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RADIATION-INDUCED LIFE-SHORTENING

(Prepared in the Secretariat)

#1½

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INTRODUCTION

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

- the existence and extent of life-span shortening in irradiated animals and man as a function of the main physical and biological variables known to influence this effect of radiation;
- whether and to what extent and within what ranges of the above-mentioned variables this effect might be attributed by careful pathological analysis to real non-tumorous conditions or, on the contrary, to specific neoplastic diseases;
- whether and within what range of doses a non-specific radiation effect may be traced and quantified;
- whether such a non-specific shortening of life might be considered akin to the normal biological aging process.

Although some of the above problems may appear too ambitious in the light of the present biological and radiobiological knowledge, the Committee believes that a review of the field with such objectives in mind may be of value at least as a selective collation of the existing information.

A. HISTORICAL BACKGROUND

2. 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 duration of life, looked older and appeared to age more rapidly than their non-irradiated controls. These and other observations led quite naturally to the establishment of a 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 in a rather articulate way. They recognized, for example, the notion that single acute exposures to radiation tended to displace upward the Gompertz age-mortality function, 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 approaches to the description of the effect. The 1955 paper by Sacher [S1] was a comparative review of radiation lethality in various mammalian species, particularly under conditions of chronic treatment for the entire duration of life.

3. It is of interest to note that, although the treatment of this subject had already proceeded quite far, there was a small coverage of it in the 1958 report of the Committee [U1], where the analysis of the biological end-point was not very sophisticated. It has been established at the time that while the pathogenesis of early death was due to the failure of self-renewing systems in the body, the precocious extinction of an animal population as revealed by actuarial analysis, would be due to different mechanisms of action. However, there seemed to have been poor discrimination in the treatment of the two subjects. No attention was given, in particular, to the actuarial approach which had already been advocated by Sacher [S2] and Brues and Sacher [B1].

4. The review presented by Mole at the First International Congress of Radiation Research [M1] critically discussed on the basis of experimental evidence the idea that experimentally observed life-shortening might be equivalent to natural aging, a phenomenon about which too little was known to warrant unsupported generalizations. However, the notion that radiation could shorten life by similar physiological and pathological phenomena as natural aging gained momentum as a result of some observations on survivors of doses in the lethal range made by Henshaw [H1] and later by Alexander [A1]. The idea was first based on actuarial observations of an increase in mortality rate from all causes of death, with an apparent shift to earlier times of diseases characteristic of the late ages. Also, the occurrence in these survivors of phenomena typical of the old age (graying of the fur, cataract, loss of reproductive capacity, etc.) tended to give support to the hypothesis. However, Upton in his 1957 [U3] and 1960 [U4] reviews warned against the establishment of close resemblances 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. Under these conditions it would, of course,

be difficult to maintain that irradiation simply advanced the onset of senescence, unless it could be accepted that the aging of various organs could be advanced to different degrees.

5. Comfort [C1] discussed similarities and differences between natural aging and radiation-induced life-shortening. His review is important for its 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. The paper by Storer and Grahn [S3] was an objective and accurate review of information available which is still of interest for reference purposes. Neary [N1, N2] analyzed the various therories of aging and regarded them as belonging to 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 also 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.

6. 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 could 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. In due course these would be followed by loss of parenchymal cells, replacement fibrosis of the organs, loss of the functional reserve capacity and, eventually, an increased susceptibility to trauma, stress and disease.

7. In recent years the contributions 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 date, some basis for a comprehensive theory of a natural and radiation-induced aging.

8. The more recent report of Walburg [W1] is essentially a critique of the concept of non-specific life-shortening, at least at the low doses of practical interest. Walburg came to the conclusion that life-shortening effects after irradiation may principally or perhaps exclusively be explained by the induction or acceleration of neoplastic diseases. This conclusion was also supported by Storer [S6]. All authors recognized that at higher doses other mechanisms of death would be prevailing.

B. METHODOLOGY

9. 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 the reasons why an animal dies than to identify with great prevision the time at which the event occurs. To ascertain the cause of death is often a difficult exercise and, in some cases, an impossible one since 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 what happens early in life, where the cause of death is more often related to a single pathological entity. In old animals the number of possible causes of death increases and the primary or precipitating cause is difficult to diagnose. Also, 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.

10. The first difficulty with much of the work reviewed, particularly with the oldest contributions, is the lack of careful pathological observations on the animals at death, let alone the refined multifactorial analysis mentioned above. Many experimental series are therefore difficult to interpret, since the representation - as accurate as it maz be in time - of the life-span shortening, marks the complexity of the biological end-points. Another difficulty lies with the fact that even when good pathology is available, this 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 each of them may be equally accelerated by radiation. Serial sacrifice experiments could, in principle, provide such information, but they require considerable time and effort and are therefore not common in the literature [K1, C3, A3].

11. Apart from the difficulties in defining and describing a complex effect like life-shortening, its quantification could also create problems by giving implicit support to one or another possible interpretation. Interesting observations 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 life-span of the control population and the life-span of the irradiated animals, $t_0 - t_D$. If it is postulated that survival after a given dose 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 is a function of the dose, then the implication is that the effect of radiation may be equivalent to natural aging. No problem arises when single acute exposures are given at young ages or in duration-of-life experiments, because under these conditions the two formulations are identical. But when experiments to 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 following one or the other approach.

12. By definition, life-shortening is an effect that must be estimated statistically by comparing irradiated and non-irradiated animal populations. There are different ways of describing and expressing quantitatively the effect. They are the mean or median life-span, the percent cumulative mortality or the age-specific mortality rate. All may be regarded as compounded expressions over the whole population of animals of specific and non-specific causes, acting and interacting within each individual to decrease its fitness and to take him to death.

13. Life-shortening is expressed in days of life lost and since the time to death is a random variable, 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 such cases the effect is given in units of time. Alternatively, the effect could be given as a percentage of control values and in such cases the percent shortening of the mean or median age at death or the percent 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 precent shortening of the mean or median survival. Although it would have been desirable to use the same way of expressing the effect throughout the present document, it was impossible to do so owing to the lack of suitable data in the documents reviewed.

14. 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. Thez do not offer any indication of the variability affecting this phenomenon in 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 in that it allows knowledge of the time when this process begins and ends and it also allows one to know 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 and the curve of per cent cumulative mortality can be readily calculated.

15. 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. Changing of this parameter in time is therefore its main disadvantage: the 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 mortalityrate curve for irradiated animals above the curve for non-irradiated controls does not reflect 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.

16. 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. 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 this parameter beyond a certain age tends to assume an exponential trend. Also, death rate curves specific for certain diseases are found to vary in shape and slope. These changes 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 to be regarded as an oversimplification in the light of the variability observed among specific injuries.

17. 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 and a non-interval technique by Kaplan and Meyer and have come to the conclusion that the latter one 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 in 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. On their basis Walburg [W1] has reanalysed some of the 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.

C. THEORETICAL FOUNDATIONS

18. Although it is the primary object of the present document 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 will be given in the next few paragraphs in a very simple form and will be limited to those hypotheses that were proposed in the field of radiation research. More comprehensive discussions of the various theories of aging will be found, for example, in Strehler [S7] and Walburg [W1].

19. Gompertz in 1925 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 much 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.

20. The Gompertz function is the logarithm of the age-specific rate of mortality which is defined as

$$\Omega\,(t) \quad = \quad -\frac{1}{N}\frac{dN}{dt} \tag{1}$$

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

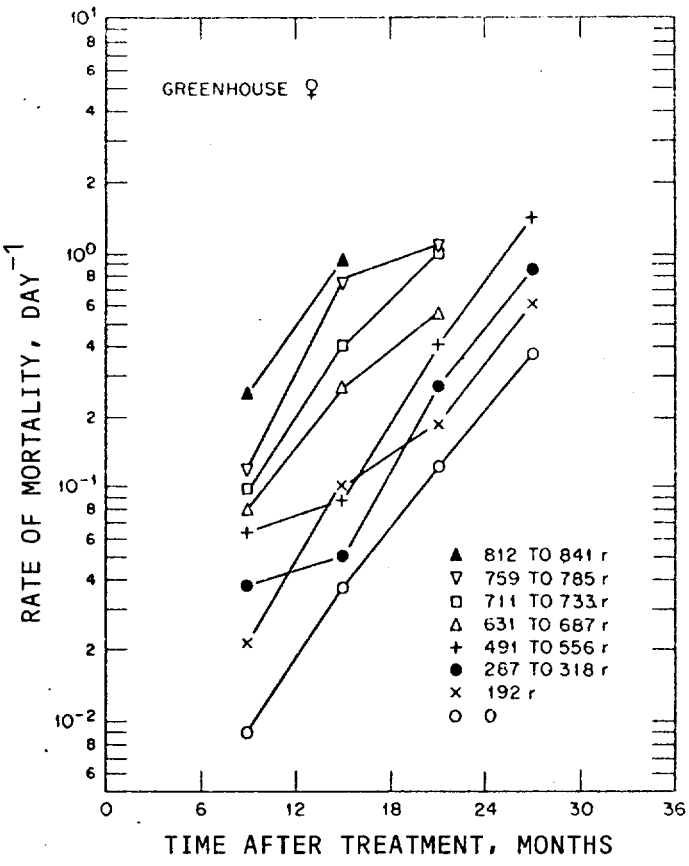
$$(t) \quad = \quad P_o\, e^{P_1 t} \tag{2}$$

where P_o 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, the amount of displacement with respect to control being a function of dose. In other words, acute irradiation would change the constant P_o in equation (2), without affecting P_1. If single exposures would affect median survival, t_{med}, linearly with dose D, then

$$t_{med}\,(D) \quad = \quad \underline{a} - \underline{b}D \tag{3}$$

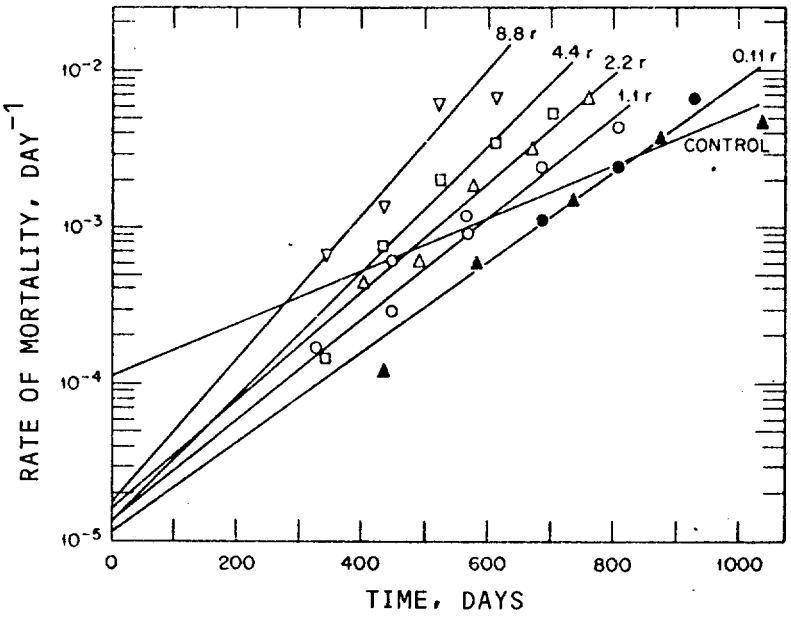
where $\underline{a}$ is the median survival time of the control group and $\underline{b}$ a dose-dependent constant. Chronic irradiation, on the other hand, characteristically increases the slope of the Gompertz function proportionally to intensity of irradiation, so that

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



A. Gompertz plots for LAF1 mice (females) after single acute doses of 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.

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

21. 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 would increase this amount of injury once and for the rest of life. However, if any new amount of injury induced summates to the residual injury present at any given time and to the underlying aging injury, one should expect a change in slope by chronic irradiation with a divergence from 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.

22. In 1952 [B2, B3] and again later in a more complete form [B4, B5] Blair formulated a "theory" 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 would proceed 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 would add in all proportions and death would occur when 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 under a variety of experimental conditions the amount of reparable injury and the kinetics of repair but was recognized later as an oversimplification of reality, leading to incorrect estimates and as such inadequate to account for the form of the dose-injury functions.

23. 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 form into an actual form of injury at a given measurable rate. The numerical parameters entering 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 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.

24. 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 pre-irradiated 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 irradiated chronically. Further work [K4, K5] suggested in fact that different recovery components with different half-times could be shown to apply to acute and chronic radiation exposure conditions.

25. 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 (240 to 1200 rad) or of fission neutrons (92 to 451 rad) to RF female mice and, after a repair period of 3 months, exposed them for the rest of their life to a dose rate of 50 rad/day. 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 than 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 per cent of any given dose, showed that such a formulation was only useful under a limited range of exposure conditions.

26. The above limited discussion of a vast amount of literature shows that short-, medium- and long-term mortality recognize different pathogenetic mechanisms whose analysis may not be performed under the same assumptions: there is probably more than one single formula that may take into account the variety of mechanisms. Also, no single recovery time or residual injury value can define all conditions of protracted exposure. The constants applicable for acute injury may to some extent predict the results of exposures within about 100 days and 1500 rad in the mouse, but for longer times and low doses a new set of relations between injury and recovery must be established [G1].

27. Neary [N1, N2] also proposed a model, based on the observation that the great majority of animals in a population die during a period in 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 inductive change is reached, the second stage sets in quite abruptly. This stage, called "development" would involve a different level of organization and would be sustained by physiological interactions proceeding autonomously and autocatalitically 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 conceptually emphasized by Mole [M6] and by Mole and Thomas [M7] in the notion of "wasted radiation". Neary suggested that small radiation doses would act essentially by shortening induction but without affecting development, and also showed that there was a good correlation between the results of his experiments on CBA mice [N3] and the formal requirements of the model. Kohn and Guttman [K6] pointed out, however, that the model, derived from experience on duration-of-life exposure, would be applicable with difficultz to acute irradiation.

28. In a paper published in 1956 Sacher (S2) proposed a model wherebz all individuals in a population are assumed to be initiallz identical. However, with time, owing to fluctuations in the phzsiological state of the animals and to external stresses, there would be a progressive change and a dispersion in the phzsiological state of the population. When a fluctuation of large amplitude in the homeostasis of an animal takes place, death will ensue. 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 having the form of a linear function between the logarithm of the mortality rate and the mean physiologic state of the population at any given age.

29. 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 kinetic, without building into the models known parameters of cell kinetics like 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 also 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 [14].

30. 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, operating soon after exposure and causing 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 would be 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: 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 because of age; and age-cumulative injury is postulated to be linear with age.

31. 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 they allowed the identification of various mechanisms of death operating with the two nuclides. The formalisms developed in this series of papers, in addition to describing the experimental data adequately, were thought to be of potential use for their interpretations.

32. 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.

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

34. 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 their variation on 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 not showing 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. It 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].

D. LIFE-SHORTENING AND AGING

1. Specific and non-specific life-shortening

35. 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 spectrum of diseases or causes of death different from the spectrum seen in the non-irradiated controls.

36. 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 equivalent 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 could be accounted for by neoplastic diseases. Even though never stated quite 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 quite legitimate and of great practical significance.

37. 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 irradiation long-term survival data should first be corrected for diseases known to be induced specifically by radiation. The concept of life-shortening appears ambiguous in that 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 recognize some basis in damage to biological structures and functions. Actually, some damage, anatomical or functional, may indeed be shown for some tissues [C4, D3, C5], but not for all, and under these conditions an increase of causes of death related to damage in those particular tissues might 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 like the blood vessels or the connective tissue, which are uniformly distributed in the body, could be the cause of non-specific life-shortening. But here again it would appear unlikely that damage to blood vessels in skin, muscle and fat tissue might result in changes ultimately affecting the vital capacity of an individual, whereas damage to blood vessels of the kidney, the brain, the heart would be expected to result in important changes affecting the capacity for survival. Thus, if the determining factor would be the anatomical location of the damaged blood vessels, again a change in the spectrum of diseases would be expected in irradiated animals, compared to unexposed ones.

38. In conclusion, the notion of non-specific life-shortening is superimposable with that of aging (advanced or accelerated) induced by radiation. The two concepts are inevitably linked with the demonstration that radiation, although advancing the instant of death, should not modify the spectrum of induced diseases. This demonstration is not only difficult in practice but probably impossible to visualize conceptually since the mechanisms that might be hypothesized for non-specific effects, would also change the spectrum of diseases appearing in irradiated animals. Such change would in itself be incompatible with the notion of aging or of non-specific life-shortening.

2. The notion of aging

39. Attempts to show that irradiation may non-specifically age animals were started by observations that radiation did produce life-shortening and that irradiated animals showed phenomena similar to those observed in old age

(graying of the fur, appearance of cataract, loss of fertility). Although it should have been clear that the resemblance was onlz superficial [M3], the hypothesis of radiation-induced aging gained momentum and stimulated much work. The interested reader might refer to the following reviews - which are only some of the many available - for more detailed evaluations of data obtained in the experimental animal [A1, U4, C2, H3, C6, C7] and in man [A4, A6, F1, B6].

40. Difficulties with experimental work on aging are related to its definition, to the lack of any direct measure of senescence except in term of life-span, and to the impossibility of deciding whether pathological processes in old animals are the causes of aging, its effects or indeed aging itself. The only generalization in this respect is that in mammals the age-specific death rate increases as a function of time in a roughly exponential fashion by a constant factor for each year of the adult life, that is, that the probability of death per unit time increases with age (Figure I). However, to take this phenomenon as a measure of aging requires first the assumption that aging within each individual is paralleled by the average changes of the population where 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.

41. It should be pointed out that radiation is by no means the only agent producing life-shortening, but other treatments have often been reported to produce similar effects in conjunction with radiation experiments. These agents included 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 these data that the effect is in general less readily induced than with radiation and that the diseases leading to precocious death are rather specific for each drug.

42. In the context of the hypothesis of radiation-induced aging, the concept has also been repeatedly discussed of differences between advanced or precocious aging on the one hand, and accelerated aging, on the other (see, for example, [C2] and [C7]). These two notions can be visualized formally in terms of the theory of radiation injury of Blair [B2, B3, B4, B5]. Actually, 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 be verified experimentally.

3. Mechanisms of aging and life-shortening

43. In spite of all 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 to be seen in irradiated tissues [U4, C7]. Some of these resemble superficially senescent changes, although there are profound dissimilarities between radiation-accelerated and senescent lesions W1, M3] at a closer inspection. Among the least equivocal van Cleave [V7] mentions the following: involution of the cartilage discs, involution of the thymus and all lymphatic tissues, lymphocytopenia, marrow hypoplasia, atrophy of the iris, atrophy and displasia of skin and degeneration of the skin collagen, degeneration of the elastic walls of the arteries, nephrosclerosis with glomerulosclerosis, dysplasia of the lens epithelium, vaculoization 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.

44. Casarett [C7] proposed a "histopathological theory" of natural and radiation-induced premature aging. It rests on the notion that morphologically 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 increase of arteriocapillary fibrosis. Functionally, a loss of selectivity of the barrier to nutrients and to wastes and a decreased efficiency of circulation would be the consequences of such changes. Under these conditions a decrease of parenchymal cells and functions would follow, with more fibrosis and loss of vasculature, in a circle becoming progessively more serious with time and leading to increased susceptibility to infection, stress, degenerative and neoplastic conditions and eventually to death.

45. Irradiation would advance 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 edema, increased fibrillar density, spotty at first and then more generalized) 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.

46. The basic notions of Casarett's model [C7] appear on the whole biologically well founded, since it is known that radiation may cause an interstitial fibrillar density and capillary fibrosis. The mechanisms of these phenomena have recently been discussed by Gerber [G1] who has examined the possible pathways responsible for fibrosis and by Hopewell [H16] who has particularly addressed himself to vascular changes. But whether the initial endothelial and connective changes operating in natural and in radiation-induced aging may indeed be the same remains to be demonstrated and so 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] seem to cast considerable doubt on the applicability of the hypothesis to the very low doses and dose-rates and to confine presumably its interest to the region of the intermediate to high doses.

47. The hypothesis could also be entertained that late effects of radiation on the duration of life might be brought about <u>via</u> alterations of the immune system and in this respect two possible mechanisms of action could be envisaged. The first would imply auto-immune diseases as possible causes of a diffuse deleterious action; alternatively, life-shortening could 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 would 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.

48. In 1972 the Committee reviewed extensively the effects of radiation on the immune response and considered the general question of radiation as it

might relate to auto-immunity and possibly in turn to aging [U15]. There were at the time few results on animals consistent with the hypothesis of a breakdown in the balance of self-tolerance leading to auto-immune conditions, and on the whole the data were thought to be inconclusive in showing positively any such effect.

49. Studies of the late effects of radiation on the immune system of mammals are still relatively few and their results variable according to the test system and radiation doses. In general, intact animals examined individually show little if any effect of age [S45] mostly correlated with the presence of reticular tissue tumours [U14]. When the immune competence of cells from irratiated animals is examined, there is often a significant decrease in cell number, but this appears to be well compensated by an increase in antibody affinity A10]. Other immune functions could, however, be significantly effected. Recent evidence about effects at the whole-body level is rather ambiguous. On the other hand, animals selected for a low antibody response showed a higher incidence of spontaneous malignancies and a shorter life-span than others of the same genetic background selected for a low response [C30]. On the other hand, 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].

50. In 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 considers that radiation could alter tissue constituents to create new auto-antigens or to release previously inaccessible components. The second possibility would act via somatic mutations leading to the emergence of auto-reactive clones. The third would act through the unbalance of natural mechanisms of regulation controlling the potential auto-immune expression. Several studies would be in favour of the third mechanism but at the present time few definitive statements are warranted.

51. The first statement might be 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 could actually be operating at high radiation exposures causing

extensive tissue damage, their possible relevance at the low doses of interest for radiation protection can only be viewed at the present state of knowledge with great reservations.

52. 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 in the mean time that might change this general proposition. Actually, a most recent reveiw of the subject [S46] confirms the above conclusion and therefore supports indirectly the view that, whatever the role of tumours in radiation-induced life-span-shortening, there is as yet no clear evidence that it might be mediated through immunological mechanisms.

53. 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 have been discussed by Walburg [W1] and their applicability to a possible effect of premature aging criticized since mortality data and causes of death in irradiated animals point to a life-shortening action related essentially to tumour induction. Also, according to this analysis, exposure of mammals to life-shortening doses of radiation almost uniformly fails to accelerate lesions characteristic of senescence.

54. Recently other hypotheses related to molecular changes have been considered. Cutler [C31] reviewed the concept of primary aging processes. With this term are covered causes which could 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 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 could, however, be more attractive when applied to information transfer molecules among which primarily DNA or chromatine. For these molecules a more systematic approach is advocated, on the basis of preliminary data on radiation and natural age-induced changes in chromatine.

55. DNA damage is, however, only the initial step in reactions of this kind, since 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 would be the factors controlling the expression of such damage. Alterations in one or both of these mechanisms would be expected to modify life expectancy. Although interesting, at present both these hypotheses have not been sufficiently formalized and their general applicability has not been extensively tested to warrant more than the present mention in the course of this document.

4. Conclusions

56. 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 on the whole rather unproductive. Data in animals an 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, partilularly 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 auto-immune conditions or a favouring influence on tumour acceleration or induction are few and contradictory. In any case, such mechanisms would not be expected to yield non-specific life-shortening without changes in the spectrum of old-age diseases.

57. Therefore, in view of the difficulties of defining aging, of the lack of reliable parameters of senescence, of the impossibility to distinguish between specific and non-specific causes of aging and between the action of 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 convincingly been shown, 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 an ill-defined effect such as aging. Pending clarification of the points previously reviewed, the relationships between radiation-induced life-shortening and aging - if endeed the latter effect exists to justify such relationships - will not be taken up again for discussion in the rest of the present document.

I. PHYSICAL VARIABLES

58. To establish a relationship between the degree of life-shortening and the characteristics of the acute or chronic exposure to radiation is important for the need to fix criteria and levels for human exposure. It may also be useful for theoretical reasons, in order to validate indirectly hypotheses and models on the nature of aging and on the similarity between natural and radiation-induced senescence. Experiments on single acutely-delivered doses are but one and the simplest out of all possible models: single-dose irradiations are not interesting in practice, but represent the most efficient treatment, since under these conditions the action of any repair system is minimal. On the opposite side, there are experimental treatments like the duration-of-life exposure which may more closely resemble the situations of interest in practice: they yield, dose for dose, less effect than the acute exposures. Between these two extremes there is a whole range of treatments where any given amount of effect can be obtained by infinite combinations of many interrelated variables. They are: 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 under "Biological variables", see 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.

59. Having thus recalled the complexity of the problem at hand, the following irradiation conditions will in turn be considered; single acutely-deli-

vered exposures; continuous life-time irradiation; the effect of dose-rate; the effect of fractionation; chronic terminated exposures; and the effects of radiation of different quality. The various contributions will be examined under the section thought to be more relevant to the subject matter under discussion. However, a certain amount of overlapping and repetition is unavoidable in order to compare the various conditions of irradiation.

A. THE EFFECTS OF ACUTE SINGLE DOSES

60. In the following paragraphs the effect on long-term survival of acutely-delivered single doses of radiation will be examined. The data will be reviewed with the criterion of considering together all information pertaining to a given species, roughly arranged according to the time of publication in order to give some historical perspective and a feeling of the state of the field at any given time. Since it was often found that data on low- or high-LET radiation were included in the paper, the review will consider together the information pertaining to different types of radiation. 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

61. 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.

62. 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 179 to 782 rad. Neutron doses in 8 groups ranged from 28 to 250 rad. 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

Table 1

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

Species and strain	Sex	Radiation	Percentage life lost/ 100 rad	Range of percentage shortening	Days lost/ rad	Form of the curve	References
Mouse 10 strains	M	98-kVp x	4.2	?	0.15	linear	G 2
Mouse BAF1	M	80-kVp x	4.2[d]	30.2	0.24	?	G 3
	M	135-kVp x	4.9[d]	30.4	0.29	?	
	M	250-kVp x	4.6[d]	27.2	0.27	?	
	F	80-kVp x	6.7[d]	39.2	0.35	?	
	F	135-kVp x	5.2[d]	32.1	0.34	?	
	F	250-kVp x	6.7[d]	39.2	0.43	?	
Mouse CAF1	F	250-kVp x	3.2-6.3	19	0.21-0.42	convex upward?	K 7
Mouse Swiss	F	250-kVp x	4.7	0-30	0.19	linear	S17
Mouse CF1	F	gamma from weapon	2.6	8-37	0.25	linear	S18
Mouse CF1	M	x rays	7.8-10.9	11-31	?	convex upward?	B 8
Mouse LAF1	M	gamma from	5.0[e]	3-45	0.37[f]	concave	U 5
	F	weapon	6.3[e]	10-51	0.47[f]	upward	
Mouse 6 strains	M	200-kVp x[c]	4.1	23.2	0.28	concave	G 4
	F		5.4	30.6	0.81	upward	
Mouse SAS/4	M+F	15-MeV x	5.4	5-44	0.40	linear	L 1
Mouse RF/J	F	250-kVp x	9.1	36.5	0.45	linear?	S19
Mouse BDF1/J	F	250-kVp x	5.1	5-50	0.45	linear	S20
Mouse RF	F	^{60}Co gamma	4.7	28-85	0.25	linear	S21
Mouse RF/Un	M	250-kVp x	-	3-31	0.56-0.03	convex	U 7
	F	^{60}Co gamma	-	5-29	0.15-0.02	upward	
Mouse C57BL/6L	F	300-kVp x	4.1[b]	3-32	0.23[b]	convex	Y 1
Mouse A/J	F	300-kVp x	5.9[b]	7-38	0.29[b]	upward	Y 1
Mouse RF	F	300-kVp x	7.7[b]	6-32	0.75	convex upward	C12
Mouse LAF1	M+F	^{60}Co gamma	2.5[b]	7-29	0.15	concave upward	G 5
Mouse B6CF1	M	^{60}Co gamma	5.3	5-42	0.45	linear	A 7
	F		5.3	6-43	0.48	linear	
Mouse (C57BLxC3H)	M	250-kVp x	2.5	0-9	0.22	linear?	C13
Mouse BALB/c	M	250-kVp x	7.3	0-66	0.54	linear?	M 8
Mouse C57Bl	M	250-kVp x	9.8	0-48	0.68	linear?	M 8
Mouse (C57BLxC3H)	M	250-kVp x	3.2	0-29	0.27	linear?	M 9
Mouse RFM	F	^{137}Cs gamma	9.6[b]	0-38		complex	S44
	M		6.7[b]	0-20		linear?	
Mouse BALB/c	F	^{137}Cs gamma	7.0[b]	0-14	0.39[b]	linear?	S44
Rat Wistar	M	250-kVp x	4.2-4.9	7-29	0.35-0.41	linear?	H 5
	F		2.8-4.0	4-24	0.15-0.22	linear	
Rat Wistar	F	250-kVp x[a]	0.4	39	0.28	?	L 3
Dog Beagle	F	250-kVp x	6.7	3-24	2.84	linear?	A 2

a/ Data derived from a single exposure of 1000 R given under 5 per cent oxygen
b/ Data derived under the hypothesis of linearity
c/ Average for all strains
d/ Data derived under the hypothesis of linearity from experiments at the LD_{50} level
e/ Figures obtained at the LD_{50} level
f/ Figures derived from Grahn and Sacher (G1)

Table 2

Life shortening after single acute whole-body neutron treatments

Species and Strain	Sex	Radiation	Percentage life lost/ 100 rad	Range of percentage shortening	Days lost/ rad	Form of the curve	Refs.
Mouse Swiss	F	thermal column	4.7	0-30	0.19	linear	S17
Mouse CF1	F	weapon neutrons	4.7	8-30	0.37	linear	S18
Mouse LAF1	M F	weapon neutrons	6.7 15.6	9-23 9-39	0.79 1.06	concave upward	U 5
Mouse CF1	F	fission neutrons	22[a]	9-45	1.06	linear?	V 1
Mouse RF/Un	M F	1-MeV neutrons	9.0-18.0 8.4-14.9	19-28 33-47	0.21-0.06 0.11-0.03	convex upward	U 7
Mouse RF/Un	F	14-MeV neutrons	6.7[a]	9-26	0.40	convex upward	D 1
Mouse BC6F1	M F	fission spectrum	35.9[b]	7-26 9-31	3.0-0.9 3.9-1.1	convex upward	A 7
Mouse RFM Mouse BALB/c	F F	fission spectrum	45-77 42-70	4-25 0-20	- -	convex upward	U 8
Rat	M	fission spectrum	10[a]	22	-	?	K 8 K 9
Guinea-pig	M	fission spectrum	12[a]	12-16	~1	?	K 8 K 9

a/ Estimate derived from a first-approximate assumption of linearity
b/ Estimate derived from data at the smallest dose of 20 rad

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.

63. In the Greenhouse series [U5] the Gompertz plot of irradiated mice showed a displacement upwards and to the left of the control curves in 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 being 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. Thus, no overall clear-cut relationship could be established between life-span-shortening and tumour incidence.

64. Some of the data from the Greenhouse experiment (male and female animals receiving up to 267 rad) were reanalised 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 concluded therefore 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.

65. Working on six mouse strains irradiation with single doses of x razs 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 reconduct the whole process culminating in life-shortening to a basic injury parameter (0.28 days of life lost/R or 19 per cent life lost for irradiation at the $LD_{50/30}$) applying to all strains and sexes. On this basic parameter other factors, specific for life-shortening due to leukaemia and ovarian tumours, would superimpose 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.

66. 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 survivors was plotted against age at weekly intervals for each dose group, the life-shortening effect for the pooled sexes fitted a good 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: simply from the point of view of survival, the irradiated animals behaved in fact like the non-irradiated controls of older ages. 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 this be considered as an aging factor, although not identical to natural aging, since the relative ages of onset of the various diseases were different in irradiated and control animals.

67. 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 performed also 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 might apply.

68. 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 10 rad/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 per cent range of life-shortening the days lost/rad at the various doses varied between 0.56 and 0.02 at progressively higher doses, with differences between male and female animals. With fast neutrons between about 20 and 50 per cent of life-shortening, the days lost/rad were between 0.21 and 0.03, again with oscillations 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 (which shows with both neutrons and x rays) could conceivably be explained by difference in the effects responsible for life-shortening, in that not all effects which might 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.

69. Data on induction of neoplasia in the above-described experiments 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 100 and 300 rad) were reanalysed 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 if 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 could 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.

70. Darden et al. [D1] also reported data on RF/Un female mice exposed to graded doses of 14 MeV neutrons (dose rate 1 - 2 rad/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 400 rad group and amounting to 151 days of 27 per cent of the control life-span. Life-shortening was an approximately constant or slowly decreasing function of dose up to about 200 rad, but at higher doses the efficiency/rad tended to decrease, as in the series by Upton [U7]. Tumour in-

duction 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.

71. 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 shape 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.

72. 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 per cent or less of normal the increased mortality is attributable entirely to induction or acceleration of tumours.

73. 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 (50-400 rad) and with 60 MeV protons (47-372 rad). The data indicated a flattening of the dose-response curve at doses in excess of 200 rad and a reasonable straight trend at the lower doses. When animals dying from thymic lymphoma and myeloid leukaemia (which were induced in up to about 40 per cent and 25 per cent, 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 more near and more parallel to the control line: the curves,

however, did not superimpose except at doses below 100 rad. Thus, not all of the observed life-shortening, particularly at the high supralethal doses, can be explained by the induction of leukaemia, as in male RF animals. A possibility does remain (but it was not examined in a most recent publication, [C15]) that ovarian tumours occurring in 50 per cent or more of the animals might account for the extra life-shortening remaining after subtraction of leukaemia.

74. 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 death 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.

75. Ainsworth et al. [A7] irradiated male and female B6CF1 mice with single doses of gamma rays (90 to 788 rad) and found that life-shortening had a reasonably linear dose-response. In the case of fission-spectrum neutron irradiation, however, the shape of the dose-response curve (20 to 240 rad) 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.

76. 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). 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.

77. Pathological observations in the course of 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 C57B1

mice other non-neoplastic causes were observed in the majority of cases. An increases and advanced incidence of specific diseases, mainly thymic lymphoma, was at the origin of the 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.

78. Very extensive data on RFM and Balb/c mice were recently presented by Ullrich and Storer [U8] and Storer et al. [S44]. The effects of dose, dose-rate and radiation quality on life-shortening and carcinogenesis were examined. ^{137}Cs gamma rays at 40-45 rad/min and 8.3 rad/day (10 to 400 rad total doses) and fission neutrons at 5-25 rad/min or 1 rad/day (5 to 188 rad total doses) were used. Dose-effect relationships for life-shortening at dose-rates will be examined here. In the RFM females a dose-squared or linear-dose-squared model could describe the data adequately between zero and 50 rad, with the dose-squared component predominating after about 4 rad. 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 47 rad, with an ensuing decrease of effectiveness giving rise to an upward convex trend up to 200 rad. No specific discussion is given of the contribution of particular diseases to life-shortening.

79. Metalli et al. [M9] irradiated hybrid male mice of the $(C57BLxC3H)F_1$ strain (100-days old, 250 kVp x rays, 100 to 700 rad). A dose of 900 rad 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 alter appreciably 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 have a spontaneous incidence of about 55-60 per cent of reticulum cell sarcoma. The incidence of this disease was still quite high at 400 rad but fell gradually at higher doses to about 5 per cent at 900 rad. On the contrary, the incidence of glomerulosclerosis (which is very low in normal animals) increased to about 70 per cent after 900 rad. 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 should probably be regarded as a fortuitous event. The data are in no way reconcilable with any theory postulating a non-specific aging effect.

80. Preliminary 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 dose, dose rate, age at exposure and genetic background on a variety of late effects, including life-shortening, by ^{60}Co gamma rays in mice. It is proposed that the present Annex should include a review of these data as soon as they will become available in a more complete form.

2. Rat

81. There are a few data on 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. They found a decrease of the survival time proportional roughly to exposure, the per cent reduction of life span/100 R being 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, since the various dose groups included a maximum of 24 animals each.

82. Wistar females surviving an acute whole-body exposure to hypoxic irradiation (250 kV 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 per cent 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].

83. Again 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/rad was found to vary from 0.60 to 0.76 to 0.52, respectively, at the above-mentioned doses [L4].

3. Guinea-pig

84. In experiments by Kimeldorf, Phillips and Jones [K8, K9] young adult male guinea-pig from a 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 100 rad-exposed animals, 730 days (12 per cent reduction); of the survivors in the lethal dose range (120 - 160 rad), 698 days (16 per cent reduction). Both values of the median life-span were significantly smaller than control survival. In a related study [K9] young adult male rats (94 to 110 days of age) were treated with 215 - 230 rad from the same neutron source. Although this dose was sublethal to the animals at 30 days, the median life-span was reduced by about 22 per cent. It was concluded that a dose range producing some acute mortality in the guinea-pig is less effective on life-span than a dose which in the rat is sublethal. The reduction in median life-span/rad is, however, comparable for the two species.

4. Chinese hamster

85. 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, 550 rad of x ray whole-body exposure caused a loss of 32 weeks (corresponding to about 30 per cent) of the life-span remaining at the age of 230 days. At higher doses, for each increment of 100 rad above 550 rad and up to 950 rad there is an additional approximately linear loss of life-span of 20 weeks up to a per cent life-span reduction of 93 per cent.

5. Dog

86. A large experiment on the life-span of 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 rays treatments to total doses 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 9.5 per cent and 20.7 per cent in the 100 and 300 R groups, respectively. The average life-span-shortening/100 R amounted to 6.7 per cent. 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.

87. 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 to some extent the pattern of early deaths) there was a significantly increased rate of mortality in the irradiated dogs with respect to normal animals, but this increase disappeared when the neoplastic deaths were exlcuded 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.

6. Other mammals

88. It is known that 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.

89. 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.

7. Conclusions

90. 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 between such very heterogeneous data appears rather surprising. The variability on each experimental point (which is available in many of the experiments, although not in all) has not been plotted since it would be expected to be reabsorbed 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 corresponding maximum effects of about 60 per cent. In order to standardize the abscissa dose scale a conversion factor of 1 R = 0.95 rad was used. The ordinate scale is simply 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.

91. 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 per cent 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

$$y = \underline{a} + \underline{b}\, D \qquad (5)$$

where y is the precentage of life-shortening, D is the dose and $\underline{a}$ and $\underline{b}$ are the coefficients of the regression. The calculated least-square solution to the above equation was

$$y = 1.615 + 0.0502\, D \qquad (6)$$

and it gave an R^2 value of 0.788. 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

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

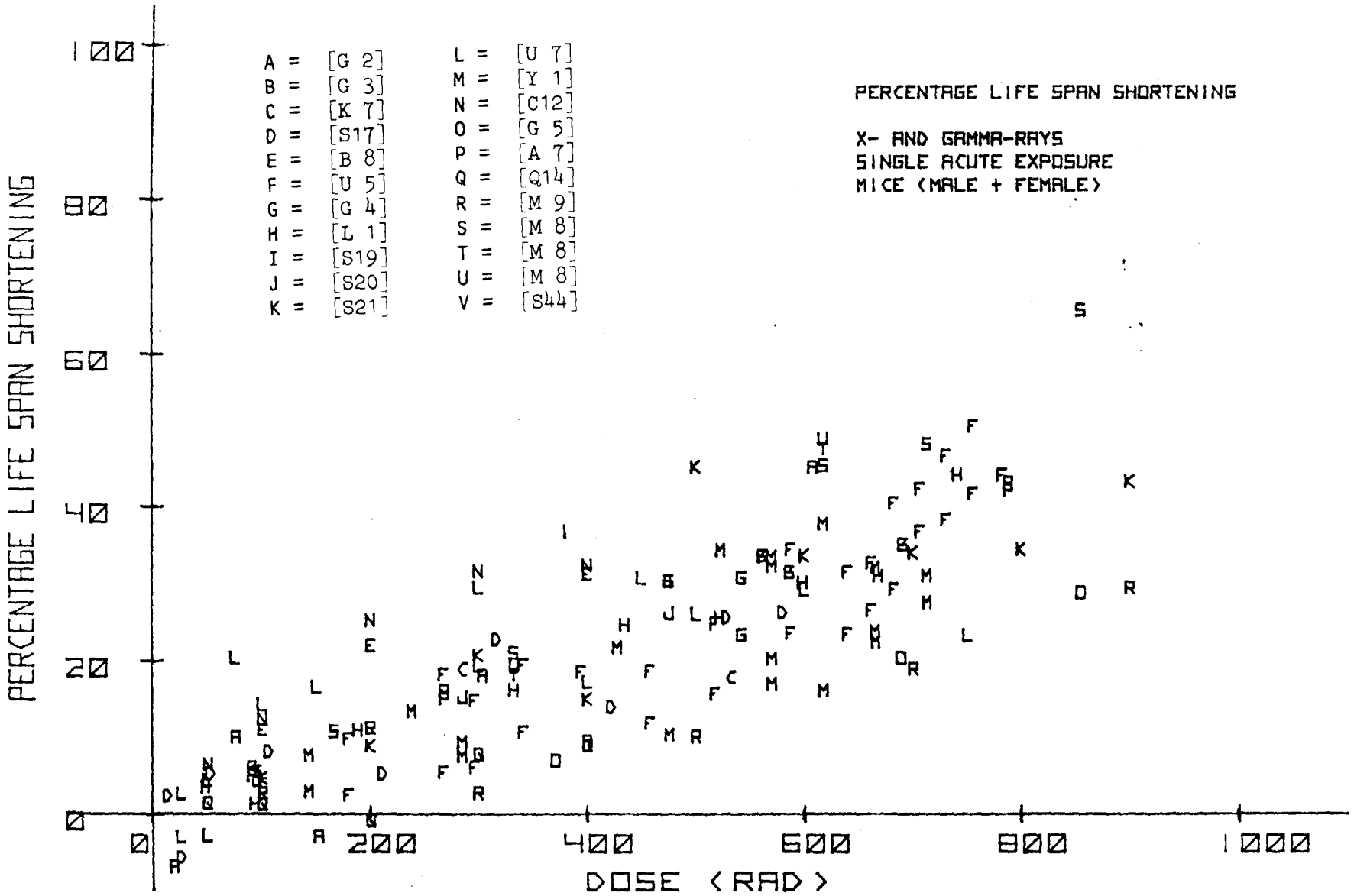


Figure II.

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

which yielded the following solution

$$y = 0.531 + 0.0638\ D - 1.94\ 10^{-5}\ D^2 \qquad (8)$$

The R^2 of this fit was 0.743.

92. It may be concluded that under the above conditions the life-shortening data for the mouse may be considered to 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 cent/100 rad down to the smallest doses. The data may, however, also be fitted by a linerar + quadratic function, where the quadratic term is negligible and not such to give rise to an appreciably different relationship within the errors of such an analysis or to substantially different quantitative conclusions.

93. 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, giving rise to a different spectrum of life-shortening diseases or pathological conditions at the various doses. That the combination of a variety of experiments should produce 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 an unreasonable proposition.

94. 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 500 rad and life-span-shortening effects up to about 50 per cent

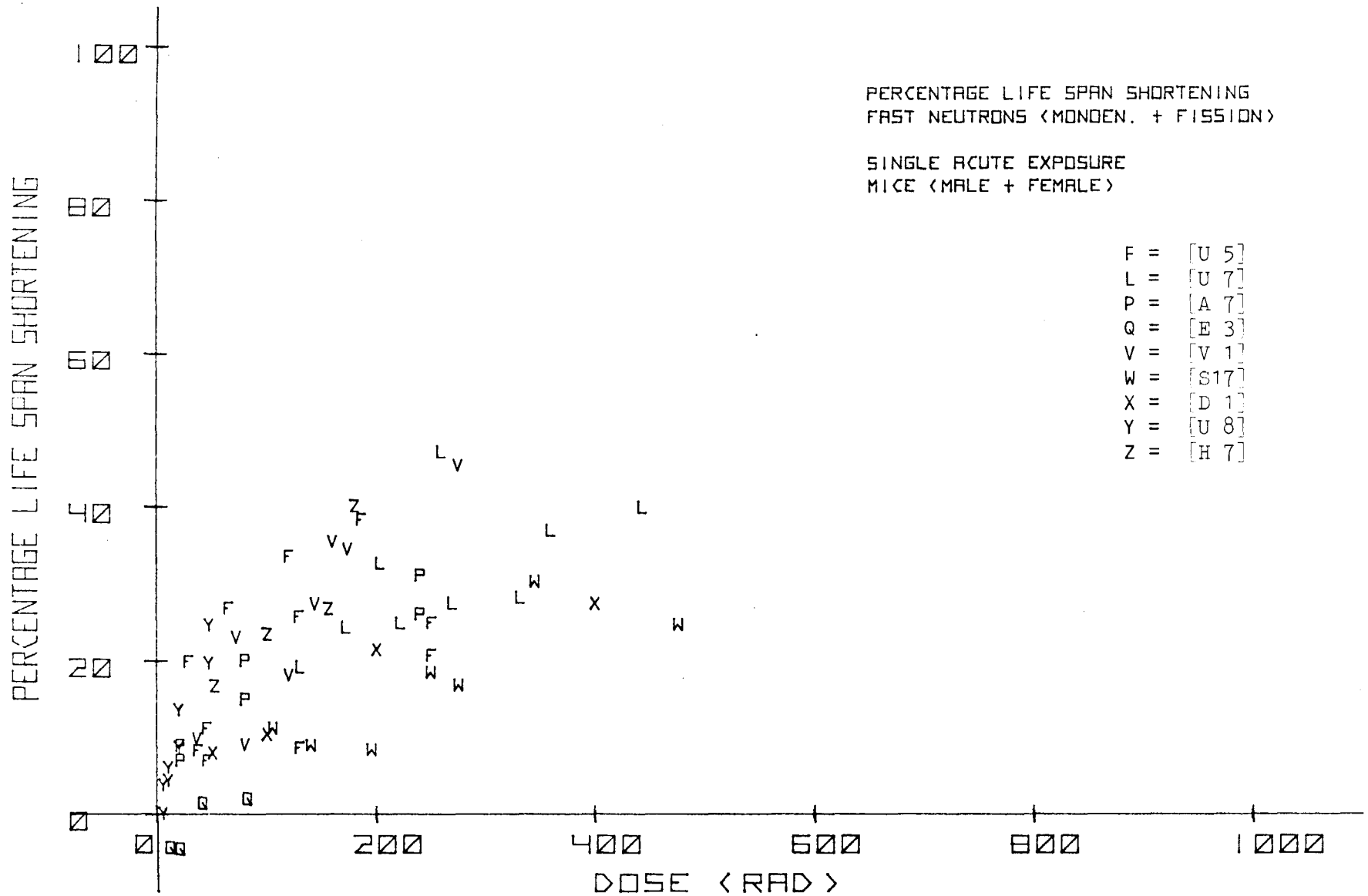


Figure III.

Dose-effect relationship for life-shortening in the mouse following single acute exposures to fast neutrons. Various experiments.

of normal. Only the results with monoenergetic-, fission spectrum- and weapon-neutrons delivered acutely were included, for a total of 15 series and 5 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

$$y = \underline{a} + \underline{b}\, D \qquad y = 5.7361 + 0.0851\, D \tag{9}$$

$$R^2 = 0.5751 \tag{10}$$

$$y = \underline{a} + \underline{b}\, D + \underline{c}\, D^2 \qquad y = 2.005 + 0.1837\, D - 277\ 10^{-4}\, D^2 \tag{11}$$

$$F^2 = 0.6860 \tag{12}$$

Clearly, none of these two relationships provides a satisfactory interpolation to the neutron data, because the first of them fails to show the initial steep rise and the latter, after showing a maximum of effect between 300 and 400 rad bends down rapidly towards lower values, an effect which would be difficult to interpret. The following relationship was also fitted

$$y = \underline{a} + \underline{b}\, \sqrt{D} \tag{13}$$

and it yielded the following solution

$$y = 0.1645 + 1.764\, \sqrt{D} \tag{14}$$

$$R^2 = 0.6837$$

The square-root relationship seemed to fit the data fairly well in that it described adequately the increase of effect seen at very low doses of neutrons and the ensuring levelling-off of the data for doses up to 500 rad, along a slope roughly parallel to the slope of the low-LET radiation dose relationship.

95. Thus, whatever the actual relationship truly applying to the life-span-shortening effect caused by neutrons in the mouse, under the conditions of the present analysis the data 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 effi-

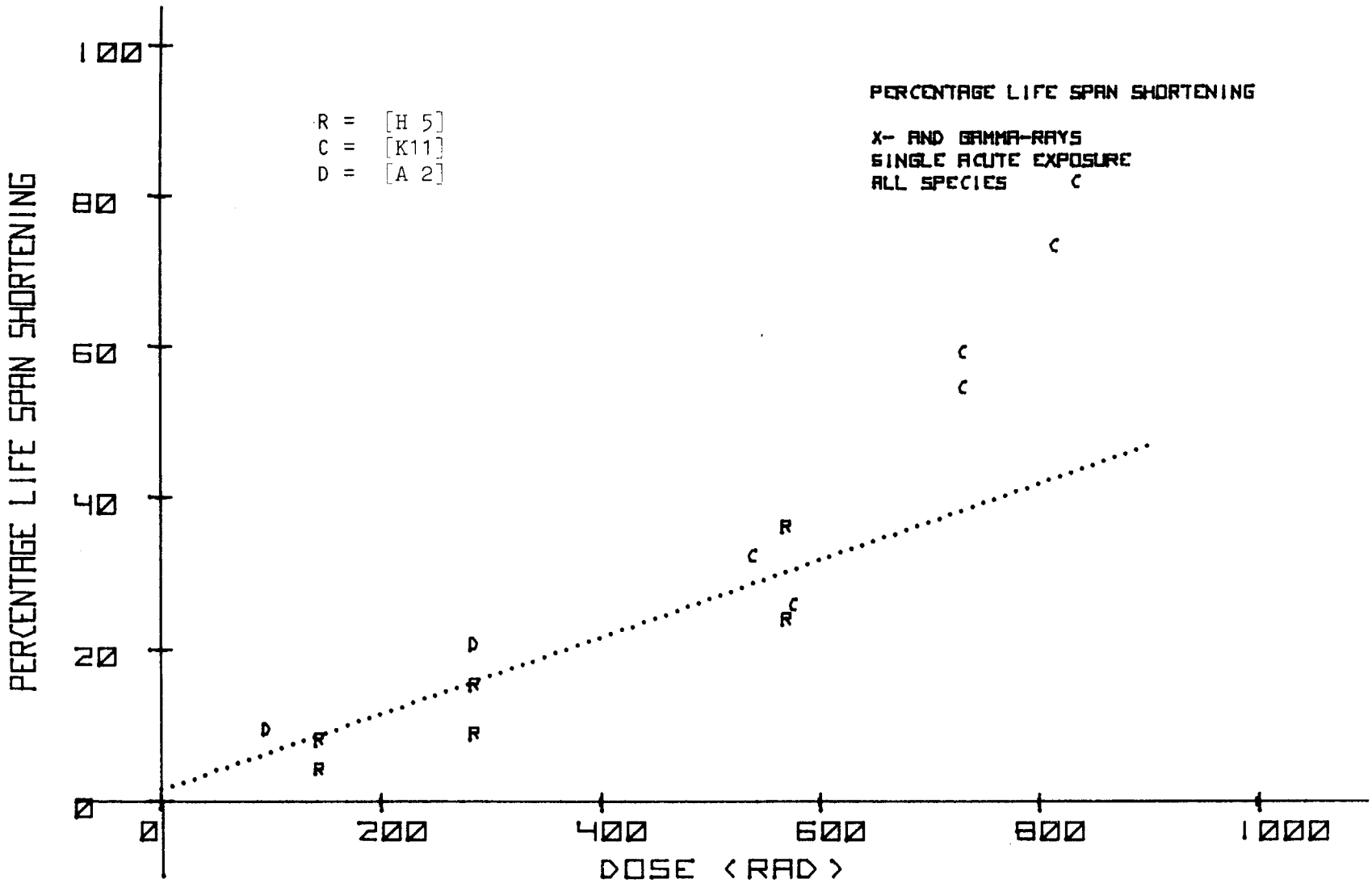


Figure IV.

Dose-effect data for life-shortening in various mammalian species following acute single exposure, 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 equ. (6).
Various experiments.

ciency will be discussed under paragraphs 192-213. Once more, it should be pointed out that there is no fundamental biophysical reason why the shape of the neutron curve should be of the form roughly described by the above equations, because the same observations pointed out for the x- and gamma-ray data under paragraph 93 would be expected to apply to the neutrons as well. However, the form of the neutron relationship is curvilinear (convex upward) within a range of effect where a linear function applies to low-LET relationships. Since saturation phenomena with respect to the expression of the biological damage might not be expected under such conditions, the only way to interpret the neutron data is by assuming that the shape of the relationship does reflect some primary biophysical difference in the mode of action of low- and high-LET radiation, particularly at the low doses.

96. 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 mouse data. At inspection, no large differences may be traced from the small series reported in the literature. This is particularly true for the rat, whose data are well superimposable up to 500 rad with the mouse response. The response of the dog has only been examined at relatively low doses and the data are perhaps on the high side of the mouse data. The chinese hamster, on the contrary, has only been examined at doses in excess of 500 rad and the data are suggestive of a concave upward trend. Between the species tested, however, the variability of the response is apparently rather small.

B. THE EFFECT OF CONTINUOUS LIFE-TIME IRRADIATION

97. 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 widely been 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 at present [N6, N7]. In this case of internal irradiation from radionuclides of long half-life it is naturally the only possible irradiation condition. Exposure for the entire life represents a base-line condition of irradiation useful for comparison with other exposure types like the acute single-dose: in respect to this latter it has the advantage of mimicking a pattern of exposure which is the most interesting in practice, since the continuous chronic rather than the short

acute irradiations are of major concern in human radiation protection. Also, some research workers [G1, G6] point out other advantages, like the linearity of the relationship between the log mean after-survival of the animals and the daily exposure level. This property might facilitate the description of the effect and justify comparisons between various animal species or various types of radiation.

98. On the contrary, others believe that the terminated exposure technique, rather than the exposure to death might be more apt to give unbiased answers. Based on evidence on 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 would amount to over one-half of the mean accumulated dose. This implied that the duration-of-life exposure conditions would be unsuitable to establish precise dose-time relationships for life-shortening. Actually, the mean accumulated dose would be overestimated on account of the wasted radiation and the mean survival time would be put in doubt by the fact that each specific biological response to radiation might take a different and characteristic time to develop. According to Mole [M6], for all these reasons terminated exposure conditions should preferably be used.

99. The concept of wasted radiation was utilized by many research workers in the field, although often without much experimental ground, 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 into a lethal condition. The biological arguments underlying the concept of wasted radiation are indeed well founded but there are different views as to the practical importance of this concept since the amount of wasted radiation appears to be 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 indeed changes in the effectiveness of a given dose with an increase of the protraction time (see paragraphs 151-191) and under appropriate circumstances

these changes could at least in part be interpreted as being due to an effect of wasted radiation. According to Grahn and Sacher [G1] this concept would already be contradicted for rather high doses and short survival times (the concept was actually derived from experiments at 200 to 25 R/day and on the $LD_{50/30}$ end-point); but for long protraction periods the idea would be injustified since no radiation may be considered as truly wasted.

100. The difficulty with the notion of wasted radiation is that in chronic exposure to death time and dose have a bi-univocal correspondence and cannot be experimentally separated from each other. Thus, it becomes difficult to isolate from an end-point like the life-span-shortening (which is measured in units of time) the dose that would have been given in excess of the minimum required to kill the animal within a given time. An additional difficulty lies in the nature of the biological event of death which is in itself 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].

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

102. The available evidence on the biological effects of chronic radiation exposure for the whole life of the animals will be reviewed in the next few paragraphs (paragraphs 103-126). This field has been reassessed at various times, among others, by the UNSCEAR Committee [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 will be considered for convenience in separate paragraphs (127-139).

1. Mouse

103. Henshaw [H1] carried out two small experiments with C3H mice with 200 kV x rays (0, 5, 10, 20 and 25 R/daY, 5 times per week). He showed a decrease of the average survival time down to 58 per cent of control at the highest exposure rate and an increase of the death rate. In a later re-examination of these data Boche [B11] showed that the excess death rate over the control death rate divided by the exposure rate was a constant within the range of exposures considered and could be taken as a characteristic of the mouse sensitivity to chronic x-radiation.

104. More complete experiments by Henshaw [H6] and Henshaw, Riley and Stapleton [H7] were reported on four strains of mice (CF1, ABC, C58 and A), selected for special characteristics, like, for example, the high spontaneous incidence of leukaemia and lung tumours. Daily whole-body exposures to fast neutrons (0.115 to 13.0 n) and of gamma rays (1 to 17.2 R) were administered 6 times weekly at high instantaneous dose rates. Most of the animals died either in a state of atrophy or with mediastinal lymphomatosis. Doses and LET dependencies were noted, as well as changes in sensitivity between strains and special patterns of response of the various diseases. In those days the main interest was in establishing the existence of a threshold dose: in this respect that of neutrons was set below 0.115 n/day and below about 1 R/day for the gamma rays. It was also noted that life-span was a sensitive indicator of damage since about ten times more radiation was required to produce a threshold pathological change than to shorten appreciably the life-span.

105. Daily doses of 0.014 n of fast neutrons (equivalent to 0.1 R/day of x rays on the basis of the relative effect of single exposure) were shown to have no definite effects on mice treated for 87 weeks. Survival time was definitely reduced at exposures of 0.14 n/day for a total of 60 n, while doses of neutrons ten times higher produced over 50 per cent death of the animals by about the 29th week at a total dose of approximately 200 n [E2].

106. Boche [B11] studied various species of animals. Wistar rats were treated with 250 or 1000 kVp x rays at exposure levels of 0.1 - 10.0 R/day. Rabbits received 1 year of irradiation and beagle dogs or monkeys were treated for 2 years at similar exposure levels. The life-span-shortening effect was shown in various ways but the different energy of radiation or

the animal sex were not found to influence the extent of this life-shortening. In dogs, rabbits and monkeys which were irradiated for only a fraction of the life-span no effect on survival times was found at exposure rates below 1 R/day. Boche's contribution emphasized particularly the importance of the net increase in mortality rate/roentgen in characterizing the relative species sensitivity.

107. In the experiments of Lorenz et al. [L6] (reported also by Lorenz [L8] in a less complete form) C3Hb female and LAF1 male and female mice were given life-span exposures of 0.11 - 8.9 R/8-hour day of gamma-radiation. There was a progressive decrease of the mean survival time with increasing daily dose. At the 4.4 and 8.8 R/day level there was an early acceleration of the death rate, which showed later (at around 20 and 24 months after the beginning of exposure) also in the 2.2 and 1.1 R group and was taken to be a manifestation of the cumulative character of the radiation injury. By plotting mean accumulated dose versus mean survival time a straight line was found to represent the data adequately over the dose interval considered. No predominant cause of death was apparent.

108. In the case of guinea-pigs exposed under similar conditions the death rate was greatly accelerated already at the 4.4. and also at the 2.2 R level, by comparison with the mice, showing that bone-marrow failure was killing the guinea-pigs at short terms. Survivors at 1.1 R/day had a shorter life-span. In this species the curve describing the mean survival time as a function of the mean accumulated dose, after an approximately linear relationship of the two variable up to 4.4 R/day was shown to bend back sharply because of the appearance of the early syndrome of pancytopenia.

109. The mouse data in the experiments by Lorenz et al. [L6] were reanalysed by Failla and McClement [F4] by the use of the Gompertz function, in such a way that the resulting curves might be internally consistent. The straight slope of the Gompertz plot (see Figure I) was taken to represent the effect of the aging process, whatever its mechanism might be. Chronically-irradiated mice had a steeper slope which phenomenon, on the above assumption, would be taken as an acceleration of aging. From the relative position of the Gompertz-lines a fictitious dose rate of radiation was calculated (amounting to 12.8 R/day) that would cause the same aging as occurred spontaneously. This analysis was used as a preliminary step to infer life-span-shortening values applicable in the human species.

110. The survival of two mouse strains (the ABC male and the CF1 female) was studied by Sacher [S2] for exposure rates between 2 to 100 R/day of x rays. The relationships between mean survival time and mean accumulated dose as a function of exposure rate, as well as the relationships between lethality following acute or repeated exposures were analysed. From these analyses a lethality function could be deduced under certain mediating assumptions about the linearity of the processes and about a defined lethal bound of injury.

111. Neary, Munson and Mole [N3] exposed male and female CBA mice to gamma rays (1.5 mR/h) or fast neutrons (three dose levels; 36.4, 3.0 and 0.9 mrad/h) spread over most of the time and almost continuously. Gross effect on the cumulative mortality curve were seen only at the highest dose-rate where the mean survival time was shortened by one third; at the medium dose-rate the mean survival times was shortened by less than 10 per cent. There was a general trend towards shorter survival with increasing dose levels: the difference of the combined data for males and females was significant at the 5 per cent level only between the group at the highest dose level and all other groups and between the control and the group at medium level. Significance could be improved if only the animals comprised between 30 per cent and 100 per cent mortality were included in the analysis. Shortening of mean survival time was examined in relation to dose-rate and to mean accumulated dose after averaging the male and female data. Having made allowance for the gamma ray contamination of the neutron field, straight lines could be drawn through the experimental points.

112. Neary et al. [N3] also analysed the data to see whether treatment was acting by accelerating the process of aging, in which case the time axis of the mortality curve would be contracted and the dispersion of life-time values would be reduced in proportion to the mean life-time. The evidence was, on the contrary, for a displacement to the left of the time axis which would be in favour, as in the case of Lindop and Rotblat [L1], of premature rather than accelerated aging.

113. All experiments on irradiation for the duration of life known until that time were reviewed by Mole in 1957 [M13] and his paper was made a part of the 1958 report of the Committee [U1]. Only 5 out 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/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/week or higher of gamma rays shortened the mouse life in a reproducible manner. There were eight experimental estimates at weekly doses of less than 10 R/week (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/week or its neutron equivalents.

114. Moos et al. [M14] and Yusken et al. [Z2] carried out experiments on CFW mice of both sexes, individually caged and irradiated with 400 kVp x rays at daily dosages of 2 - 512 R. The survival time of the mice descreased as the daily dose increased but the decline was not very rapid up to 8 R/day. Exposure of up to 4 R/day allowed the animals to accumulate 600 - 1400 R before one-half of the mice died. About 2900 R of accumulated radiation was given at 16 or 32 R/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/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.

115. Of particular interest to the problem of life-time irradiation are the data by Sacher and Grahn [S4] on more than five thousand 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/day and corresponding mean survival times from about 500 days to 6 hours. The daily doses between 5 and 2500 R (giving mean after survival times of 5 or more days) were delivered during 12 or 15 hours/day; higher daily doses were given almost continuously. Dosimetry was particularly accurate and fully discussed.

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

$$C_L\,(t^*) \quad = \quad \frac{1}{I}\left(1 - \frac{t^*}{t_o}\right) \qquad (15)$$

where I is the daily exposure in roentgen, 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). For mean after-survivals in excess of 60 days a plot of the log mean after-survival versus the daily dose was found to be very nearly linear: 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.

117. 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/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 less 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 the female mice; also, some diseases were accelerated in the irradiated mice and some were not.

118. Sacher and Trucco [S13] analysed a model for mammalian radiation lethality and recovery, based essentially on the kinetic characteristics of self-renewing cell populations. The model assumes that 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 monotone function of the size of the population and the other is a monotone 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.

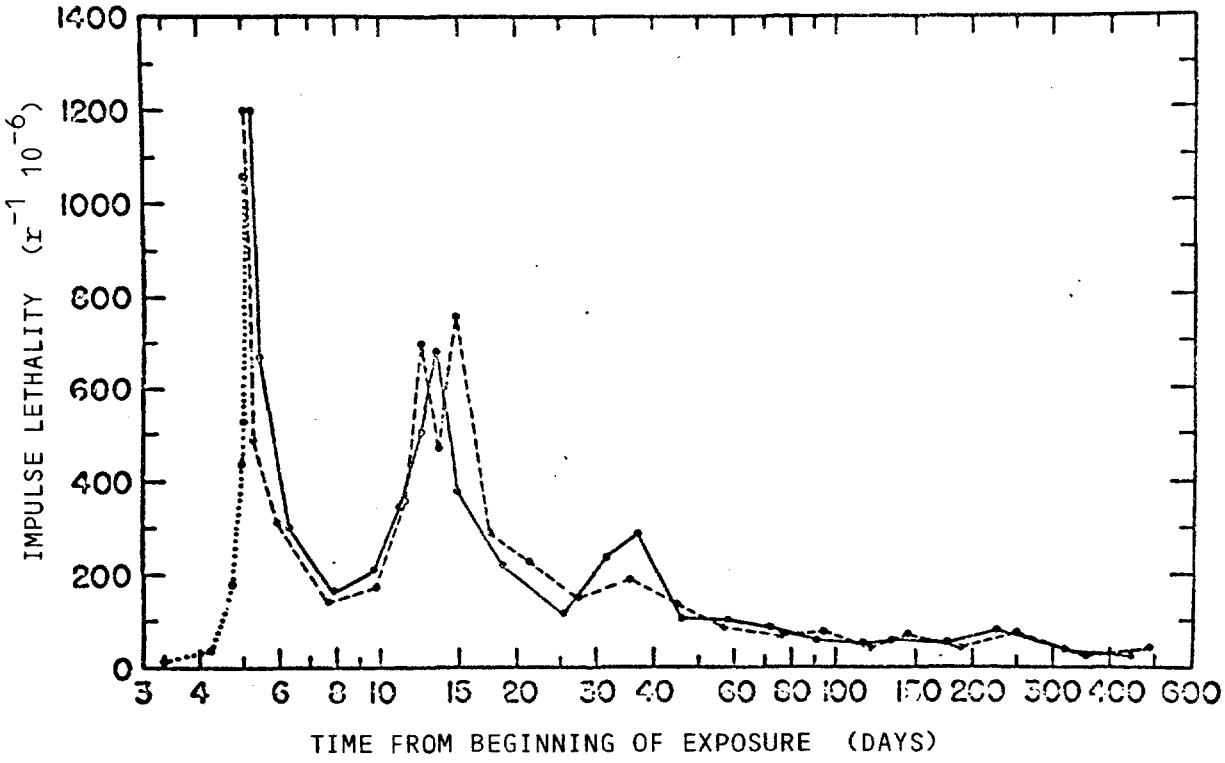


Figure V.

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. Data from Sacher and Grahn [S4].

However, the formulation of this theory is not sufficiently developed and may be regarded as a first attempt towards a more comprehensive treatment.

119. In another paper Sacher, Grahn, Fry et al. [S5] examined the late effects of gamma-radiation in 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/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.

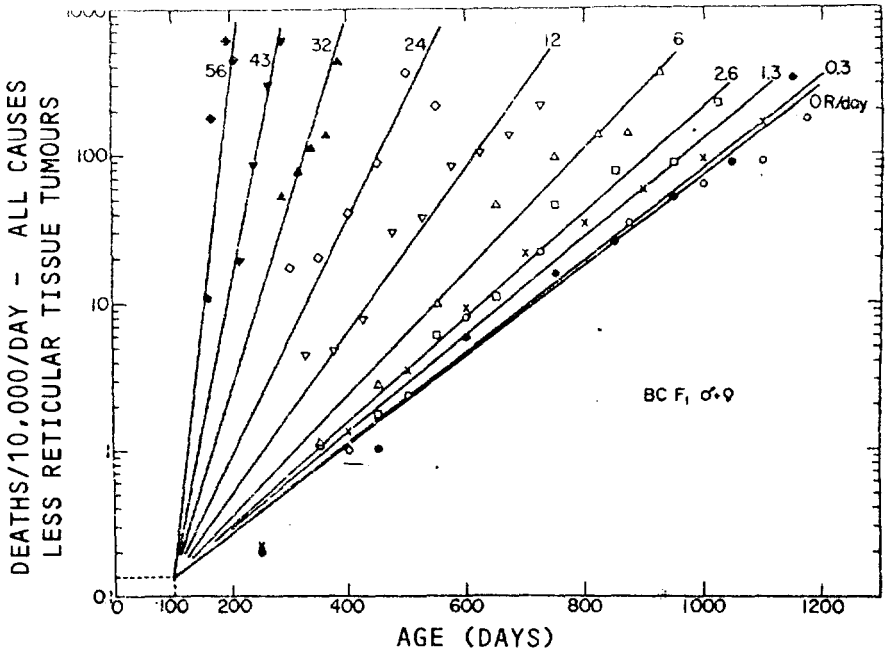
120. The Gompertz transforms of these data (see Figure VI) for all causes of death were slightly convex upward and formed a fan of lines of increasing slope with increasing dose-rate with small differences between genotypes. When the

These slopes plotted on a semilogarithmic scale as a function of the exposure rate (R/day) gave in turn straight relations thus justifying the conclusion that the slope of the Gompertz lines increased 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.

122. The 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/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 upon irradiation a steady increment of mortality associated with neoplastic disease as both the age and the daily dosage increase up to a few R/day. An excess mortality from non-neoplastic conditions with respect to controls is seen only at 6 R/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 would be related entirely to the increase in incidence and to the shift in the time of appearance of the neoplastic diseases.

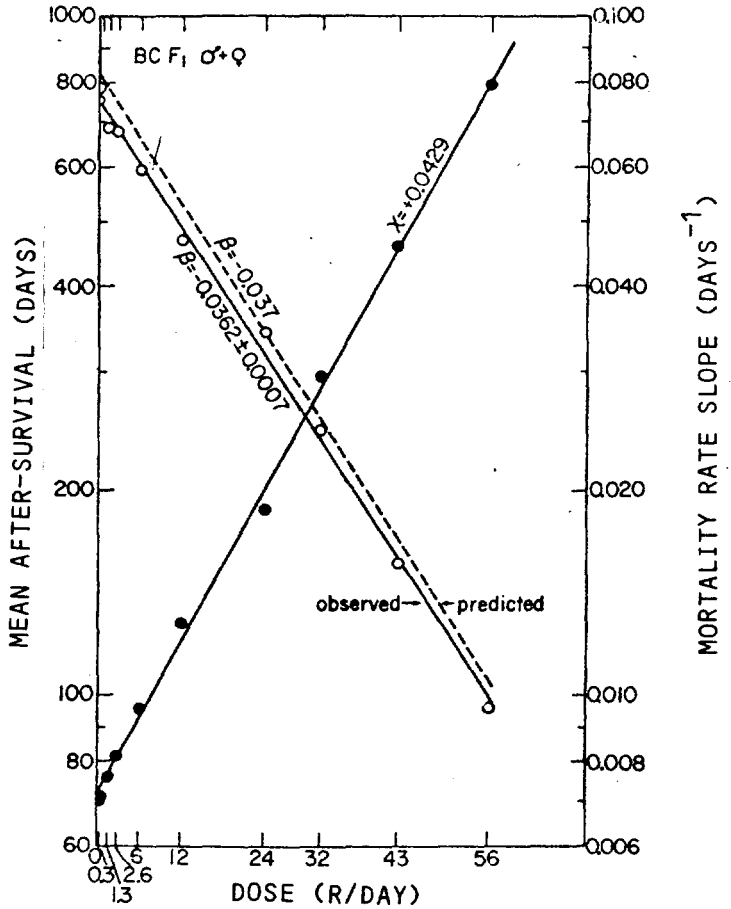
123. Sacher [S14] pointed out that when the slope of the Gompertz curves obtained at various daily doses is plotted as a function of the daily dose on a double logarithmic scale for two mouse strains, the LAF1 [S4] and BCF1 [S5] the resulting relationship can be resolved into two straight branches (see Figure VIII). At exposure rates below 24 R/day the data lie close to a first-power line while above this value they conform closely to a second-power trend. At about 24 R/day the contribution of the two terms is equal. These observations would be consistent with the hypothesis that life-shortening at dose rates in excess of the above-cited value is predominantly due to a type of cytogenetic injury viewed as lethal rearrangements following chromosome breakage (dicentrics). On the contrary, at lower dose rates one-event lethal aberrations (terminal deletions, dominant point-mutations) would predominantly or exlcusively be involved. Life-shortening by fast neutrons would obey single event kinetics.

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. *(Data in panels A and B are from Sacher, Grahn, Fry et al.* [S5]

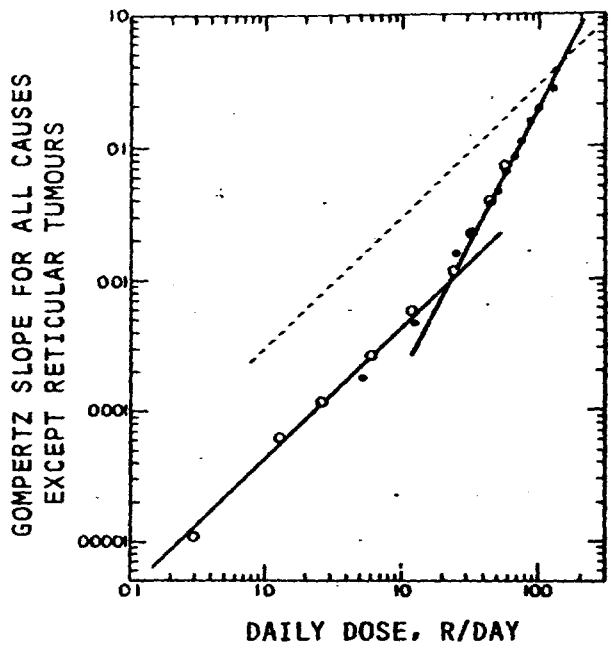


Figure VIII.

A plot of life-shortening to daily dose for mice treated with life-time gamma rays 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].

2. Guinea-pig

124. One hundred-day old male and female guinea-pig 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/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.

3. Goat

125. The survival of goats was followed by Hupp et al. [H8] and by Hupp [H9] on 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 dose level. The lethality pattern observed was quite different than that of mice and rats. Females exhibited little exposure rate response in the range of 7-40 R/day, while males accumulated the maximum exposure at 7 R/day. Rats and mice, on the contrary accumulate maximum exposures at 30-50 R/day [G6].

4. Dog

126. 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 0.06 R/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/day in 10 minutes for 5 days/week for a total of 25, 32 and 42 weeks. Other two groups received 300 and 375 R whole-body at rates of 10 and 64 R/min, respectively. For these latter groups no survival data were reported. More recent data for the dog are also to be found in [N7] (see paragraph 235).

5. Internal irradiation

127. 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.

128. 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 2200 μCi/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 880 μCi/kg but at still higher doses, in spite of a decreased incidence of the bone tumours, life-span further decreased, showing the beginning of a specific non-tumorous mechanism of death.

129. Finkel's [F5] data were reanalised 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 (1.0 or 0.2 μCi/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].

130. Similar observations can be made regarding the rat data of Moskalev, Streltsova and Buldakov [M16] as reanalysed by Mays and Lloyd [M11], since the average time from injection to death tended to lengthen as the dose decreased from 500 to 0.005 μCi/kg. A dose-related life-span-shortening was reported by Brooks et al. [B12] in hamster injected with ^{90}Sr (0.2 to 5.0 μCi). The 60 per cent survival times ranged from 90 days with 2.0 μCi/g to 1100 days at 0.2 μCi/g. In this species, however, myeloproliferative diseases rather than osteosarcoma were the most common pathological conditions observed.

131. Another volume seeker, ^{45}Ca, was studied in single injections by Finkel et al. [F5], and her data were also reanalysed 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.

132. 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.

133. There is some information regarding bone-seeking alpha-emitters. In a reanalysis 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 from injection) was seen at increasing skeletal dose, even when the incidence of bone tumours at doses in excess of 3.1 μCi/kg 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.

134. 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].

135. 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) and included into the Utah experiment 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 efficiency of the various nuclides relative to ^{226}Ra taken equal to one were $^{239}Pu = 6$; $^{228}Th = 8$; $^{228}Ra = 2.5$; $^{90}Sr = 0.07$ to 0.24. These differences could best be interpreted in relation to the local site of energy absorption and to the type of radiation, the surface-seeking alpha emitters being substantially more effective than the volume-seekers.

136. In 1970 Eyring and Stover [E1] examined the life-span-shortening from internal irradiation by ^{239}Pu and ^{226}Ra reported for the beagle dog experiments at the University of Utah [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 per cent 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 per cent survival times followed a linear function of dose at the low doses. This difference was taken to show that although both nuclides were effective in inducing osteosarcoma, ^{226}Ra acted by inducing specific changes in one or more compartments, while ^{239}Pu induced small changes which appeared to be adjuvants to the changes occurring through the aging process.

137. The analysis of life-shortening was also extended to ^{228}Ra, ^{228}Th and ^{90}Sr in subsequent publications [S25, S26]. When the precentage 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 per cent was obtained when the tumour incidence reached 100 per cent. 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 2120 rad, where the occurrence of osteosarcoma was between 92 and 100 per cent but practically no life-shortening was found at skeletal doses between about 370 and 950 rad, although sarcoma incidence in these groups was between 10 - 20 per cent and 42 per cent, respectively.

138. From an analysis of data on yong 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 is confirmed also in the case of a medium size mammal injected with a variety of bone-seeking radionuclides.

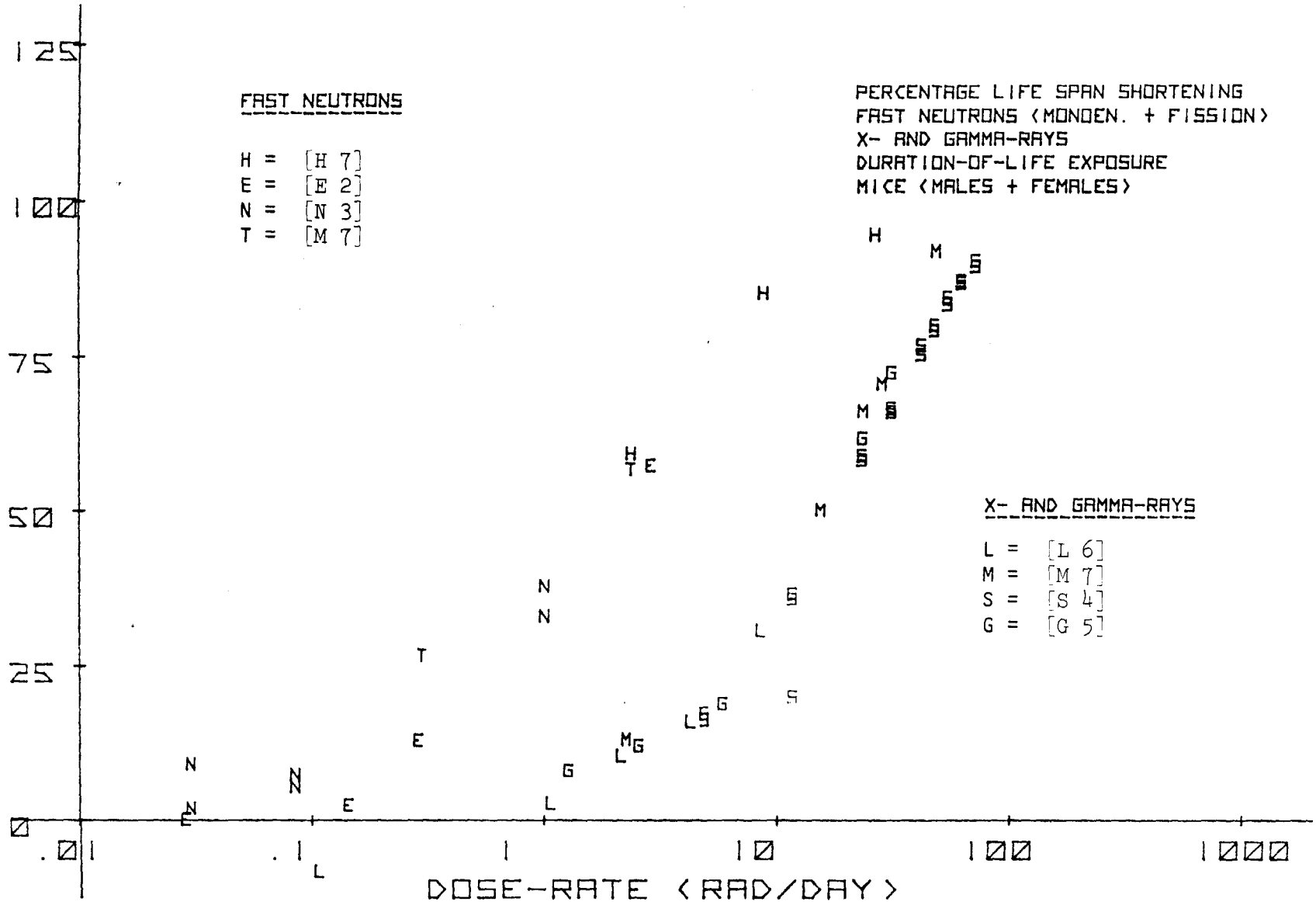


Figure IX.

The relationships between dose-rate and the life-shortening effect following duration-of-life exposures of fast neutrons and low-LET radiations in the mouse. Various experiments.

139. 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 recently [M19]. Survival time of the animals and latency time, frequencey, location and histotype of the tumours were analyzed as a function of the dose rate and of the dose distribution. An acceleration of the tumour induction time (and therefore of aftersurvival 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].

6. Conclusions

140. 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 in the mouse to examine both types of dependencies and to attempt some descriptive analysis.

141. Figure IX shows on the ordinate the percent life-shortening induced after exposure at the dose rates indicated on the abscissa in rad/day. All data available on various strains and sexes have been grouped, separately for the case of neutron and low-LET radiations. The graph includes therefore all the variability expressed in this type of experiments. It should be pointed out that the data by Moos et al. [M14, M15], although following qualitatively a similar trend, have quite different quantitative relationships and could not be considered with the other series. The x- and gamma-ray data include 5 different series performed on 4 strains of male and female mice; the neutron data include 5 series on 3 strains and both sexes.

142. 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

$$y = 100\ (1 - e^{-\frac{aA}{}}) \qquad (16)$$

where A is the dose-rate in rad/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

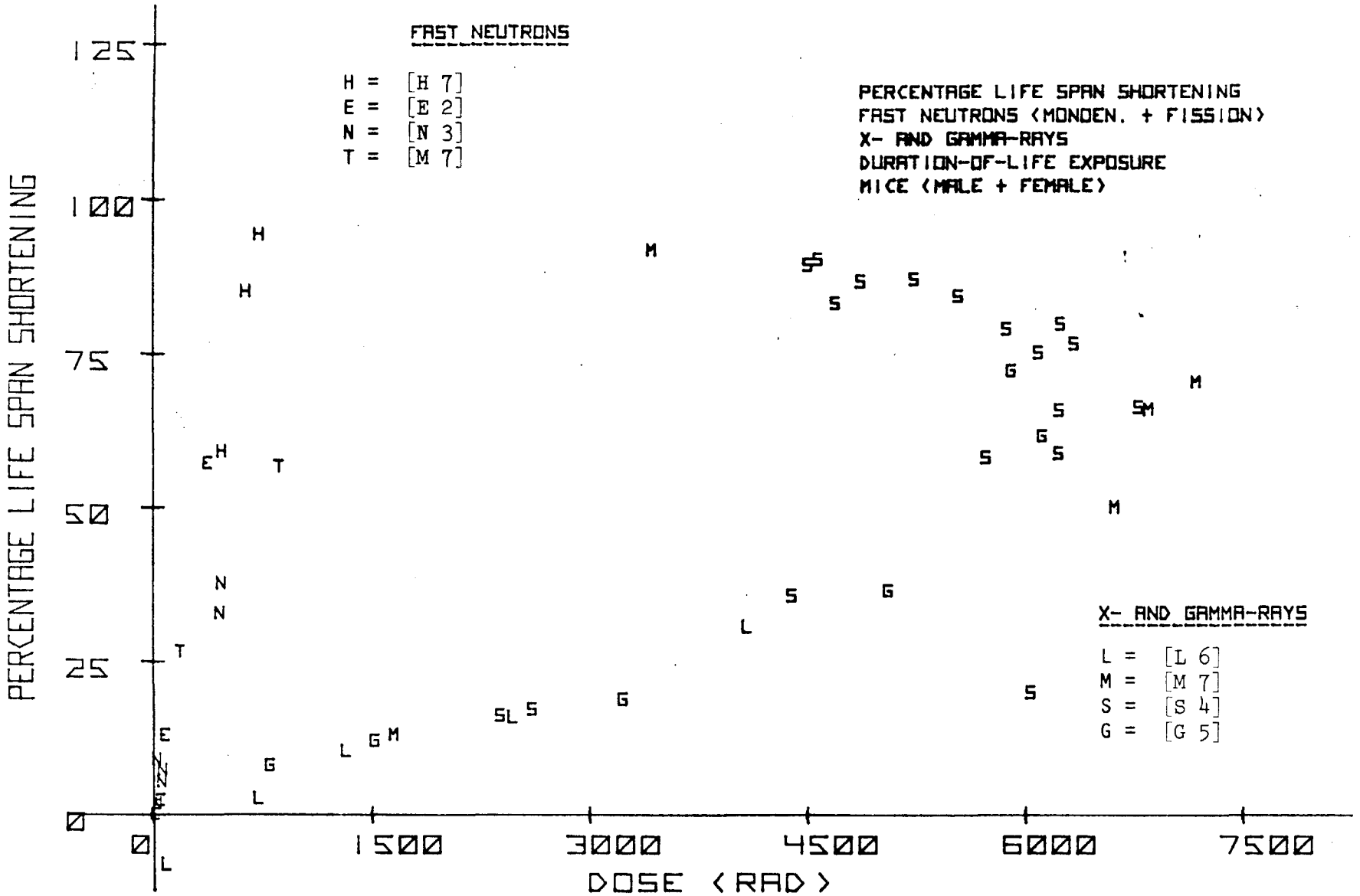


Figure X.

The relationships between the total accumulated doses of fast neutrons and low-LET radiations in the mouse, following exposure for the duration-of-life. Various experiments.

$$y = 100\ (1 - e^{-0.0379\ A}) \tag{17}$$

and in the case of neutron irradiation

$$y = 100\ (1 - e^{-0.3748\ A}) \tag{18}$$

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 to merge of the x-ray and neutron data in the high-dose region of the graph. The relationship

$$y = 100\ (1 - e^{-a\sqrt{A}}) \tag{19}$$

which fits the neutron data with the following values

$$y = 100\ (1 - e^{-0.4883\ \sqrt{A}}) \tag{20}$$

seemed more adequate for that purpose. But an even better interpolation was obtained by least-square fitting the data with the relationship

$$y = 100\ (1 - e^{-0.4883\ A^{X}}) \tag{21}$$

solved as

$$y = 100\ (1 - e^{-0.4883\ A^{2/3}}) \tag{22}$$

It should be noted that even in the case of chronic radiation exposure the low doses of neutrons appear somewhat more effective than the high doses in bringing about life-shortening damage (see paragraphs 211 - 213).

143. Another type of 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 same experimental series shown in Figure IX are plotted in Figure X, separately for the x- and gamma-ray and for the neutron series. At increasing doses the life-shortening effect of low-LET radiation also increases in an apparently linear fashion at the low doses and then with a progressively accentuated upper concavity up to doses of about 6000 rad administered for the duration of life at dose rates of about 20 rad/day.

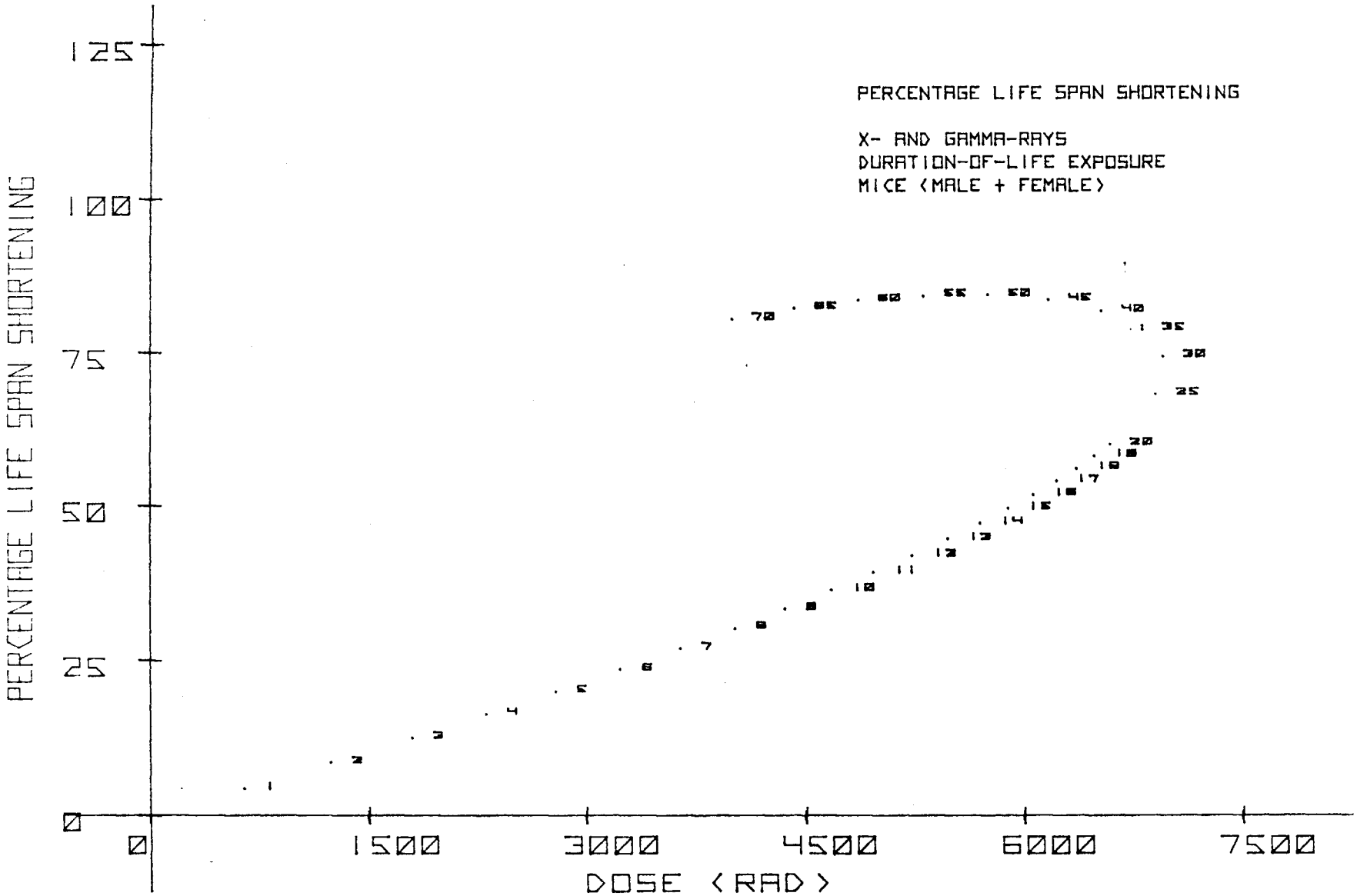


Figure XI.

Best fit to the low-LET radiation data in Figure X. The numbers in the body of the graph are the dose rates (rad/day) at which the doses specified in the abscissa are cumulated during the entire life of the animals.

144. At higher dose-rates the life-shortening continues to increase but, owing to the progressive reduction of life, the dose accumulated decreases and the curve bends over towards the origin. Such an effect had previously been 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 it may be noted that 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.

145. Simply 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 interpolate the phenomenon reasonably

$$y = \underline{b}\, D\, e^{\underline{c}A} \tag{23}$$

where y is the percentage of life-span-shortening, D the dose and A the dose-rate, $\underline{b}$ and $\underline{c}$ being proportionality constants. Such a relationship could not be fitted adequately 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

$$T = T_o\, e^{-A/A_o} \tag{24}$$

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

$$D = A\, T \tag{25}$$

it follows that

$$D = A\, T_o\, e^{-A/A_o} \tag{26}$$

A plot of total absorbed dose <u>versus</u> 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

$$D = 664.11\, A\, e^{-0.0351} \tag{27}$$

with an $R^2 = 0.98$.

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

$$y = 0.00662\, e^{+0.0159} \qquad (28)$$

in which the functional relationship between A and D is given by the above expression (equation 27). Figure XI 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 rad/day) specified at the various points along the fitted curve in the body of the graph.

147. 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 would 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 remarked that the experimental points in excess of about 60 per cent 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.

148. 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 per cent life lost for 100 rad) is divided by the slope of the curve for duration-of-life exposure obtained, for example, at a dose-rate of 1 rad/day (total dose about 700 rad) the loss of efficiency is by about a factor of 7. In the case of neutrons an estimate of efficiency requires that a function be fitted to the data in Figure X. If a linear rationship is interpolated only for the purpose of the present comparison, the equal effect ratios between acute and chronic neutron exposures at 50 per cent, 20 per cent and 10 per cent of life-shortening are, respectively, 0.6, 1.4 and 2.5.

149. The guinea-pig, the goat and dog have also been exposed for the duration-of-life and have revealed differences with the mouse 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) might 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/day, as compared to the 20 - 40 R/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 3.5 rad/day, while in the mouse the relevant figure would be in the region of 20 rad/day.

150. A large variety of injected, ingested or inhaled radionuclides have been studied for their capacity to induce life-shortening. The largest experience refers to 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 a specific mechanism of death might produce short-term mortality. This conclusion is very clear-cut and not surprising, since 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.

C. DOSE-RATE, DOSE FRACTIONATION, CHRONIC TERMINATED EXPOSURES

151. Other experiments are available where radiations of different types were given at various instantaneous dose-rates in chronic terminated or in fractionated exposures to animals of various species. The experiments were made sometimes to examine the effect of a given regime of chronic terminated exposure; in other instances, to study changes in the instantaneous dose-rate; in still other cases in order to compare the effects of splitting a single dose into fractions separated by various time intervals. In all 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: the subdivision to follow will consider separately the effect of dose-rate, of dose fractionation and of chronic terminated exposure, in an attempt to draw more systematic conclusions about the different radiobiological variables.

1. Instantaneous dose-rate

152. The papers where instantaneous 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. It is evident that, unless the dose-rates used are very high, the effect of the duration of the exposure cannot be separated from the effect itself of the instantaneous intensity of irradiation.

153. Vogel, Frigerio and Jordan [V1] reported that between 1 and 4.4 rad/min of fission neutrons the effect of life-span was independent of dose-rate, while there was dependence for gamma rays in the range of 1 to 13 rad/min, the efficiency of the treatment being 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 8 rad/min or 0.2 rad/min (36-174 rad total dose). Survival did not differ within the above dose-rates.

154. Vogel and Jordan [V3, V4] irradiated the same mice with fission neutrons and gamma rays (1 to 35 rad/min). Four weekly doses of 200 rad/week of ^{60}Co gamma or 100 rad/week of neutrons were employed, delivered at variable

dose-rates. For both radiations, the lower the dose-rate, the longer was the life-span of the animals. Lindop and Rotblat [L10] reported on the changes in effectiveness (expressed in weeks of life-shortening/100 rad) as a function of the instantaneous dose-rate at the extremely high intensities of 77 to 158.000 rad/min. They showed that the maximum effectiveness (5.7 to 6.2 weeks/100 rad) was at around 1000 rad/min, but could not explain the loss of effectiveness at still higher dose-rates. Oxygen depletion induced by these high intensities could not be responsible for such an effect, since it was also seen in mice made artificially hypoxic.

155. Upton, Randolph and Conklin [U7] and Upton, Randolph and Darden [U10] used variable dose-rates of gamma rays (80-1 rad/day) or of fast neutrons (11 to 0.004 rad/day) to induce life-shortening on RF/Un male and female mice (total doses of 10.000 and 1.000 rad, 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 (6.7 or 80 rad/min) 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 per cent 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 per cent of the mice. In male animals, the loss of efficiency of the gamma rays was even higher, amounting to 0.1 upon continuous administration ad to 0.04 for irradiation protracted up to 50 per cent survival.

156. Spalding et al. [S21] performed experiments on RF female mice irradiated with gamma rays (2.5 to 250 rad/hour, 100 to 1200 rad 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, 0.1 - 100 rad/min, 100 - 300 rad 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.

157. 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 modi-

fication of the shape of the dose-effect relationship in the range 50 - 400 rad from a very complex pattern at 45 rad/min to a nearly linear shape at 8.3 rad/day. The large difference in effectiveness was related to an upward displacement of the regression line in the 0 - 50 rad range in the high-dose rate groups. Balb/c females showed a similar trend, in that the 50 rad 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 50 rad, similar to the one identified by Sacher [S2] in female mice given 200 rad or more. The response to neutron irradiation of high (25 rad/min) or intermediate (1 rad/day) dose-rate was somewhat different. In RFM mice the low-dose-rate was less effective at 24 rad but more effective at 188 rad than the high dose-rate. In Balb/c mice little dose-rate dependence was seen at low doses but at 188 rad the low intensity was more effective. The results are somewhat less clear at doses below.

2. Dose fractionation

158. The experiments reported in the next few paragraphs (159-172) 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 together in producing the final effect. They cannot be disentangled from each other under most of the experimental conditions used. Often the ocmparison 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.

159. In the mouse Sacher[S2] performed experiments on the life-shortening of 400, 800 and 1200 R when 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, was 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 (see also paragraph 194) did not show any change in RBE upon fractionation but the authors themselves 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.

160. 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 longevity 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 indeed 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.

161. Mole [M1, M20, M21] reported that when 1000 R or x rays were delivered in 10 daily fractions of 100 R the mean survival time was shortened by 10 per cent, 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 per cent. 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.

162. Cole et al. [C18] examined in 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 per cent in the mice receiving the single exposure to less than 10 per cent in the group receiving eight fractions. Therefore, in these experiments nephrosclerosis was mainly responsible for early death after the single dose, whereas malignancies specifically accounted for more than half of the deaths in the fractionation groups.

163. According to Vogel, Frigerio and Jordan [V1] fractionating 275 rad 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 rays given as a single exposure or in two fractions administered 8 days apart on male and female CAF1 mice. Regarding specifically the effect of fractionation, here again the results were unclear in showing any significant improvement in survival.

64. Vogel and Jordan [V5] examined on CF1 female mice the effect of fractionating a weekly dose (300 rad of ^{60}Co gamma rays or of 60 rad of fission neutrons) into 1, 3 or 6 equal dose fractions per week. Both radiations were delivered at aprroximately 1 rad/min and the treatments were continued for a total of 13 consecutive weeks, so that the mice were exposed to almost 4000 rad of gamma rays or 780 rad 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.

165. Silini and Metalli [S27] showed in a small experimental series that survival time could be improved by a schedule of fractionation where a conditioning dose of 150 was followed by 350 R given at seven time intervals between zero and 48 hours. A positive regression of the data amounting to an 8 per cent improvement in survival time was detected. The kinetics of the phenomen followed a pattern reminiscent of the short-term intracellular type of recovery described in cultured cells by Elkind and collaborators [E4].

166. 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 <u>versus</u> fractionation interval was negative in 3 our 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 what seen in other studies [G4, U11].

167. Ainsworth et al. [A7] reported that fractionation of a gamma dose of 838 rad into 24 doses of 35 rad administered over 23 weeks produced a sparing effect by approximately three-fold. On the contrary, a similar regime of fractionation with fission spectrum neutrons produced an increased life-shortening, which is a rather unusual observation in fractionation experiments. 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.

168. Storer et al. [S44] exposed RFM and Balb/c mice to 7 weekly doses of fission neutrons of 6.7 rad for 7 weeks (total of 47 rad) or to 23.5 rad once every 4 weeks over 28 weeks (total 188 rad). Animals exposed to 47 rad fractionated had a life-span not different from those given single high dose-rate exposures or exposures at 1 rad/day. Balb/c animals receiving 188 rad had a survival time significantly shorter than that following a single exposure. RFM animals given fractionated treatment up to 188 rad experienced the same survival as after single exposure and a significantly longer survival than following exposure at 1 rad/day. It was concluded that the cause of death may critically determine the effectiveness of the fractionated exposure, although the authors were unable to provide a basis for their observations.

169. Data on the effect of dose fractionation on life-shortening were described in the Wistar male rat by Hursh et al. [H5] irradiated with x rays. While the life-shortening caused by an acute exposure of 600 R was marked (19 per cent of the control) animals receiving 20 R x 30 days had a life-span similar to that of the controls. Sixty R x 10 days produced an intermediate effect between the previous two conditions. A pneumonia infection occurring about one year after the start of the experiment complicated the survival picture of the animals. Also, since the range of control values in these experiments was extremely variable and different from previous data, all this series seems rather inconsistent.

170. Data on x-ray dose fractionation were 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 frac-

tion. The effect was dose-dependent in that it could be seen at the two highest but not at the low exposure. 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 per cent of the sparing effect obtained by halving the total exposure in the 0 - 446 R exposure range.

171. 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 difference 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.

172. 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 per cent as treatment time increased from 7 to 84 days.

3. Chronic terminated exposures

173. The papers discussed in the next few paragraphs (173 - 180) 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 factors such as the protraction of dose ad-

ministration 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 came to death, thus allowing estimates of the relevant factors under conditions in which the "wasted radiation" component (see paragraphs 98-101) would not be effective.

174. The early contributions of Evans [E2] and Lorenz et al. [L6] should only be cited 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/week for progressively longer times (4 to 30 weeks) and for the duration of life were tested. For neutrons, 16 or 2 rad/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 more 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.

175. 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 (see paragraphs 18-34). 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 under paragraph 199.

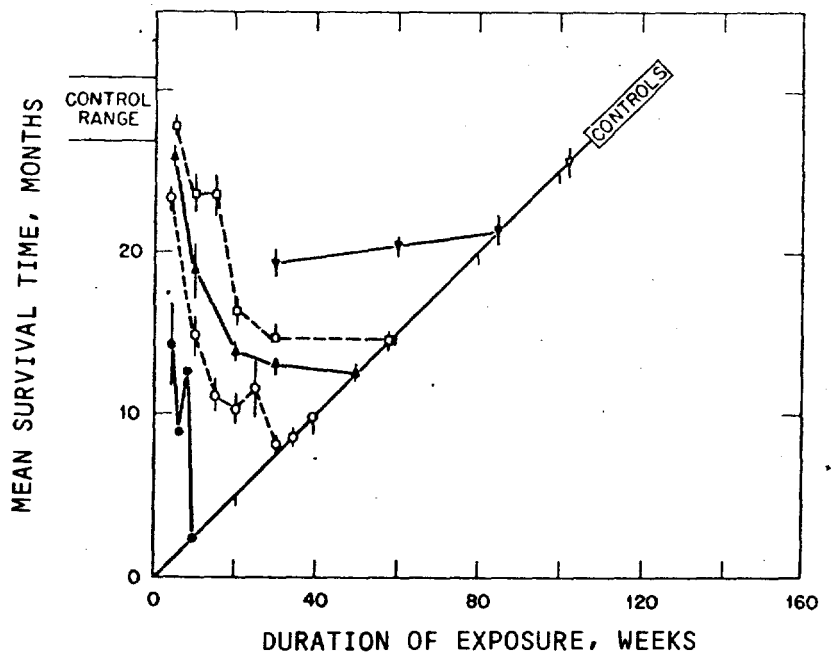


Figure XII.

Mean survival times of female CBA mice after chronic terminated and duration-of-life exposures to gamma rays and fast neutrons.

The nominal weekly doses are: gamma rays, ● 350 R, o 210 R, □ 110 R, ▽ 16 R; fast neutrons, ▲ 16 rad, ▼ 2 rad.

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. 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/hour or 0.2 R/hour of ^{60}Co gamma radiation. The cumulated total doses 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 small 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.

177. 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 daily exposure levels below 20-30 R/day. 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 - 50 R/day to 12 or less R/day.

178. Spalding et al. [S28] exposed 13 groups of adult female RF mice to ^{60}Co gamma rays at 2.76 rad/hour until a predetermined dose (from 457 to 3.008 rad) 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 0-47 rad, the effect would be about 0.18 days/rad, a value which is on the low side of those usually found for low-LET radiation (see Table 1).

179. 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/day no effect on survival was noted. This was also true for monkeys.

180. 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/day) 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 344 R (258 rad) delivered at 15 R/min to about 4000 R (about 3000 rad) at 10 R/day. Over this range of exposures the leading cause of death was haemopoietic damage. At 5 R/day or lower no definite LD_{50} could be determined: the haemopoietic function continued at a nearly normal rate and survival was prolonged. The large number of malignancies other than leukaemia observed among the few animals dead up to the time of the report suggested that in irradiated animals tumours of the soft tissues would be significantly increased with respect to controls. It is yet too early to see whether a non-specific component in the life-span-shortening might become apparent at the lowest dose-rates.

4. Conclusions

181. On the whole, the modifications of life-shortening induced by changing the instantaneous dose-rate are rather variable. The conditions examined cover acute, fractionated and chronic irradiation, as well as various types and energies of the radiations. For single acute doses of low-LET beams, changing the dose-rate from 0.4 to 40 rad/min did not significantly alter the effect [S21]. When the intensity varied between about 80 and about 150 000 rad/min [L12] the effectiveness of the treatments differed as a maximum by a factor of 1.6. Thus, acute treatments show little dependence on the instantaneous dose-rate down to 0.4 rad/min. At lower dose-rates, down to about 1 rad/day, it becomes difficult to resolve changes due to the instantaneous dose-rate and those attributable 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 per cent survival of the irradiated animals [U7]. With such extremely protracted irradiations the form of the dose-effect relationship may change with respect to the very acute exposures with resulting lower effectiveness at lower intensities, but with various reduction factors for different total doses [U7, U8].

182. Examples have been reported where a relatively high loss of effectiveness was seen at doses of the order of 50 rad or less, while proportionately lower reduction factors would be applicable at higher doses. Modifications of the form of the dose-effect relationships are not surprising, since changes of the damage, repair and repopulation at the various doses would superimpose to irradiation. All these variables would be expected to change profoundly as a function of time and dose and therefore the situation operating under a given set of irradiation conditions would hardly be comparable to that of acute irradiation and could not be interpreted according to the same principles governing the response to an acute insult.

183. In the case of neutrons, changing the instantaneous dose-rate between 8 and 0.2 rad/min does not result in an appreciable loss of effectiveness [V1]. The data available at lower dose-rates (25 to 0.004 rad/day) 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 rnage of variation. There has been experience in changing the instantaneous dose-rate (from 13 to 1 rad/min) 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 (1 to 35 rad/min) did, however, show some reduction of effectiveness even in the case of neutrons [V3, V4].

184. Thus, the dependence of life-shortening on instantaneous dose-rate is modest for low-LET radiation and doubtful for neutrons, for treatments lasting a few hours to a few days. Only when extremely low dose-rates and correspondingly long irradiation times are involved, x- and gamma-rays (but not neutrons) show consistent reductions of effectiveness, of the order of a factor of 10 or 20. Under these conditions, however, there is no way to discriminate between the effect of lowering the dose-rate and that of protracting the treatment time, which implies re-equilibration of the organism's adaptation system.

185. Experiments performed by splitting a given dose into two or more fractions separated by a few hours to a few weeks have repeatedly been performed. The simplest instance is one where two dose fractions, equally or unequally divided, are administered within fractionation times of the order of a few hours to one day. Two experiments with such a scheme [G1, S27] have yielded little increase in survival by the split dose: life-shortening was within 5 - 8 per cent of the single-dose survival time in the first case and the results were essentially negative in the other.

186. Experiments using two dose fractions in the range of 100 rad or more total dose for fractionation times of 1 day or longer are more numerous [U11, C18, K6, A2]. Fractionation intervals ranged from 2 days to 8 weeks. Splitting the dose usually produced less life-shortening. In two cases [K6, U11] a sparing effect of the order of 3 - 20 per cent was reported. In the other two cases, no effect of dose fractionation [C18] or a negative effect, that is, an increased life-shortening, was observed [A2]. When fractionation intervals of progressively longer duration were tested with a given scheme, a tendency to a longer life-span with 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].

187. It is very difficult to see an overall trend for more complex fractionation patterns. On different species, treatment schemes involving from 3 to 90 dose fractions administered from 3 days to about 23 weeks have been tested. Very seldom is the fractionation pattern comparable within each experimental series, since for the same total dose both the dose per fraction and the total treatment times are changing. In some cases [S2, A2, A7, H5, L4, R3] dividing the dose into smaller and smaller fraction 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., and 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 oberservations. The outcome of a given fractionation treatment depends critically on the characteristics of the biological system as they reflect on the pathology of the animals at death. It is difficult therefore to give a numerical value to the effect of fractionation except to say that the effect, when present, is not very large and the biological variables appear in general more important in determining it, than the actual change in the dose-time relationships induced by dose fractionation.

188. Four neutron dose fractionation experiments have also been reported on mice. In the first [V1] splitting a dose into 3, 4 or 10 fractions in 3, 4 and 12 days did not result in any significant change in the mean after survival. The second series [V5] involved changing the number of fractions/week (1,3,6) for a given weekly dose (60 rad) and a fixed time of treatment (13 weeks) and was similarly negative. In the third series [A7] fixed doses (80 and 240 rad of neutrons) were given singly or subdivided into 24 fractions administered over 23 weeks and such a scheme produced a significant increase of life-shortening. Similar observations were also made in the last series [S44]. It should again be emphasized that the physical parameters of fractionating the dose are not prevalent over the changes of the pathological expression of the damage which largely determine the life-shortening effect.

189. 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 reviewed in paragraphs 173-180 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 re-

lationships 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, are the variables determining the final outcome of any given course of irradiation. There are not enough data on any single species for analysing such a broad statement into any coherent model of action, particularly since published data have essentially been obtained on two mouse strains [M7, U7] and other series [S11, S21, L6] have contributed relatively less information.

190. These data, involving x- and gamma-ray and neutron irradiations were analysed by Grahn and Sacher [G1] and their conclusions may be accepted provisionally. Apparently (see Figure XIII) the curve describing life-shortening as a function of total dose accumulated for doses of 1500 rad or less and/or for protraction periods of 50 days or less shows an abrupt slope transition

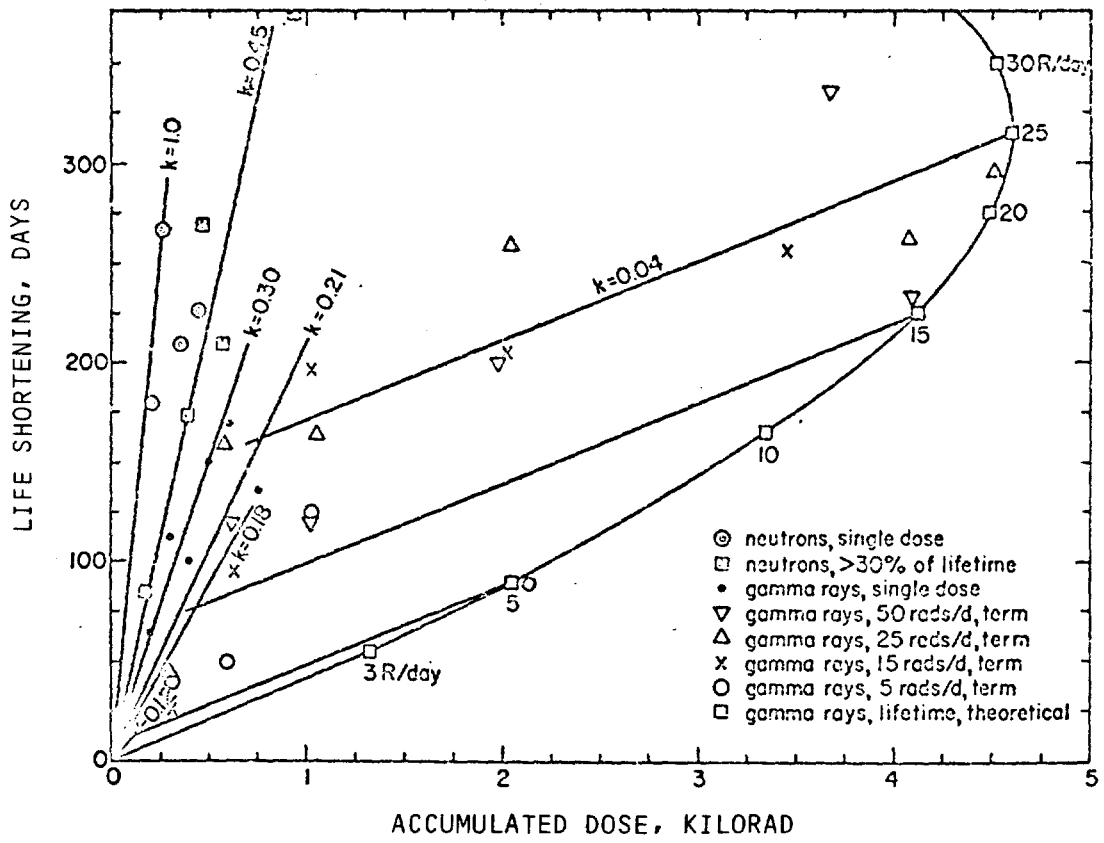


Figure XIII.

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]

from an initial portion where the effectiveness of the treatment is of the order of 20-30 days of life-shortening per 100 rad to a final slow-rising portion having an effectiveness of 4-5 days per 100 rad. This final slope would apply 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 would be clear at 50 to 100 rad/day but less so at intensities of 10 to 15 rad/day. This flattening of response noted by Mole [M1] and by Sacher [S1] might be related to the establishment of an equilibrium between radiation injury and recovery mechanisms, which would be related to the kinetic modifications of the tissues that are important for long-term survival [S5, L13, L14, L15].

191. It may therefore be expected reasonably that the breaking point or transition in the dose-effect relationships would also depend 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 recover 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. RADIATIONS OF DIFFERENT TYPES AND ENERGIES

1. Data

192. The action of different radiations 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 radiations 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. Short of these conditions, the higher effectiveness of a densely-ionizing

radiation may be measured by an "Equal Effectiveness Ratio", a quantity defined as the ratio of the standard radiation dose to the densely-ionizing radiation dose producing the same level of effect. The present document will not discuss the theoretical foundations of these concepts which are reviewed elsewhere [K10, R4] and are discussed in other annexes of the UNSCEAR report. It will only consider evidence regarding life-shortening, according to the order of publication.

193. The early experiments on neutron RBE by Henshaw [H6], Evans]E2], Gowen [G8] and Neary et al. [N3] will simply be cited. They were analysed by the 1958 report of the Committee [U1] which discussed all data in the rodent irradiated chronically and summarized them in one graph [M13] (see Figure XIV). The percentage mean survival time was plotted versus the gamma-ray or the fast neutron exposure- or dose-rate in R or rad/week. The data appeared to be superimposable when the gamma- and neutron-scales were in the ratio of 1:13. From this it could be deduced (in spite of some uncertainties in the comparison of data from different laboratories) that the RBE between fast neutrons and gamma rays applicable to life-shortening in the rodent for chronic duration-of life-exposure was about 13.

194. A study of x rays (250 kVp, 185 rad/min) and of fast neutrons (fission spectrum, 2.7 x 10 neutrons/cm^2/sec) was performed in CF1 female mice by Curtis and Gebhard [C17]. In a first series, single doses (474-641 of x rays and 280-330 rad of neutrons) were used; in another experiment mice received 35 per cent of the $LD_{50/30}$ of both radiations once a week for 4 weeks; in a third series 50 per cent of the $LD_{50/30}$ was given once every two weeks for 4 weeks. The RBE for life-shortening was estimated at 1.7 for all series. 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.

195. 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 16-17 rad/week of fast neutrons or of 210 and 110 R/week of gamma rays were found to be equivalent both for terminated and for duration-of-life exposures. For all levels of re-

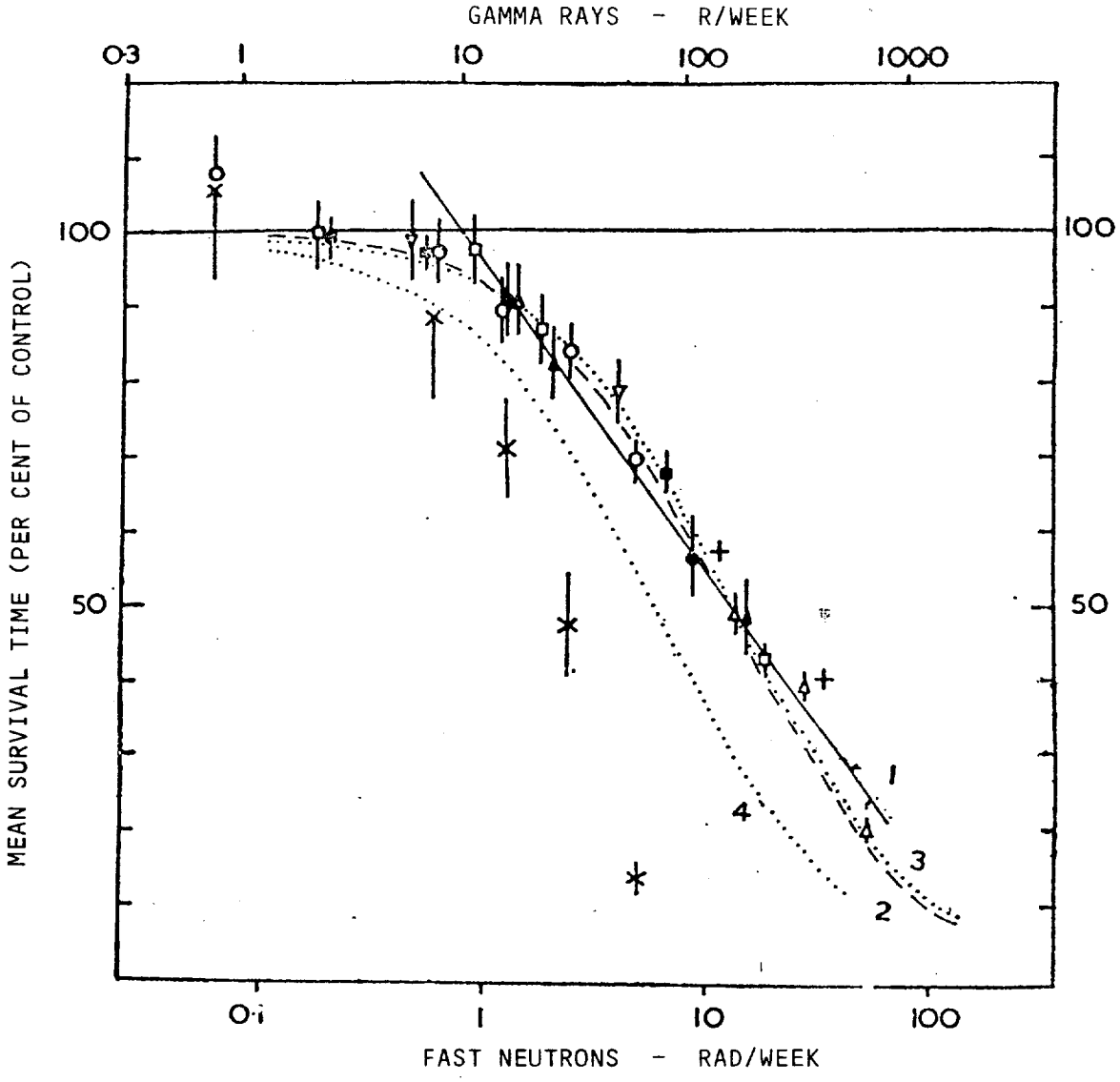


Figure XIV.

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, as plotted by Mole [M13] *and included in the UNSCEAR 1958 report* [U1].

sponse the neutron data were intermediate between the effects of these two intensities of gamma rays and nearer to those of the 110 R/week. The RBE was therefore estimated to be between 13 and 7, but nearer to the latter figure.

196. In a subsequent paper by the same group [N8] the RBE value was discussed for CBA mice irradiated chronically with fast neutrons with the neutron facilities described in [N3]. The dose-rates of the 0.7 MeV neutrons were 2.2 rad/day or 0.3 rad/day. Gamma irradiations were run at 15.8 or 2.3 rad/day. Complete life-table data and cumulative survival curves were obtained in repli-

cate 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.

197. 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.

198. 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 4.4 and 13 rad/min, respectively. Groups of animals were given 13 brief exposures, each corresponding to 2.2 - 70 rad/day of neutrons and 6.5 - 208 rad/day 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 1 rad/min 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.

199. Curtis, Tilley and Crowley [C19] reviewed the literature data on life-shortening by 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, while for neutrons equal efficiencies by acute and chronic exposures were the most common finding. Accordingly, the neutron RBE of about 2 for life-shortening by acute doses might 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 support indirectly the hypothesis that mutations in somatic cells might be at the origin of natural and radiation-induced aging.

200. Sixteen-weeks-old female CF1 mice received 100 rad/week of fission neutrons for 4 weeks at dose-rates of 1, 3, 6 and 35 rad/min; or 200 rad/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, lifetime was reduced by about 65 per cent by neutrons and by about 50 per cent 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 35 than with 1 rad/min.

201. 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 1 rad/min. CF1 female mice were exposed according to a complex pattern of fractionation in which 13 weekly doses of 300 rad of gamma rays were delivered into 1, 3 or 6 equal fractions per week. Since the arbitrary RBE value chosen was 5, the corresponding total weekly dose of neutrons was 60 rad, delivered into 1, 3 or 6 fractions per week. The data showed that the postulated RBE of 5 was too high.

202. Upton, Randolph and Darden [U10] reported that with fast neutrons the life expectancy of RF female mice was shortened by 0.8 days/rad, irrespective of dose-rate, whereas the life-shortening efficiency of the gamma rays decreased from about 0.3 days/rad at 7 rad/min to about 0.15 days/rad at 5 rad/day. The RBE increased therefore with decreasing dose-rate from about 2.7 to 5.4.

203. In the experiments of Upton, Randolph and Conklin [U7] variable dose-rates of x and gamma rays (80 - 1 rad/day) and of fast neutrons (11 to 0.004 rad/day) were administered to RF mice. There were also groups treated at about 100 rad/min of both radiations. Gamma rays at the low dose-rates were invariably and consistently less effective than at the high dose-rates. Neutrons, on the contrary, showed less dependence on the intensity. The RBE evaluated on the basis of the average life-shortening effect (days/rad) 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 per cent of the mice, a further increase of the effectiveness to about 14 took place. Without knowledge of the dose-rate-RBE relationships it was impossible to foresee whether higher RBE's 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 (0.000003 - 0.01 rad/min as opposed to 85 rad/min) it was felt that neutrons of still higher energy might prove less effective.

204. Clapp et al. [C12] published a large experiment in which the effects of acute doses of 300 kVp x rays (50 to 400 rad) were compared with those of 60 MeV protons (47 to 372 rad). Irradiation conditions were such that comparable LET values were obtained. The proton mean LET was in fact estimated to be approximately 1.5 keV/μm within the animal's body. As expected on the basis of LET considerations, protons were found to be 0.36 times as effective as x rays for life-shortening and were in general slightly less effective on the basis of 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.

205. 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 of this latter radiation was therefore dose-dependent and changed between 2.0 and 2.4 for doses causing between 25 per cent and 45 per cent of life-shortening. For doses causing 4 per cent life reduction the RBE was between 6.8 and 7.6. Fractionation of the treatment into 24 doses given over 23 weeks, up to a total dose of 80 rad of neutrons or 838 rad of gamma rays, caused an increase of the RBE between 13.5 and 10.5 in male and female animals, respectively.

206. 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 50 rad. Such a trend would be predicted by the dual radiation action theory of Kellerer and Rossi [K10]. At doses above 50 rad 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).

2. Conclusions

207. Except for a study of thermal column radiation [S17] and another on 60 MeV protons [C12] - for which, as expected, the RBE was found to be near unity - experience on life-shortening refers only to neutron irradiations. Fission and degraded-fission spectrum neutrons, weapon and monoenergetic neutrons were used in the various cases. The only species on which data are available is the mouse, where inferences may be drawn about the RBE changes as a function of dose fractionation and protraction and, to some extent, as a function of the dose level.

208. For acute doses in the region of a few tens to a few hundred rad of x and gamma rays (and equivalent doses of neutrons) RBE figures of 2 to 3 have generally been found [U5, S18, S44]. Direct comparisons of single and brief daily courses of irradiation were reported by Vogel, Frigerio and Jordan [V1] and by Vogel and Jordan [V3, V4, V5, V6] at neutron dose rates of between 1 and 35 rad/min: under these conditions the RBE is very similar to that applying to acute single doses (2.8) with maximum oscillations between 2 and 5. These figures are also similar to those of Upton, Randolph and Darden [U10] (2.7 to 5.4) obtained by changing the instantaneous dose-rate form 7 rad/min to 5 rad/day, for total doses of up to 600 rad. The data of Curtis and Gebhard [C8, C17] are in this respect an exception in that the RBE is similar for single and for fractionated doses and, on the whole, very low (1.7). The evidence reviewed shows some increase of the RBE upon short fractionation courses and with decreasing dose-rate down to a few rad of neutrons per day, from figures of 2 - 3 applying to acute treatments to figures of about 5 - 6. More consistent changes are found for extremely long courses of irradiation. RBE values of between 9 and 15 were quoted under similar conditions by Neary, Munson and Mole [N3] and Neary, Hulse and Mole [N8]. These latter are in fair agreement with the figure of 13 that may be obtained from the 1958 report of the Committee [U1].

209. For more precise evaluations the data of Upton, Randolph and Conklin [U7] are of particular interest because they examine the RBE changes as a function of the dose-rate, with a spectrum of dosages between the acute and the long chronic exposures. The RBE changes in this series from figures of about 3 at high dose rates to figures of about 8 for protracted exposures or even up to about 14 for very prolonged treatments. Ainsworth et al. [A7] also reported differences in the RBE of fission neutrons between 2.0 - 2.4 up to 10 - 15 for weekly dose fractionation over 23 weeks and total doses a few hundred rad of gamma rays and a few tens of rad of fast neutrons.

210. Only the most recent reports allow an analysis of the RBE changes as a function of dose. Ainsworth et al. [A7] pointed out that the effectiveness of neutrons increased from values of 2.0 - 2.4 at doses causing 25 - 45 per cent of life reduction to values of 6.8 - 7.6 at doses producing 4 per cent reduction. Ullrich and Storer [U8, S44] reported that the RBE figures of 2.9 - 3.0 observed for doses about 50 rad would increase for progressively lower doses as the inverse of the square root of the dose, in accordance with theoretical predictions [K10]. There is therefore a tendency of the RBE to increase as the dose decreases and in both the cases cited this effect is brought about by the upper convexity of the neutron curve at low doses, rather than by the upper concavity of the dose relationship applying to the low-LET radiation.

211. From the analysis of the mouse data in Figures II and III the RBE values that would be obtained for acute single doses of neutrons by pooling all available experience would differ at different doses. The effectiveness of the neutron treatment obtained by dividing the doses of the two radiations producing 50 per cent life-shortening would be 1.2. At 20 per cent of the effect the corresponding value of the RBE would be 3.2 and it would further increase to 6.6 at 10 per cent of the effect. For doses in the region of 1 rad of neutrons or less the efficiency would be about 50. These are of course average figures obtained from the best fit of the data, as specified under paragraphs 90-95.

212. 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 per cent 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; this same value would go to about 17 at 20 per cent of effect and to about 25 at 10 per cent of effect. At dose rates corresponding to 1 rad/day of low-LET radiation (and proportionately lower neutron intensities) 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. If the assumptions made in paragraph 148 are utilized to this effect, the relative neutron effectiveness values applying to 50, 20 and 10 per cent of effect would be, respectively, about 11, about 14 and about 16.

213. 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.

3. SPECIFICITY OF LIFE-SHORTENING

214. After the overall quantitative analysis in the preceding paragraphs, the problem of the specificity or non-specificity of the effect should now be reviewed. 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. Reported experiments of this kind are indeed 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 in fact 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 based 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.

215. 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 rodent, does lead 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 seen after irradiation must be attributed to tumour induction.

216. The first large 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 since the dose relationships for tumour induction had variable form, some neoplasms being increased and some decreased with increasing dose. These data gave impulse to the idea that radiation might cause non-specific aging by advancing in time all diseases by about the same degree for each given dose. However, a more recent reevaluation by Walburg [W1] with 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.

217. 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 this series was that life-shortening was due to a forward displacement in time of all causes of death, without any changes in the relative probability of each cause. It would be of interest to reconsider these data with a more refined statistical test [H2] to assess the reliability of the conclusions, particularly since the pathology and the statistics of this experiment were criticized [W1]. It should in any case be pointed out that the authors did recognize differences in the relative time of onset of the various diseases between control and irradiated animals: one may wonder therefore how these data could be interpreted, as they were at the time and long thereafter, to support the existence of a non specific effect of aging.

218. 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 tumoural and degenerative diseases of the 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 when the tumour deaths were excluded. This indicates that tumours did contribute substantially to life-shortening, at least in the dose range of 100 to 300 rad of gamma rays. 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.

219. Grahn, Fry and Lea [G5] ascribed to excess tumour mortality the life-shortening observed up to about 400 rad, 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.

220. 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 author's opinion and to the reanalysis of Walburg [W1].

221. 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/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/day an excess mortality from non-tumorous conditions becomes apparent. It should also be added that whatever conclusion may be drawn up to the present from the Argonne series on the life-time irradiation of dogs seems to be in agreement with the above conclusion.

222. 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, appears 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 taking some animals to premature death. 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. 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. BIOLOGICAL VARIABLES

223. In the following paragraphs (223-289) 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, which appears to be 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 differntial 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 paragraphs 314-324 with other modifying biological conditions.

A. GENETIC BACKGROUND

224. Among the genetic variables, the inter-species and intra-species differences should be considered separately. In the first case, the objective 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 naturally 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 easiness of obtaining crosses of inbred genotypes. Before discussing long-term effects, it should be recalled that in respect to early radiation death the susceptibility of inbred strains differs by less than a factor of two and that resistance to early death is generally associated with physiological vigour. Also, a short life-span, when it is due to a high incidence of leukaemia, does not seem to influence the response to the acute radiation syndrome [V7] while it does, as it will be seen, for the longer-term survival.

1. Inter-species differences

225. Attempts at inter-species comparisons in relation to life-shortening with the objective of an extrapolation between species and eventually of a projection to man, were discussed and proposed repeatedly. An appraoch based on the actuarial Gompertzian analysis of survival paramaters 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) might hold for mammalian species of different life-span, a common origin for the curves and a time-scaling factor might be chosen in such a way that actuarial functions belonging to various species might 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) might decrease the human expectation of life by 10 per cent. Even exposure to background radiation could, in principle, be responsible for about one year of life lost, with respect to a purely ideal situation where background radiation would not be present.

226. On the basis of experiments already reviewed in paragraphs 103-104 and of other experiments by Henshaw [H1], Boche [B11] identified in the parameter alpha (the excess death-rate/week divided by the exposure level in R/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 insult. 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.

227. In summarizing the effects of long-continued whole-body irradiation of mice, guinea-pigs and rabbits, Lorenz [L7] 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 that 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 hu-

man 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 per cent or higher of the control values would hardly be justifiable. On the other hand, it is only in this region of effects that extrapolation could be of any interest.

228. 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 paragraph 116) 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 ten in the steady-state or plateau values of their cumulant functions, while intra-species differences were within a factor of four. However, the evidence available for long-term mortality showed considerably less species variation.

229. 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.

230. 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 days/R [N1]. In Neary's model [N1] if the life-shortening/rem is taken to be the same for man as for the mouse, the absolute life-shortening for the two species would be calculated at 0.08 day/rem of chronic radiation. Thus, a person accumulating what was at the time a maximum permissible life-time dose of 200 rem would suffer a life-shortening of 16 days, instead of the figures of up to one year calculated on Boche's [B11] assumptions.

231. On the basis of data obtained in the mouse exposed to acute ^{60}Co gamma doses (110 to 1200 rad) Spalding, Johnson and McWilliams [S21] attempted some extrapolation. They found that if a mouse-to-man relationship of 1 day to

1 month could be assumed, similar conditions of exposure in man might be expected to cause a reduction of the mean after survival time of 9 to 10 days/rad of gamma-ray exposure.

232. Grahn and Sacher [G1] based their extrapolations on the linearity of the log mean after-survival in days as a function of daily dose in rad or R, for mean after-survival of 25 per cent or more of the control values. This linear trend of the mean after-survival had been shown previously to hold for the mouse [S4] (see Figure XV). The coefficient of this regression is a species constant [G9] and reflects the days of life lost per rad or the fraction lost per day. It may therefore allow, when two points referring to a given species are known, to define the slope of the curve applying to that species. The ratio of the life-shortening coefficients would be in a direct proportion to the ratio of life expectancies for non-irradiated populations or to the ratio of the age-specific mortality rate slopes. A radio susceptibility scale could 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 16500, 4000, 1400 and 500 days, respectively. It could therefore be deduced that the relative sensitivity of the various species (expressed in per cent life-shortening for exposure of 1 rad) 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].

233. Grahn [G6] explored further the problem of inter-species comparisons, starting from the notion of the exponential decline of mean after-survival with daily dose, already mentioned repeatedly (see 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 and McClement (20:1) [F4]. In consideration of these other estimates Grahn selected for his calculations a ratio of 1:30 and established that the daily dose to induce a 50 per cent reduction of life expectancy in man would be 0.65 R/day, to be compared with a 19.4 R/day in the mouse. Calculations for man and for other species showed that the guinea-pig would be 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.

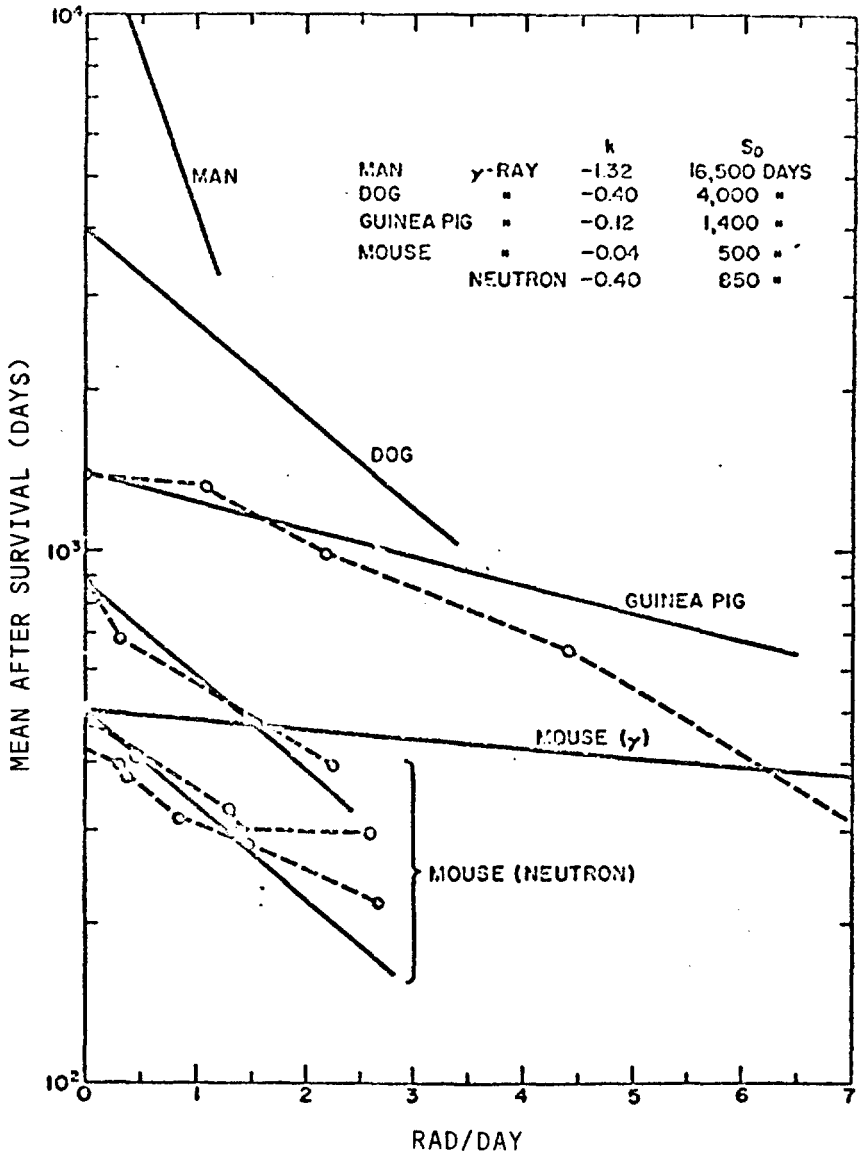


Figure XV.

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

234. 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 depend inversely

on the body size or on the size of the eyeball; the susceptibility to the induction of bone tumours, which might 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 like mortality or life-shortening should be particularly pursued. He further expanded these concepts [M3] and pointed out that in principle life-span-shortening may be considered a meaningful parameter if and only when the spectrum of diseases in different animal populations receiving various doses is found to be 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.

235. 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]. The comparison was carried out in terms of the radiation-specific death-rate [S14, S29] (see also Figure VIII)

$$e = (1/t_r) - (1/t_o) \qquad (29)$$

being the difference of the reciprocals of survival times for the exposed and the control animals. It was found in both species that plotting the log of the radiation-specific death-rate against the log of the dose-rate (rad/day) gave rise to a dose-response with a slope of 2, indicating that the death-rate 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 20 rad/day in the mouse. At lower dose rates in this species the slope change to 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 3.5 rad/day, but this suggestion will have to be proven by appropriate experimentation. The only point available for dogs below 1 rad/day [C16] lies quite close to the curve for the mouse sensitivity of the two species at the level where injury becomes independent of dose-rate.

236. Grahn, Sacher, Lea et al. [G16] returned again to the problem of extrapolation from mouse to man on the assumptions [G6] that: (a) the Gompertz slopes for mouse and man are in the inverse ratio of their susceptibility; (b) the previously-mentioned ratio of 30:1 for mouse : man applies; and

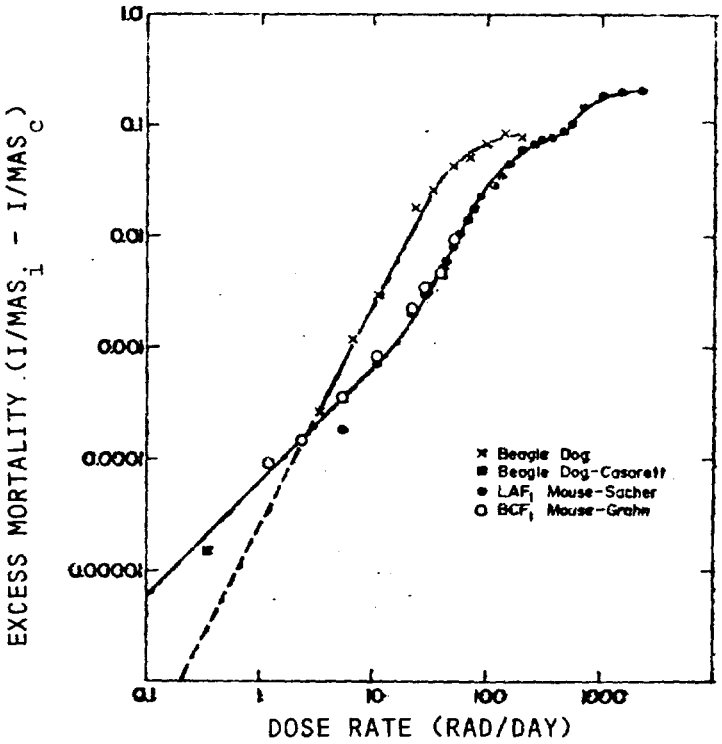


Figure XVI.

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

(c) 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 250 rad (i.e. 5 rem/year 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 years-old man.

237. 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 all species (with the exception of the black rat) had a "death rate to dose-rate" relation where 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 coordinates of the breaking points showed a linear relationship, indiciating that the species variation to chronic irradiation is due to a sin-

gle 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 under paragraphs 54-55, although filling the gap between the two approaches requires clearly much confirmatory work.

2. Intra-species differences

238. 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 (30 - 360 rep exposures) the S mouse were shown to be considerably more resistent than the Ba ones and this pattern of response was similar to that observed after 98 kVp x-irradiation (exposures of 20 - 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.

239. 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 effects. Weighted regression lines of life-shortening on 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 eleven exposure levels between 220 R/day and 6 R/day, 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.

240. A more refined analysis of the above data [G4] allowed the conclusion that all genotypes exhibited a radiation induced life-shortening effect depending on a single common primary injury parameter. For acute single-dose exposures the parameter could be expressed by the number of days of life lost/unit dose, equalling 0.28 days/R. This parameter could be combined with others to give equations predicting the life-shortening for any combination of normal life expectancy, dose, 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 per cent. 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 correlated to each other in that each had a common relationship to the normal life-span.

241. Gowen and Stadler [G11] published also a large series of experiments where 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/day) for 22 hours/day. The design and the analysis of this research, although involving irradiation for the duration-of-life, was centered more on the capacity of irradiation to stop the reproductive functions of these mice, than to shorten their life-span.

242. Other analysis 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/day 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 four 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.

243. 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) four 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. Since these differences correlated well with the weight of the animals, it was suggested that the variation in susceptibility to life-shortening might be at least partially accounted for by genetically-determined differences in the maturation rates of the various genotypes. In fact, during growth the weight of the animals may be an expression of the maturation rate rather than of the general state of health of the animals, as it is during adulthood.

244. After fission neutron irradiation at both high (25 rad/min) or low (1 rad/day) 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]. In another report by Spalding et al. [S22] experiments in progress were reported on RF/J and C57BL/6J mice, whose results will be added to the present document as soon as they will become available.

B. SEX AND BODY WEIGHT

245. 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 separately all these observations would probably be unnecessary since in many cases they are incidental and not particularly relevant to the main physical or biological variable discussed in each specific paper. In the following paragraphs (246-254) only those papers are reviewed where such effects were particularly well substantiated and discussed. Emphasis will be 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

246. In the experiments of Neary, Munson and Mole [N3] (see paragraphs 111-112) the mean survival time of the female animals was significantly greater at the

5 per cent level than that of the males. When only the mean survival times between 30 per cent and 100 per cent mortality were considered in order to exclude early mortality, this sex difference remained evident.

247. 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 together as a function of dose and fitted by linear regressions: the reduction of mean after survival for a given dose increment was about twice in female than in male animals [G10]. Ovarian disfunction 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 per cent in the female and 29 per cent in the male sex. 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.

248. 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/R and for the females 0.81 days/R (all strains pooled). Difference tended to disappear when corrections were introduced for animals dying of leukaemia and of ovarian tumours. 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/100 R. Combination of this primary injury term with other secondary parameters could provide equations predicting the final long-term effect for any combination of normal life expectancy, leukaemia incidence, ovarian tumour incidence and dose [G4].

249. 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/day of 400 kV x rays.

250. In the series by Kohn and Guttman [K6] (see also paragraphs 263-264) 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 250 rad, although the slope of the female dose-effect relationship between 250 and 400 rad 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 might be a manifestation of the increase and fall of ovarian endocrine function. Such a hypothesis would be in accordance with the fact that continuous low-level treatment with estrogen 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.

251. 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, Randolph and Conklin [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.

252. Sex differences in A/J strain in regard to radiation-induced life-shortening (x rays, single exposures, 150 - 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.

253. 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 of 0 - 50 rad was also reported by Storer et al. [S44].

254. In experiments by Moskalev, Petrovich and Streltsova [M22] performed on rats treated with fast neutrons (8.5 - 510 rad) or 500 MeV protons (28 - 1008 rad) 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

255. Body weight as a variable affecting long-term animal survival was investigated by Holland and Mitchell [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 being 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 animal 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, might 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 and Mitchell [H10] would be compatible with the hypothesis that body weight might be a measure of the rate of maturation and it would not be inconceivable under these conditions that body weight could be a parameter better correlated with radiation resistance than chronological age. It could also be further suggested, as the authors do, that some of the strain-specific differences in radiation sensitivity already discussed in paragraphs 238-244 might 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

256. The available data on shortening induced by in utero irradiation will first be examined. According to Nash and Gowen [N9] who evaluated in multifactorial experiments the life-spans of 647 mice irradiated in utero with exposures of 20 - 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 would indicate that after the neonatal period there is little permanent damage of the in utero irradiation.

257. 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 dose levels of 300 - 400 R and in age groups of 40-70 days of age. 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 took them to death in 6 to 7 months for causes which were not clear: signs suggestive of a polyarteritis

were noted but these signs appeared too mild to have contributed to death and were also seen in females that had no effect on life-span. The relatively low susceptibility of fetal mice to life-shortening was unexpected and could not be explained [U12].

258. Friedberg et al. [F8] tested the effect of fast neutrons (15 rad) on mouse embryos in the pronuclear-zigote 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.

259. 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 13-16 per cent. 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.

260. In 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 5 days before birth resulted in a long-term survival not significantly different from controls.

261. 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 would imply a general decrement of fitness as a result of pre-natal exposure.

2. Irradiation during the extra-uterine life

262. 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.

263. Kallman and Kohn [K7], Kohn, Kallman and Berdijs [K1] and Kohn and Guttman [K6, K14] studied the life-shortening response of 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 40 - 45 rad/min with two single doses of 260 or 520 rad and a fractionated dose of 260 x 2 rad 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 reanalysis 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.

264. 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 250 rad. 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 in fact 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) was as such an inadequate explanation for these data because the irradiated animals appeared to age abnormally and usually, but not necessarily, died sooner than controls, the effect depending on age at exposure, sex and dose [K6].

265. 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 400 rad of x rays life-shortening amounted to 40 per cent of con-

trols in the age interval from 1 day to 3 months; it was then gradually decreased to 32, 14 and 7 per cent of controls at 6, 12 and 18 months of age, respectively. Thus, while the acute response to radiation appeared to increase, the life-shortening response decreased as a function of age. This effect cannot be traced to the incidence of leukeamia 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 factor 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 at the young ages than at the older ones.

266. Upton, Kimball, Furth 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 in 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 days) or old (140-150 days) mice within the daily range of doses of 8 to 128 R/day. However, such differences were seen at exposure rates of 2, 4 and 256 R/day, and the old mice were less resistant under these conditions. The greater variability of the radiation response in the young mice and the increased frequency of natural death in the older animals could account for the observed differences.

267. 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 rad 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 per cent 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/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/day 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-shortenining action.

268. Lindop and Rotblat [L12] made a systematic study of the age factor giving small single sublethal exposures of 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 weeks-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 life to live than the same reduction produced at a young age. When the effect was expressed as a precentage 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 per cent and a minimum of 3 per cent reduction of the remaining life-span.

269. 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/100 R. Under hypoxic conditions a considerable reduction of the life-shortening effect was found at all doses, 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.

270. 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]. Irra-

diation 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.

271. 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 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.

272. 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 dose 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 doses 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}.

273. Thirty-four samples of previously-exposed animals were tested at ages ranging from 120 to 960 days with 100 R/day 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 challenge treatment was not actually measuring a pheonomenon 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 morbility in these groups.

274. In addition to presenting data on CBA female mice given acute doses of radiation (450 rad 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 is not independent of 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 refers also to similar unpublished data obtained with protracted exposures to gamma rays and fission neutrons. Such observations might 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 how opposing conclusions might be reached by different analyses of the same experimental data.

275. 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 lenghtening of life of the order of 53 to 65 days.

276. 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-lenghtening in mice irradiated at very old ages. The compatibility of these findings was tested in relation to five different hypothesis. 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 with advancing age the sensitivity to the induction of certain diseases decreases, irrespective of the time required for their expression; or, alternatively that radiation given in old age might have a therapeutic effect on some neoplastic growths in these animals.

277. Ainsworth et al. [A7] examined the problem of age-sensitivity in B6CF1 male mice after single doses of 80 rad of fast neutrons or 269 rad 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 sparing of effect with age 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 would thus be proportionately greater with low- than with high-LET radiation.

278. A very comprehensive experiment is presently in progress at the Los Alamos Scientific Laboratory to study the late effects of whole-body gamma-irradiation on C57BL/6J and RF/J mice. Genetic background, dose, dose-rate and age at irradiation are the main variables under investigation. For what concerns the effect of age, newborn, 2, 6, and 15 months old animals are being treated. A preliminary report covering the influence of genetic background has already been made available [S22] and the next draft of the present report will include other new data as they will appear.

279. The data available for another mammalian species, 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 220 rad 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 littermate controls. The magnitude fo these effects was inversely related to age at exposure from post-infancy up to middle age (10 months). At even older ages there was no discernible change in life-span with respect to control rats. In the opinion of the authors these data would be compatible with Neary's theory [N1] postu-

lating an induction period in life which may be shortened by various treatments and an ensuring 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.

280. 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 might have altered to an unknown extent any more precise estimates of life-shortening.

D. CONCLUSIONS

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

282. It is easy to understand that different species might show a different response in relation to the longevity of each species and to its specific physiologic and pathologic characters. Much less easy is to trace a common parameter or a set of parameters on which one could evaluate the sensitivity of a species in order to construct a susceptibility scale which might facilitate inter-species comparisons or extrapolations. The analysis of survival parameters according to the actuarial model of Gompertz; the calculation of semi-empirical parameters like 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. As to the man, its susceptibility is reported in one case to be higher (perhaps by a factor of two) and in another case to be similar to that of 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 might be included could 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.

283. 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. No 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 more thouroughly analyzed) 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 for acute single doses the number of days lost per unit exposure equals 0.28 days/R. On this basic dose-response relationship all the factors mentioned above (in addition to other factors for sex and age) would superimpose to give the compounded final value of effect applying to each particular situation.

284. In few of the data reported either no difference or small differences in sensitivity to life-shortening were reported between male and female animals:

Table 3

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

Irradiation condition	Approximate sensitivity: more sensitive		more resistant	Refs.
Chronic x-irradiation	monkey	rat, dog and mouse about equal	rabbit	[B11]
Acute x- or γ-irradiation		rat and mouse about equal		[U 1]
Chronic γ-irradiation	man	guinea-pig, rat, dog and mouse about equal		[G 1] [S23]
Chronic γ-irradiation	guinea-pig	man, dog and mouse about equal		[G 6]
Chronic γ-irradiation		dog and mouse about equal		[N 7]
Chronic γ-irradiation	goat	mouse		[H 9]

they refer to the SAS/4 strain [L1, L2], to the CFW strain [M14], to the RF/Un strain [U7] and to the B6CF1 strain [A7]. The data in the LAF1 mouse are contradictory since in the series by Upton et al. [U5] the female appeared to be more sensitive, in that by Sacher and Grahn [S4] the females were more resistant at survival times of 130 days or more. In the case of the CAF1 mouse [K6] age at irradiation and sex appeared to interact, owing probably to changes in the endocrine balance, so that in early life the female and in old age the male appeared as the most sensitive sex. In all other cases comprising the following inbred strains: CBA, Balb/c, A/Jax, A/He, C3CF1, B6RFMF1, C3CB6RFM; invariably a higher sensitivity of the female animals was observed. The sensitivity factors reported were between 1.5 and 4. Ovarian disfunction induced by irradiation and the incidence of ovarian tumours were 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. Only in the case of the CAF1 mouse [K6] the ovarian tumours were reported to be uncorrelated with the higher sensitivity of the female and in that instance it appeared that irradiation in late life did actually show a higher sensitivity of the males. The observation therefore does not contradict the conclusion to be

drawn from the vast majority of the data that, within strain, sex has a constant effect in the sense that female animals are more sensitive to radiation-induced life-shortening, which effect is mostly manifested by an increased incidence of tumours of the female genital tract.

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

286. As to the effect of age, after allowing for other factors influencing the reduction in longevity (genetic background and sex) most data agree in showing 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.

287. Regarding the effect of extra-uterine age, the data are rather numerous but only limited to the mouse and the rat. In both these species invariably irradiation late in life 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.

288. Among the many hypotheses considered it appears that, at least under some conditions, the effect of age might be attributed to a decreased susceptibility of certain pathological conditions. Another possibility is that radiation in old age may have some therapeutic effect on some (presumably neoplastic) conditions already under development at irradiation. Caution should be used in the analysis of data where animals are started on irradiation courses at variable initial ages since different analytical appraoches to the data, in additio to implying different hypotheses of action, may lead to variable conclusions as to effect of age on the animals radiosensitivity.

289. In two large sets of experiments [S19, S20] a number of texts ($LD_{50/30}$, survival time after daily exposures to 100 R, recovery rate after split doses) were performed on RF or BDF1 mice at various times following a conditioning dose of radiation. The experiments showed that each test measured the damaged inflicted to different cellular systems and that each system aged according to a different rate. The data showed also that normal animals exhibited a sharp decline of their radiation resistance in old age. Previous irradiation induced an increased susceptibility and an earlier onset of the decline, which was interpreted as the expression of the earlier onset of morbidity in the irradiated animals.

III. MODIFYING EFFECTS

A. PHYSICAL TREATMENTS

290. Among the treatments that modify the life-shortening response to irradiation those of a physical, chemical or pharmacological, and biological nature will in turn be reviewed. It should be realized that information available on these subjects is very heterogeneous and not suitable for generalized conclusions. Among the physical treatments, those referring to irradiation given in combination with low- or high-temperature treatments should be included.

291. Carlson et al. [C21] exposed male Sprague-Dawley rats to 20°C and 5°C to ^{60}Co gamma-irradiation for 8 hours/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/24 hour-day and the exposed ones 895-931 mR/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 per cent longer than their respective non-irradiated controls, the half-lives observed being: 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.

292. 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 50 rad/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 0.093 day/rad.

293. 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/day during the year that irradiation lasted 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/day. The age at which 50 per cent 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/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, since the different species or environmental conditions might have been responsible for the negative observations of Bustad.

294. Paradoxical effects induced by relatively low doses of radiation which increased, rather than decreased, the expectation of life are not uncommon in the papers reviewed. In addition to the experiments just cited on the rat [C21, C22], observations on mice by Lorenz and co-workers [L6] are to be mentioned. Here, mice exposed throughout life to 0.11 R of gamma rays daily had an increased after-survival with respect to controls. This increase was not statistically significant, but was confirmed in a subsequent test. There were differences between groups concerning the air conditioning and temperature of the animal quarters which made the data uncertain. No reduction of the mean after-survival of three different strains of mice exposed to 5 R/day and to cumulative exposures of about 2500 R was observed by Sacher and Grahn (cited by Sacher and Trucco [S32]. Yuhas [Y3] also reported life-span lengthening when old animals (15, 18 and 24 months old) were exposed to 10 fractions of 140 R of x rays given over 12 days, wheras the same amount of radiation administered to 4 or 9 months old animals produced some life-shortening. It should also be recalled that life-lengthening in animals irradiated in their old age is by no means a strange finding [K6] (see paragraphs 262-280).

295. 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 two authors proposed [S32] a modification of the theory that makes it possible to account for paradoxical observations of the type described. Radiation (particularly at low doses) would induce 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 would also be decreased. In essence, the decreased variability among the exposed than among the control animals would be the main effect of the irradiation and the improved survival at relatively low doses would result from it as an occasional consequence.

296. In experiment 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 $0^{\circ}C$. Reduced longevity was among the effects (retarded growth, cataract, fur graying tumours) seen at long-term in the whole-body-irradiated (but not in the adrenal-irradiated) rats. It amounted to about 20 per cent 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 per se 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].

297. 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. [01] irradiated C57BL/10 mice on the brain with 500 rad 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.

298. 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.

B. PHYSICO-CHEMICAL AND PHARMACOLOGICAL TREATMENTS

1. Anaesthesia, oxygen and hypothermia

299. The effects of hypoxia induced by various treatments will first be examined. Lindop and Rotblatt [L12] showed some protective action of anaesthesia (Nembutal, 60 mg/kg, i.p.) against early and late death. Protection appeared to decrease with dose-rate in the interval 480-162 000 rad/min. 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 Rotblatt [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, 40 000 rad/min) they had a considerably reduced life-shortening effect, by comparison with 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.

300. Hypoxic hypothermia was also tested by Hornsey [H12] in respect to the possible modification induced by this treatment on life-span. While hypothermia induced at the time or irradiation offered considerable protection 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 greated 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

301. On the subject of chemical radioprotection Maisin et al. [M33] reported that mercaptoethylamine [MEA] (10 mg/rad, 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/day) and 2-aminoethylthiosulfuric acid (1000 mg/kg/day) 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/hour. Mortality data were indistinguisable 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 efffects at drug levels accepted by the mice [A8].

302. Cosgrove et al. [C23] tested on (101xC3H)F1 female mice following a wide range of x-ray exposures (300 - 1800 R) the effect of the radioprotective drugs aminoethylthiouronium (AET) with or without parallel treatment with isologous bone marrow infusion. The 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 graying 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 per cent).

303. 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 graying of the fur.

304. An attempt to maximizing 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 syngeic bone marrow and 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. Graying 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.

305. 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/day for 24 days or at 4 mg/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 depending 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; also, 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.

306. Yuhas [Y1] reported that the radioprotective agent WR-2721 [S - 2-(3-amino propylamino) ethylphosphorothioic 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.

307. Storer [S30] investigated on A/J and C57BL/6J male and female mice the effect of four radioprotectors administered i.p. 15' prior to irradiation. They were: paraaminopropiophenone (PAPP) at 40 mg/kg, mercapto-ethylamine (MEA) at 200 mg/kg, amynoethylthyouronium (AET) at 200 mg/kg and 5-hydroxytryptamine (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.

308. 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.

309. 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 essentially that both the irradiated and the irradiated-AET-protected mice die when an accumulated exposure of about 2000 R is reached, whereas mice protected with the above-mentioned mixture may sustain exposures up to 4000 R, independently of the size and frequency of the radiation dose fractions, making due allowance for early mortality.

310. Another 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, prior to irradiation with 400 R (250 kV 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 could be calculated for long-term survival, which 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

311. Syngeneic marrow transplantation was not very effective in protecting against reduction of longevity in Cosgrove's et al. [C23] experiments. This treatment did inhibit 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.

312. Experiments on the late somatic effects in syngeneic radiation chimaeras were performed by Covelli et al. [C13] on (C57BLxC3H)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 900 rad of x rays were not influenced by the number of cells injected (in the range of $8\ 10^4$ - $1\ 10^7$ cells/mouse). Irradiation with 900 rad of 250 kVp x rays followed by bone marrow treatment was very effective in decreasing the occurrence of reticulum cell sarcoma in long-term survivors but led to an enhancement of tumour incidenc (particularly in the malignant tumours) 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

313. In order to investigate on the frequently reported finding of a greater sensitivity of the female animals of life-shortening (see paragraphs 246-254) Holland et al. [H13] investigated the effect of ovariectomy on RFM mice. Castration had little effect on overall mortality rate, both alone or in com-

bination with irradiation (300 R). It had, on the contrary, significant effects on specific spontaneous or radiation-induced diseases, since 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 their increased incidences 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/day and found that females had a greater sensitivity than males, judging on survival time. However, when the females were ovariectomized their survival came nearer, although still lower, to that of the males. Thus, acute survival might be influenced by ovariectomy, as opposed to long-term survival.

D. PARTIAL-BODY IRRADIATION

1. Mouse

314. Although selective partial-body exposure might be in principle a good methodology to study the pathogenesis of the individual causes of death responsible for life-span-shortening, data on this subject are comparatively few. In the mouse Kallman and Kohn [K7] reported on CAF1 females exposed acutely 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 95.0g). 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.

315. 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 100, 200 or 400 rad, shielded animals 200, 400 or 800 rad 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.

316. 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.

317. 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, 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.

318. 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.

319. In other experiments conducted on ddN female mice (10 weeks of age) by the same group of workers [S43] the effects of 600 R given whole-body or of 800 R given only to the head, the trunk or the lower body were compared. The mean survival times and per cent life-span-shortening observed in the various groups were as follows: control: 69.2 weeks; whole-body exposure: 43.0 weeks 6 per cent/100 R; exposure of the trunk: 59.7 weeks, 2 per cent/100 R; lower body exposure: 62.7 weeks, 1 per cent/100 R; head exposure: 66.1 weeks. The life-shortening effects observed in the irradiated groups were all significant, except for the group with head exposure. 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 arly 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

320. 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 per cent; 850 - 1000 R to the abdomen alone reduced the life-span by 18-34 per cent. 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 oropharingeal 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.

321. 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 were 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].

322. 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 exlcusive of the gastrointestinal tract (which was surgically exteriorized and shielded) to 1300, 3500 or 5000 rad. A dose of 1300 rad to the intact abdomen resulted in 100 per cent 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 3500 or 5000 rad 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.

323. Carsten and Innes [C26] working on female rats of the CFN strain irradiated with 250 kVp x rays showed that 650 rad given to the lower body or 1300 rad 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 per cent 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.

3. Chinese hamster

324. 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 ascertained only of the ovary. Progressive capillary glomerulosclerosis was observed as in all animals examined and this lesion was accelerated by irradiation.

C. CONCLUSIONS

325. It appears, in conclusion, that keeping the animals under environmental temperature conditions which are thought to be suboptimal may decrease, rather than enhance, the life-shortening effect of a radiation treatment. Also, 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 unconventional 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 induces invariably some protection against the life-shortening action or radiation, but the extent of this protection is probably less than that produced by the same treatments against acute radiation effects.

326. 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.

327. 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 is not a factor to be considered among the causes of natural aging or of radiation-induced life-span-shortening.

328. 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 hundreds of rad or higher are given to sections of the body are clearly unsuitable for studies on the pathogenesis of life-shortening, because under these conditions localized structive 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 factor that in all strains or rodent tested and at doses of a few hundred rad 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 EXPERIENCE

A. INTRODUCTION

329. In the present chapter the evidence about the existance of a non-specific life-shortening effect in the human species is discussed. The evidence available comes from three different sources: groups of persons (radiologists, radiology technicians, physicians) exposed occupationally during the course of their professional life; patients who have undergone radiation treatments for different pathological conditions, but 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 fall-out accident in 1954. The data will be discussed separately, since the modalities 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.

330. The studies performed on humans are subject to a number of limitations, mostly related to the lack of any control over the variables to be examined. 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 in this respect. Often the time elapsed between irradiation and the epidemiological survey is insufficient to reveal effects which take a very long time to develop. This requires frequent updating to keep the time-course of the phenomena under control. 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 to be expected in a normal population.

331. 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 between the control and the test sample add variability to the data and uncertainty to the conclusions.

332. 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 well 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. Concerning the radiation dose records, they are mostly uncertain or not known at all, as for occupational exposures where presumptive evidence must often be used instead of more precise statements of dose. In these cases no analyses of dose-response relationships are possible, but only contrasts of broad categories of exposed versus unexposed groups. At the other extreme, doses are very well known for radiotherapy patients. Exposures in Hiroshima and Nagasaki have also posed dosimetric problems but the newest results on the T65 doses and shielding conditions, together with clinical evidence about the presence of early symptoms of irradiation, make the assessments fairly reliable [02].

333. 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.

B. DATA FROM OCCUPATIONALLY EXPOSED PEOPLE

334. 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 white males 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 per cent) were classified as full-time specialists. During the five years covered by the study there were 12.419 doctors dead in the age group 35-47 and 2.029 of these (or 16.3 per cent) were medical specialists. The mortality ratio from all causes of specialists was 78 per cent, taking the death rate of all physicians to be 100 per cent. 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.

335. 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 white males having reached 25 years of age was 65.6 years. Radiologists died on the average 5.2 years earlier than other non-radiologist physicians, who died at 65.7 years. Also, the non-radiologists known to be exposed ro radiation did show some life-shortening (they lived on the average 63.7 years) although less than that of non-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.

336. 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 per cent of the deaths from specified causes occurring among non-irradiated physicians were due to leukaemia, against a 2.33 per cent among other specialists having had some contact with

radiation and 3.65 per cent 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 factor could be radiation.

337. 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.

338. 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.

339. 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 in fact have a slightly longer life-span than other non-exposed doctors.

340. 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 very high, whereas the average exposure of those registered as specialists after that date had been within the limits recommended.

341. 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.

342. Regarding expectation of life, observed deaths were 463, less 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. The finding should not be interpreted to mean that radiologists have an increased life expectancy because of their profession: actually, artifacts due to the possible absence of particularly unhealthy individuals in the group considered, or to insufficient corrections for social class and occupations, or to inadequacies of the standards chosen for comparison were discussed as possible sources of the slight deficiency of deaths due to causes other than cancer.

343. As to cancer mortality, a significant excess was found among radiologists entering practice before 1921, the excess being confirmed 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.

344. Seltser and Sartwell [S38] returned again to the problem of mortality of American radiologists, 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 (ophtalmologists and otorinolaringologists) rate of exposure to radiation. The mortality experience in these groups conformed to the 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.

345. 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.

346. 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 birthplace: 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.

347. Seltser and Sartwell commented on the fact that the reduced survivial (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 conclusions) 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.

348. 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 Britain than in the United States; the fact that in Britain 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 themselves; 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 Britain [V7]. It should be pointed out, however, that both the British 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.

349. 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 days/R.

350. New data on the effects of ionizing radiation or radiologists were reported in 1966 by Warren and Lombard [W4]. The study comprised 5.982 certified radiologists which were compared with all United States physicians in 1949-1951, with the United States male population aged over 25 years in 1950 and with a group of 3.176 Massachussets 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 after 40 years of age, but more common before 40 in the general population. In recent years the excessive incidence of leukaemia in radiologists decreased. From the above findings Warren and Lombard concluded that radiation protection measures had been effective in providing adequate safeguards for the radiology specialists.

351. Miller and Jablon [M27] searched for late radiation effects among men trained as radiology technicians 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 that 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 radiologists: 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.

352. 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 anemia and these numbers were significantly higher than would be expected to occur among the population at large. Leukaemia was found in 5 cases, in 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.

353. 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 Ophtalmology and Otolaringology. 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 per cent of the decedents. The persons under comparison were about 30000 among all Societies for a total number of deaths of about 6500.

354. 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. Mortality from all causes depended on the decade of entry. During 1920-1939 death rates of radiologists were higher than those of any other specialty 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 tumours 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.

355. 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 1920-939 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, since American radiologists are the only human population where life-shortening effects of radiation, over and above those related to an excess tumour induction, has 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.

356. Very 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 American white females. An increased death rate was observed in comparison with the expected rate in the exposed population (240 cases versus 188.5 expected).

357. Bone cancer (22 causes 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 101) 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 only: subjects with a body burden lower than 50 μCi or those with a burden of 50 or more μCi. 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.

358. Another paper by Stehney et al. [S39] is more specifically concerned with the possible presence in this group of women of a life-shortening effect ascribable to causes other than bone sarcoma and head carcinoma. The study was performed by the life table method using age- and time-specific mortality rates for United States white females for the comparisons. There were 1235 women exposed before 1930: they were on average 20 years old at employment and about 44 per cent 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 per cent 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 cleaned from 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 contemporary white females

362. 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 U.S.A. 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 per cent 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 in stage I and stages II and III, respectively. There was also a grouping according to the regional dose delivered into low (2 - 22 Mgm rad), middle (23 - 31 Mgm rad) or high doses (32 - 54 Mgm rad) which allowed survival to be evaluated as a function of dose. It was also reported that the incidence of leukaemia appeared in these patients to be lower than among patients treated for ankylosing spondilitis or for metropathia hemorragica.

363. Indirect information of a negative nature may be derived from a study of nearly 3000 children irradiated in infrancy 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 is not surprising in view of the small portion of the body irradiated.

364. In 1965 Court-Brown and Doll [C28] reported on a sample of 14.554 persons (12.161 mean and 2.393 women) treated for ankylosing spondylitis at various radiotherapy centers in Great Britain and Northern Ireland during the years 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 and adequate follow-up information in 98 per cent of the cases were available. The number of expected deaths in these patients if they had suffered only 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.

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.

C. DATA FROM RADIOTHERAPY PATIENTS

359. Doses administered to patients surviving radiotherapy are rather well known and may be taken as the independent variable against which any possible life-shortening could 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.

360. Studies reported on patients are few and all of them negative, in that none show life-shortening attributable to radiotherapy. Sørensen [S40] studied patients treated for cancer of the uterine cervix in 1922-1929 in Copenhagen, surviving for at least 5 years after treatment and having been followed for the 20 years thereafter. Out of 798 eligible patients, 184 met the above requirements: they were 49.1 years old at the time of treatment and the average radium treatment received was about 6500 mg-hours, equivalent to 4.4 Mgm rad. 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 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 per se had decreased the survival rate of the patients without recurrence.

361. 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 fro 10 or more years after treatment. Radium treatment alone (6 Mgm rad) or radium in conjunction with x rays (37 Mgm rad) 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, Bailar and Zippin [K20] who had access to the original records: their conclusion was the same.

365. 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 anemia, 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 hand a prevalence of 1.3. This latter increase regarded all conditions examined and the total expierience was sufficiently large for it to be highly significant.

366. When mortality was examined as a function of the post-irradiation period, all causes of death other than cancer and aplastic anemia were in a constant relationship to the expected mortality. In contrast, for leukaemia and aplastic anemia mortality increased within the first 5 years of observation and then fell off; deaths for cancers of heavily-irradiated sites were increased approximately two-fold at six or more years and up to 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.

367. 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 resistence 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.

D. DATA FROM A-BOMB SURVIVORS

368. The effect of radiation on aging and life-shortening in a Marshallese 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 opafication 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.

369. The situation for the Marshallese series is completely at variance with that of the A-bomb survivors in Japan, which is providing information on long-term radiation effects, including life-shortening, that will eventually form the most exhaustive source of data in the human species. The earliest reports of this 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].

370. The report covering the period up to 1966 [B22] was based on the T-65 dose estimates and included 16.356 deaths over 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.

371. 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. This latter disease in the data reported was higher by an order of magnitude than any other cause of death. The authors could not conclude with certainty for 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.

372. 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 [02], 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.

373. 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 increases, but difficulties with the diagnosis made this finding uncertain. All other non-neoplastic conditions were apparently unaffected.

374. 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.

375. The latest available analysis 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

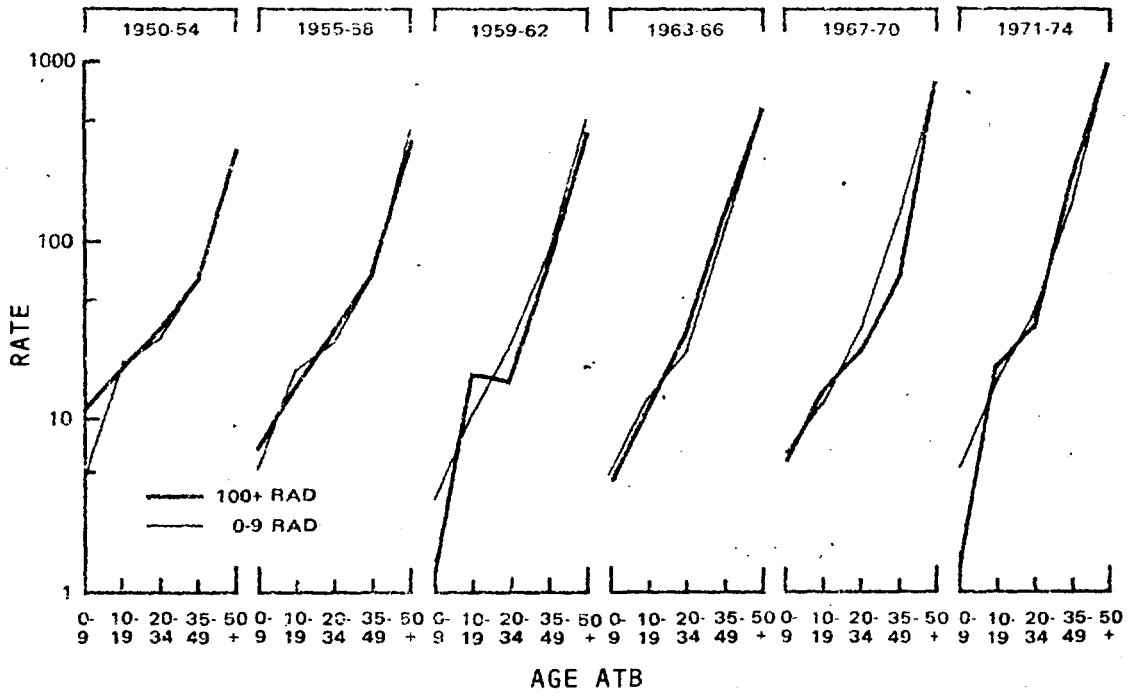


Figure XVII.

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 100+ rad (heavy line) or 0-9 rad (light line). The rates were adjusted for city and sex within time periods. Data from Beebe, Kato and Land [B24].

death rates for all non-tumorous causes (taken at 4 years intervals and adjusted for city and sex within each time period) separately calculated for the group receiving 0-9 rad and that exposed to 100+ rad were superimposable (see Figure XVII). This finding, as repeatedly pointed out, cannot be reconciled with the hypothesis that radiation may accelerate natural aging, but rather shows that any life-shortening present in the sample is associated with cancer induction.

376. The contrast between the Japanese data and the data on occupational exposure of American radiologists 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 et al. [M28, M29] (see paragraphs 353-355). 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 exposure between the Japanese survivors and in the United States radiologists. 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 with known T-65 doses.

377. 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; but 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, for 55 of 203 children no information was available and the sample size is yet too small and too young for any conclusion about a possible excess death from non-specific causes.

D. CONCLUSIONS

378. 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 choise of controls.

379. 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. There is no way to derive from the data, since 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.

380. True shortening of life has only been seen in the series from the United States. Reasons to justify the absence of life-shortening among British radiologists 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 rations 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 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].

381. In spite of the small samples 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.

382. 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 induction were often seen [K17, K18, M27, K19]; in one case life-shortening was reported [K18], but not in others.

that applying to the surveys on occupationally-exposed people and much less than that carried by the studies on A-bomb survivors.

387. Induction of leukaemia and of a variety of tumours has been throughout the years the experience of the Japanese survivors of the A-bombs. These pathological conditions have produced some shortening of life, whose magnitude can be accounted for entirely on their basis. The absence of non-specific life-shortening among A-bomb victims is undisputable not only because this conclusion has been confirmed during more than thirty years, but because the sample size (and therefore the accuracy of the finding) leaves little margin for other conclusions.

388. The negativity of this survey is remarkable for a number of reasons. Firstly, the quality of the radiaton received: at least in the case of Hiroshima, this had a substantial neutron component and therefore, in accordance with the evidence discussed under paragraphs 192-213, it could have been expected to be considerably more effective. Secondly, 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. Thirdly, the absolute amount of radiation absorbed over the whole body (or the order of 100 rad or more) which 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.

389. In conclusion, the evidence concerning a non-specific radiation-induced life-shortening effect in man has been shortly reviewed in the preceding paragraphs. This review has produced essentially negative answers, except for the old American radiologists. 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. What is more, the data on the American radiologists are also in sharp contrast with the much larger and more reliable experience on the A-bomb

383. What may safely be concluded from the data on occupationally-exposed people is that of neoplastic diseases, particularly leukaemia and skin cancer, are real effects, particularly in old radiologists. Some life-span reduction may also have been present in old radiologists who were presumably exposed to very 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 lower than 1 R/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 an appreciable shortening of life in the human species.

384. In principle, radiotherapy patients have a number of favourable characteristics of 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 paragraphs 314-324).

385. The experience on the ankylosing spondylitis patients [C28] does show at a first sight a small but significant prevalence of unspecific mortality. However, a more 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 and thus the survey seems inadequate to validate the existence of a radiation-induced non-specific shortening of life.

386. 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

survivors where any life-shortening action observed over more than 30 years can reasonably and entirely be accounted for by the induction of neoplastic conditions. And the differences of exposure between the United States radiologists and the A-bomb survivors were such that, on the basis of general radiobiological knowledge, non-specific life-shortening would rather have been expected from the latter than from the former series.

390. 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.

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