [G8]. He studied two strains, the S mouse with a medium longevity and the Ba mouse with a long life span. Upon irradiation in the course of a nuclear test the S mice were shown to be considerably more resistant than the Ba ones and this pattern of response was similar to that observed after 98 kVp x-irradiation (exposures of 20 to 960 R). There were no good pathological observations reported, and it was argued that the resistance of the S strain to Salmonella might at least partly account for the differences observed, although the full basis of the radioresistance of these mice was thought to be more complex.

235. Grahn [G10] reported on the chronic lethality of five mouse strains: BALB/c, A/Jax, A/He, C3H1/He and C57BL/6. The survivors of single 200 kVp x-ray acute exposures (400 to about 700 R) were kept for

analysis of late effect. Weighted regression lines of life shortening versus dose showed no significant differences between the strains in either sex, although females were more sensitive per unit dose. There was no correlation between life-span reduction and control life expectancy, although such a relationship could be shown in respect to $LD_{50/30}$. In a second series daily ^{60}Co gamma exposures were tested at 11 exposure levels between 220 R d^{-1} and 6 R d^{-1}, covering the full range from acute to chronic responses. Partial data from crosses of BALB/c x C57BL/6 were also included. Preliminary data showed strain differences at all exposure levels; survival times were quite variable between strains but closely reflected genetic differences in control survival. The greatest life-shortening effect was seen in strains with a high incidence of leukaemia.

236. The conclusion of a more refined analysis of the above data [G4] was that all genotypes exhibited a radiation-induced life-shortening effect dependent on a single common primary injury parameter. For acute exposures the parameter could be expressed by the number of days of life lost per unit exposure, equalling 0.28 days R^{-1}. This parameter could then be combined with others to give equations predicting the life shortening for any combination of normal life expectancy, dose, and incidence of neoplastic conditions. After correction for leukaemia and ovarian tumour induction, life shortening for both sexes following exposure to 570 R was 111 days and exposure to the same $LD_{50/30}$ caused a constant proportion of life lost amounting to 19%. In duration-of-life experiments mean survival time and mean accumulated dose varied directly with control survival and therefore at each exposure rate strains having different control survival lost the same proportion of their life expectancy. With a few exceptions, the mean accumulated dose and the acute $LD_{50/30}$ were shown to be related to each other in that each had a common relationship to the normal life span.

237. Gowen and Stadler [G11] published also a large series of experiments in which ten different mouse strains (four pairs for each genotype) were initially exposed from mating to death to ^{60}Co gamma-irradiation (0.6 to 2.7 R d^{-1}) for 22 hours per day. The design and the analysis of this research, although involving irradiation for the duration of life, was centred more on the capacity of irradiation to stop the reproductive functions of these mice, than to shorten their life span.

238. Other analyses by the Argonne group [S5, G9] contain comparisons of the relative life-shortening effect of ^{60}Co irradiation to death in genetically different mouse strains and indicate the constancy of the slope of the relationship expressing the log mean after-survival against exposure rate. The linearity of this relationship over the exposure rate range between zero and 56 R d^{-1} was established for BCF1, C57BL/6, BALB/c and A/Jax male and female mice [S5], thus confirming previous findings with the LAF1 mouse [S4]. The control survival of the male and female mice of the 4 genotypes cited (8 groups in total) ranged from 466 to 796 days and these differences in life span curves were nearly parallel and were displaced from one another by the same amount of displacement of the control survival times.

239. The problem of the genotype relationship to long-term survival has also been considered by Holland and Mitchell [H10] who irradiated (300 R, 300 kVp x rays) 4 strains of male and female inbred mice (C3Hf/Wg, C57BL/6, RFM/Un, BALB/c), C3CF1 and B6FRMF1 hybrids and a cross between these two hybrids, C3CB6RFM. Females were shown to be, in general, more sensitive than males by a factor of 1.5. Within the same sex, substantial differences in sensitivity were also shown among strains. As these differences correlated well with the weight of the animals, it was suggested that the variation in susceptibility to life shortening may be at least partially accounted for by genetically-determined differences in the maturation rates of the various genotypes. After fission neutron irradiation at both high (0.25 Gy min^{-1}) or low (0.01 Gy d^{-1}) dose rate no appreciable difference in life shortening was found between RFM or BALB/c female mice in the experiments of Ullrich and Storer [U8].

240. Life tables for different strains of inbred and hybrid mouse strains have been reported, with data on life expectancy for parental, F1 F2, F3 and the first three backcross generations [G17]. These data refer to non-irradiated animals, but they could be used in radiation work on the basis of the repeatedly cited invariant life-shortening relationships with dose common to all mouse genotypes (4 days per Gy or 28 days per Gy for life-time and single acute exposure, respectively [G4]). In another paper Storer [S57] reported life table data on 9 inbred and 5 hybrid strains of mouse, non irradiated or exposed to 250 or 450 R of 250 kVp x rays. All these data may be regarded as initial attempts to a genetic analysis of the radiation susceptibility to life shortening in mammals. Such attempts must however be improved considerably in order to clarify the simple relationships of the kind mentioned above and how these may be translated into a variety of disease states in different mouse genotypes.

B. SEX AND BODY WEIGHT

241. Very often in the course of the papers reviewed mention is made of differential effects in the two sexes for various strains of animals. To review all these observations separately is probably unnecessary as in many cases they are incidental and not particularly relevant to the main physical or biological variable discussed in each specific paper. In this section only those papers are reviewed where such effects were particularly well substantiated and discussed. Emphasis is given to contributions where pathological observations were performed, in an effort to ascribe the differential effects to diseases or conditions affecting preferentially one of the sexes.

1. Sex

242. In the experiments of Neary et al. [N3] the mean survival time of the female animals was significantly greater ($P < 0.05$) than that of the males. When only the mean survival times between 30% and 100% mortality were considered in order to exclude early mortality, this sex difference remained evident. Sex differences in BALB/c, A/Jax, A/He, C3Hf/He and C57BL/6 mice were evident when data for female or for male animals of all strains were pooled and fitted by linear regressions as a function of dose. The reduction of mean after-survival for a given dose increment was about twice in female as in male animals [G10]. Ovarian dysfunction resulting in ovarian tumour formation was suggested as the possible cause of this difference. Grahn and Sacher [G3] also showed a

greater sensitivity of the females with respect to chronic life-shortening injury. With x rays of three different energies the reduction of life span averaged in animals surviving the $LD_{50/30}$ about 37% in the female and 29% in the male. Female mice were uniformly more sensitive than males when irradiated with gamma rays or fast neutrons [U5]. This was again attributed to the induction of tumours of the ovary or to hormonal disturbances. However, the RBE for neutrons against gamma rays was not significantly different between the two sexes.

243. After single-dose irradiation of one hybrid and five inbred strains of mice (200 kVp x rays, doses between 0.85 and 1.15 times the $LD_{50/30}$) strain differences within sex were not significant. The two sexes had, however, significantly different responses averaging for the males 0.28 days lost per R and for the females 0.81 days per R (all strains pooled). Differences tended to disappear when corrections were introduced for animals dying of leukaemia and of ovarian tumours. It should in fact be recalled that there are sex differences in the induction of leukaemia among different mouse strains [U14]. Life shortening in all strains after an acute treatment about the $LD_{50/30}$ seemed to be characterized by a single parameter applicable to all strains and sexes and expressed as a constant number, 28 days of life lost per 100 R. Combination of this primary injury term with other secondary parameters may provide equations predicting the final long-term effect for any combination of normal life expectancy, leukaemia incidence, ovarian tumour incidence and dose [G4].

244. In the experiments of Lindop and Rotblat [L1] the shapes of the survival curves were similar for males and females SAS/4 mice but showed small consistent differences in favour of a higher resistance for males. These differences were not such, however, to warrant a separate analysis of the life-shortening effect in the two sexes. Moos [M14] also reported no difference in longevity response with respect to the sex of irradiated animals (mice, CFW strain, 40–50 or 140–150 days of age) in the interval of daily dosage between 2 and 256 R d^{-1} of 400 kVp x rays.

245. In the series by Kohn and Guttman [K6] the animal's sex was shown to be an important factor for life-span shortening in CAF1 mice. During much of the adult life the female animals reacted to doses below 25 Gy, although the slope of the female dose-effect relationship between 2.5 and 4.0 Gy was less than that of the males. Late in life the females became less sensitive than the males. Here again, changes in the endocrine balance were reputed to be at the origin of such phenomena, in the sense that the female's changes in sensitivity may have been a manifestation of the increase and fall of ovarian endocrine function. Such a hypothesis is in accordance with the fact that continuous low-level treatment with oestrogen hormone increased the age-specific mortality rate of the BALB/c female mouse after x-irradiation [K13]. It is of interest that in the CAF1 strain the reduction of life span was not correlated with the induction of ovarian tumours, which were actually depressed and not enhanced at the doses used.

246. Sacher and Grahn [S4] showed that LAF1 female mice after life-time irradiation were slightly more sensitive than males in the 5–10 days period of survival but became consistently more sensitive in the 17–40 day period. In the mice surviving during the periods of 10–15 and of 40–130 days the difference between sexes was either much smaller or non-existent; at survival times in excess of 130 days females accumulated consistently higher doses than males. In the large experiments of Upton et al. [U7] on RF/Un mice no obvious effect of sex can be traced from the data. Protraction factors in male animals irradiated with gamma rays at low dose rates appeared to be in the same direction as in female animals but considerably more pronounced. Consequently, RBE data were different in the two sexes.

247. Sex differences in the A/J strain in regard to radiation-induced life shortening (x rays, single exposures, 150 to 600 R) were also seen by Storer [S30]. At exposures of 600 R the female animals lost nearly four times as many days of life as did the male mice. Qualitatively similar results in male and female mice were observed in the experiments of Ainsworth et al. [A7] and the apparent quantitative differences in response after single and fractionated gamma-ray and fast-neutron experiments could not be attributed with certainty to differences in body size (and therefore absorbed doses), to hormonal unbalance resulting from damage to the ovaries or to differences in the spontaneous or induced tumour incidence.

248. Holland and Mitchell [H10] studied life shortening (300 R of 300 kVp x rays) on four inbred male and female mouse strains (C3H, BALB/c, RFM, C57BL/6), on two hybrid strains (C3CF1 and B6RFMF1) and a four-way cross between both F_1 hybrids, C3CB6RFM. At the time of irradiation the mice were 5–6 weeks of age. In all strains and crosses a significant life-shortening effect was observed. Females were about 1.5 times more sensitive than males of the same strain and these data suggested a general and constant effect of sex under all conditions. Unfortunately, the data on the various modes of death are not yet available for a more complete interpretation of these observations. A higher sensitivity of RFM female mice accounted for by a rapid rise of life shortening over the dose range up to 0.5 Gy was also reported by Storer et al. [S44].

249. In experiments by Moskalev et al. [M22] performed on rats treated with fast neutrons (0.085 to 5.1 Gy) or 500 MeV protons (0.28 to 10 Gy) observations on life shortening were also reported. The average life expectancy of rats irradiated with the fast neutron beam did not depend on the animal's sex. The data by Rust et al. [R2] on the guinea-pig showed that the females were more responsive to life shortening by chronic gamma-ray exposure. This differential effect could not be correlated with the induction of tumours of the female generative organs.

2. Body weight

250. Body weight as a variable affecting long-term animal survival was investigated in mice by Holland et al. [H10]. Within the same sex, there were substantial differences in sensitivity among the strains tested and these differences were highly correlated with body weight at 6 weeks of age. The heavier animals were less resistant to radiation, i.e., showing a higher degree of life shortening. Previous analysis of body weight versus radiation resistance based on early effects and on mature animals had given opposite results [Q1, G12, R5] in that, within the same strain, adult animals with a higher body weight were shown to be more resistant.

However, in adult animals body weight is thought to reflect the general state of health and fitness and it is conceivable that the heavier (i.e., the healthier) animals, may be more resistant to a given radiation insult. If the comparison is among different strains and on maturing animals, given a more or less uniform state of health, the data of Holland et al. [H10] would be compatible with the hypothesis that body weight may be a measure of the rate of maturation and it is not inconceivable under these conditions that body weight is a parameter better correlated with radiation resistance than chronological age. It may also be further suggested, as the authors do, that some of the strain-specific differences in radiation sensitivity already discussed in subsection II.A.1 may be due to differences in the rate of maturation of the various strains or to other non-specified processes which are in turn highly correlated with maturation rate.

C. AGE AT IRRADIATION

1. Irradiation in utero

251. The available data on life shortening induced by in utero irradiation are examined first. According to Nash and Gowen [N9] who evaluated in multifactorial experiments the life spans of 647 mice irradiated in utero with exposures of 20 to 320 R at four different gestational ages, the reduction in longevity induced by the radiation treatment depends on the genetic constitution and sex, as well as on the dose and on the gestational age at irradiation. Rugh, Duhamel et al. [R6] followed the long-term survival of mice irradiated with mid-lethal in utero doses at 0 to 5 days post-conception (p.c.) and found no modification of the life span in animals that survived later than 30 days post-partum. This observation indicates that after the neonatal period there is little permanent damage of the in utero irradiation.

252. Non-inbred male and female RF mice were exposed to x irradiation in utero at ages ranging from 9.5 days p.c. to 1 year of extra-uterine age. Shortening of life span by doses of 50–400 R was more effective per unit dose at the higher exposure levels of 300–400 R and in age groups of 40–70 days. For exposure in utero life shortening was consistently less marked than for exposure after birth, but irradiation with high doses in utero (300 R at 14.5 days p.c.) gave rise to growth and developmental effects in a very high percentage of the animals (particularly males) which caused death in 6 to 7 months for causes which were not clear [U12].

253. Friedberg et al. [F8] tested the effect of fast neutrons (0.15 Gy) on mouse embryos in the pronuclear-zygote stage for their ability to shorten the life span or to induce tumours in animals surviving at least 30 days after birth. No differences were found between irradiated and control animals of the same sex for the following end-points: mean ages at death, cumulative mortality distributions and incidences of the principal neoplastic diseases. Sasaki et al. [S49] observed a significant shortening of life in mice irradiated at 16–18 days p.c. with 200 R of x rays. Mean life span was reduced by about 13% to 16%. Slight changes of the tumour spectrum were observed, with no excess of lympho-reticular tissue tumours. Female mice had a higher incidence of lung and pituitary tumours, while a prevalence of lung and liver tumours was found in males.

254. For the rat there are data by Reincke et al. [R7]. In her experiments Wistar animals were administered a single whole-body x-ray exposure of 270 R at 5 days before birth and at 13, 49 and 121 days after birth. Among other observations, life expectancy was reduced by about 3 to 6 months and this reduction was not influenced apparently by the age at exposure. In a subsequent paper Reincke et al. [R8] reported that 220 R five days before birth resulted in a long-term survival not significantly different from controls.

255. Sikov, Resta and Lofstrom [S31] studied the long-term mortality of rats surviving at the time of weaning, exposures of 20 or 100 R at 10 days p.c. and of 50 or 185 R at 15 days p.c. Life-span reduction appeared to be greater in females than in males where the effects observed were of doubtful significance. An interesting observation was that the $LD_{50/30}$ of an irradiation performed at 100 days of age decreased as a linear function of the dose of a previous irradiation carried out in the pre-natal period at all developmental ages. In the opinion of the authors such a linear dependence may imply a general decrement of fitness as a result of pre-natal exposure.

2. Irradiation during extra-uterine life

256. Experiments where the effect of the extra-uterine age has been examined as a biological variable affecting radiation-induced life span shortening are fairly numerous and cover a variety of different species, strains and conditions of irradiation. Kallman and Kohn [K7], Kohn, Kallman and Berdijs [K1] and Kohn and Guttman [K6, K14] studied the life-shortening response to x rays of male and female CAF1 mice, with special regard to the influence of age at irradiation. Exposure conditions were: 250 kVp x rays at a dose rate of about 0.4 Gy min^{-1} with two single doses of 2.6 or 5.2 Gy and a fractionated dose of (2.6 x 2) Gy given 8 days apart. Mice were irradiated when young (144 and 164 days of age) or old (385, 550 and 730 days) and followed with detailed pathology at death. The age interval covered in the mouse would correspond in man to a range of ages between 18 and 65 years. The last publication of Kohn and Guttman [K6] gives an account of the whole set of data, including a re-analysis of other previous data obtained on BALB/c mice irradiated at 5 months, 1.2 or 1.4 years of age. In general, some reduction of the life span was observed, although in some cases evidence of life shortening was small or even absent.

257. Old adult mice tended to show less life shortening than young ones, although the difference was not the same in all strains used owing to genetic differences. During much of the adult life the female animals were more sensitive to doses below 2.5 Gy. Later in life, however, the females, at least in the CAF1 strain, became less sensitive than the males. The life shortening in older animals was not associated (as in younger ones) with an increased induction of neoplasia, but rather with a decrease. In the CAF1 mice irradiation tended to reduce the number of animals dying with tumours and the tumour-bearing animals lived as long or longer than the non-tumorous ones. Aging (both premature or accelerated) as such was an inadequate explanation for these data because the irradiated animals appeared to age abnormally and usually died sooner than controls, the effect depending on age at exposure, sex and dose [K6].

258. Boone et al. [B19, B20] on CF1 female mice at ages from 1 day to 18 months reported changes in life shortening as a function of age at exposure. More precisely, after 4 Gy of x rays life shortening amounted to 40% of corols when in the age interval from 1 day to 3 months; it was then gradually decreased to 32, 14 and 7% of controls at 6, 12 and 18 months of age, respectively. Thus the life-shortening response decreased as a function of age. This effect could not be traced to the incidence of leukaemia or of ovarian tumours which were evaluated separately in these experiments. In other strains the situation may, however, be different. In the C57BL mouse, for example, age is a condition which alters the sensitivity to lymphoma induction. Kaplan [K15] showed in fact on animals at 2 weeks and at 1, 2, 3 and 4 months of age that lymphoma incidence is higher and the appearance time earlier for irradiation at the young ages than at the older ones.

259. Upton et al. [U5] considered in detail the variable "age at exposure" in relation to the life-shortening effects in both sexes on 9–12 week old mice. No differences were found of any significance for either sex and this observation was at variance with what was seen in the same animals with regard to early mortality, which was highest among young animals. Moos [M14] was also unable to find differences between the longevity of young (40–50 d) or old (140–150 d) mice within the range of doses of 8 to 128 R d^{-1}. However, such differences were seen at exposure rates of 2, 4 and 256 R d^{-1}, and the old mice were less resistant under these conditions.

260. In a series conducted on about four thousand RF/J female mice Storer [S19] examined the age-dependent changes in radiation sensitivity in normal and previously-irradiated animals. He obtained life-table data on all these mice, about one-half of which received at the age of 90 days 400 R of 250 kVp x rays. The rate of mortality from all causes in the irradiated mice showed marked departures from the Gompertz equation and this dose of radiation shortened the median life span to 63% of the control animals. Mortality rates for all causes other than leukaemia gave reasonably good Gompertz fits to the control and irradiated populations: life shortening amounted to 24 days per 100 R under the assumption of linearity between dose and effect. No latent period was found between exposure and the time when the mortality increase became detectable. The mortality rate of irradiated mice was at all times higher than in control animals. The $LD_{50/30}$ of the control and irradiated mice tested between 120 and 560 days of age declined linearly with age without effect attributable to the previous 400 R exposure. The mean after-survival following exposure to 100 R d^{-1} also declined with age in a complex manner, irradiated animals being generally more sensitive than controls. Finally, recovery rate tested by split exposures was found to decline sharply with age: the rates estimated in previously-irradiated animals were much lower than those in non-irradiated animals of the same age. From all these data Storer [S19] concluded that the tests applied were in fact measuring the damage inflicted to different cellular systems each of which aged at a different rate, in contrast with the notion of a non-specific life-shorteninig action.

261. Lindop and Rotblat [L12] made a systematic study of the effects of age, giving small single sublethal exposures of 15 MeV x rays to SAS/4 mice. They found that radiation given at 4 weeks of age produced an effect that was linear with dose in the range of 50–780 R. The life shortening produced by 100 R was about 4 weeks for mice irradiated at the age of 1 week; it increased to about 6 weeks for 5 week-old animals and then decreased steadily to a minimum of approximately 2 weeks for animals irradiated when 70–90 weeks old. A given reduction in life time in old animals represents a much greater loss of the remaining life than the same reduction produced at a young age. When the effect was expressed as a percentage of the remaining life span the increase in response at 5 weeks of age was still evident, followed by oscillations of the response between a maximum of 6% and a minimum of 3% reduction of the remaining life span.

262. In a subsequent paper [L16] life shortening was studied as a function both of the age and of the oxygenation conditions of the animals. For animals breathing air, assuming linearity of response at all ages, the life-shortening effect at 1 day and at 1, 4, 8 and 30 weeks of age was found to decrease as a function of age from 7.6 to 2.7 weeks per 100 R. Under hypoxic conditions a considerable reduction of the life-shortening effect was found at all exposures, amounting to a factor of three for mice irradiated at 8 and 30 weeks of age. However, when the mice were irradiated at 1 day or at 1 week of age hypoxia changed the linearity of the dose-response relationship to a convex upward curve, such that the protection afforded by hypoxia at low doses was large but at high doses small. The authors could not suggest a firm interpretation for such findings.

263. Johnson [J2] set up a simulated experiment where he computed the life shortening as a function of age at irradiation utilizing parameters and life-functions taken from Sacher's [S2] analysis of the LAF1 male mice exposed to fission neutrons and gamma rays in the Greenhouse experiments [U5, F2]. Irradiation was simulated by a displacement of the Gompertz function on the time axis. Johnson was thus able to show that a decrease in the life-shortening effect with increasing age was a necessary consequence of the hypothesis that ionizing radiation accelerates certain of the processes that characterize natural aging. The relationship of life shortening to age at irradiation varies however according to the actual form of the Gompertz function.

264. Age-dependent changes in the response to radiation (250 kVp x rays) were also observed in other experiments by Cosgrove et al. [C20] where LAF1 mice were given from 300 to 1200 R whole-body or partial-body when 10 weeks or 1 year old. At any given exposure level, a higher incidence of glomerulosclerosis was observed in animals irradiated at the younger age, presumably because the older animals did not survive long enough to develop as high an incidence of the diseases. Longevity was also reduced and the incidence of ovarian tumours increased in the young but not in the old irradiated animals.

265. Some data by Storer [S20] in mice are of interest to the problem under discussion. BDF1 females, when three months old, were exposed at doses of 0, 100, 300, 500 R of 250 kVp x rays. Median survival time was found to be reduced linearly with exposure and the slope of the linear non-threshold regression function amounted to a life-span reduction of 45 days/100 R. The changes in radiation response with advancing age and for various radiation exposures were evaluated in two ways: beginning at various ages, samples of previously-irradiated surviving animals were tested for their ability to survive successive daily exposure of 100 R; or, alternatively, they were tested for their LD_{50}.

266. Thirty-four samples of previously exposed animals were tested at ages ranging from 120 to 960 days with 100 R d^{-1} and resistance was assessed as mean survival time after initiation of this treatment. Resistance was found to follow a long plateau (the duration of which was dose-dependent) and to decline sharply at advanced ages. Pre-irradiated animals were less resistant than non-irradiated control mice of the same age and showed an earlier onset in the decline of resistance. Since the variability in radiation resistance increased with age and the differences in sensitivity between irradiated groups were reduced when the relevant comparisons were conducted at equal levels of mortality, Storer [S20] concluded that the test treatment was not actually measuring a phenomenon intrinsic to the aging process but was more simply an estimate of the incidence of diseases in the population examined. Similarly, the $LD_{50/30}$ test showed that resistance followed the same dependence on age as after the protracted exposure test. The conclusion was that the earlier onset in the decline of resistance of the more heavily exposed animals was in fact correlated with the earlier onset of morbidity in these groups.

267. In addition to presenting data on CBA female mice given acute doses of radiation (4.5 Gy of 250 kVp x rays at four ages from 100 to 670 days), Mole [M2] pointed out some difficulties in the analysis of such data. If the mean after-survival time is taken as the criterion of effect, then it is clear that the radiosensitivity of the animals decreases with age. But if it is assumed that the radiation-induced mortality depends on the mortality of the non-irradiated animals and the Abbott's correction is used to derive the net radiation-induced life shortening, then the curves of cumulative mortality show little difference with age. Mole also refers to similar unpublished data obtained with protracted exposures to gamma rays and fission neutrons. Such observations may imply that the life-shortening process proceeds independently of natural aging and thus the two phenomena are not correlated. However, in the absence of further information about natural aging itself, it should simply be realized that opposing conclusions may be reached by different analyses of the same experimental data.

268. In experiments by Yuhas [Y3] the sensitivity was studied of 4 to 24 months old C57BL/6J female mice to the life-shortening effects of 1400 R of 300 kVp x rays. Radiation was given in 10 equal fractions within 12 days. In the 4 months old animals the resulting life shortening amounted to 148 days but in older animals the same dose was considerably less efficient: in fact, life shortening amounted to only 30 days at 9 months and at the three oldest ages (15, 18 and 24 months) there was actually a lengthening of life of the order of 53 to 65 days.

269. The decreasing response with increasing age confirmed previously-reported data by Lindop and Rotblat [L12], Kohn and Guttman [K6], Jones and Kimeldorf [J3]. The data also confirmed the life lengthening in mice irradiated at very old ages. The compatibility of these findings was tested in relation to five different hypotheses. The data could not be accounted for in terms of insufficient time for expression of injury; or of the identity of normal and radiation-induced senescence; or of selective changes in the population of mice induced by early mortality; or by normal "attrition". They were instead consistent with the hypotheses that the sensitivity to the induction of certain diseases decreases with advancing age, irrespective of the time required for their expression; or, alternatively, that radiation given in old age may have a therapeutic effect on some neoplastic growths in these animals.

270. Ainsworth et al. [A7] examined the problem of age-sensitivity in B6CF1 male mice after single doses of 0.8 Gy of fast neutrons or 2.69 Gy of gamma rays. The mice were 115, 194 or 278 days old at the time of exposure. Irrespective of whether life shortening was expressed as a per cent reduction of the after-expectation of life or as per cent life shortening, there was some decrease with age of the effect per unit dose and this was shown to be greater after gamma than after neutron irradiation. The contribution of this change in sensitivity to the "sparing" effect of fractionation during a long course of treatment is thus proportionately greater with low- than with high-LET radiation. Life shortening and carcinogenesis by x rays in mice irradiated neonatally was also studied recently by Sasaki and Kasuga [S61] who attributed the reduction in mean life span to the high induction rate of liver and pituitary tumours and of thymic lymphoma.

271. The data available for the rat are similar to those just discussed for the mouse and show a dependence of life shortening on the age of irradiated animals. Jones and Kimeldorf [J3] treated male Sprague-Dawley rats with about 2.2 Gy of fast neutrons obtained by the Be (p,n) B reaction. They belonged to 5 different age groups of 1, 3, 10, 15 and 21 months. Survival rate and life expectancy were decreased and the age-specific death rate was increased by comparison with sham-irradiated litter-mate controls. The magnitude of these effects was inversely related to age at exposure from post-infancy up to middle age (10 months). At older ages there was no discernible change in life span with respect to control rats. In the opinion of the authors these data may be compatible with Neary's theory [N1] postulating an induction period in life which may be shortened by various treatments and an ensuing period of development, which would be relatively constant in duration. In the male Sprague-Dawley rat the period of development would begin in the age range of 10 to 15 months.

272. In a subsequent paper [J4] the relevant data for tumour induction were reported. There was an excess proportion of animals with one or more palpable tumours (compared to the control groups) after exposure at all except the oldest age (21 months), in spite of a significant life shortening only after exposure at the three younger ages. The percentage of animals with palpable tumours was higher in all groups (even for the group exposed at 21 months) in comparison with the control tumour-bearing animals. It should be recalled that this strain of rats has normally a very high incidence of radiation-induced tumours, particularly of the skin and skin adnexa, which may have altered to an unknown extent any more precise estimates of life shortening.

D. CONCLUSIONS

273. From all the data reviewed it may be concluded that among the biological variables determining the life-shortening response to irradiation there is sufficient data for discussions on the genetic constitution and on the influence of sex and of age at irradiation.

274. It is easy to understand that different species may show a different response in relation to the longevity of

each species and to its specific physiologic and pathologic characteristics. It is less easy to trace a common parameter or a set of parameters from which one can evaluate the sensitivity of a species and thus construct a susceptibility scale for inter-species comparisons or extrapolations. The analysis of survival parameters according to the actuarial model of Gompertz; the calculation of semi-empirical parameters such as the excess death-rate divided by the exposure rate in chronic irradiation experiments; the evaluation of the life-shortening effect normalized as a percentage of the control value and as a function of the acute $LD_{50/30}$; the hypothesis of a common life-shortening effect per unit dose normalized according to the respective life span of the species compared; were all criteria proposed in order to achieve the scopes mentioned above. On the basis of one of these parameters approximate scales of radiosensitivity were in fact proposed, of which the majority were obtained from gamma-ray chronic irradiation data (see Table 3). Most of these data agree in showing that the rat, the dog and the mouse are about equally sensitive, while (on the basis of very scanty data) the rabbit would appear to be less susceptible and the monkey, the goat and the guinea-pig perhaps more sensitive in terms of life lost per unit dose. Susceptibility for man is reported in one case to be higher (perhaps by a factor of two) and in another case to be similar to that of the dog and the mouse. It does not appear from the data that the differences between the various mammalian species tested is very large and the range within which all species may be included may possibly be a factor of two in both directions (taking the mouse and the dog to be in the middle of an ideal radiosusceptibility scale) or about a factor of five over the whole range of radiosensitivity of the species tested.

275. Intra-species or inter-strain variability has also been studied in the mouse, the species where different genetically-homogeneous strains are more easily available. When adequately looked for, differences between various strains (for the same sex) were easily observed. Little formal genetic analysis of the radiosensitivity parameters has been attempted and most of the data refer to irradiation for the duration of life. In general the amount of life shortening is correlated with the control mean survival time, in the sense that the proportion of life lost per unit dose is similar for the various strains having different life spans. Life shortening is also correlated with the expression of the pathological characteristics of the strains, since animals prone to the development of leukaemia and of ovarian tumours (the cases which have been more thoroughly analysed) show a greater amount of life shortening per unit dose. It is possible that the differences in response of the various strains may also reflect the maturation rate of the genotypes irradiated, as some data on the correlation of the response with the weight of maturing animals would suggest. When allowance is made for all these variables the mouse appears to respond according to a basic parameter, whereby the number of days lost per unit exposure for acute single doses equals 0.28 d R^{-1}. On this basic dose-response relationship all the factors mentioned above (in addition to other factors for sex and age) combine to give the final compounded value of effect for each particular situation.

276. In a few cases of the data reported, either no difference or small differences in sensitivity to life shortening were reported between male and female animals. In most other cases however invariably a higher sensitivity of the female animals was observed. The sensitivity factors reported were between 1.5 and 4. Ovarian dysfunction induced by irradiation and the incidence of ovarian tumours were generally reported to cause this differential effect, which tended to disappear when the data were appropriately corrected for the incidence of tumours of the genital tract or of leukaemia. The conclusion to be drawn from the vast majority of the data is that, within strain, sex has a constant effect which is mostly manifested by an increased incidence of tumours of the female genital tract.

277. The data for the rat show no obvious difference in results for either sex, while the results for the guinea-pig, in analogy with most data for the mouse, show an increased sensitivity of the females attributable to tumours of the genital tract. Body weight may also be a biological variable of interest in the final expression of life shortening, but it appears to be of rather minor importance.

278. With regard to the effect of age, after allowance for other conditions influencing reduction in longevity (genetic background and sex) most data show that irradiation in utero of the mouse produces less marked life shortening than irradiation during post-gestational ages. There may even be no long-term effect at all on the irradiated animals, particularly those surviving irradiation at the early gestational ages. The experience in the rat shows some reduction of the life span for irradiation of the foetal animals, but the effects observed are of doubtful significance and in any case not substantially different from the effects of the same doses given soon after birth.

279. With regard to the effect of extra-uterine age, the data are rather numerous but only pertain to the mouse and the rat. In both these species irradiation late in life invariably produces—all other factors being equal—less life shortening than treatment at younger ages. In the one case where no effect of age was found [U5] the range of useful ages examined was too short for any effect to be seen. In some instances the reduction of life shortening with age is preceded by a phase of increased susceptibility of the animals up to the time of sexual maturity [L12]. In other cases irradiation in old ages may even produce (for moderately high doses) an increase, rather than a decrease, of the duration of life [Y3] or no change with respect to control [J3]. The change in sensitivity between young and old animals may be up to a factor of three when the life shortening per unit dose is considered; if the effect is evaluated in terms of the percentage loss of the remaining life span, this amounts to a few per cent. In some experiments a correlation may be established between the degree of life shortening and the induction of tumours or of nephrosclerosis, but in other cases no such correlation may be found.

280. If life shortening is primarily or exclusively due to the induction of excess tumours, each of which has a distribution of times of expression, the age-dependence of life shortening may be due to the influence of latency on the life tables of the irradiated population. Thus, because of competing risks, some lives will be over before the induced cancers are expressed, an effect which obviously increases with the age at exposure. No specific test of this possibility has been reported in the literature. It may, however, account for all age-dependence. If it should only account for part of it, then the remainder may be attributed to a decreased susceptibility of certain pathological conditions. Another possi-

bility is that radiation in old age may have a therapeutic effect on some (presumably neoplastic) conditions already under development at irradiation. Caution should be used in the analysis of data from experiments in which animals were started on irradiation courses at variable initial ages as different analytical approaches to the data, in addition to implying different hypotheses of action, may lead to variable conclusions as to effect of age on the animals' radiosensitivity.

III. MODIFYING FACTORS

A. PHYSICAL TREATMENTS

281. Among the treatments that modify the life-shortening response to irradiation those of a physical, chemical or pharmacological, and biological nature are reviewed in this chapter. It should be realized that information on these subjects is very heterogeneous and not suitable for generalized conclusions. A review on life shortening, including also some original data, centred on various chemical and biological modifying factors, has been recently published [A16]. Among the physical treatments, those referring to irradiation given in combination with low- or high-temperature treatments have already been reviewed in subsection I.B.6.

282. In experiments by Gambino et al. [G13] Long-Evans female rats were irradiated over the whole body or only on the adrenals with 500 R and then exposed for three hours daily to 0°C. Reduced longevity was among the effects (retarded growth, cataract, fur greying, tumours) seen at long term in the whole-body-irradiated (but not in the adrenal-irradiated) rats. It amounted to about 20% of the normal control life span and it was not modified by the cold treatment. Other effects were also not modified, except perhaps for a slight reduction of the accelerated tumour onset seen in whole-body irradiated animals. Interpretation of these data is made difficult by the fact that the cold treatment as such has produced life-span reduction and changed the spectrum of diseases with a prevalence of inflammatory pulmonary conditions and a relative decrease of neoplasia [H11].

283. Some information is also available in regard to the modifying effects of a specific stress on long-term mortality of irradiated animals. Ordy et al. [U1] irradiated C57BL/10 mice on the brain with 5 Gy of 20 MeV deuteron beam with a highly significant decrease in longevity of the irradiated animals. They also observed a reduction of the late mortality in the animals undergoing periods of daily stress (cold, electrical shock, or both). Such an effect appeared to be statistically significant in some, although not all, groups of animals and was observed irrespective of whether they had been irradiated or not.

284. Reincke et al. [R9] submitted Wistar rats at 120 days of age to starvation for 9 days, water deprivation for 6 days or forced swimming. Animals that had passed through such severe stress before irradiation (280 R of x rays, single dose), lived longer than those receiving irradiation only. The differences in the survival curves were significantly different in three out of six possible comparisons. No influence of stress was observed on the tumour incidence. There was also no obvious difference in the swimming ability and in the decline of this ability with age between normal mice and mice irradiated with a single acute dose of 2.24 Gy of x rays at 20 weeks of age [N12].

B. PHYSICO-CHEMICAL AND PHARMACOLOGICAL TREATMENT

1. Anaesthesia, oxygen and hypothermia

285. The effects of hypoxia induced by various treatments will first be examined. Lindop and Rotblat [L12] showed some protective action of anaesthesia against early and late death. Protection appeared to decrease with dose rate in the interval 4.8–1620 Gy min^{-1}. Protection could not be ascribed to low oxygen tension in tissues by the anaesthesic drug, because there was no summation of effects by the anaesthesia and dose rate, particularly at the high dose rates. In other series of experiments Lindop and Rotblat [L12, L16] showed that when SAS/4 mice, anaesthetized with 20–60 mg/kg of Nembutal and breathing nitrogen 30–50 second, were exposed to a beam of fast electrons (15 MeV, 400 Gy min^{-1}) they had a considerably reduced life shortening, in comparison to other animals exposed in air. The protective effect of hypoxia was influenced by the age at exposure in that a dose-reduction factor of about 3 due to the nitrogen breathing was observed in animals of 8 and 30 weeks of age. In mice of 1 day or 1 week of age the shape of the dose-life shortening relationship was changed from linear to curvilinear, giving rise to a larger protection factor at low doses and a very small one at high doses.

286. Hypoxic hypothermia was also tested by Hornsey [H12] with respect to the possible modification induced by this treatment on life span. While hypothermia induced at the time of irradiation offered considerable protection (a factor of about 2.8) to the haemopoietic system whose failure is responsible for the early death of the animals, it did not protect to the same extent against long-term death. For the same dose administered to normal and to chilled animals the expectation of life was greater for the latter, but the nature of the data did not allow any precise estimate of the protection factor afforded by hypoxic hypothermia. Thus it appears that the protection by hypoxia already shown against the acute radiation effects extends also to the long-term effects, although perhaps not to the same degree.

2. Chemical radioprotective drugs

287. On the subject of chemical radioprotection Maisin et al. [M32] reported that mercaptoethylamine [MEA] (10 mg/rat, given 5 minutes prior to irradiation) was active in reducing the mortality rate during the first month post-irradiation but was incapable of modifying the late rate of mortality following irradiation of the head (1000–2000 R) or of the abdomen (900–1500 R). This drug was also without effect on the late mortality following irradiation of the abdomen and of the whole body with 600 R. In another series of experiments, MEA (425 mg kg^{-1} d^{-1}) and 2-aminoethylthiosulfuric acid (1000 mg kg^{-1} d^{-1}) were administered in the drinking water to Swiss mice that were exposed for the duration of life to ^{60}Co gamma rays at dose rates from 1 to 5 R h^{-1}. Mortality data were indistinguishable from those of controls drinking tap water and it was therefore concluded that neither of the drugs (which are active in the prevention of early mortality) had a protective action against chronic irradiation effects at drug levels accepted by the mice [A8].

288. Cosgrove et al. [C23] tested the effect of the radioprotective drugs aminoethylthiouronium (AET)

on (101 × C3H)F1 female mice following a wide range of x-ray exposures (300–1800 R) with or without parallel treatment with isologous bone marrow drug treatment was found to have a marked protective effect against early lethality, but its effectiveness in protecting against a reduction in longevity was equivocal. No effect was found on tumour induction, nephrosclerosis and lens opacities while induction of thymic lymphomas and greying of the fur were reduced by the drug treatment. Thus AET protected against some but not all long-term somatic effects and in no case the dose reduction factor approached that obtained against the acute lethal effects of radiation (40–50%). In another experimental series performed on male and female LAF1 mice by the same workers [C20] administration of AET before irradiation led to some reduction of kidney sclerosis but was again without effect in regard to the induction of tumours of the ovary or to the greying of the fur.

289. An attempt to maximize protection against 9 MeV irradiation was reported by Shewell and Wright [S33] who combined four different methods of protection: administration of cysteamine before irradiation, irradiation during nitrogen hypoxia, and administration of syngenic bone marrow and of antibiotics after irradiation. The $LD_{50/30}$ for the protected mice (C3H/Bi, 15 weeks old) was increased by a factor of 3.8 with respect to unprotected animals and this factor persisted throughout the long-term follow-up of the mice surviving early lethality. Greying of the hair and epilation also gave a dose-reduction factor of 3.8, but the appearance of radiation cataracts did not conform to the same pattern. It was therefore concluded that the protection afforded against the different effects had variable dose-reduction factors for each effect tested.

290. In Nelson's [N10] experiments irradiation followed various fractionation schedules: 80 R at intervals of 1 day up to total accumulated exposures of 640–1920 R; 80 R at intervals of 3 days for the whole life span; 160 R at intervals of 1, 3 and 7 days up to exposures of 480–1760, 1600–3250 and 2880–5760 R, respectively. Cysteamine at 4 mg per day for 24 days or at 4 mg per day twice a week was used as a chemical protector. The drug treatments by themselves, as well as the injection of physiological saline twice a week for the whole life, modified drastically the mean and median survival time of the irradiated animals. However, cysteamine unequivocally protected against mortality. The magnitude of the protective action depended on the accumulated exposure and on the time interval between fractions. At low accumulated exposures radiation injury was insufficient to show significant differences between protected and control animals, while for high exposures radiation injury was supralethal. The effect of fractionation intervals was often variable. No single dose-reduction factor could be derived from these experiments since the values of this factor vary in each series with exposure, fraction size and fractionation interval. However, cysteamine was shown to protect not only against the acute injuries but also against fractionated doses in the sublethal range. Any more precise assessment would be unwarranted owing to the toxicity of the drug and to the adverse effect of the administration procedure which influenced the survival of the animals rather substantially.

291. Yuhas [Y1] reported that the radioprotective agent WR-2721 [S – 2-(3-amino propylamino) ethyl-phosphorothioic acid] protects against acute death more efficiently than it can protect against the life-shortening effects of radiation, although the exact extent of this protection could not be directly and precisely estimated. It has, however, been shown [D6] that the ability of the drug to protect against life shortening varies with the size of the dose of radiation.

292. Storer [S30] investigated on A/J and C57BL/6J male and female mice the effect of four radioprotectors administered i.p. 15 min prior to irradiation. They were: paraaminopropiophenone (PAPP) at 40 mg/kg, mercaptoethylamine (MEA) at 200 mg/kg, amynoethyl-thiouronium (AET) at 200 mg/kg and 5-hydroxytrypt-amine (5 – HT) at 100 mg/kg. X rays of 300 kVp were given acutely at 150, 300, 600 R to the control animals and at proportionately higher exposures to the protected mice. Dose-reduction factors in the region of 1.5–1.8 were found for the various drugs with respect to the $LD_{50/30}$ of the x rays and the drug treatments had no significant effect on the longevity of the non-irradiated mice. Within the range of exposures tested, mean survival time decreased as a function of dose (with some sex and strain differences in the amount of response) with concave upward relationships, although the hypothesis of linearity could not entirely be rejected. The pooled data (all strains and sexes and drugs together) for control and for protected mice showed that mean life shortening was a curvilinear function of dose both with and without drugs and that the radioprotective treatment did afford some protection against life shortening. However, the extent of protection varied with strain, sex and drug. PAPP was found to be the most effective, followed by MEA, 5–HT and AET. The average dose-reduction factor for all agents and mouse groups was 1.35. All this shows that protection against life shortening is qualitatively and quantitatively different from protection against the acute lethal effects and results from a complex interaction of factors depending on strain, sex, drug and dose of radiation.

293. Other experiments on the subject of chemical radioprotection were reported by Maisin et al. [M8, M23] and summarized in Maisin et al. [M10, M24]. BALB/c and C57BL mice were given 100–2000 R acute exposures of 250 kVp x rays; causes of death were classified among 12 different groups and analysed for competing risks of death. In the BALB/c strain life shortening had a linear dependence on dose, except perhaps at very high doses. When AET or a mixture of radioprotectors (glutathione, cysteine, AET, MEA and 5-hydroxytryptamine) were administered prior to irradiation with various schedules of administration, they showed a significant protective action against late death. Under the hypothesis of linearity, the dose reduction factor for AET was estimated to be 1.23 ± 0.05 and that for the radioprotective mixture 2.1 ± 0.2, which values are significantly smaller than those applying to acute lethality (1.7 and 2.8 respectively). Radiation-induced shortening of life was attributed to specific diseases (thymic lymphoma, myeloid leukaemia, glomerulosclerosis, non-tumorous lesions of the lung). Protection was most effective against thymic lymphoma, but was also discernible for leukaemia and nephrosclerosis. In the C57BL mouse the data, although less complete, were essentially similar.

294. Maisin and his collaborators [M24] performed also another experiment where the mice were given fractionated treatments. Using a variety of different doses and fractionation intervals they showed for the irradiated-AET-protected mice a dose-reduction factor of 2.1 at 50% life shortening. Radioprotectors decreased significantly the incidence of thymic lymphoma, but

did not modify other causes of death. A paper was also reported on the same subject by Philip [P2]. In this case AET (300 mg/kg body weight) or 5-HT (75 mg/kg) were given i.p. 10 min prior to irradiation with 400 R (250 kVp x rays) to young Swiss female mice. Single exposures of 100, 200 and 400 R were also given to normal, non-protected mice. Life-span shortening, incidence of thymic or myeloid leukaemia, and the occurrence of tumours of breast, ovary, lung and uterus were the end-points evaluated. Dose reduction factors of 1.7 for AET and 1.4 for 5 – HT were calculated for long-term survival. These values were close to those obtained for short-term survival. For the induction of all tumours the respective dose-reduction factors were 1.5 and 1.4; for the induction of thymic lymphoma 1.8 and 1.6.

C. BIOLOGICAL TREATMENTS

1. Bone marrow transplantation

295. Syngeneic marrow transplantation was not very effective in protecting against reduction of longevity in Cosgrove's et al. [C23] experiments. This treatment inhibited the induction of thymic lymphoma, in accordance with other data [C13, K16, I12, C24] but did not alter the incidence of glomerulosclerosis, solid tumour induction (ovary, breast, lung, uterus) or lens opacities.

296. Experiments on the late somatic effects in syngeneic radiation chimaeras were performed by Covelli et al. [C13] on (C57BL × C3H)F1 male mice. Bone marrow treatment was effective in increasing survival of the animals within 60 days, but the mean and median after-survival of the mice irradiated with 9 Gy of x rays were not influenced by the number of cells injected (in the range of 8 10^4 to 1 10^7 cells/mouse). Irradiation with 9 Gy of 250 kVp x rays followed by bone marrow treatment was very effective in decreasing the incidence of reticulum cell sarcoma in long-term survivors but led to an enhanced incidence of other tumours (particularly of the malignant ones) by comparison with untreated animals. Irradiated bone-marrow-treated animals had a greatly enhanced and accelerated appearance of nephrosclerosis which was by far the most important cause of death between 600 and 700 days of treatment under these conditions.

2. Other treatments

297. In order to examine further the frequently reported finding of a greater sensitivity of the female animals to life shortening (see section II.B.) Holland et al. [H13] investigated the effect of ovariectomy on RFM mice. Castration had little effect on overall mortality rate, both alone or in combination with irradiation (300 R). It had, on the contrary, significant effects on specific spontaneous or radiation-induced diseases, as it reduced the incidence of lymphosarcoma and pituitary, harderian and adrenocortical adenoma and it increased the incidence of lung adenoma. For two other diseases, septic metritis and severe glomerulosclerosis, castration interacted with radiation in nullifying the increased incidence brought about by radiation. Although not strictly comparable, these findings seem at variance with those of Hamilton et al. [H14] who exposed LAF1 mice to 145 R d^{-1} and found that females had a greater sensitivity than males, judging by survival time. However, when the females were ovariectomized their survival became closer to, although still lower than, that of males. Thus, acute survival might be influenced by ovariectomy, as opposed to long-term survival.

D. PARTIAL-BODY IRRADIATION

1. Mouse

298. Although selective partial-body exposure may, in principle, be a good method for the study of the pathogenesis of the individual causes of death responsible for life-span shortening, data on this subject are comparatively few. In the mouse Kallman et al. [K7] reported on CAF1 females exposed to 250 kVp x rays. Partial-body irradiation was performed bilaterally on the thorax (weight of irradiated tissues about 7.6 g); on the right hemithorax (3.5 g) and on the pelvis (5.0 g). Three hundred and 500 R given to the whole body produced an appreciable shortening of life. Partial-body exposure on the chest or on the pelvis was much less effective than whole-body irradiation in terms of tissue dose units. The smallest whole-body doses were more effective than the larger per unit dose but the reverse was true in the case of partial-body exposure. In the partial-body exposure of one region the loss of life per unit absorbed dose (dose per unit volume of tissue) was not a constant in these experiments.

299. Boone [B8, B9] worked on mice of the same strain and sex irradiated on the whole-, lower- or upper-body with x-radiation in single doses. Whole-body irradiated animals (150 mice for each group) received 1, 2 or 4 Gy, shielded animals 2, 4 or 8 Gy and shielding was adjusted in order that the total weight of the tissues included in the irradiation fields would be the same. The integral dose to shielded animals was therefore equivalent to that received by unshielded ones receiving one-half of that dose. Inspection of the data showed a non-linear dose-effect relationship in all cases, with upper convexity. Whole-body exposure was most efficient for induction of life shortening; shielding of the lower body least efficient; shielding of the upper body was intermediate between the two. The only pathological data given were those referring to overall leukaemia and they are insufficient for any conclusion. Also, the significance of the differences observed between control and treatment groups and between the treatment groups themselves appears dubious.

300. Cosgrove and Upton [C25] exposed RF female mice to 250 kVp x rays, under Nembutal anaesthesia and the conditions studied were: irradiation on the whole body with 100 R or 300 R; 300 R to the upper, middle or lower third of the body: non-irradiated controls. Life shortening was appreciable after 100 or 300 R given whole-body but survival of the shielded groups was slightly, if at all, different from that of non-irradiated controls. Whole-body irradiation at both exposure levels increased the incidence of thymic lymphoma and in the 300 R group myeloid leukaemia was also increased; but none of the diseases was increased in shielded mice. Since partial exposure of any third of the body to 300 R produced less life shortening than did 100 R to the whole body, the effect was not correlated with the integral dose.

301. The experiments of Cosgrove, Upton et al. [C20] on LAF1 female and male mice are more concerned

with the induction of nephrosclerosis than with life shortening, but were performed on partially-shielded animals. They showed that shielding of the kidney prevented the induction of glomerulosclerosis and exposure of the kidney alone was as effective as whole-body irradiation for induction of this disease. Longevity was reduced by irradiation of the whole body or by exposure of the lumbar area to 1200 R at 10 weeks of age, but not when the same dose under the same conditions was given at 1 year of age. Partial-body exposures below 1200 R gave an insignificant reduction of the mean age at death.

302. Sato, Tsuchihashi and Kawashima [S34] reported that whole-body, head or trunk exposure to 400 R induced significant life shortening in ddN female mice irradiated when 10 weeks old with 200 kVp x rays. Lower-body exposure to the same amount of radiation did not result, on the contrary, in any reduction of the life span. Per volume dose, life shortening was maximum for the head exposure. Gompertzian plots of all groups were linear, but they did not bear any simple relationship between partial- or whole-body irradiation. Other experiments on ddY female mice [S60] yielded dose-effect relationships for life shortening by whole- or partial-body irradiation. Mean survival times following whole-body exposure decreased by about 7% per Gy. A dose of 1 Gy to the head or the lower body produced 8.5% and 9.7% shortening, respectively, but there was almost no further reduction up to 7.6 Gy. After irradiation of the trunk with 1.9 Gy life shortening amounted to about 14% of the control value and beyond this dose to about 1% per Gy.

303. An analysis of causes of death was carried out only for part of the experiments mentioned above. Histological data are available for animals receiving 6 Gy whole-body, 8 Gy on the head, trunk or lower body, or for non-irradiated controls [S43]. The increase in incidence of all tumours and of malignant lymphoma was significant in the whole-body exposed group. Head exposure enhanced the induction of tumours of the pituitary gland; trunk exposure that of ovarian tumours (with a depression of malignant lymphomas); lower body exposure gave the same tumour spectrum as the control. Judging by the mean after-survival of mice dying for the same cause, an earlier appearance of all causes of death (and particularly of the lymphoma) in irradiated than in control groups was apparent. The larger life shortening produced by the whole-body treatment was attributed to the high incidence of lymphoma and to the early appearance of lymphomas, lung and mammary tumours. The lower incidence of lymphoma in the partially-shielded mice was responsible for the low life-shortening efficiency of these treatments.

2. Rat and hamster

304. In the rat Maisin et al. [M23] and Dunjic et al. [D7] performed a study of the mean duration of life of a homozygous strain exposed under various conditions. They found that 600 R given whole-body gave a reduction of life span of about 41%; 850–1000 R to the abdomen alone reduced the life span by 18–34%. There were also groups irradiated over the thorax only (600–3000 R) or over the head only (600–2000 R). The survival curves had distinctly different shapes depending on the region of the body exposed and on the various modes of death showing at characteristic doses: pulmonary and oesophageal syndromes for thorax irradiation and delayed head or oropharyngeal syndromes for irradiation of the head. The authors suggested that the survival curve after whole-body irradiation could be a composite of the survival curves for partial irradiations of various types, an explanation that fails to account for the life shortening at doses far lower than those responsible for the modes of death mentioned above.

305. In other experiments young female Wistar rats were irradiated on the whole body or on sections of it (head, upper abdomen, whole body except the upper abdomen) with a single exposure of 1000 R of 250 kVp x rays under anaesthesia and therefore under slight anoxia. Mean and median survival times of the groups receiving partial- or whole-body exposure were all reduced compared to controls. Life shortening observed after partial-body irradiation was in approximate proportion to the weight of the irradiated tissues. Nephrosclerosis was not seen unless the upper abdomen was included in the irradiation field and, except for the kidney, the spectrum of diseases observed at death in control, partial-body or whole-body irradiated animals was very similar. Inflammatory diseases of the thoracic organs and benign and malignant neoplasms predominated [L17].

306. The results of Taketa [T2] were also obtained in the rat (adult male Sprague-Dawley, 9–11 weeks old) and involved exposure of the intact abdomen exclusive of the gastro-intestinal tract (which was surgically exteriorized and shielded) to 13, 35 or 50 Gy. A dose of 13 Gy to the intact abdomen resulted in 100% of the animals dying within 4 days of exposure. The same dose given to the abdomen without the intestine allowed survival of the animals to a mean life span of 262 days. But an increase of the dose to 35 or 50 Gy under the same conditions shortened the life span of the rats to 82 or 33 days, respectively. Results with the lower or the upper abdomen irradiated separately (with exteriorized and shielded intestine) were less clear.

307. Carsten and Innes [C26] working on female rats of the CFN strain irradiated with 250 kVp x rays showed that 6.5 Gy given to the lower body or 13 Gy administered to the upper body had a life-shortening effect of about 90 days (against a control value of about 700 days). The effect was statistically different from the control life span, but was very similar for the two treatments. Mammary adenofibromas developed in 60% of the normal aging mice. Acceleration of these tumours was induced by irradiation of the lower, but not of the upper, body. These tumours were a major cause of death in both the irradiated and the non-irradiated rats.

308. Chinese hamsters were irradiated whole- or partial-body with 250 kVp x rays [K11]. Judging by the life span, the upper half of the body appeared more vulnerable than the posterior half and the response to the whole-body exposure was largely determined by irradiation of the anterior half. This observation seems quite unique to this species and at variance with data obtained in the mouse [K7, B8, C25] and in the rat [D7, L17]. A significant increase of the incidence of tumours in irradiated animals was seen only for the ovary. Progressive capillary glomerulosclerosis was observed in all animals examined and this was accelerated by irradiation.

E. CONCLUSIONS

309. In conclusion, it appears that stress of a rather non-specific nature (cold, starvation, water deprivation, physical exercise, electric shock) may have some influence on the life span of the irradiated animals, owing presumably to some interaction between the effects of stress and of radiation exposure. These data are, however, too few, the treatments tested too unspecific and their underlying mechanisms too obscure to warrant undue generalization. Hypoxia induced by various techniques invariably results in protection against the life-shortening action of radiation, but the extent of this protection is probably less than that produced by the same treatments against acute radiation effects.

310. Treatment shortly before irradiation with a number of radioprotective chemicals (MEA, AET, 5-HT, cysteamine, PAPP and others) affords a certain amount of reduction of the life-shortening effect, by comparison with irradiated untreated controls. The nature and the dose of the drug; the dose of radiation in relation to the form of the relationship and to its possible modification by the drug treatment; the strain and sex of the animals; are all variables that may to some extent modify the final outcome of the drug-radiation interaction. The effect on longevity of these drugs is often smaller, sometimes marginal, by comparison with the effect produced by the same drug treatments on early mortality: dose reduction factors in the region of 1.4 to 1.8 may be derived. Some protective effect is also found with fractionated courses of treatment but not with duration-of-life exposures and low drug levels. The protective action of a single drug may cumulate with the effects of other drugs and with the action of concomitant treatments like anoxia, bone marrow transplantation, antibiotics. Whether the protective effects of the drugs on the life span operates through a decreased induction of tumours or of other non-specific conditions is not clear. However, the incidence of some diseases such as kidney sclerosis (which is responsible at medium-to-high doses for life span shortening) may be decreased by the action of radioprotective drugs.

311. Isologous marrow infusion acts essentially on short-term lethality: late survival is not correlated with the size of the marrow inoculum or with the amount of marrow shielded. The only long-term effect that appears to be affected by transplantation or shielding of haemopoietic cells is the induction of thymic lymphoma or of myelogenous leukaemia. These data, together with other findings [P3, S35, S36] may be viewed as evidence that marrow exhaustion does not contribute to natural aging or to radiation-induced life-span shortening.

312. The only generalization to be gained from the experiments where whole- and partial-body irradiation were compared is that partial-body exposure in the range of medium-to-low doses is less effective (both per unit dose and per integral dose) than whole-body irradiation for induction of life-span shortening. Experiments where doses of many Gy are given to sections of the body are clearly unsuitable for studies on the pathogenesis of life shortening, because under these conditions localized destructive lesions to the irradiated organs are decisive for survival or death of the animals. Data are unsuitable for other firm conclusions on the causes of death contributing to the loss of life-time. It appears however that inclusion of the kidneys in the irradiation field is a prerequisite for induction or acceleration of nephrosclerosis, a disease that in all strains of rodent tested and at doses of a few Gy largely contributes to life-span shortening. The tumour spectra and the pathogenesis of each tumour type are too variable for any meaningful generalization. In cases where leukaemia contributes substantially to the reduction of life, the lower incidence of this disease resulting from the shielding of the haemopoietic system [K12, K16, I2, C24] could explain the low efficacy of the partial-body irradiation in respect to life shortening.

IV. THE HUMAN DATA

A. INTRODUCTION

313. In this chapter the evidence for a non-specific life-shortening effect in the human species is discussed. The evidence available comes from three different sources of epidemiological studies: groups of people (radiologists, radiology technicians, physicians) exposed occupationally during their professional life; patients who have undergone radiation treatments for pathological conditions, mostly for tumour therapy or for control of ankylosing spondylitis; a large number of survivors of the A-bomb experience in Japan in 1945 and a few hundred people exposed in the Rongelap fallout accident in 1954. The data will be discussed separately, since the conditions of the exposure are different in the three groups and the characteristics of the sample size and of the epidemiological observations are also quite different.

314. The studies performed on humans are subject to a number of limitations, mostly related to the lack of any control over the variables in question. In general, the sample size is small for effects which have often a marginal incidence over the whole population studied. The life span study on the A-bomb survivors, numbering about 80 000 irradiated persons, is an exception. Often the time elapsed between irradiation and the epidemiological survey is insufficient to reveal effects which take a very long time to develop. In the case of radiotherapy patients there is the concomitant presence of an important disease which causes a decrease of survival completely unrelated to the radiation exposure and induces a prevalence of associated disabling conditions altering the spectrum and the time of occurrence of the causes of death expected in a normal population.

315. Finding suitable control groups to match the irradiated group is always a problem: the distribution of ages, the geographical location, the differences in the socio-economic status and in the living and working conditions between the control and the test sample are often quite large. When the effects to be studied are small the choice of an appropriate control group may often be decisive in order to assess their presence and magnitude. Although in many cases corrections can be applied to allow for obvious differences, a subtle difference may remain unrecognized and may thus alter to an unknown extent the interpretation of the data. In all cases differences in the composition of the control and the test sample, difficult to be recognized add variability to the data and uncertainty to the conclusions.

316. In retrospective studies the accuracy of the records is often a problem. For some groups (physicians, radiotherapy patients) the high standard of the medical care makes the records on causes of death very

useful and well documented. But in other instances records are poor and causes of death only approximately known. Uncertainties may apply only to some and not to all causes of death and the ability of the epidemiologist lies in identifying these sources of errors and properly allowing for them. Radiation dose records are mostly uncertain or unavailable; as in the case for occupational exposures where presumptive evidence must often be used instead of more precise statements of dose. In these cases no analysis of dose-response relationships are possible, but only contrasts of broad categories of exposed versus unexposed groups. At the other extreme, doses in the treatment volume are very well known for radiotherapy patients, but may not be easy to estimate for all tissues of importance outside the beam.

317. Radiation dose distribution in time is often unknown and variable within the ascertained or presumptive period of occupational exposure; the radiation beams are often of very low energy and therefore likely to be absorbed superficially; irradiation of the hands, arms or upper part of the body makes the sample of occupationally exposed individuals very inhomogeneous. And, in addition to the above-mentioned factors, the acute, fractionated or chronic conditions of the exposures make it difficult to compare the results of the various series. The interplay of all these variables would naturally call for multifactorial types of analysis, which however have not been specifically applied to the field of life shortening.

B. DATA FROM OCCUPATIONALLY EXPOSED PEOPLE

318. Following a number of papers where an increased rate of leukaemia in radiologists, as compared to other medical practitioners, had already been reported [M25, M26, U13], in 1947 Dublin and Spiegelman [D8] published some preliminary data on United States physicians during the period 1938–1942, showing essentially that physicians experienced the same longevity and mortality as a male test group of the same age in the United States. No evidence of diseases associated to radiation exposure was found in that study, but in a subsequent paper [D9] this research was extended to the mortality of medical specialists during the same period. Among 175 146 medical doctors listed in the American Medical Directory in 1940, 37 610 (or 21%) were classified as full-time specialists. During the five years covered by the study there were 12 419 doctors who died in the age group 35–47 and 2029 of these (or 16.3%) were medical specialists. The mortality ratio from all causes for specialists was 78%, taking the death rate of all physicians to be 100%. Radiologists were reported to have a mortality ratio of 0.90, dermatologists of 0.98, pathologists of 0.60. Radiologists showed a high rate of mortality from cancer and leukaemia and among 95 recorded deaths of radiologists leukaemias were higher than in any other speciality.

319. In 1956 Warren [W2] reported on 82 441 physicians dead during the period 1930–1954 inclusive. He found that physicians had a mortality rate about the same as that of the general adult population. In 1950 in the United States the average age at death for a male test group having reached 25 years of age was 65.6 years. Radiologists died on the average 5.2 years earlier than other non-exposed physicians, who died at 65.7 years. Also, the non-radiologists known to be exposed to radiation did show some life shortening (they lived on the average 63.7 years) although less than that of radiologists. Failla and McClement [F4] estimated that radiologists received an accumulated exposure that could vary from rather low values to about 1000 R, with a possible whole-body exposure of 500 R in 35 years of practice.

320. Warren [W2] found that deaths from leukaemia among physicians were 120 over the period 1950–1954, which rate was about three times that for the general adult population. During 1930–1954, 0.63% of the deaths from specified causes occurring among non-irradiated physicians were due to leukaemia, against a 2.33% among other specialists having had some contact with radiation and 3.65% of leukaemia deaths in radiologists. Also, the average age at death of physicians dying from leukaemia was 60 years, whereas radiologists with leukaemia died on average at 55.8 years. Not only radiologists and medical specialists exposed to some radiation had a shorter mean life span than other non-exposed doctors, but they seemed to die younger from practically every cause of death, neoplastic, degenerative, infectious or other stated or non-stated causes. This suggested that radiologists were subject to some factor lowering their resistance to disease and hastening aging. The fact that other specialists exposed to some radiation had mortality values intermediate between radiologists and non-exposed physicians was taken as a further evidence that such a common causative agent may be radiation.

321. In a subsequent paper Warren [W3] added two years to his previous series and compared the life span of radiology specialists (averaged over periods of 5 years) with the duration of life of the United States male population at large. He found that the mean age at death of radiologists before 1945 was less than 60 years, while after that date it increased progressively to approach by 1955 the average age at death of the general male population. This observation implied that during the period 1930–1955 there had been a lower rate of mortality of the radiologists as compared to the average male population, so that, in spite of a general tendency to an increased life span, the average age at death for the two populations compared had by the end of the period come very near.

322. Seltser and Sartwell [S37] examined the comparability of the groups in Warren's [W2] study, in order to see whether there might be other differences that could account for the apparent life shortening of the radiologists, compared to non-radiologist physicians. They tested the hypothesis that the observed differences might result from an unequal age distribution among the samples under comparison and found in effect that the age distribution of radiologists differed from that of the other physicians: radiology being a relatively new medical specialty, there were proportionately fewer radiologists in the older age groups where the mortality intensity was heavier. And when the expected age distribution at death was recalculated using data from 1940 and 1950, it was concluded that radiologists would in fact be expected to die at younger ages, just because there were proportionately fewer elderly radiologists. This finding raises some doubt on the comparison method adopted by Warren [W2]: it shows that the average age at death is in this particular case a misleading parameter, while comparison of age-specific death rates in the two groups would be a more reliable method of analysis. Seltser and Sartwell, however, did not prove that the exposure to radiation of radiologists had no effect on their life span.

323. Similar reservations about the method used by Warren [W2] were expressed by Lewis [L18] in a review on radiation-induced leukaemia. He pointed out after appropriate calculations that a difference of at least 6 years in excess in the life span of radiologists would be expected by comparison with other non-exposed physicians, solely on the basis of differences in the age distributions among the two samples compared. If this were true, radiologists might have had a slightly longer life span than other non-exposed doctors.

324. At approximately the same time the results were published of a survey on British radiologists by Court-Brown and Doll [C27]. The study concerned life expectation and cancer mortality among 1377 male radiologists, mostly diagnosticians, who had been members of specialist societies in Great Britain during 1897–1956. It proved impossible to assess the exposure to radiation of this group: it was simply assumed that the average dose received prior to 1921 (when the first recommendations on radiation protection were issued) was high, whereas the average exposure of those registered as specialists after that date had been likely to be within the limits recommended.

325. Mortality data were calculated from the population at risk at each age and in each year. The expected numbers of deaths were first estimated by assuming that mortality might be the same as for all men in England and Wales in the same age groups and over the same time period. Expected deaths were also calculated according to those expected in the upper social class or in the medical class as a whole, with some corrections concerning the relative mortality of people in various social groups aged 65 or more. By similar methods the number of deaths to be attributed to all types of cancer (appropriately corrected for occupation and social class) were obtained. All the data were kept separate for radiologists registering before or after 1921.

326. With regard to life expectation, the observed deaths were 463, fewer than expected on any of the assumptions mentioned, which would have been between 499 and 525. If deaths attributable to cancer were excluded, the relative differences between observed and expected cases became more marked and approached statistical significance. Thus, there was no evidence that occupational exposure to radiation caused a detectable non-specific shortening in the expectation of life. As to cancer mortality, a significant excess was found among radiologists entering practice before 1921, the excess being confined to tumours of the skin and pancreas (and possibly to leukaemia). No excess mortality from cancer was found in those entering radiology after 1921, although the time elapsed up to the completion of the study was insufficient to ensure that the cancer hazard had been totally expressed.

327. The study on British radiologists was recently updated by Smith and Doll [S59] to include observations up to the beginning of 1977, by which time about 55% of the 1338 persons had died. A reliable estimate of the dose received by these individuals proved impossible, but it was calculated that those entering the profession between 1920 and 1945 might have cumulated a whole-body dose of the order of 1 to 5 Gy. As in the previous study, the mortality of the radiologists was compared with that of all men in England and Wales, all men in the upper social class and all male medical practitioners. Radiologists entering the profession before 1921 had a 75% higher cancer death rate than other medical practitioners. Leukaemia, tumours of the pancreas, lung and skin were significantly elevated. The cancer death rate among those who had started the profession after 1920 was not significantly elevated. Data were not available to examine non-cancer mortality by individual causes. However, it was confirmed that the overall non-cancer death rate among radiologists was significantly lower in two out of three comparison groups than that of other classes under comparison. Thus, an extension by 20 years of the study provided no support for the concept of a non-specific life-span shortening.

328. Seltser and Sartwell [S38] returned again to the problem of mortality of radiologists of the United States, in comparison with other medical specialists. Their new study covered the period 1935–1958, during which the mortality experience of 33 616 members of several United States medical specialty Societies was analysed, in order to test the hypothesis of a possible increase in mortality due to occupational radiation exposure. The Societies were selected in such a way that their members had a postulated high (radiologists) intermediate (internists in general) or low (ophthalmologists and otorhinolaryngologists) rate of exposure to radiation. The mortality experience in these groups conformed to the above hypothesis and the median age at death was about 5 years greater among the lowest-exposure than the highest-exposure groups. The method followed for the comparison was to determine person-years of exposure, specific for age and calendar time, and to relate these to mortality. There were three periods along which comparisons were made: 1935–1944; 1945–1954 and 1955–1958.

329. Comparison of matched and paired subjects for low- and high-exposure groups were also carried out and they gave results consistent with those of group comparisons. The differences in mortality increased with age but decreased with calendar time for all except the oldest age classes. There was no excess mortality of radiologists in the 35–49 classes of age over the period 1945–1958, suggesting that by that time the hazards had been controlled. The increased risk of mortality was distributed over a number of assigned causes of death. In the Societies with a postulated high exposure mortality due to cancer, cardiovascular-renal diseases and all other causes combined was increased. Leukaemia showed the highest ratio of observed/expected deaths at all ages combined. In general, with the exception of leukaemia and other cancers, the mortality ratios were highest in the oldest groups of age. The excess of leukaemia and all cancers combined was greatest during the last working years and the excess in other causes during the post-retirement years.

330. From the above data Seltser and Sartwell [S38] inferred that occupational exposure to ionizing radiation on the part of radiologists had in the past produced a non-specific life-shortening effect. But the validity of this conclusion depends on the demonstration that the groups compared are similar in all respect, except for radiation exposure. The authors examined certain characteristics of the samples compared such as the geographic distribution of the groups, the region of residence, the size of the living communities, the birth-place: none of these comparisons revealed any difference among groups. Exclusion from the comparisons of the first five years after the members had joined the Societies, in an attempt to eliminate a possible selection due to persons with poor

health not joining the profession [C27], did not modify the conclusions. And the same was true for another possible cause of selection due to the unfit persons not entering the profession with the highest radiation risk. Factors known to affect the survivorship of other populations (smoking, diet, alcohol consumption, family longevity) could not be tested, but were not deemed to have caused significant differences among the population groups tested.

331. Seltser and Sartwell commented on the fact that the reduced survival (about 5 years) among radiologists for the years 1935–1944 was remarkably near to that obtained by Warren [W2]. This occurred in spite of the fact that the method used by this latter author (but not his conclusion) was criticized by Lewis [L18] and by the same Seltser and Sartwell [S37]. Whether Warren [W2] reached the right conclusion with the wrong method, or not, the results from his and from Seltser and Sartwell's study are in any case in good accordance.

332. The differences with respect to the negative findings of Court-Brown and Doll [C27] could first be explained, in the opinion of Seltser and Sartwell [S38], by the methods of analysis. The absence of a comparison between medical specialists in the British series would be a weakness, since specialist physicians have a more favourable survival experience than males in the general population, at least in the United States. Also, the numerical adequacy of the British data might be questionable, since with groups of the order of 1000 persons a life-shortening effect of as much as 10 years could go undetected, even if present. Other differences of substance may have regarded the more careful and earlier adoption of safety measures in the United Kingdom than in the United States; the fact that in the United Kingdom most radiological practice was carried out in hospitals and therefore much of the exposure might have been taken by radiology technicians and not by the specialists; the wider use of fluoroscopy than of radiography and also the greater number of films used per radiological examination in the United States than in the United Kingdom [V7]. It should be pointed out, however, that both the United Kingdom and the United States series agree in showing that since adoption of radiation protection limitations any hazard attributable to radiation can no longer be documented.

333. Two papers from Japan on a small group of radiology technicians were also reported. In the first one [K17] estimates of radiation injuries such as leukaemia, cancer of the skin and tumours of the inner organs were carried out but no mention was made of life-span shortening associated with the exposure of this group of people. The second paper [K18] reported that during the period 1933–1963 there were 52 radiology technicians dead in three Japanese prefectures. The corrected death rate corresponding to this number was significantly higher than that in the population at large employed in similar professions and aged over 15 years in 1955. There was some tendency of the death rate to increase with increasing occupational exposure, but no correlation with the age at which exposure first began. Except for skin cancer which was significantly higher, other causes of death were similar in this group as in the general population. Life expectancy in each age class was shorter than in male persons of comparable social and working conditions which were over 15 years of age in 1951 and 1952. A life-span shortening amounting to 6.6 years in the x-ray technicians was found, corresponding to an estimated loss of 0.92 d R^{-1}.

334. Another paper on the mortality of Japanese radiology technicians was made available to the Committee [S53]. During the period 1955–1965 the number of these technicians was estimated to be 74 721 and the observed number of deaths in this group was 91 (for male Japanese of the same age classes 325 were expected). Leukaemia deaths did not exceed the expected value, although the relative risk of leukaemia was an order of magnitude higher for people who had been employed for over 29 years. Seventeen deaths were registered in 1964 and 1965 (80 would have been expected for male Japanese of the same age classes) with an average age at death of 47.7 years (against 48.0 expected). The estimated exposure ranged from 9 to 37 R during the ten years of observation. Since there were no significant differences between observed and expected values, it should be concluded that radiation-induced life shortening was not proven in this population sample.

335. New data on the effects of ionizing radiation on radiologists were reported in 1966 by Warren and Lombard [W4]. The study comprised 5982 certified radiologists which were compared with all physicians of the United States in 1949–1951, with the male population of the United States aged over 25 years in 1950 and with a group of 3176 Massachusetts dentists. Although the number of certified radiologists increased more than three-fold from 1940 to 1960, their mean age did not change at all and remained between 46 and 47 years. The mean age at death of radiologists was 55.8 years in 1934–1939; 59.3 years in 1940–1949; 64.5 years in 1950–1959 and 70.1 years from 1960. The rate of this increase was higher than that of the general male population, so that, from 1960 on, the two curves expressing the increase in the average age at death versus time crossed with each other. The life shortening observed in preceding years could not be attributed to any one cause in particular, such as leukaemia, but was the aggregate of shorter life spans associated with many causes of death. Leukaemia had a higher risk (about 5 times) among radiologists than among the male population at large, but it occurred rarely and only after a number of years of occupational exposure. It was more common in radiologists than among the male population at large, but it occurred rarely and only after a number of years of occupational exposure. It was more common in radiologists after 40 years of age, but more common before 40 in the general population. In recent years the excess incidence of leukaemia in radiologists decreased. From the above findings Warren [W4] concluded that radiation protection measures had been effective in providing adequate safeguards for the radiology specialists.

336. Miller and Jablon [M27] searched for late radiation effects among men trained as radiographers in the United States Army during the Second World War. The mortality experience of this group of people (6560 persons in total) was compared over the period 1946–1963 with that of other groups trained by the Army as pharmacy (1522 persons) or medical laboratory technologists (5304 persons). It was difficult to ascertain the radiation dose but it was concluded from ancillary evidence, in the absence of more complete records, that they received substantially greater radiation than did patients exposed to x rays for diagnosis. Causes of death were investigated and in only 1 out of 16 possible comparisons between exposed and non-exposed groups there was a statistically significant difference of any interest in the present context. It referred to an excess of tumours of the respiratory tract

which was elevated among radiographers: however, the difference between expected and observed values was due in part to the low mortality rate from this cause of death in the control samples. No significant excess of leukaemia was found among the radiographers, but in a study of this size a two- to three-fold increase in the risk of leukaemia could have gone undetected. No information on life-span shortening was reported as such.

337. There was yet another report from Japan on the mortality and causes of death of radiology technicians during the period 1966–1972 [K19]. Among these technicians affiliated to the Japanese professional association there were during the above-mentioned period 134 deaths, a number much lower than expected, owing probably to some inadequacy of the survey. Out of these deaths, 6 were due to skin cancer and 2 to aplastic anaemia and these numbers were significantly higher than would be expected to occur among the population at large. Leukaemia was found in 5 cases, indicating no significant difference with the number expected. Concerning the average age at death, 52.7 years was the value found among radiology technicians, while the expected value would have been 48.6 years. A very recent evaluation of the doses absorbed by persons dying from neoplastic and non-neoplastic causes was reported [A17]. Statistical tests to investigate a possible relationship between dose and mortality showed no correlation for the majority of causes of death from malignant tumours and for the cancer versus non-cancer causes.

338. The mortality rates of United States radiologists in comparison with other medical specialists were re-examined by the Johns Hopkins University group [M28, M29] in two reports published in 1975 up to a total follow-up of 50 years. The comparison regarded male members of the Radiological Society of North America who were contrasted with fellows of the American College of Physicians and members of the American Academy of Ophthalmology and Otolaryngology. The information through 1954 available from the previous study by Seltser and Sartwell [S38] was updated for new members and decedents up to 1969. Deaths and causes of death were traced for 99.5% of the decedents. The persons under comparison were about 30 000 among all Societies for a total number of deaths of about 6500.

339. In the first paper [M28] the mortality rates from all causes were calculated by the life-table method of analysis with age- and time-adjustments of the death rates in such a way that cumulated rates could be compared within any 10 year cohort and across societies. No specific study of the influence of life style was included in this or the following [M29] study. Mortality from all causes depended on the decade of entry. During 1920–1939 death rates of radiologists were higher than those of any other specialist group for both cancer and non-cancer causes. The differential between the rates for radiologists and other specialists was lower in the 1930–1939 cohort and it disappeared in the 1940–1949 cohort. So did the graduation of death rate radiologists > internists > other specialists which was noticeable in earlier periods. Removing the deaths from cancers in the 1940–1949 cohort led to a disappearance of the difference between radiologists and non-radiologists noticed in earlier cohorts. The all-cancer mortality rates for radiologists were higher than those of other specialists up to the decade ending in 1949. The next decade had not aged sufficiently to show the expected peak of cancer mortality in the 60–64 years age group. It was pointed out that self-selection of the persons entering any one group and the life style after entering the specialty would have little influence on the data: thus, the presumed radiation exposure of the specialists under comparison would appear as the only reasonable way to explain the mortality differences and their trend over time.

340. In a companion paper [M29] the specific causes of death contributing to the excess risk of mortality in radiologists were examined. In the 1920–1929 cohort the radiology specialists, in addition to the previously-noted cancer mortality [M28], showed also the highest death rate for diabetes, cardiovascular-renal diseases, stroke, hypertension and suicide. After this early period radiologists ranged highest among other comparison groups only for cancer mortality. The excess of leukaemia observed in the 1920–1939 cohorts subsequently disappeared. During the same period, however, lymphoma mortality, particularly multiple myeloma, increased significantly in radiologists entering their profession in 1930–1949. Except for this latter finding, which was discussed in relation to possible effects of radiation on the immune system, the data reported confirmed and extended previous observations. The authors were aware of the peculiarity of their findings, as radiologists of the United States are the only human population where life-shortening effects of radiation, over and above those related to an excess tumour induction, have been observed. They specifically commented on this point and reaffirmed the validity of their observations. They also added [M28] that it may be premature to state conclusively that such an effect has disappeared in the 1940–1949 cohort, since relatively few persons in this cohort (193 out of 1011) had passed through the ages when mortality is higher: examination of an additional 5–10 years period might be required to determine whether such an effect has been reduced through a decrease of the occupational exposure.

341. More recently Polednak et al. [P4] reported on the mortality of a group of women employed in the dial-painting industry in the United States. A cohort of 634 subjects working in this industry during 1915–1929 was traced from employment lists. Mortality in these subjects was compared on the basis of death certificates with the general mortality rate of a comparable female test group. An increased death rate was observed in comparison with the expected rate in the exposed population (240 cases versus 188.5 expected).

342. Bone cancer (22 cases versus 0.3), cancer of non-specified sites (18 versus 2.6), cancer of the colon (10 versus 5) diseases of the blood and haemopoietic organs (4 against 1) and external causes (31 against 10.1) were also increased, as compared to the general population. Mortality from selected causes was also examined as a function of the year of first exposure, time period of observation and age at first exposure. The mortality ratios from all causes and all cancers in women exposed after 1925 were lower than in women exposed in 1915–1924, in good agreement with the fact that the work regulations for the dial painting industry came into operation at about that time. Large-scale measurements of radium burden on these women were begun in 1954 and an anlysis of the relationships of radium body burden to mortality was performed only on women alive in 1954 who had been measured at least once between 1954 and 1975. Only 360 women in the group were available for an analysis as a function of dose and therefore the comparison with respect to cause-specific

mortality was performed between two groups: subjects with a body burden lower than 1.8 MBq or those with a burden of 1.8 or more MBq. Mortality ratios from all causes higher than 1 were observed only in the groups with the higher body burdens (1.91). Among these, all malignant tumours, bone tumours and other unspecified neoplasms were also significantly elevated. Among women with less than 50 μCi body burden, tumours of the large intestine were the only significantly increased cause of death.

343. Another paper by Stehney et al. [S39] is more specifically concerned with the possible presence in this group of women of life shortening ascribable to causes other than bone sarcoma and carcinoma of the head sinuses. The study was performed by the life table method using comparable age- and time-specific mortality rates for females for the comparisons. There were 1235 women exposed before 1930: they were on average 20 years old at employment and about 44% of the persons in the group had died by the end of 1976. The observation times thus covered a period of between 45 and 60 years. Regarding death from all causes, 529 deaths before the age of 85 were observed versus 461 expected and the cumulative survival of the group was significantly less than expected, starting at 10 years after employment. When mortality rates for bone sarcoma and head carcinoma were subtracted from the mortality rate for all causes, there was no significant difference at the 5% level in the total population (455 cases observed against 460 expected) or at any of the time intervals considered. A correction for the effect of competing risks was also made on the data after exclusion of the radium-related tumours and the difference between observed and expected survival was similarly non-significant also under these conditions. When calculations on the expectation of life were performed at one year intervals from zero to 59 years after the first employment, differences between expected and observed mortality were again not apparent. The conclusion from this study is that when radium-tumour deaths are removed from the exposed sample the average survival is indistinguishable from that of the contemporary control group of the same age. Thus, to the precision obtainable with such a small sample size, only the radium-related tumours contributed significantly to life shortening of this population, with no evidence of non-specific effects.

344. The epidemiological data on uranium miners in Czechoslovakia [K25], the United States [A13] and Canada [G18] are discussed in Annex L in connection with the combined action of radiation and tobacco smoke on lung tumour appearance. The problem of life shortening has not been addressed specifically in published work on these series. However, to the extent that standardized mortality rates may indicate the prevalence of death mechanisms or causes, the data available can not be interpreted to show non-specific life shortening. The Hanford series [M31, G20] and the Portsmouth Naval Shipyard Series [R12] are similarly negative in respect to any such effect having been observed in the employees of a large atomic plant and of a nuclear shipyard.

C. DATA FROM RADIOTHERAPY PATIENTS

345. Doses administered to patients surviving radiotherapy are rather well known and may be taken as the independent variable against which any possible life shortening may be tested. The limitations with this group of people are due to partial-body exposure and to the possible effects of the disease initially requiring radiotherapy. The relevant data should thus be taken critically. Sørensen [S40] studied 184 patients treated for cancer of the uterine cervix in 1922–1929 in Denmark, surviving for at least 5 years after treatment and having been followed for the 20 years thereafter. Sørensen found that survival was not correlated with the stage of the disease at diagnosis. Each patient lost on average 3.5 years of life by comparison with the mortality experience of the female Danish population. This excess of deaths was exactly accounted for by patients who died during observation time for a recurrence of the neoplasia and there was no evidence that irradiation as such had decreased the survival rate of the patients without recurrence.

346. Newell [N11] attempted to establish some correlation between integral radiation dose and longevity in 217 women treated by radiotherapy at Stanford University in 1924–1947. The patients affected by cervical carcinoma in stages I and II had survived for 10 or more years after treatment. Radium treatment alone or radium in conjunction with x rays were used in the therapy. From the data Newell concluded that no life shortening attributable to radiation had occurred in the patients. The data were also evaluated independently by Kohn et al. [K20] who had access to the original records: their conclusion was the same.

347. A third series was reported by Kohn, Bailar and Zippin [K20, Z1] on about 500 cases of cervical carcinoma treated with x rays and/or radium obtained from two cancer registries in the United States. These women were treated prior to the age of 55 and survived at least 5 years after treatment. By the time of the last report about 38% of the women had died and this fact limited objectively the weight of the conclusions. The patients were grouped according to the stage of the disease at the time of treatment and according to the regional dose delivered. There was no evidence of radiation-induced life shortening. It was also reported that the incidence of leukaemia appeared in these patients to be lower than among patients treated for ankylosing spondylitis or for metropathia haemorrhagica.

348. Indirect information of a negative nature may be derived from a study of nearly 3000 children irradiated in infancy to shrink their allegedly enlarged thymus. These infants were followed in time and compared with about 5000 non-irradiated siblings. In spite of a four-fold increase in tumours, particularly of the thyroid, among the irradiated subjects, the report [H15] shows good agreement between observed and expected numbers of death. This indicates the absence of excess non-specific mortality, which may not in any case be surprising in view of the small portion of the body irradiated. The data of Peters et al. [P5] on 61 patients given local irradiation to suppress stomach hyperacidity after partial gastrectomy are inconclusive as to the presence of non-specific life shortening.

349. In 1965 Court-Brown and Doll [C28] reported on a sample of 14 554 persons (12 161 man and 2393 women) treated for ankylosing spondylitis with one or more courses of radiotherapy at various centres in the United Kingdom during 1935–1954. These patients had been followed for periods varying from 5 to 25 years up to the end of 1959 with reasonably good records of the

treatment; adequate follow-up information in 98% of the cases were available. The number of expected deaths in these patients if they had suffered only a normal mortality rate were computed from the numbers of person-years at risk for each sex, age group and calendar period and they were multiplied by the sex and age-specific mortality rates for each corresponding period. These calculations were performed for all causes of death, all cancers, the principal types of cancer and the respiratory diseases. The total death rate among the patients was about 1.8 times as high as the corresponding national death rate. When the various causes of death were analysed separately, the following observations were made.

350. In the test sample (by comparison with the general population) deaths attributable to arthritis and other forms of rheumatism were very high (about 100 times on average); deaths attributable to clinical conditions known to be associated with ankylosing spondylitis were on average 2.9 times more common; deaths from conditions attributable to irradiation (aplastic anaemia, leukaemia, cancers other than leukaemia) were about two times as common; deaths due to diseases from which the mortality could be similar to that of normal population had a prevalence of 1.3. This latter increase regarded all conditions examined and the total experience was sufficiently large for it to be highly significant. When mortality was examined as a function of the post-irradiation period, all causes of death other than cancer and aplastic anaemia were in a constant relationship to the expected mortality. In contrast, for leukaemia and aplastic anaemia mortality increased within the first 5 years of observation and then fell off; deaths from cancers of heavily-irradiated sites were increased approximately two-fold at 6–15 years after treatment. Many different types contributed to this excess, in a rough proportion to their natural incidence. Deaths from cancers originating in other lightly-irradiated tissues were not increased significantly.

351. The interesting observation in the present context is the increase in deaths due to non-specific causes and not grossly related to spondylitis or to irradiation. The authors [C28] pointed out a number of reasons that might account for this finding. Firstly, non-specific deaths might contain a small proportion of rare conditions related to spondylitis (lesions of the aortic valves, regional enteritis, proneness to accidents). Secondly, patients in this group carry other conditions known to be associated with spondylitis (amyloid degeneration, nephritis) that might decrease resistance to non-specific causes of death. Thirdly, the inaccuracy of the diagnoses at death, the possible effect of drugs and the use of imperfect death-rate values for the calculation of the expected numbers of deaths were discussed as other possible reasons. Finally, the constancy in time of the ratio between the number of deaths observed other than those presumably related to radiation over the expected number calculated from national mortality rates suggested that the above excess mortality was likely to be dependent on the spondylitis itself and unrelated to the form of the treatment.

352. The 1965 study of Court-Brown and Doll [C28] included many patients who had been treated with x rays more than once. This fact could complicate the interpretation of the late effects of the overall treatment, since subsequent irradiations may have contributed to the excess of death observed. A very recent study by Smith and Doll [S62] reports on about 14 000 patients with ankylosing spondylitis given a single course of x rays between 1935 and 1954. They were observed for an average follow-up time of 16.2 years, after a mean bone marrow dose of 3.47 Gy. The numbers of deaths expected by cause were estimated by multiplying the person-years at risk by the corresponding age- and sex-specific mortality rates for England and Wales. Mortality from all causes combined in the test sample was 66% greater than for members of the general population. Although the study was mainly concerned with cancer mortality, it did show that there was also a substantial excess of deaths from non-neoplastic conditions, which appeared to be associated with the spondylitis itself, rather than its treatment. However, the excess of deaths from leukaemia and cancers of the heavily irradiated sites in the test sample was attributable to radiation exposure. The authors concluded that, on the whole, the data did not support the suggestion that radiation could produce a non-specific effect of life shortening affecting death rates from causes other than cancer.

D. DATA FROM A-BOMB SURVIVORS

353. The effect of radiation on aging and life shortening in an Oceanic population irradiated in 1954 was summarized in a report by Conard [C29]. A number of changes connected with aging was investigated and among them the opacification of the eye lens, the presence of chromosomal aberrations in perypheral lymphocytes, immuno-haematological and nephrosclerotic changes. Regarding life shortening in particular, the number of persons exposed was too small to allow any reliable assessment. The population under study includes in fact a control group and two irradiated groups of 334 persons in total, exposed to a maximum of 175 R from fission-product gamma radiation.

354. The study of the A-bomb survivors in Japan, is providing information on long-term radiation effects, including life shortening, that will eventually form the most extensive source of data on the human species. The earliest reports of the A-bomb series are particularly concerned with the description of the sample [B21] and with mortality from all causes [J5] and from specific causes up to 1960 [J6, A6].

355. The report covering the period up to 1966 [B22] was based on the T-65 dose estimates and included 16 356 deaths among about 109 000 people, comprising irradiated and control groups. When malignant neoplasms were excluded from the analysis, there was no evidence that radiation might aspecifically shorten life and the excess mortality of the irradiated sample could best be explained in terms of disease-specific effects, particularly leukaemogenesis and, more generally, cancerogenesis.

356. Mortality data from the Japanese sample up to 1970 [J7] allowed the following conclusions. Although late radiation effects on human mortality could to some degree resemble non-specific manifestation of accelerated aging, the most notable effect remained by far the induction of tumours and leukaemia. The authors could not conclude with certainty on the absence of an excess mortality, for example, from diseases of the circulatory system or from cerebrovascular conditions: but it appeared most unlikely, if there was indeed any excess, that it could approach the excess of tumour induction.

357. The problem of longevity in irradiated human populations with special reference to A-bomb survivors up to 1972 was reviewed by Anderson [A9]. He concluded that evidence for a tumour-independent shortening of life was equivocal and, in his opinion, this experience would be at variance with other reported experience in man. For this reason, judgement on the interpretation of the Japanese data should be reserved pending further evidence. However, from their review of thirty years experience with the A-bomb survivors [O2], Finch and Beebe [F1] could find no convincing evidence for a generalized increase in mortality from natural causes other than cancer, in contrast with the requirements of the hypothesis of accelerated aging.

358. A re-examination of the mortality experience of A-bomb survivors up to September 1974 was performed by Beebe, Land and Kato [B6]. The number of deaths from non-neoplastic diseases, whose increment could in principle be suggestive of a non-specific life shortening, was at the time about 14 000 among 82 000 survivors. In the irradiated sample, cerebrovascular diseases, other circulatory diseases and diseases of the digestive system showed no evidence of an increase. Deaths from diseases of blood or blood-forming organs were apparently increased, but difficulties with the diagnosis made this finding uncertain. All other non-neoplastic conditions were apparently unaffected.

359. When all diseases except tumours and diseases of the haemopoietic system were pooled together, their combination produced no further evidence of a relationship to radiation dose. Although the sample group in the Life Span Study could indeed be regarded as a highly selected group, there was no evidence that selection due to survival from early effects, as suggested by others [S41, R10], might have favourably influenced the subsequent mortality. It was concluded therefore that the views that ionizing radiation may cause premature aging in man or that the carcinogenic effect is only a part of a more general acceleration of aging find no support in the Japanese experience: radiation effects on long-term mortality do not appear diffuse but rather specific and focal and principally cancerogenic.

360. The latest available analyses of the mortality experience of Hiroshima and Nagasaki survivors should also be reported for completeness [B23, B24], although the information contained in them is essentially that discussed in Beebe, Land and Kato [B6]. These contributions showed that age-specific death rates for all non-tumorous causes (taken at 4-year intervals and adjusted for city and sex within each time period) separately calculated for the group receiving 0–0.09 Gy and that exposed to 1 + Gy were superimposable (see Figure XVII). This finding, as repeatedly pointed out, cannot be reconciled with the hypothesis

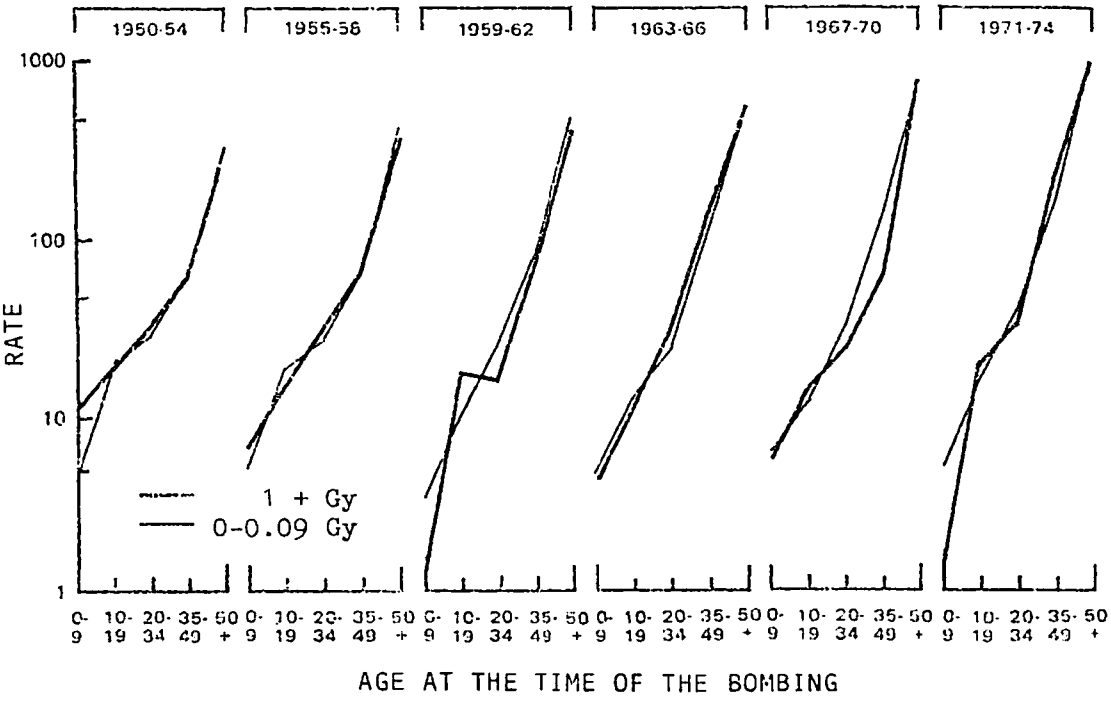


Figure XVII. Death rates (per 100 000 persons per year) from all diseases except neoplasms by age at the time of the bombing in Hiroshima and Nagasaki, during the period 1950–1974, plotted for each 4-year period separately for the group receiving 1 + Gy (heavy line) or 0–0.09 Gy (light line). The rates were adjusted for city and sex within time periods. Data from Beebe, Kato and Land [B24]

that radiation may accelerate natural aging, but rather shows that any life shortening present in the sample is associated with cancer induction. The results shown in Figure XVII did not change even when the observations were extended up to 1978 on the same cohort [K23]. The survival curve excluding deaths from malignant neoplasms for this cohort does not differ by dose over the whole period 1950–1978 [K23]. However, it is important to note that the most pronounced putative effects might be expected among the younger age groups where to date relatively few deaths from non-malignant causes have occurred.

361. The contrast between the Japanese data and the data on occupational exposure of radiologists of the United States and their mortality prior to 1950 was specifically discussed in the last publications [B23, B24], particularly in view of the most recent evidence of Matanoski [M28, M29]. It was pointed out that either the contrast groups in the occupational experience (radiologists against other medical specialists) were confounded by factors other than irradiation or that there are intrinsic differences in the nature of the radiation response between the Japanese survivors and the radiologists of the United States. Since the latter

hypothesis would be against a massive body of evidence collected on other mammals, one should logically be inclined to favour the first interpetation, particularly in view of the much more reliable experience from Japan, which is now based on about 20 000 deaths among about 80 000 A-bomb survivors.

362. Mention should also be made of an up-to-date report concerning the mortality experience of children exposed in utero to the A-bombs [K21]. There were 203 deaths among 1923 subjects during 1945–1976. The mortality ratio increased with dose in both cities. The increase was linear with dose in children dying within the first year of exposure, particularly within the first month; however, there was no increase between 1 and 9 years and only the suggestion of a further increase after 10 years of age. The excess mortality was significant only for children exposed during the third trimester of pregnancy, but loss of the embryos and foetuses might have been present in an unknown percentage of pregnancies before term. Regarding the causes of death, no information was available for 55 persons (out of a total of 203 deaths) most of whom died within one year after birth: loss of this information was due to the confusion in the official vital statistics reporting system which arose immediately after the war. The sample size is yet too small and too young for any conclusion about a possible excess death from non-specific causes.

E. CONCLUSIONS

363. The data on occupationally-exposed groups of workers do not lend themselves to complete dose-effect analysis and, in the absence of precise dose evaluations, conclusions must rely on comparisons between groups of exposed and non-exposed individuals. Under these circumstances, the homogeneity between the control and the test samples is critical because in many series the effects are marginal and their statistical significance may depend on the choice of controls.

364. The data on radiologists leave no doubt that particularly in the early days of radiology leukaemia and cancer were indeed induced in these persons. Observations in favour of this conclusion have been confirmed in all studies [D9, W2, W3, C27, S38, W4, M28, M29]. However, in some instances a higher incidence of neoplastic conditions was not accompanied by an increased death rate and shortening of life [D9, C27], while in others [W2, W3, S38, W4] there was a true loss of life amounting to 5 to 6 years, following exposure for the whole working life. Not all of this life shortening may be accounted for by leukaemia and cancer induction, and other non-neoplastic conditions contributed to it. Some of these may have been due to non-stochastic damage, such as skin necrosis, leading to death in the earlier series. There is no way to derive from the data, as there is no knowledge of dose, an approximate value of the life shortening per unit dose. There is unanimity in the conclusion that the induction of neoplastic conditions, accompanied or not by life shortening, has disappeared in more recent years, presumably after the adoption of radiation protection measures.

365. True shortening of life has only been reported in a series from the United States [W2,W3,W4,S38]. Reasons to justify the absence of life shortening among radiologists of the United Kingdom have indeed been given and the absence of effect could be accounted for by objective reasons and on methodological grounds. It has been pointed out that with samples of the order of 1000 persons prevalence ratios of the order of 2 to 3 for leukaemia and life-shortening effects of the order of 5 to 6 years can hardly be resolved. It should also be realized that induction of neoplasia is not necessarily linked to life shortening. Within the large limits of variation cited above an excess mortality ratio of 1.5 to 2.0 could be compensated by a lower rate of death from other causes, leaving the death ratio from all causes unchanged with respect to controls [S42].

366. In spite of the small sample size (about 1200 persons) the data on the mortality experience of dial painters convincingly showed that the only causes of death significantly contributing to the life-span shortening in these women are bone sarcoma and carcinoma of the head sinuses, tumours known to be specific risks for ^{226}Ra and ^{228}Ra exposure. To the precision possible with such sample size, therefore, non-specific mortality was not seen, in spite of the known presence of non-stochastic injury in these subjects, for example, in the bone. On the other hand, exposure under these conditions was localized and not extended to the whole body.

367. The experience on the radiology technologists, both from Japan and from the United States, is considerably more limited (and therefore much less significant) than that on radiology specialists. However, on the whole, it does not appear in contrast with the latter. Here again, induction of leukaemia and of some forms of cancer were often seen [K17, K18, M27, K19]; in one case life shortening was reported [K18], but not in others.

368. What may safely be concluded from the data on occupationally-exposed pioneer radiologists is that neoplastic diseases, particularly leukaemia and skin cancer, are real effect. Some life-span reduction may also have been present in these persons who were presumably exposed to high doses; however, this effect was reported unanimously to have disappeared in more recent years in radiology specialists entering their profession after the radiation protection rules have been in operation. If this conclusion is true, it should logically follow that within the range of doses recommended since that time (that is for exposure rates of 1 R per week as a maximum) no reduction of life span can be expected and any residual prevalence of leukaemia and tumour induction would be insufficient to cause a statistically detectable shortening of life.

369. In principle, radiotherapy patients have a number of favourable characteristics for epidemiological studies (knowledge of the dose, good standard of medical follow-up) which might counterbalance some negative aspects (small samples, death associated with the primary disease). In practice, the three small series available on women surviving radiotherapy for uterine cancer [S40, N11, Z1] have yielded negative answers in respect to life shortening. The size of these surveys is certainly inadequate for any firm conclusion, but a negative finding would not be unexpected under conditions where only a small fraction of the body was irradiated. It is known from animal experimentation that life shortening is less likely to be observed after partial-body exposure (see section III.D).

370. The experience on the ankylosing spondylitis patients [C28] does show at a first sight a small but significant prevalence of unspecific mortality. However, a thorough analysis of the causes of death,

discussion of the epidemiological evidence and consideration of the time-course of the excess mortality raise some doubt on the reality of this observation. On these grounds a dependence of the excess non-specific mortality on the spondylitis itself cannot be rejected. Thus, the survey seems inadequate to validate the existence of a radiation-induced non-specific shortening of life.

371. On the whole, therefore, the evidence coming from radiotherapy patients is negative for the presence of the life-shortening effect under discussion. Naturally, the weight to be attached to these data is relatively smaller than that applying to the surveys on occupationally-exposed people and much less than that carried by the studies on A-bomb survivors.

372. The incidence of leukaemia and various other malignant tumours is increased among the survivors of the A-bombs. These diseases are associated with a measure of life shortening and appear to account entirely for the observed shortening of life in the exposed groups, irrespective of dose. The absence of significant non-specific life shortening is important because this conclusion is based upon a large amount of data on person-years at risk. However, the limited experience in connection with the younger age groups where few deaths have occurred should be kept in mind in this regard.

373. The negativity of this survey is remarkable because the modality of the irradiation (acute, high dose rate) would be expected to produce a maximum of life shortening by comparison, for example, with the low dose rate occupational exposures. Also, the absolute amount of radiation absorbed over the whole body (of the order of 1 Gy or more, but for 90% of those exposed below 2 Gy) should also have produced a substantial life-shortening effect. But since there is no evidence to support the hypothesis that a selection of the early survivors might have favourably influenced the subsequent long-term mortality experience [R10], the conclusion must be accepted that up to the present time there is in this large sample of persons no evidence of a diffuse non-specific effect of life shortening. Any long-term effects are, on the contrary, very specific, focal and essentially cancerogenic.

374. In conclusion, the evidence concerning a non-specific radiation-induced life-shortening effect in man has been reviewed in the preceding paragraphs. This review has produced essentially negative answers, except for the pioneer radiologists of the United States. The data from this group of people are, however, in contrast with a massive body of data in experimental animals where such a non-specific effect, particularly at low-medium doses of radiation, cannot be substantiated. The data on the pioneer radiologists of the United States are in contrast with the much larger body of information on the A-bomb survivors. In the latter situation, the degree of life shortening observed can be accounted for by the increased prevalence of a variety of malignancies, although data on the survivorship of younger age groups are still limited. It may be noted in this connection that the early radiologists that experienced a degree of life shortening were exposed at a relatively early age.

375. Pending further evidence therefore, it should be concluded that radiation-induced life shortening in man is essentially due to the induction of specific neoplastic conditions. Non-specific effects on the life span, suggested in one instance, have not been proven beyond doubt: the weight of these data is therefore insufficient to modify the above conclusions.

V. GENERAL CONCLUSIONS

376. The Committee has reviewed in this Annex most of the existing data in animals and man on the subject of radiation-induced life span shortening and has considered the effect thereupon of the major physical and biological variables. The analysis of the Committee has been centred particularly around the possible existence of non-specific mechanisms of premature death, the dose levels at which these mechanisms might operate and their possible relationship to the physiological processes of aging. A non-specific life-shortening action and an aging effect of irradiation were claimed in earlier times on the basis of gross experimental observations of irradiated animals. The Committee believes, however, that a critical reappraisal of previous findings and the availability of more precise and significant new information have now made these concepts untenable.

377. The Committee has briefly reviewed the current concepts concerning natural aging and the possible mechanisms at the molecular, cellular, tissue and whole-body level that might be responsible for senescence. The Committee has also examined the interactions between such mechanisms and their expression in an animal population as statistical events causing the population's extinction in time. It has concluded that there are at present great difficulties in defining aging in ways other than by actuarial parameters and that it is impossible to decide whether the changes revealed by experimental observations in senescent animals are the causes of aging, effects of aging or indeed aging itself. The Committee has therefore decided to confine this Annex to the analysis of life shortening as such, pending further clarification of the notion of aging.

378. All available data consistently show that irradiated animals do experience on the average a shorter life span than their non-irradiated controls. However, the notion that such an effect may be due to the same spectrum of causes taking normal animals to death (although appearing earlier in time) may not be substantiated by experimental evidence. Thus, the idea of a non-specific effect of irradiation superimposable on physiological aging becomes conceptually improbable and logically unnecessary. This is particularly true at doses below the mean lethal dose where life shortening may be accounted for solely on the basis of radiation-induced tumour induction. Under these conditions life shortening becomes a compounded but very imprecise way of expressing by actuarial values the acceleration or higher incidence of tumour appearance in an irradiated animal population. However, at doses well in the lethal range a non-specific component of life shortening may become apparent, which may be substantiated by diffuse damage to the capillary blood vessels or to the connective tissues.

379. The Committee has reviewed and independently analysed the existing life-shortening data on mice submitted to a single acute dose of radiation of *both* high- and low-LET. While in each given experimental series the dose-effect relationships could be of many different forms, pooling many series resulted in an

apparently linear relationship for low-LET and an apparently convex upward relationship for fast neutron exposure. The different forms of the two relationships cannot be explained at present, but the fact that a linear function of dose may reasonably describe life shortening in a highly non-homogeneous population where different strains, ages and sexes are represented has interesting practical implications. Information on other mammalian species such as the rat, the hamster and the dog have also been examined in comparison with the mouse to which most data refer.

380. Single acute irradiation is undoubtedly an easy and efficient way to induce and study life shortening, but long-term irradiation at low doses is the most relevant exposure condition in practice. The existing data on rodents irradiated for the whole duration of their life was examined by the Committee as a function of the dose rate and of the total cumulated dose, for exposure to electromagnetic beams. The lower efficacy of the long-term as compared to the single-dose treatment has been confirmed for x and gamma rays. In the case of neutrons, long-term treatments have in some instances shown reduced life shortening compared with single doses and in others increased life shortening, particularly in more recent studies. Under long-term conditions of exposure phenomena of apparent life lengthening have been reported whose significance has also been discussed. The special case of chronic exposure to many injected, ingested or inhaled radionuclides has been studied but has revealed no life shortening in excess of that attributable to the induction of specific tumours caused by the various nuclides.

381. A variety of observations exist in experimental animals concerning the effect on life shortening induced by changes in the dose rate, dose fractionation and chronic exposure terminated before death of the animals. The Committee has reviewed this information and has concluded that all these treatments, but each to a variable degree, result in a level of life shortening which is intermediate between that of the acute and of the life-long treatments. Repair and repopulation mechanisms are operating under such circumstances. These mechanisms appear to depend markedly on dose and time parameters as well as on a large number of biological variables, following complex relationships.

382. A linear relationship for gamma rays, as suggested in paragraph 379 implies no dose rate dependence. Therefore fractionation of the dose or continuous irradiation at low dose rates should not reduce life shortening per unit dose. This however is at variance with the Committee's conclusions about the experimental observations (paragraphs 380 and 381). Thus a linear-quadratic relationship which can provide for the observed effects and which is equally likely according to the analysis in paragraph 95, might be preferable to a simple linear dose-response relationship. At low doses and dose rates the form of the response would be essentially linear in either case, but not with the same slope.

383. For neutrons, the convex upward shape of the dose-response relationship for single doses intrinsically implies an increased effect when the dose is fractionated or when low dose continuous irradiation is used. As has already been noted, the experimental results with neutrons have been mixed. In some cases, life shortening appeared to be reduced by lengthening the exposure, in other cases (particularly in more recent experiments) it is increased by fractionation. It is possible that real differences in dose-effect relationships for different tumour end-points do exist, and that these account for the complexities observed in the life shortening response for different strains or species.

384. The RBE of fast neutrons up to 14 MeV, as compared to low-LET radiation, has been assessed from published data and from the Committee's own analysis. For acute doses in the region of 0.01 Gy of neutrons, the RBE cannot be determined precisely. The predicted values could be about 10, but values as high as 50 might be possible, depending upon the assumed shape of the dose-response curves. Low-LET radiation appears to be about seven times less effective in studies with duration-of-life exposure than it is for single exposures. At low dose rates and duration-of-life exposure neutrons could be 20 to 40 times more effective than low-LET radiation.

385. The vast majority of the data reported on rodent and non-rodent species of mammals submitted to radiation of different types delivered at various dosages appeared, when appropriately analysed, to be consistent with the notion that life shortening after doses up to about the $LD_{50/30}$ can be accounted for essentially by an acceleration or an increased net incidence of tumours causing premature death. No data were found to clearly support the concept that radiation may advance in time or accelerate the appearance of diseases normally associated with senescence, without any change in the type and the relative incidence of these diseases.

386. The spectrum of radiation-induced diseases and the consequent life shortening depend largely on the specific physiological and pathological characteristics of the irradiated animals. The Committee has reviewed the evidence pertaining to the changes in life shortening seen in different species of animals. Such data had been obtained in the hope of constructing a scale of radiosensitivity values to aid in the extrapolation of findings from animals to man. The conclusions to be derived from such data may, however, hardly be taken as useful generalizations in view of the large differences pointed out above. Comparisons between strains of the same species, the mouse, have also been attempted and have revealed interesting regularities in the life-shortening response, in spite of the strain-related specificities. The formal genetic analysis of these findings is not yet sufficiently advanced to allow the identification of the common principles underlying the precocious death of animals through a variety of specific causes.

387. Extensive data led the Committee to conclude that the sex of the irradiated animals is also a significant variable affecting the susceptibility to life shortening: female animals are in general more sensitive than males, mostly owing to their higher rate of genital tract tumours and leukaemia in mice. As to the effect of age, irradiation in utero seems to produce usually less life shortening for a given dose than irradiation during the post-natal ages. Irradiation early in extra-uterine life also produces, all other conditions being equal, more life shortening than treatment in older ages. Physical conditions (temperature, stress), chemical treatments (oxygen, radioprotective substances) and partial-body irradiation have been studied in respect to their influence on life shortening. The presence and the extent of these effects have been assessed by the Committee.

388. Data derived from irradiation of human subjects were the object of special attention in this Annex. They were obtained through epidemiological investigations carried out on persons exposed in the course of their professional life (radiology specialists or technicians, dial painting workers), on patients treated with radiation for various pathological conditions (tumours, ankylosing spondylitis) or on survivors of the atomic explosions in Japan. The Committee has investigated the reliability of the different series from the point of view of exposure conditions, dose assessment, methodology of study and significance of the conclusions.

389. With regard to occupational exposure, it has repeatedly been shown that a component of life shortening observed in radiology specialists exposed in the United States during the early days of clinical radiology cannot be accounted for solely on the basis of tumour induction. Such a component has apparently disappeared at about the time when radiation protection recommendations limiting exposure to less than 1 R per week came into practice. Analogous investigations carried out on a group of British radiologists were unable to reveal such an effect. Numerous other studies conducted on radiology technicians or on dial painters (these latter series carry less weight due to the smaller size of the groups) were also negative for the presence of non-specific life shortening. The Committee therefore concluded that the existence of such an effect is doubtful under the conditions of the above studies or, more conservatively, that exposures to 1 R per week or less does not cause any detectable non-specific shortening of life in man.

390. With regard to medical exposure, investigations on patients treated with localized radiotherapy for cancer of the uterus did not reveal any life-shortening effect. A survey on spondylitis patients was inadequate to validate the presence of life shortening associated to the radiation treatment rather than to the disease itself requiring radiotherapy. Although the importance to be attached to these conclusions is limited by the modality of the treatment (partial-body) the conditions are also, in general, against the notion of non-specific life shortening.

391. The epidemiological series in man which carries by far the highest degree of significance and reliability for the numerosity and the accuracy of the observations is that on the A-bomb victims. For the last thirty years and up to the present stage of the observations this series has indisputably shown that there is no evidence of life shortening that could not have been explained by an increased appearance of leukaemia and solid tumours.

392. In essence, the review of the Committee has been unable to substantiate in experimental animals and in man a non-specific effect of life shortening below the mean lethal dose. While the presence of such an effect cannot be excluded for higher doses, there is no firm evidence that diffuse non-specific mechanisms causing premature death in the irradiated animals may be operating at the low doses and dose rates of significance to the radiation protection of man. On the contrary, long-term radiation effects are very specific and essentially cancerogenic under these conditions. In the light of present data, a higher incidence of tumours fully explains the life shortening seen in the irradiated populations.

VI. RESEARCH NEEDS

393. Given the above conclusions, the Committee believes that experimental research specifically designed to analyse the physical and biological variables affecting radiation-induced life shortening only should not be assigned high priority. It is, however, advisable that the collection of data on life span might proceed in parallel with other experiments planned for different purposes, in particular for the study of induction of neoplasia. Specific recommendations as to the general strategy and the detailed topics to be followed in this field have been issued in previous reports of the Committee. In order that the best use might be made of data on life span shortening obtained in the course of long-term experiments, these data should be collected and analysed according to methodological needs repeatedly discussed in the preceding text.

394. For the actuarial analysis of the data, use of the following methodologies is recommended:

(a) Analysis of mean and median ages at death and survival times following standard statistics, both as absolute parameters and relatively to the control values;
(b) Analysis of the extinction curves of the irradiated versus the control population;
(c) Analysis of age-specific mortality rates in irradiated and control groups;
(d) Corrections of the life-shortening data to account for the effects of competing diseases by methods which have been shown to enhance the capacity to discriminate between specific and non-specific causes of death;
(e) The use of multifactorial models in the analysis of complex physical, physiological and pathological interactions.

395. Attention has been repeatedly drawn to the fact that in order to assess specificity or non-specificity of life shortening detailed clinical surveillance during life and pathological examination of the animals at death is necessary. Although the assessment of causes of death is difficult in animals, it is essential if the data to be gathered are to be of the most use. Serial sacrifice experiments, whether included in life-span studies or not, would be particularly valuable to investigate the evolution in time of the diseases contributing to premature death. Attention should also be drawn to the renewed importance of interspecies extrapolation, not only for life shortening but for tumour induction as well, because of the lack of human information for some types of radiation, including neutrons. In this regard experiments in species intermediate in life span between mouse and man are of special importance. Questions of particular interest at this time relate to the sensitivity of embryos to life shortening and to tumour induction among the different species.

396. The Committee's recommendation for a low priority to be assigned to research solely on radiation-induced life shortening derives from the opinion that such an effect may be explained at low doses and dose rates by tumour induction, with addition, at higher dose rates, of specific non-stochastic effects described in Annex J. It is perfectly compatible with the well established fact that gaps still exist in knowledge of the life-shortening effects of radiation in mammals. The

Committee has identified many areas which could profitably be explored among which are:

(a) The analysis of physical and biological factors contributing to the life-shortening effect in complex regimes of long-term irradiation;
(b) The analysis of the causes leading to an apparent life lengthening for irradiation at low doses and dose rates and the influence of biological variability or repair phenomena thereupon;
(c) The problem of RBE, particularly at low doses and dose rates, of radiations of different qualities;
(d) The dose levels at which non-stochastic effects as well as tumour induction might become of importance in the causation of death after whole or partial-body irradiation;
(e) The extent and mechanisms of life shortening after pre-natal irradiation;
(f) The influence of modifying factors, including radiosensitizing and radioprotective treatments;
(g) The role played by the different pathological conditions in determining the form of the dose-effect relationship for life-shortening;
(h) The comparison of life-shortening effects in different species.

397. The Committee believes that the collection of data about the effect of radiation in causing or contributing to deaths in men should continue to be given the highest priority. This applies not only to the series on the atomic bomb victims which will undoubtedly be followed with care, but to all other groups and particularly to those undergoing occupational exposure and to patients treated by radiation for benign diseases and for cancers with a good prognosis. The final conclusions drawn from such data will be of immediate relevance to the knowledge and prevention of radiation effects in the human species. This recommendation is made since further knowledge is needed regarding deaths from non-stochastic damage, in addition to cancer induction, at as wide a range as possible of both dose and dose rate.

398. The loss of life expectancy by affected individuals in whom a tumour has been induced by radiation is an important factor in risk estimation. It involves a knowledge of the frequency of induction of each tumour, the average latent period and the average age of the population at risk. The lost time per affected individual can then be used as a basis for comparison of hazards between occupations involving exposure to ionizing radiation and, for example, lost time due to accidents (fatal and non-fatal) in a range of industries [14]. These estimates can also be used to derive an average loss of life span for the entire population at risk from a given average dose. It would be useful to have direct estimates of the life shortening per unit dose for populations such as the Japanese survivors, when these are feasible.

Table 1

Life shortening after single acute whole-body x- or gamma-ray treatments

Species and strain	Sex	Radiation	Percentage life lost per Gy or per 100 R	Range of percentage shortening	Days lost per Gy or per 100 R	Form of curve g/	Ref.
Mouse							
10 strains	M	98 kVp x	4.2	?	15	linear	[G2]
BAF1	M	80 kVp x	4.2 a/	30.2	24	?	[G3]
	M	135 kVp x	4.9 a/	30.4	29	?	
	M	250 kVp x	4.6 a/	27.2	27	?	
	F	80 kVp x	6.7 a/	39.2	35	?	
	F	135 kVp x	5.2 a/	32.1	34	?	
	F	250 kVp x	6.7 a/	39.2	43	?	
CAF1	F	250 kVp x	3.2-6.3	19	21-42	convex upward?	[K7]
Swiss	F	250 kVp x	4.7	0-30	19	linear	[S17]
CF1	F	gamma from weapon	2.6	8-37	25	linear	[S18]
	M	x rays	7.8-10.9	11-31	?	convex upward?	[B8]
LAF1	M	gamma	5.0 b/	3-45	37 c/	concave	[U5]
	F	from weapon	6.3 b/	10-51	47 c/	upward	
6 strains	M	200 kVp x d/	4.1	23.2	28	concave	[G4]
	F		5.4	30.6	81	upward	
SAS/4	M+F	15 MeV x	5.4	5-44	40	linear	[L1]
RF/J	F	250 kVp x	9.1	36.5	45	linear?	[S19]
RF	F	60-Co gamma	4.7	28-85	25	linear	[S21]
RF/Un	M	250 kVp x	-	3-31	56-3	convex	[U7]
	F	60-Co gamma	-	5-29	15-2	upward	
C57BL/6L	F	300 kVp x	4.1 e/	3-32	23 e/	convex	[Y1]
A/J	F	300 kVp x	5.9 e/	7-38	29 e/	upward	[Y1]
RF	F	300 kVp x	7.7 e/	6-32	75	convex upward	[C12]
LAF1	M+F	60-Co gamma	2.5 e/	7-29	15	concave upward	[G5]
B6CF1	M	60-Co gamma	5.3	5-42	45	linear	[A7]
	F		5.3	6-43	48	linear	
(C57BLxC3H)	M	250 kVp x	2.5	0-9	22	linear?	[C13]
BALB/c	M	250 kVp x	7.3	0-66	54	linear?	[M8]
C57BL	M	250 kVp x	9.8	0-48	68	linear?	[M8]
RFM	F	137-Cs gamma	9.6 e/	0-38		complex	[S44]
	M		6.7 e/	0-20		linear?	
BALB/c	F	137-Cs gamma	7.0 e/	0-14	39 e/	linear?	[S44]
B6CF1	M	60-Co gamma	5.1 e/	0-40	42 e/	linear	[T4]
	F		5.2 e/	0-45	43 e/	linear	
Rat							
Wistar	M	250 kVp x	4.2-4.9	7-29	35-41	linear?	[H5]
	F		2.8-4.0	4-24	15-22	linear	
	F	250 kVp x f/	0.4	39	28	?	[L3]
Dog							
Beagle	F	250 kVp x	6.7	3-24	284	linear?	[A2]

a/ Data derived on the hypothesis of linearity from experiments at the LD_{50} level.
b/ Figures obtained at the LD_{50} level.
c/ Figures derived from Grahn and Sacher [G1].
d/ Average for all strains.
e/ Data derived on the hypothesis of linearity.
f/ Data derived from a single exposure of 100 R given under 5 % oxygen.
g/ As given by the authors.

Table 2

Life shortening after single acute whole-body neutron treatments

Species and strain	Sex	Radiation	Percentage life lost per Gy or per 100 R	Range of percentage shortening	Days lost per Gy or per 100 R	Form of curve c/	Ref.
Mouse							
Swiss	F	thermal column	4.7	0-30	19	linear	[S17]
CF1	F	weapon neutrons	4.7	8-30	37	linear	[S18]
LAF1	M	weapon	6.7	9-23	79	concave	[U5]
	F	neutrons	15.6	9-39	6	upward	
CF1	F	fission neutrons	22 a/	9-45	6	linear?	[V1]
RF/Un	M	1 Mev	9.0-18.0	19-28	21-6	convex	[U7]
	F	neutrons	8.4-14.9	33-47	11-3	upward	
	F	14 MeV neutrons	6.7 a/	9-26	40	convex upward	[D1]
BC6F1	M	fission	35.9 b/	7-26	300- 90	convex	[A7]
	F	neutrons		9-31	390-110	upward	
RFM	F	fission	45-77	4-25	-	convex	[U8]
		neutrons	42-70	0-20	-	upward	
B6CF1	M	fission	-	0-25	-	convex	[T4]
	F	neutrons	-	0-31	-	upward	
Rat	M	fission neutrons	10 a/	22	-	?	[K8] [K9]
Guinea-pig	M	fission neutrons	12 a/	12-16	~ 100	?	[K8] [K9]

a/ Estimate derived from a first-approximate assumption of linearity.
b/ Estimate derived from data at the smallest dose of 0.2 Gy.
c/ As given by the authors.

Table 3

Approximate scales of sensitivity of various animal species for the life-shortening effects of irradiation

Irradiation condition	Approximate sensitivity			Refs.
	More sensitive		More resistant	
Chronic x-irradiation	Monkey	Rat, dog and mouse about equal	Rabbit	[B11]
Acute x- or γ-irradiation		Rat and mouse about equal		[U1]
Chronic γ-irradiation	Man	Guinea-pig, rat, dog and mouse about equal		[G1] [S23]
Chronic γ-irradiation	Guinea-pig	Man, dog and mouse about equal		[G6]
Chronic γ-irradiation		Dog and mouse about equal		[N7]
Chronic γ-irradiation	Goat	Mouse		[H9]

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