IONIZING RADIATION: SOURCES AND BIOLOGICAL EFFECTS

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ANNEX J

Non-stochastic effects of irradiation

CONTENTS

Introduction

1. The main purpose of this Annex is to review damage to normal tissues caused by ionizing radiation. Only the so-called "non-stochastic" effects are considered, i.e., those resulting from changes taking place in large numbers of cells. In its publication 26 the ICRP suggests that "non-stochastic effects are those for which the severity of an effect varies with the dose and for which a threshold may therefore occur" [I1]. In contrast, "stochastic" effects are those for which the probability (rather than the severity) of an effect occurring is a function of dose. In this Annex effects such as the induction of cancer, hereditary defects, teratogenesis and life shortening are specifically excluded.

2. This Annex will therefore review radiation effects on normal tissues, in animals and in man, in order to determine the threshold dose levels for non-stochastic effects. It should be pointed out immediately that the threshold will depend entirely on the end-point adopted and on the sensitivity of the measuring technique. For example, functional changes in some tissues may only be detected after several tens of Gy, whereas structural abnormalities may be detected after much smaller doses by using an electron microscope. The concept of threshold dose presents difficulties throughout the discussion. Consideration is given to radiation quality, dose rate, fractionation and the volume of tissue irradiated. In general, permanent rather than transient biochemical changes have been emphasized.

3. Another important parameter is the time at which a radiation response occurs. In gut, microscopic changes can easily be detected using histological techniques after hours or a few days, in skin after a week and in liver the reaction may take months or years to develop. These differences result in part from the different cellular proliferation characteristics of the cells involved, to which some attention is paid. However, other basic factors (e.g., genetic, hormonal, nervous) are certainly involved in the time of onset of late radiation injury.

4. The precise way in which ionizing radiation causes cells to lose their reproductive integrity is not understood. There is, however, good evidence pointing to the most sensitive sites being in the region of the cell nucleus rather than in the cytoplasm. A considerable body of circumstantial evidence suggests that some part of the chromosome is the primary target [H6], especially the DNA molecule [H64], but there is also evidence implying that effects on membranes are involved in the primary damage [A26]. The two possibilities are not mutually exclusive. However, detailed discussion of fundamental radiobiology is beyond the scope of this report.

5. The topic of this Annex is extremely wide. By no means have all aspects been considered, but an attempt is made to be interpretive rather than to simply compile available data. The basic premise is that the non-stochastic response of a tissue depends on the level of cell killing (which is in itself a stochastic process). Therefore the first chapter is devoted to basic concepts of cell survival, to the factors influencing tissue response to fractionation or continuous irradiation and to the empirical formulae proposed to estimate the doses producing the same level of injury under different treatment schedules. The second chapter is a discussion of radiation effects on individual animal tissues. The third is a review of data obtained on humans, mostly derived from radiotherapy results but including also a small number of radiation accident reports. The effects of radiation quality are discussed in chapter IV with most emphasis on fast neutrons. A review of the effects of radionuclides introduced into the body is given in chapter V. Chapter VI is a brief review of studies of radiation damage to the vascular system.

6. Experiments and clinical findings have resulted from irradiations with photons of differing energies. Sometimes these have been specified in the original reports, but often they have not. Also, doses in early reports have been quoted in roentgen (R). However, differences in effects due to different photon energies are considered to be negligible. Moreover, in view of the uncertainties in estimating the dose in most of the early work, it is reasonable to assume that 1 Gy is not significantly different from 100 R.

I. BASIC CONCEPTS OF RADIATION EFFECTS ON CELLS AND TISSUES

A. CHARACTERISTICS OF CELL SURVIVAL

7. The relationship between the dose of radiation and the reduction in cell surviving fraction is a cell survival curve. Knowledge of survival curves is basic to an understanding of "non-stochastic" effects, and their shape is an indication of how cells will respond to many small dose fractions or to continuous exposures. Cell survival is defined as the capacity of the cell to undergo sustained proliferation, a survivor being able to produce a "clone" or a "colony". Cell survival may be measured in vivo or in vitro.

8. The effects of radiation are dependent on the stage of a cell in its mitotic cycle. Basically there is a specific period, designated S, during which DNA is synthesized (in proliferating cells). There is a period between mitosis M and S, which is known as G_1; the interval between S and the next mitosis is known as G_2. Almost the first observable effect of radiation on cells both in vivo and in vitro is that they are temporarily prevented from entering mitosis. This is often referred to as the G_2 block or mitotic delay [E1]. For cells in vitro 10 Gy seems to produce a delay of approximately one cell cycle in duration. Denekamp [D1] analysed both in situ and in vitro results covering a wide range of cycle times and found a similar result for cells in situ, namely, that in general 10–15 Gy causes a delay of approximately 1 cell cycle duration.

9. After irradiation, cell death for most cell types occurs when the cell attempts to divide. Death does not always occur at the first division. After low doses of radiation cells may complete 1, 2 or even 3 divisions before failing. In some cases, however, cells die in interphase, the most notable example being the lymphocyte. Schematic examples of survival curves for mammalian cells irradiated with low-LET radiation are shown in Figure I. No systematic differences have been demonstrated between such curves derived from animal or from human cells. For low-LET radiations, such as x rays, gamma rays or electrons, survival curves may be continuously bending, i.e., effectiveness of the radiation

may increase with increasing dose, or they may become exponential at large doses, with slope defined as $-\frac{1}{D_o}$. D_o (the mean inactivation dose) is the dose required to reduce the surviving fraction by a factor of e on an exponential curve.

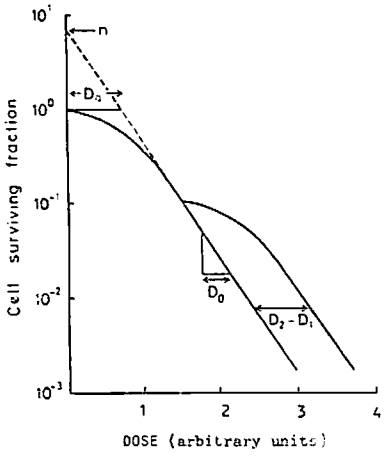

Figure I. Diagrammatic representation of a single- and split-dose cell survival curve. The "shoulder" region is characterized by the extrapolation number n or the quasi-threshold dose D_q. D_o is the dose to reduce survival to 37% on the exponential part of the curve. The parameters are related by: $\log_e n = D_q/D_o$

10. At lower doses the radiation is less effective and there is a shoulder region. Exponential curves may be extrapolated to determine n or D_q, as shown in Figure I. The sizes of these parameters indicate the capacity of the cells to accumulate sublethal damage [E2, F1]. With low-LET radiation and for cells in vitro n normally varies from 1 to 20 for the majority of cell types. With high-LET radiation, (e.g., neutron or alpha particles) n and D_q are both smaller, indicating less capacity for accumulation of sublethal damage. D_o is also generally less for high-LET radiation. Sublethal damage can normally be repaired in a few hours. This is of great importance in interpreting dose fractionation and low dose rate effects.

11. Survival curves have been measured for cells in situ as well as in vitro. The former has been achieved for cells of bone marrow, small intestine, stomach, colon, testis, cartilage, skin, as well as for a range of experimental tumours. In general the values of n and D_q are greater for tissues in vivo than for cells in vitro. This is also true when D_2-D_1 is measured, where D_1 and D_2 are the single dose and dose in two fractions, respectively, to produce the same level of tissue damage. Since D_2-D_1 is analogous to D_q from the cell survival curve, this means that the cells in organized tissue have a greater capacity to recover from sublethal damage than cells in vitro.

12. An example of evidence that the gross tissue response reflects that of its constituent cells is obtained from a comparison of the LD_{50} in 4 days (gut damage [Q1]) with cell survival by counting the number of surviving crypts [W1]. It was seen that for a variety of different types of treatment, different dose rate and LET, the reduction in the proportion of surviving cells resulting in 50% death of the mice was the same for all treatments [H1].

13. Various models for describing the shapes of cell survival curves have been proposed [I4, S33]. The simplest is the single exponential model, fitted by

$$S(D) = e^{-kD}$$

where S(D) is the surviving fraction after dose D, and

$$k = 1/D_o$$

A population of cells may consist of 2 or more subpopulations, each following an exponential curve. In this case

$$S(D) = a\,e^{-k_aD} + b\,e^{-k_bD} + \ldots$$

where a, b, etc. are fractions of the total population. This model describes a curve with a series of exponential slopes, the initial slope depending on the most sensitive cells and their proportions [S76]. The multitarget single-hit model is described by

$$S(D) = 1 - (1 - e^{-k_nD})^n$$

where k_n is the sensitivity of each of n targets, each of which must be hit to kill a cell. This curve has zero initial slope, a finding which is not supported by the majority of recent data. A model incorporating a finite initial slope is the modified multi-target single-hit curve, is given by

$$S(D) = e^{-k_1D}[1 - (1 - e^{-k_nD})^n]$$

where $dS/dD = -k_1$ for $D \to 0$. Thus the initial slope is given by $-k_1$. The final slope of the curve is given by $-k_o$, where $k_o = k_1 + k_n$. This model describes a curve with a finite initial slope, consistent with many experimental findings. A continuously bending survival curve, which has often been adequately used to describe survival curve data is:

$$S(D) = \exp - (\alpha D + \beta D^2)$$

where α and β are constants. This model also has a finite initial slope but continues to bend, the rate of the change in slope depending on the values of α and β.

14. It is possible to construct curves with almost any shape, but is normally not possible to distinguish experimentally between the more realistic models. Nevertheless knowledge of cell survival characteristics at low dose levels is extremely important in order to extrapolate data from single doses to many dose fractions or to continuous irradiation.

15. Cell sensitivity to ionizing radiation depends on the phase of the cell generation cycle. This phenomenon has been widely investigated, mainly in vitro. In general, cells exhibit a bimodal response during the cell cycle, in which a peak of resistance appears early in G_1 and another late in S. The greatest sensitivity occurs at mitosis (and G_2) and at the G_1-S border. In cell lines with a short G_1 the peak in G_1 may not be evident, but the general features are the same [S1]. The response of a normal synchronous cell population will thus reflect the different responses of cells in different stages of sensitivity.

16. There are, however, variations from one cell line to another [S1]. Cell cycle times vary from a few hours (e.g., intestinal mucosa) to many weeks or even months in some tissues (e.g., lung or kidney). These very long

cycle times are due to extended G_1 periods, the other phases differing less markedly from those in more rapidly dividing tissues. With high-LET radiations, e.g., fast neutrons, the fluctuation in sensitivity through the cell cycle is qualitatively similar to that for photons. However, the extent of the fluctuations is much less with high-LET radiation [W2, M1].

B. RESPONSE TO FRACTIONATED IRRADIATION

17. When radiation is split into two or more dose fractions the total dose required to produce a given level of damage is altered. This is due to a number of factors [W3]: repair of sublethal damage; repair of potentially lethal damage; other slower repair processes; repopulation of surviving cells; reassortment of cells in their mitotic cycle; and reoxygenation of hypoxic cells. These factors have been shown to occur to a different extent in different tissues, so that the effect of dose fractionation is tissue dependent.

1. Repair of sublethal damage

18. Cells are capable of absorbing energy which results in sublethal damage and only with increasing dose is this converted to lethal damage. Thus survival curves may be exponential at large dose levels but usually have a pronounced shoulder in the low dose region. This region of relatively inefficient killing is due to the accumulation of sublethal damage. Sublethal injury may be repaired in a few hours and repair is manifest by a return of the shoulder region (D_2-D_1 or D_q) for the second treatment (Figure 1 [E2]). Thus, repair of sublethal damage is the operational definition of repair between two radiation doses. Accumulation of and recovery from sublethal damage are smaller for cells in vitro than for the cells of many tissues in situ, possibly owing to the greater intercellular contact between cells in solid tissues. When cells have been grown as multicell spheroids in which they are in contact through desmosome-like junctions, the capacity of those cells to accumulate and repair sublethal damage is also markedly increased [D2]. The extent of repair of sublethal damage is very large in some tissues, e.g., intestine, skin, lung but much less in others, e.g., the haemopoietic system. It may be measured as the difference between the single dose or two fractions which produce the same level of injury. i.e., D_2-D_1. Values for some tissues are given in Table 1.

19. As the number of fractions is increased and the dose per fraction decreased, the proportion of dose that is effective in killing cells, relative to that which is used in accumulating sublethal damage is decreased. For very small doses per fraction, only about one-third of the dose is effective in some tissues. This means that in these tissues, to produce the same reaction in an extended fractionation regime as in a single treatment, three times more dose must be given.

2. Repair of potentially lethal damage

20. The technique by which cells are cultured after irradiation will affect the radiation response. It is possible to decrease radiation sensitivity by various means, including delaying plating [P3, H5]. This type of repair has been called "repair of potentially lethal damage" (PLD). It is operationally defined as the repair which takes place after irradiation, depending on the environmental conditions and usually tested by stimulating cells into division. There is a tendency for cells to exhibit repair of PLD when they are grown into crowded conditions so that their number is no longer increasing. They then develop the capability of repairing radiation damage before being called upon to divide. In general this causes an increase in D_o of the cell survival curve. The phenomenon has been shown to occur in tumours [S2] but techniques are not yet available for demonstrating repair of PLD in normal tissues. There is, however, no reason why the phenomenon should not occur in normal tissues and it may play an important role in determining tissue radiation response. Repair of PLD is normally complete within a few hours. Repair of chromatid aberrations in testes and bone marrow has also been observed with a similar time course [B40].

3. Slow repair

21. Various types of slow repair have been identified. Van den Brenk et al. [V2] and Reinhold and Buisman [R3] investigated the response of capillary endothelium to irradiation. The technique used by both groups was to stimulate cell proliferation in these otherwise slowly dividing tissues at various times after treatment. By this means these authors observed a repair process with a half-time of about one week, analogous to repair of potentially lethal damage, but taking much longer. Curtis [C1], using chromosome abnormalities as the end-point for damage to mouse liver, also observed a very slow removal of damage, manifest by a steady disappearance of the abnormalities. This type of repair may also be analogous to a slow repair of PLD, although McKay et al. [M50] believe that there is no repair of chromosome damage in liver of Chinese hamsters. In mouse lung there appear to be two phases of repair of sublethal damage as measured by an increasing D_2-D_1 with time between two fractions, the second phase taking about 100 times longer than the first [F17]. This second phase of slow repair is thought not to result from cellular proliferation [C31].

4. Repopulation

22. Following irradiation cells undergo a period of mitotic delay, after which there may be renewed proliferation. Tissue damage is repaired in this way, often rendering radiation decreasingly effective as the period of protraction of the dose is increased. It is known, at least in some tissues (e.g., skin and intestine) that cell proliferation after irradiation is stimulated by homeostatic control in response to the presence of dying cells or to products of cell lysis. Two techniques have been used to estimate compensatory cell proliferation. Where cell survival can be estimated by a clonal assay (intestine), the survival ratio with various intervals between dose fractions can be measured. Where clonal assays are not available and only gross tissue response can be assessed, repopulation is measured in terms of the increase in D_2-D_1 as doses are separated beyond the time during which sublethal damage is repaired. However, it is difficult with these techniques to distinguish between repopulation and slow intracellular repair processes. Long-term changes in proliferation resulting from irradiation have been reviewed by Beer [B78].

5. Reassortment

23. Since, as described earlier, cell sensitivity varies with the mitotic cycle, a dose of radiation will preferentially kill the sensitive cells, leaving mostly those in the resistant phases as survivors. After irradiation the remaining resistant cells are at first delayed and then move towards the more sensitive phase. Thus a second dose will be more effective if given some time after the first treatment than if given immediately afterwards. This process is in competition with the repair processes, all of which render the population less sensitive with time after a first irradiation. In addition mitotic delay is not constant for cells at all stages of the cell cycle and the net effect of irradiation is to cause a temporary accumulation of cells in the G_2 phase. This process adds to the partial synchrony of the population caused by preferentially killing the sensitive cells. All these processes combined cause a tissue to express a pattern of sensitivity to a second treatment with peaks and troughs, at times depending on the kinetics of the various phenomena. The effect of reassortment becomes extremely complicated with many fractions or with irradiation at low dose rates and cannot be predicted with any certainty.

6. Reoxygenation

24. It is well known that hypoxic cells are more resistant to low-LET radiation than are well oxygenated cells. The factor by which the dose must be increased to produce the same level of damage in hypoxic as compared to well oxygenated conditions is normally 2.5–3. Most experimental tumours and some normal tissues have been shown to contain hypoxic cells, e.g., mature cartilage. Radiation will sterilize selectively the well oxygenated cells. It may also cause a reduction in respiration and after removal of the dead cells and shrinkage of the tissue, all surviving cells will have a greater proximity to blood vessels. Therefore after irradiation many of the surviving hypoxic cells become better oxygenated, a process which has been termed reoxygenation [T2]. This is extremely important for tumours. However, in most normal tissues, a majority of cells are well oxygenated and if there is any reoxygenation these tissues will, in a protracted regime of irradiation, respond as if all their cells were well oxygenated. It is therefore unlikely that hypoxia and reoxygenation are important mechanisms in most normal tissues.

C. IRRADIATION AT LOW DOSE RATE

25. It is clear from the above considerations that dose rate is a very important parameter. This is especially true for low-LET radiation. As the dose rate is reduced and the time of irradiation is therefore extended, the overall effectiveness is reduced. This is due to two separate processes: (a) during the exposure there will be repair of sublethal damage occurring; (b) if the dose rate is low enough cellular repopulation can occur. Both of these repair processes cause the radiation to be less effective. Changes in the distribution of cells along their mitotic cycle may also be a contributing factor. The subject has often been reviewed, e.g., by Rajewsky et al. [R37] and by Hall [H6].

26. The effect of repair of sublethal damage on sensitivity may be dealt with by considering low dose rate as if it were many small fractions. This was the approach taken by Lajtha and Oliver [L1] who assumed that sublethal damage would be repaired with a half time of 1.5 hours. If many small fractions are given, the survival curve becomes shallower and the extrapolation number is reduced, as illustrated in Figure II. As the dose rate is reduced and treatment time protracted a greater proportion of the dose is inflicted as sublethal damage and is repaired. Ultimately a point is reached where effectively all the sublethal damage is repaired and there can be no further effect of decreasing the dose rate based on sublethal damage. The limiting slope is shown by the upper solid line in Figure II. The magnitude of this dose rate effect will depend on the inherent ability of the cells to repair sublethal damage. This is a very large effect for many, but not all organized tissues. In general the effect occurs between dose rates of about $2\ 10^{-3}$ – 1 Gy min^{-1}. Outside of these rates there is little or no further effect attributable to recovery from sublethal damage.

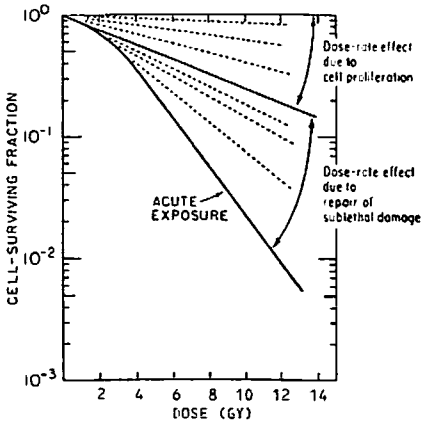

Figure II. Illustration of the dose rate effect due (a) to repair of sublethal damage and (b) to cell proliferation [H6]

27. In addition to repair of sublethal damage, in rapidly dividing tissues there may be an effect of proliferation during exposure if the dose rate is sufficiently low and if exposure time is long compared with the normal length of the cells' mitotic cycle. Cell death will then be balanced by cell proliferation causing a further reduction in biological effect as the dose rate is progressively reduced. There may also be a proliferative stimulation of cells not in the division cycle.

28. The dose rate at which the cell death rate cannot be balanced by the birth rate is critical, since that is the dose rate above which the tissue will gradually be destroyed. The critical dose rate is very tissue dependent. For the rat intestine it is about 4 Gy per day [Q2]. The figure is high because of the high proliferative capacity of the intestinal mucosa. For the bone marrow the threshold is about 0.5–1 Gy per day for the erythropoietic system in mice and rats [B1]. White cell and platelet levels in rats are maintained at 0.5 Gy per day [L2] and a steady state of granulocyte precursors develops. However, it was also shown in the rat that 0.5 Gy per day caused a reduction in the level of lymphoid cells in bone marrow, thymus, spleen and in the blood. In mice, and particularly in the rabbit and guinea pig, it was suggested that the threshold steady state dose was lower than 0.5 Gy per day [B41]. Testis has a far greater intrinsic sensitivity. Only if the dose rate is below a few hundredth of Gy per day [B2] can rats and mice maintain reproduction for 10 generations or more.

Obviously the repair potential for developing sperm cells is extremely limited.

29. Little is known of the effects of low levels of continuous irradiation on non-stochastic effects in slowly proliferating tissues. It may be expected that critical dose rates will be much lower than for rapidly proliferating tissues, which seem readily able to compensate for the damage.

D. RESIDUAL INJURY

30. The extrapolation from single doses to treatments extending over years, i.e., over a significant proportion of the recipient's life time, is very difficult to make in the present state of knowledge. Some information may be obtained from the data on fractionation, but this is not generally available for more than 30 fractions and for treatment times longer than a few weeks. These data do not answer the questions about long term recovery potential which are related to the complete repair of parenchymal cell damage through proliferation; to the role of slow repair in this capacity; to the presence and extent of irreparable damage, for example, to the vascular system, as mentioned in section II.A. and discussed further in chapter VI.

31. Experiments in which a "priming" treatment (a single dose or a series of doses) is followed some time later by a test treatment can be of help in answering some of these questions. The priming treatment is normally below tolerance and the "residual" damage at a given time is estimated by the response of the tissue to a further test treatment. The results of Denekamp [D3] and of Brown and Probert [B3] in mice, show that by about 6 months after the priming treatment the tissue responsible for the early skin damage has almost totally repaired and only about 10% of the priming dose is "remembered" [D5, F5]. This early reaction is the result of killing of the basal epidermal cells, so clearly their repopulation can restore the tissue to near normal. The same is true for the rapidly proliferating mucosal epithelium of the intestine. Human skin can also almost fully recover, as assessed by early reactions [H7].

32. Brown and Probert [B3] also investigated the end-point of late deformity in the mouse foot. In their experiments 35–40% of the priming dose appears to be "remembered" if assayed for late foot deformity. It was suggested that different components of the limb were responsible for late reactions and that for these there was less repair. The accuracy of the Ellis formula for partial tolerance (see section I.F.) with time after treatment was tested in the same set of experiments and found to give a fairly close prediction of the results from 1 to 10 months after the priming treatment.

33. Hendry et al. [H8] investigated residual injury using necrosis of the mouse tail as the end-point. The results were consistent with those for early skin damage in that the residual injury in the tail was 10% of the first treatment after 6 weeks. However, if a further "priming" treatment was given, the residual injury was increased to 35%, at which level it remained for repeated "priming" treatments, each separated by 6 weeks [H9].

34. Thus it appears that rapidly proliferating systems can almost fully repair a radiation injury, whereas tissues responsible for late injury have a reduced repair potential and would, therefore, be expected to accumulate more damage during protracted irradiation. The relationship, if any, between the early and late reactions has been the subject of much debate and is still not resolved [D5, B3, F5, F6, P4, D6, R35].

35. Residual injury has also been investigated after neutron irradiation. Hendry et al. [H8], using necrosis of the mouse tail, observed that the residual injury was greater after a treatment with neutrons than after x rays. A similar set of experiments was performed on mouse foot skin by Field et al. [F7]. In this case both the early and late reactions were assessed after test doses given 6 months after the priming irradiations. In general, residual injury after neutron irradiation was greater than after x rays. Skin reaction increased with increasing priming dose, but was not dependent on whether this was x rays or neutrons. Residual injury, manifest as late deformity after x ray priming doses, was only slightly greater than for early reactions, but the residual injury measured for the same end-point after neutron priming doses was larger.

36. An interpretation of these observations is that recovery from tissue damage leading to late reactions is at least partly due to slow repair and that this is absent with neutrons and possibly other high-LET radiations. Thus the RBE for late damage might be expected to increase for protracted irradiations if there were less long-term recovery after neutrons than after photons. Such an observation was made from a skin experiment in which the RBE measured for short overall treatment times was compared with treatment over 6 months. The RBE for the latter was about 30% higher [F9]. However, it is not known whether or not this concept may have general validity.

E. MODIFIERS OF RADIATION RESPONSE

37. Perhaps the most important modifier of the response to radiation is oxygen. Its absence protects cells and tissues by a dose factor of 2.5–3 in comparison with fully oxygenated cells and tissues. The fact that some normal tissues may be partially hypoxic and thereby protected to some extent has already been discussed (section I.B.6). Drugs which are vasoconstrictors may also protect tissue by causing hypoxia. Some drugs are radiation protectors, e.g., the sulphydryl compounds such as cysteamine, 2-β-aminoethylthiouronium (AET) and the compound WR2721. Other drugs are radiation sensitizers, e.g., many of the anti-cancer agents including the antibiotics, some alkylating agents, sulphydryl-binding agents and antimetabolites. The halogenated pyrimidines such as BUdR and IUdR are also sensitizers. A rather special group of drugs essentially sensitize only hypoxic cells. The best known are the nitro-imidazoles and these may be useful in connection with radiotherapy of cancer. Heat also sensitizes to radiation with temperatures in excess of 41°C, and sensitizing factors of 3 or 4 have been reported. These factors will be important for patients undergoing radiotherapy, although it seems rather unlikely that the response of whole human populations to irradiation would be significantly affected by any of these modifying factors. Many of these factors are considered in detail in Annex L; reviews are also to be found in [R50 and P59].

F. ISOEFFECT FORMULAE

38. Data relating the total dose, number of fractions and overall treatment time for a given degree of normal tissue damage are all derived from radiotherapy results or animal studies aimed at providing useful information for the radiotherapist. Isoeffect formulae to fit these data have been suggested. Whether or not these formulae are accurate over the therapy range of treatment times and number of fractions is the subject of much debate. It is even more dubious whether these relationships may be extrapolated beyond the therapy range, but they can certainly be useful in giving an indication of the dose required to produce a given level of damage in long protracted irradiations.

39. In 1918 [K2] the results of experiments on human skin indicated that radiation was less effective if given in many fractions. Regaud and Ferraux [R4] confirmed this observation on skin and also indicated an improved therapeutic ratio by fractionation. The subject was further studied in the 1930s, [e.g., R5 and M2]; and it became standard radiotherapy practice to treat in many fractions. A classic paper appeared in 1944, by Strandqvist [S3]. He constructed isoeffect curves for the cure of skin cancer and for various levels of damage to skin, i.e., erythema, dry desquamation, moist desquamation and necrosis. The total required dose was plotted against the overall treatment time, both on logarithmic scale. The topic was further considered by Cohen [C2] who also published data for skin damage and for tumours. Skin damage was taken from McComb and Quimby [M2] and Reisner [R5] for erythema and from Paterson [P5], Jolles and Mitchell [J1] and Ellis [E3] for tolerance.

40. It was initially thought that the number of fractions was less important than the overall treatment time. However, this view was changed in the 1960s as the meaning of repair of sublethal damage became clearer [F10]. Ellis [E4], on the basis of Cohen's earlier publication suggested separating the factors for overall treatment time T (days) and number of fractions N giving the empirical formula

$$\text{total dose} = (\text{NSD})\, N^{0.24}\, T^{0.11}$$

where NSD is known as the nominal standard dose; its "units" are designated as the ret. The NSD is a "constant" referring to the maximum single dose which a particular normal tissue can tolerate in radiotherapy. It will depend, therefore, to some small degree on the judgement of the physician. It is not considered reasonable to extrapolate the Ellis NSD formula to less than $N = 4$ or $T = 5$ and it is questionable whether or not the formula holds for very large values of N and T. In addition, the exponents of N and T will vary, to some extent, from tissue to tissue. The formula was, however, based on human data.

41. The main limitation of the concept of NSD is that the formula is applicable only at the level of normal tissue "tolerance". Various modifications have been made to make it possible to apply the formula to levels of injury lower than tolerance. One of these is the concept of "partial tolerance" (PT)

$$PT = \text{NSD}\, N/N_{TOL}$$

where N_{TOL} is the number of fractions to give full tolerance and N is the number actually given. By this means PT becomes an additive quantity, unlike NSD. For convenience in radiotherapy Orton and Ellis [O1] introduced TDF (time dose factor) which is proportional to partial tolerance, but is independent of specific values of NSD.

$$TDF_f = N\,(d\ 100)^{1.538}\,(T/N)^{-0.169}\ 10^{-3}$$

where d is the dose per fraction in Gy.

42. An alternative generalization of the NSD formula is that of the Cumulative Radiation Effect (CRE) [K3] where

$$CRE_f = \left(\frac{T}{N}\right)^{-0.11} d\, N^{0.65}$$

where N is the number of fractions given and T is the overall time for those fractions including the first and last treatment days. CRE is applicable at less than tolerance, as is the case for TDF. Like NSD, CRE is also based on human data. Differences between CRE and TDF have been discussed by Turresson and Notter [T28].

43. Both CRE and TDF have been generalized for low dose rate continuous irradiation, such as implant brachytherapy [K48, O14]. Thus $CRE_c = k'\ r\ T^{0.71}$ where r is the dose per day, T is the overall treatment time in days, and k' is a normalizing constant between CRE_f and CRE_c or $TDF_c = k''\ (r\ 100)^{1.35}\ T\ 10^{-3}$ the symbols having the same meanings as for CRE_c.

44. Recently these models have been subjected to critical testing both clinically and experimentally on pig skin by Turesson and Notter [T28, T29, T30]. Attention was focussed on CRE. In the clinical study there was good agreement between CRE_f and acute skin reactions for a variety of treatment schedules with different fractionation and overall treatment times. The agreement with late reactions was less good. The same was true for the experimental study with significant differences between prediction and observation with small numbers of large dose fractions. A modified CRE formula was thus proposed [T28] where

$$CRE = L(d)\left(\frac{T}{N}\right)^{-0.11} d\, N^{0.65}$$

where L(d) is a correction factor for reactions following doses per fraction of size d. For early reactions $L(d) = 1$. This is also the case for late reactions with $d = 2$ Gy. For $d = 10$ Gy, L(d) rises to 1.18. Turesson and Notter [T28] also compared the predictions of both CRE_c and TDF_c for low dose rate continuous irradiation at two dose rates (1.20 and 0.54 Gy h^{-1}). It was observed that the normalization constant k was significantly different from the proposed values and that the irradiation was more damaging than implied by these formulae. Turesson and Notter proposed revision in the values of k' in CRE from 0.80 to 0.57 and in k'' in TDF from 2.02 to 1.57. The modifications proposed to both TDF and CRE require further experimentation.

45. The N factor is related to the number of dose fractions, and is thought to be primarily influenced by repair of sublethal damage. As this is usually complete in a few hours it is theoretically possible to give several fractions per day without changing the N factor. Extensive repair of sublethal damage will normally be consistent with a large N factor, i.e., a large sparing of fractionation and vice versa. Techniques are not yet available to determine repair of potentially lethal damage in normal tissues in situ, but if it occurs, it also will cause the N factor to be increased.

46. The T factor is more difficult to explain. In rapidly proliferating tissues it is probably due to cellular repopulation, in which case a power function, such as $T^{0.11}$ is unlikely to be universally applicable. In slowly proliferating tissues T may be due to "slow repair" for which a power function would be more appropriate. McKenzie [M75] attempted to derive the CRE formula from a cellular survival model with Gompertzian repopulation. The agreement obtained with the N factor was good, but T could not be explained by this model.

G. CELL PROLIFERATION AND ITS RELATIONSHIP TO THE TIME OF EXPRESSION OF RADIATION INJURY

47. Cell proliferation is important for two reasons. Firstly, it is related to the time of death of cells in tissue and thus to the time after irradiation when damage becomes apparent. Secondly, it is a mechanism by which a tissue is restored to near-normal after irradiation. In addition, radiation can perturb the cell proliferation kinetics of a population, and as the cell kinetics can influence the response of the cell population to any further dose of radiation, these mutual interactions are of importance in the response of tissues to single doses and fractionated irradiation. Changes may take place many years after irradiation, such as cell death which has been reported after treatment of the breast region of female babies for haemangiomas [F44, K36].

48. Most adult normal tissues show no net growth under normal circumstances but an exact balance of cell production and cell loss. This may result from very slow production and slow loss as in lung or kidney, or from more rapid production and loss as in most epithelial tissues. The cell production is determined by the cell cycle time (intermitotic time T_c) and the fraction of cells in the proliferation cycle (i.e., the growth fraction or GF). The cell loss may be by migration (as occurs in the villus of the intestine) or by differentiation and death (as for blood cells formed in the marrow).

49. In the last two decades, experimental techniques have been developed to investigate the proliferation rates of cell populations both in vitro and in vivo. These include labelling studies with radioactive precursors of DNA, based on the work of Howard and Pelc [H10]. The cell cycle time and the growth kinetics of a wide variety of tissues, both normal and malignant, have since been studied, in undisturbed growth and also after injury by various agents, including radiation. Because of the difficulties in measuring per cent labelled mitoses curves in populations which are not in steady state of growth, continuous labelling by repeated injections of tritiated thymidine (^{3}HTdR) has also proved to be a useful technique [D7, H63]. More recently techniques of cytofluorometry have been introduced. In addition, some tissues have been studied after radiation injury by comparing the doses needed to inflict a given level of injury if two dose fractions are separated by a varying interval of time (Table 1).

50. In the response of any cell population to a dose of radiation, there is initially a delay in the progress of cells around the cell cycle (mitotic delay), which is dependent on the radiation dose administered, the stage of the cycle and the cell cycle time. The cells accumulate in the premitotic G_2 phase and are blocked from entry into mitosis for some time. The radiation damage is then expressed in dividing cells as a loss of their proliferative capacity. Most cells die at one of the mitoses subsequent to the radiation-induced mitotic delay. At high doses (10–20 Gy) cells die at the first post-irradiation division, but after smaller doses (i.e., a few Gy) many or most cells die at a second or third division. There are a few exceptions to radiation death occurring at mitosis, e.g., lymphocytes and germ cells, which can die during interphase without any attempt to divide. For most somatic cells, however, the expression of radiation damage is delayed until mitosis is attempted. After 10 Gy this may occur within 12 hours in the intestine, within 4–5 days in skin, and presumably not for many weeks in tissues with very long turnover times such as liver, lung and kidney [D1]. Since most tissues consist of a variety of cells with different proliferation rates, the expression of radiation damage is likely to occur at different times in the different cell compartments and be further complicated by various feedback processes.

51. Organ functions may be impaired either when the majority of cells have died or else when a critical subpopulation has started to express its damage. For this reason it has been suggested that radiation damage in many organs may have a common pathway of expression in the form of endothelial cell death. Endothelial cells are generally thought to have a very long turnover time of 2–4 months as measured by simple tritiated thymidine uptake studies [T3]; however, it seems likely that this may result from a very small proportion of the cells ($\sim$ 1%) cycling with a cell cycle time of about 20 hours [H4, K4]. The role of vascular damage will be discussed more extensively in chapter VI.

H. NORMAL TISSUE KINETICS: CHANGES AFTER IRRADIATION

52. In normal tissues there is a finely balanced homeostatic mechanism, such that a significant drop in cell numbers below the normal level is compensated by an increased rate of cell production. This increased production may occur in different ways, e.g., from a shortening of the cell cycle time, as in the small intestine and skin [D7, L3, H11], or by an extra division in the amplification process of cell production, as in the bone marrow or in the small intestine [L4, L5]. Recognition of cell depletion and compensatory proliferation may take place in most normal tissues.

53. Accelerated proliferation in response to injury can be very rapid when the injury results in immediate cell destruction such as from mechanical trauma, incision or burns caused by caustic chemicals. Shortly after such injuries to skin (within 6–48 hours) a wave of DNA synthesis and cells in mitosis are observed near the site of cell death.

54. The compensation appears to occur when cell depletion has been recognized, and since the expression of radiation damage is usually delayed until a subsequent mitosis, the compensatory proliferation after radiation injury is also delayed. In skin, for example, the proliferation kinetics do not alter for at least one week after either a single dose or the beginning of a course of repeated doses that will each kill a substantial

proportion of the cells [D3, D7, H11, D8]. Thus a course of radiation therapy, as usually administered over a period of 4–7 weeks, will not induce proliferation until the second and third weeks as more and more cell depletion is recognized. More rapidly dividing tissues, such as intestine, will respond earlier [W5, L6, C3] but more slowly dividing tissues such as lung, liver, kidney, muscle, nervous tissue and vascular and connective tissue, are not likely to commence compensatory proliferation in response to cell death until a long time after irradiation [D5]. This has recently been demonstrated in mouse bladder epithelium [S4].

55. The cell cycle time varies enormously in different normal tissues. It is well known for several rapidly dividing tissues but little detailed information is available for the very slowly dividing tissues [D36].

56. The relationship between tissue kinetics and radiation response is of great importance. Recently Michailowski [M70] has suggested a refinement to the accepted concepts, on the basis that tissues fall into two categories, i.e., types H and F. In type H (hierarchical) there exists a defined stem cell compartment, differentiating into histologically distinguishable functioning cells. Radiation-induced tissue damage will result from inadequacy of the mature cell compartment which depends on the life span of the functional cells. A similar model has been the accepted view for many years. In type F (flexible) all cells are thought to be capable of proliferation and specific tissue functions. In these tissues radiation will lead to a dose-dependent loss of functional cells through their mitotic death, both following exposure and during the next phase of compensatory proliferation, resulting in accelerated expression of the radiation damage ("avalanche"). Consequently the more severe damage following larger doses of radiation is seen earlier than milder reactions produced with smaller doses. Likely examples of type H tissue include the epidermis and the intestinal epithelium. Type F tissues would include the dermis, endothelium, liver parenchyma. Late reactions in type F tissues can therefore never be totally excluded and may be precipitated by some unrelated trauma, such as infection or mechanical injury. Similar phenomena are well known in radiotherapy.

I. SUMMARY

57. Radiation-induced tissue injury of a "non-stochastic" nature is likely to have its origin in the sterilization of a large proportion of the critical cells of that tissue, although these cells may be a small proportion of the total cells. The consequent injury results from the natural loss of post-mitotic cells which are not replaced or loss of cells which are stimulated into division. The characteristics of cell survival are of great importance in this context, particularly at low doses, in gaining an understanding of the response of tissues to fractionated or continuous irradiation. Various processes of repair and repopulation will increase the threshold level of dose when irradiation is given over a long period or when a second period of irradiation is encountered some time after an earlier exposure. Attempts to express these parameters have been made in terms of iso-effect formulae. The timing of tissue injury depends on the cells' natural proliferation characteristics and also on kinetic changes characteristic of the tissue which result from the irradiation itself.

II. EFFECTS OF EXTERNAL IRRADIATION ON TISSUES OF EXPERIMENTAL ANIMALS

58. Animal tissues often closely resemble those in man and respond to irradiation in a similar way. It is therefore of value to consider data on animals. These have frequently been irradiated with a wide range of doses, both in single treatments and in many different fractionated regimes. From examination of the non-stochastic response of different animal species, cautious extrapolation to man seems justified and at least will increase confidence in the extrapolation of data directly derived from the human [F11].

59. It was recognized long ago that most cells die from radiation damage only when they attempt to divide. The rate of proliferation is therefore an important determinant of the timing of response to irradiation. Rapidly proliferating tissues exhibit early responses to irradiation and also reach a peak of injury sooner than the more slowly proliferating tissues. Rapidly proliferating tissues are also capable of considerable repair of damage due to cellular repopulation, which may be important during fractionation or low-dose-rate irradiation. This is in contrast to slowly proliferating tissues which are less able to repair damage during irradiation through repopulation.

60. The tolerance of normal tissues to irradiation is organ specific. It also varies with the volume which is irradiated, bigger effects occurring in bigger volumes. Experiments on some organs are limited to specific regions as in grid therapy [B52], but there is little information available on this topic.

A. SKIN

61. The earliest evidence of the damaging effects of ionizing radiation on tissues came from skin reactions observed after radiotherapy [S5, M3]. The accessibility of the skin for observation has subsequently resulted in its being the most studied and documented normal tissue regarding its response to radiation. Several important principles may be illustrated by reference to results of skin damage.

62. After irradiation of the skin there are a variety of observable changes [R1]. There may be several waves of erythema leading to dry desquamation and depilation. Healing may still occur. For larger doses there may be moist desquamation and permanent pigmentation. Blood vessel and connective tissue damage can lead to ulceration and necrosis with no epithelialization possible. Repair from moderate doses often takes place from the wound edges and therefore large irradiated areas produce greater reactions and are slower to heal. Damaged tissue may be replaced by fibrosis in man, pig and goat, but not normally in the skin of rodents.

63. The relationship between kinetic parameters and radiation response can readily be demonstrated in skin. Mouse skin has a cell cycle of 4–5 days for most of the cells of the basal layer and a transit time of 10–15 days through the superficial 2–3 layers of differentiating cells [H11]. Mitotic activity in mouse skin is totally depressed 2–4 days after 5 Gy [K45]. Desquamation occurs after 20–30 Gy for moderately large areas, at 15–20 days, in agreement with the transit time through the differentiating layers [H11, F11, F12]. Skin which has been stimulated before irradiation, e.g., by plucking, develops a reaction earlier, and skin with more super-

ficial layers (pig or man) reacts later. Large doses cause considerable mitotic delay, followed by extensive cell death in the basal layer, but the rate of progression of cells into the more superficial layers is unchanged, at least for several days [E6]. Eventually the lack of cell production results in significant lack of basal layer cells and this may be the signal for more rapid compensatory proliferation [F11]. The proliferative response is thus delayed by 1–2 weeks after single large doses of about 20 Gy or after starting multiple small doses of a few Gy. After surgical or mechanical wounding, however, a deficit is recognized immediately and proliferation is faster within 24 hours [R48, F11].

64. The level of cell depletion affects the rate of compensatory proliferation and in skin the cell cycle time can shorten from its normal value of 4–5 days, down to 2 days after moderate damage, or to 18–24 hours after severe depletion [W4, D7, D8]. This delayed compensatory response is unusual. The only other form of injury producing a delayed response is that of a deep thermal burn involving the dermis [W9]. After the initial lag, compensatory proliferation will commence during a course of daily radiation fractions and presumably continuous irradiation and in mice can be sufficiently effective to heal the radiation-induced desquamation even though daily irradiation at over 10 Gy per week is continuing [F13]. Mucosal or epithelial healing is also sometimes observed during prolonged clinical radiotherapy.

1. Single doses

65. Skin damage has been assessed in animals by estimating the early or late changes on arbitrary scoring scales or by measuring the survival of individual cells in the basal layer of the epidermis. Pig skin has been used in radiobiological studies by several groups. It has many features in common with man, i.e. colour, the presence of relatively few hair follicles, sweat glands and a layer of subcutaneous fat. The gross response of pig skin qualitatively resembles that of man. The quantitative study of pig skin was pioneered by Fowler and his colleagues [F10]. They irradiated a number of rectangular fields on the flank. The very early erythema was not scored but the next two waves of erythema and desquamation were. Long-term damage was assessed by the degree of induration, which is taken as a measure of fibrosis, but more recent studies have improved on this late end-point [B4, W10]. To establish dose-effect relationships average reactions were taken over various time periods and these values related to the dose. An example is shown in Figure III. The smallest single dose found to produce an observable effect was about 10 Gy.

66. Non-uniform exposures of pig skin have been reviewed by Wells et al. [W38] and Osanov et al. [O13]. It was not possible to produce visible damage with 0.7 MeV beta rays to fields less than 10^{-2} cm^2 with doses up to 100 Gy, due to sparing by repopulation of hair follicle cells. With increasing energies of beta rays less dose was required to produce visible damage. The basal layer was clearly seen as being the critical cell component. Thus a 1 cm^2 field of 15 Gy to the basal layer was approximately the minimum dose which produced a visible injury.

67. Rodent skin reactions have been assessed by several workers, e.g., [F2, F12, B5, L7]. In mice, feet show a wave of damage starting at 7 days after irradiation, peaking at about 20 days and healing, according to the dose, by 30–50 days. Rat feet show a distinct wave of damage, at higher dose levels, which is not seen in mice. The feet of both rats and mice and the ears of mice ultimately become deformed after large doses and the deformity is permanent. In rodents the minimum single dose to produce a visible reaction is at least 10 Gy.

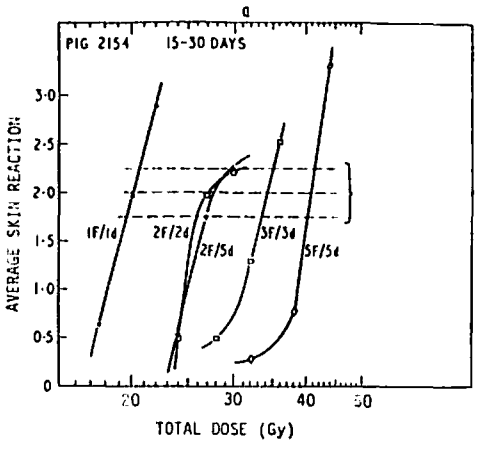

Figure III. Dose-effect curves for pig skin irradiated with x rays, obtained from the average reaction between 15 and 30 days after irradiation. A score of approximately 0.5 indicates the threshold erythema. The number of fractions given and overall treatment time are indicated in the figure [F1]

68. Both in animals and in humans the correlation between early and late radiation reactions is a matter of controversy. The early reactions of erythema and desquamation are due primarily to damage to the basal layer of the epithelium whilst late damage is more complex, probably involving damage to endothelial cells and increased blood vessel permeability. However, little is known for certain about the processes leading to later damage. A good correlation between early and late damage has been seen by some authors [F5, F6, D6], but others have observed late injury developing many years after irradiation without corresponding early reaction [W10, A2]. More recently [F7], mice feet were irradiated with graded doses of x rays (or fast neutrons) given once per week for 25 weeks. The threshold for production of an erythema was 3 Gy per week, but even after 10 Gy per week for 25 weeks the reaction faded when irradiation ceased. No late damage was observed with 10 Gy per week to a total dose of 250 Gy. The result was similar with neutrons up to 12.5 Gy.

69. A method for estimating survival curves for mouse skin cells was developed by Withers [W4]. The technique used was to isolate a defined area by heavily irradiating a moat around it. The small test areas were then given a series of graded test doses and the dose which allowed one or more nodules to grow in the test area was determined. A nodule was assumed to have grown from a single cell. The usable dose range was extended by varying the test area but practical considerations limited the applicable dose range to between 8 and 25 Gy. The survival curve obtained had D_0 = 1.35 Gy, similar to many values obtained in vitro. From split dose experiments the D_2-D_1 was about 3.5 Gy, and the extrapolation number n was found to be about 12. Similar experiments by Emery et al. [E7] gave a value of D_2-D_1 of 5.7 Gy but a similar value of D_0 to that found by Withers [W11]. By comparing the survival curves

with the dose effect curves for skin reaction it can be found that 15 Gy leaves only one cell per mm^2 surviving and produces a very mild skin reaction indeed. After a few days the skin cell doubling time is reduced to about 22–36 hours [E7, W11]. Presumably this rapid repopulation is sufficient to prevent a severe reaction following this degree of cell killing.

70. If a sufficient area of skin is irradiated, death of the animal can result. LD_{50} values, calculated at 30 days for this end-point have been measured in rats. Values in the range of 44–50 Gy for external irradiation with ^{90}Sr beta rays, and 17–30 Gy for x rays have been quoted [A38, A39, S36].

2. Fractionation effects

71. When the dose to the skin is fractionated, more radiation is required to produce a given level of injury. Fractionation experiments have been performed by varying the number of fractions, but keeping the overall treatment time constant to determine the N factor; or by keeping the number of fractions constant to determine T (see section I.F.).

72. Experiments to determine N have been based on an experimental design of Dutreix et al. [D9]. These authors aimed at estimating repair between small doses. If a single dose D_1 is split into two fractions at total dose D_2 to give the same effect, then D_2-D_1 is the additional dose required by splitting the treatment, as discussed earlier. If each of N fractions is split into two fractions to a total dose D_2N given in the same overall time as D_N in N fractions, then the additional dose per fraction is given by

$$D_r = \frac{D_{2N} - D_N}{N}$$

The experiments of Dutreix et al. [D9] indicated that D_r became zero when the dose per fraction was 3 Gy or less. This means that fractionating to doses smaller than 3 Gy resulted in no further sparing effect. These results, however, were subject to considerable statistical uncertainty. Results of some similar animal experiments [F15] are summarized in Figure IV. It is seen that D_1 becomes small, but does not approach zero at 3 Gy per fraction and possibly not until the dose per fraction is zero. However, it is extremely difficult to resolve the situation at doses less than 2–4 Gy, although this is the important region for extrapolation to many small fractions.

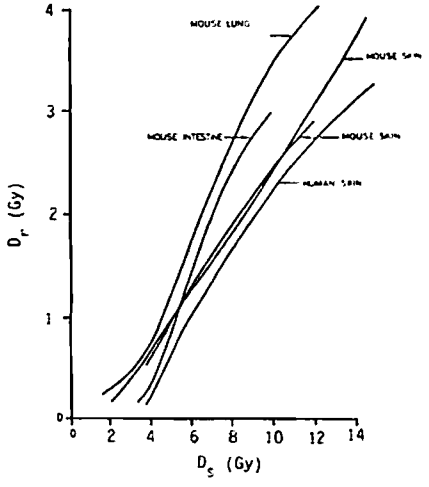

Figure IV. A plot of the additional dose per fraction, D_r, against the dose per fraction, D_s, for various tissues [F15]

73. An alternative approach which may be made from similar experiments is to derive the ratio of the initial to final slope of the survival curve, in order to make the extrapolation from a single dose to an infinite number of fractions, excluding the effects of repopulation. The initial slope determines the effect of giving an infinite number of fractions. The method of analysis is given by Field et al. [F13] who derived a slope ratio of 1:5 or 1:6 [F13, F15]. This value may be compared with 1:3 from Dutreix et al. [D9].

74. Douglas and Fowler [D10] extended mouse skin experiments to 64 fractions. All treatments were given in a total time of 8 days with the advantage that repopulation could be considered negligible during this period [D8]. Their techniques also avoided the use of anaesthesia. The results indicated that there was additional recovery down to the smallest doses given ($D_s \simeq 1.9$ Gy) in agreement with Field et al. [F13] but contradicting Dutreix et al. [D9]. From the results Douglas and Fowler [D10] derived a slope ratio of 1:5.5. They also favoured a survival curve with the form

$$S = \exp - (\alpha D + \beta D^2)$$

75. Denekamp and Harris [D11] measured the slope ratio in a different way. They gave mice feet a series of daily small "priming" doses of 1.5, 2.5 and 3.5 Gy, respectively, and measured the size of a single large test dose required to produce a given reaction. The results were subject to a moderate degree of scatter, but most of the derived values were in the range of 1: 4 to 1: 7. The results were found to be inconsistent with the multi-target single-hit curve, which was also the conclusion of Field et al. [F13]. The results of such experiments may also be compared with the Ellis formula. The value derived for N between 4 and 30 fractions varied between 0.24 and 0.33 [F13, D12] but there are indications that the curve relating log total dose to log number of fractions becomes flatter above 30 fractions [D10].

76. The T factor in a rapidly proliferating tissue, such as the skin, is primarily due to cellular repopulation between fractions. Vascular autoradiographic studies have been made of the proliferation of irradiated areas of skin and mucosa. The results generally showed a reduction in cycle time both in the irradiated zone and in the border region, indicating healing [H11, D13, B6, Y1]. After a long time (up to 1 year) the skin appeared thinner and the cycle time was slightly elongated [Y1, L8].

77. An alternative method of measuring proliferation after irradiation is by estimating D_2-D_1, D_2 being the dose given in two fractions and D_1 the equivalent single dose. When two treatments are separated by up to 1 day the change in D_2 is primarily due to sublethal damage. Beyond 1 day an extra dose is required to counteract repopulation. Since the D_o value for the skin epidermal cells is known to be approximately 1.35 Gy [W4, E7], D_2-D_1 may be interpreted in terms of doubling time. Various estimates of the doubling times in skin have been obtained in this way (Table 2). Several authors have estimated a value equivalent to 0.3 Gy/day [D3, F10, C4]. This value corresponds to a doubling time of

about 3–4 days in experiments covering a wide range of dose per fraction and intervals between doses from 1 to 5 weeks. Higher dose increments and therefore shorter doubling times have been estimated by Comas [C5] and by Fowler et al. [F16]. Both Withers [W4] and Emery et al. [E7] used the Withers cloning technique to estimate the repopulation rate. However, this type of experiment requires the hair to be plucked before irradiation, which may initiate a slightly faster rate of proliferation. The doubling times estimated in this way were 1–3 days. From human skin, Dutreix et al. [D14] estimated a cell doubling time of 1–1.5 days from the rate of growth into irradiated areas.

78. Repopulation during and after multifraction experiments has been measured using a radiobiological [D8] and a labelling technique [D7] in order to estimate the extent and timing of stimulated repopulation after irradiation. Daily fractions of 3 Gy of x rays were given on 4, 9 or 14 occasions. After 4 fractions there seemed to be little proliferation as judged from the skin reaction experiments and the labelling studies indicated an extended period of division delay, lasting for approximately 5 days after the last fraction. There was a small reduction in doubling time after 9 days but after 14 days proliferation was very rapid with a doubling time of less than 1 day. This more rapid proliferation returned to normal in the second week after the end of the fractionated treatment.

79. In conclusion, skin has an enormous capacity to repair radiation damage so that very large doses must be given, if the treatment is in many fractions, in order to produce erythema threshold changes (Table 3). However, microscopic changes in the finger ridges of monkeys have been observed with fractionated doses of about 10 Gy [G32]. The two main types of repair are recovery from sublethal damage and repopulation. The former is characterized by the N factor in the Ellis formula, which is in the region of $N^{0.3}$. Alternatively it may be described by the slope ratio, which on average is about 1:5. Thus on the basis of repair of sublethal damage alone the single dose may be increased by 5 times if given over a very long period. The other repair process is repopulation of surviving cells. When injury is manifest, proliferation increases until the population is restored to normal or near normal. Observations on mice and on radiotherapy patients substantiate this view.

B. GASTROINTESTINAL TRACT

1. Oesophagus

80. The histological changes observed in irradiated oesophagus are similar in the mouse and rat [P1, J2, K5]. More than 20 Gy in a single treatment produce mitotic death of the cells in the basal layer of the oesophageal epithelium. This is first seen at about 3 days after irradiation using a dose which kills about 20% of mice by 8 days. Hornsey and Field [H2] observed that this dose caused almost complete loss of the basal layer. Between one and two weeks after irradiation the pattern is more mixed with recovery occurring by repopulation in competition with further denudation. If the degree of damage to the basal layer is sufficiently severe the keratinized layers will not be replaced as they are lost, the underlying tissues will be exposed and radiation ulcers will result. Death occurs usually between the second and third weeks. After a reduction in food intake, animals become inactive, they suddenly lose weight and die. The probable cause of death is dehydration. Round-cell inflammatory infiltration in the submucosa and muscularis are possibly contributing factors [P1]. Mice which do not die appear to recover totally by repopulation of the basal layer. After 4 weeks surviving animals appear normal. The syndrome in mouse may be similar to the acute oesophagitis seen in patients during thoracic irradiation. However, late effects occur in patients, such as telangiectasia and fibrosis, which are only observed in animals after high doses, i.e., greater than 30 Gy in a single treatment, which is well beyond the LD_{50} for pulmonary damage.

81. The LD_{50} endpoint for damage to the oesophagus was developed by Phillips and Margolis [P2]. It was found that in anaesthetized mice the oesophagus is protected from radiation by hypoxia [P1, H2]. Whether or not the oesophagus of man is radiobiologically hypoxic is not known. In fractionated or low dose rate irradiation the tissue would, in any case, be expected to reoxygenate, so the oxygenated values of LD_{50} will be more applicable.

82. The results of Phillips and Ross [P1] and of Hornsey and Field [H2] on 3 mouse strains are in good agreement regarding the LD_{50}, as single dose values are close to 30 Gy. If the single doses are corrected for hypoxia, 20 Gy may be appropriate for the fully oxygenated oesophagus. An LD_{50} of 20 Gy has been measured for rats after irradiation of the thorax only, animals dying between 16 and 30 days [A19].

83. The repair capacity of the oesophageal epithelium is very large, values of D_2-D_1 between 5.5 and 8.5 Gy having been reported [H2, P1]. These values might be even larger if the single doses were not affected by hypoxia. The slope of the isoeffect curve is about 0.4. It incorporates both N and T in this case as the available data do not allow separation of the factors. Proliferation of the basal cells is rapid with a cycle time of about two days [L9]. However, Phillips and Ross showed a very small effect of increasing the temporal separation of two doses of x rays, for which there is no obvious explanation.

84. In summary, the reaction of the oesophagus is unlikely to be a limiting factor with thoracic irradiation, either for single or fractionated treatments. Oesophageal cells have a considerable ability to recover from sublethal damage and the cellular proliferation is high so that the tissue is able to withstand high levels of single and fractionated irradiations. Animals without signs of oesophageal reaction may die later from pulmonary damage.

2. Abdominal organs

85. Total body acute exposure of 10 Gy or more results in the gastrointestinal syndrome with death occurring between 3 and 10 days later, depending on species [M74]. The characteristic symptoms are nausea, vomiting and diarrhoea, leading to dehydration, electrolyte imbalance, loss of weight and infection. These symptoms are attributable to the depopulation of the intestinal epithelial lining. Loss of the cells in the crypts of Lieberkühn will lead to denudation of the villi owing to lack of replacement when the cells are naturally worn off. A close relationship between cell survival and the probability of death has been established by Hornsey [H1] who found that the

relationship was unaffected by either dose rate or radiation quality. A detailed review of gastrointestinal response to irradiation is given by Maisin et al. [M43].

86. Any whole-body radiation dose large enough to cause death from gastrointestinal syndrome is larger than that required to cause death at a later time from damage to the haemopoietic system [H3, B7]. Typical LD_{50} values at 5–8 days for six species range from 8 to 15 Gy [B7]. If the intestine is irradiated in isolation, the doses must be increased and the animals survive longer. If less than the whole intestine is irradiated the LD_{50} is further increased. Values of 13.2, 18.6 and 17.7 Gy were obtained in rats for treatment of the whole abdomen, front region or back region only [Z5]. It has been found that the small intestine is the most sensitive part of the gastrointestinal tract [B7]. Apart from lethality studies, there have been experiments using absorption changes, protein and fluid loss, electrolyte balance and changes in the incorporation of DNA precursors [B77, G42, M74, S72, T25, V19].

87. Withers and Elkind [W1, W5] developed two methods of estimating cell survival in irradiated small intestine by scoring either macrocolonies (visible to the naked eye) or microcolonies (visible in histological sections). From these studies a D_o of 1.3 Gy and D_2-D_1 of 4–5 Gy were derived. The value of D_o is similar to that from many other cells and tissues. The value of D_2-D_1 is similar to that derived from LD_{50} experiments and is also similar to values from other organized tissues (see Table 1). The large value of D_2-D_1 obtained indicates that the intestine has a very large capacity for accumulation and repair of sublethal damage. Withers [W12] presented results from which a slope ratio for jejunal crypt cells of about 3 may be derived.

88. Vatistas and Hornsey [V3] measured dose-effect relationships for the leakage of molecules of plasma protein size into the intestine. Radioactive PVP was used and the activity in the faeces was measured. Doses greater than 2 Gy of x rays produced increased leakage. The effect is not due to damage to the intestinal epithelium but to increased blood vessel permeability.

89. A recent quantitative method of assessing changes in the gut due to irradiation is the measurement of the absorptive surface [M5]. This is done from histological preparations. A minimum value is seen at about 3 days after irradiation and the technique can detect single doses of 3 Gy or greater.

90. With fractionated or low dose rate treatments the major repair component in the intestine is compensatory cellular proliferation. The natural cell cycle time in intestine is short, and it has a very high capacity for rapid proliferation. For example, the cycle time may be shortened to about 7 hours [L3].

91. Sato et al. [S32] observed numbers of cells in crypts and villi of mice where the trunks only had received 10 Gy x rays. The results confirmed the high degree of compensatory feedback and proliferation in the crypts. The timing of onset of this compensation varies with normal cell cycle time and tissue structure, being fastest in the jejunum and somewhat slower in stomach and colon (for a review see [D1]).

92. The potential for compensatory proliferation makes the intestine relatively unresponsive to fractionated or low dose rate treatments. Studies on rats [Q2, L10, W13] indicate that irradiation at 4 Gy per day produces an initial depopulation of the crypt cells, after which a new equilibrium develops. The cell number remains constant but their rate of proliferation is much increased. The animals appear to withstand this daily dose.

93. Maisin et al. [M6] studied the response of mice given 2 Gy daily to the abdomen. The animals survived this treatment up to the maximum total dose given, which was 60 Gy in 6 weeks. Compensation took the form of a reduced cell cycle time and an increase in the size of the stem cell compartment. The villi were, however, reduced to about 70% of normal and the number of cells per villus to about 60% of normal. The animals could not tolerate 3.5 Gy given daily.

94. In contrast to small intestine, far less is known about the responses of stomach or large bowel to irradiation. Changes in the characteristics of gastric emptying have been detected with single doses as small as 0.5 Gy [T27], but these changes are transient. Absorption changes [O15] and effects on gastric acid and bioelectric potentials were noted above 1.3 Gy [V20]. Gastric mucosa has typical survival curve characteristics [C32]. New methods to assess large bowel response are just becoming available [H65].

95. In conclusion, it is clear that the gut can withstand very large daily doses of radiation. All the studies mentioned have concentrated on the early forms of radiation injury but other major problems may arise later and very little information exists on late damage to the intestine. Quantitation of fibrosis and of changes in bowel habits are being attempted in several laboratories but no dose-response curves have yet been published.

C. CARTILAGE AND BONE

96. A growing long bone consists of an ossified shaft, the diaphysis, having metaphyses with an epiphysial growth cartilage at each end. The effect of irradiation is to reduce the growth potential, by sterilizing the stem cells in the epiphyses. The result is that the bone becomes permanently stunted. The phenomenon is therefore especially important in the young where growth is most active.

97. Kember [K6] developed a technique for estimating cell survival parameters for cells of growing cartilage in the tibia of young rats. He derived a D_o value of 1.65 Gy and an extrapolation number of 6 [K1]. Although the technique did not allow very precise measurements, these values of D_o and n were similar to those obtained for other types of cell.

98. Stunting of growth of bones has been investigated by various workers. Early measurements by Bisgard and Hunt [B8] indicated that in rabbits more than 3 Gy was required to cause measurable stunting. In a review of the older literature, Wells [W14] quoted values between 1 and 5 Gy for the threshold doses to cause stunting in various animals. In his own experiments on mouse tibia, Wells [W14] found a threshold of about 2 Gy and a 10% reduction caused by 4 Gy. On average 1% stunting was caused by 0.33 Gy.

99. Dixon [D15] performed similar experiments on the tails of 7-day old rats. The technique used allowed very accurate results and no threshold was observed. In these experiments 1% stunting was caused by approxi-

mately 0.2 Gy. By varying the oxygen concentration breathed by the rats, Dixon [D15] concluded that the epiphyseal stem cells were uniformly slightly hypoxic; the sensitivity was increased by about 10% when pure oxygen was breathed.

100. The effects of dose fractionation were examined by Dixon [D5] on rats. Considerable dose sparing due to recovery from sublethal damage was observed. D_2-D_1 increased with increasing dose to a maximum value of about 4 Gy. Kember [K1] using the clonal assay, obtained a value for D_2-D_1 of 3.5 Gy. These values are similar to those found with other tissues (Table 1).

101. In summary, growing cartilage appears to be one of the more sensitive tissues. The threshold dose for causing permanent stunting of bone growth is small or perhaps non-existent. The rate of stunting per Gy in growing rodents may be 3–5%.

D. HEART

102. The response of the heart to ionizing radiation has been the subject of few investigations, but there is little doubt of its radiation resistance. After moderate doses only histological techniques have revealed changes. Kurohara and Casarett [K5] noted degenerative changes in the rat myocardium after 24 Gy in a single treatment. At 28 days there was a loss of striation and granularity in the cytoplasm of myocardial cells. Fajardo and Steward [F35] showed identical pathology in rabbit and man: 20 Gy caused death of 4% of rabbits between 70 and 150 days after irradiation from injury to the pericardium or myocardium and often with congestive heart failure. The histological results indicate that the primary damage is to the capillary endothelium often leading to loss of capillary function. Insufficient microcirculation leads to fibrosis.

E. LUNG

103. The lung is a highly differentiated and complex tissue in which the capacity for cellular proliferation and hence restoration of the normal structure is poor. Therefore this tissue cannot easily restore function after large parenchymal losses. On the other hand, the respiratory system has a large reserve capacity which can compensate for losses in functioning parenchyma so that even after loss of an entire lung the other is usually adequate for respiratory requirements. It may thus be expected that pulmonary function is an insensitive index by which to measure the effects of irradiation up to doses which become life threatening. As a result, dose-effect relationships based on physiological changes tend to assume "all or none" threshold characteristics.

104. The pathological changes in irradiated lung have been described by various authors [K5, J3, P6, V4, M7, A20]. Changes tend to be patchy and are dose-dependent although not strongly. They occur in three phases. Microscopically, little effect is seen in the first days after irradiation, after which and for the first month or so, damage to the epithelial cells of the alveoli may appear, associated with fibrin-rich exudation. After low doses, although they may be sufficiently large to cause late changes, these early sequelae are very slight or even totally absent. Between 3 weeks and lasting for several months radiation pneumonitis is seen; it is characterized by fibrin-rich membranes lining the alveoli together with desquamative and consolidative changes and cellular infiltration. The walls of the alveoli become thickened. Late changes include further thickening of the reticulum and condensation resulting in atelectasis, fibrosis and loss of respiratory function.

105. The epithelium of the air passages, the hyaline cartilage and muscle appear to be relatively resistant and are not considered to be limiting components in the radiation response of the respiratory organs. However, other factors which tend to complicate the pathologic picture are: obstruction to air passages; infections and inflammatory reactions; capillary permeability changes; and haematologic changes.

106. The most important constituent of lung connective tissue is collagen [C28]. This has been often studied as a measure of lung fibrosis, both microscopically and biochemically [K46, C29, D50, G40, L11]. However, if the hemithorax of mice is irradiated, changes in relative collagen content occur much later than the time of death when both lungs are irradiated [K46, L11]. The indications are therefore that the pulmonary syndrome in mice leading to death as described above, results primarily from pneumonitis and its complications and not from fibrosis. Changes in elastin [F53] have also been reported.

107. Physiological studies have been performed on dogs, rats and mice by various authors [M8, S6, T4, T5, T6]. With doses greater than 10 Gy in a single dose or 30 Gy fractionated over 8 weeks there was a decrease in the diffusion of carbon monoxide, suggesting an alveolocapillary block and consistent with the histologically observed thickening of the alveolar walls. After doses of this magnitude or greater, a reduction in a variety of lung function parameters followed.

108. In general it appears that the time course of radiation-induced changes in lung is relatively independent of species. In all species the latent period for the onset of acute radiation pneumonitis is 1 to 3 months, similar to that in man. Also the doses required to cause measurable changes in physiology are similar to or greater than doses to kill animals from pulmonary insufficiency, i.e., greater than 10 Gy in a single treatment.

109. Following irradiation with single doses of x rays of approximately 12 Gy or higher (or equivalent fractionated doses) animals die from acute pneumonitis between about 3 and 7 months after irradiation. After lower doses, surviving animals may develop long-term changes leading to pulmonary fibrosis [T31]. Radiopneumonitis is thought to result primarily from direct effects on parenchymal cells with secondary damage to the vascular connective tissue. Fibrosis is thought to be a consequence primarily of damage to capillaries with secondary effects on the parenchyma [A20, K5, P6, M7]. Van den Brenk [V4] suggested that the primary target cells are the type II alveolar cells which produce surfactant, a lipoprotein preventing adhesion and collapse of the alveoli on expiration. A reduction in surfactant would lead to an unbalance of osmotic and hydrostatic pressures resulting in accumulation of fluids in the alveoli, a characteristic of radiation pneumonitis which however could also result from damage to blood vessels. Various studies of the function of type II cells have been made. Total lung lipids, total phospholipids, lipid turnover and surface tension have all been measured, but the results do not yield a clear picture [S69, G40, P38, P39, P40, M76, G41].

110. Perhaps the most sensitive end-point for assessing damage to lung in experimental animals is the probability of survival late after irradiation. Phillips and Margolis [P2] observed that mice die from lung damage from about 80 days after irradiation and that no further deaths occur beyond 160 days. They estimated the LD_{50} at 160 days for a variety of treatment regimes with x rays. The mice died with obvious signs of respiratory failure, the lungs were wet, indicating vascular leakage. This was also indicated by isotope studies [H52]. Bacterial infections were rare and the main damage was to the alveoli. Field et al. [F17] reported very similar results to those of Wara et al. [W15]. They may be summarized as follows: the LD_{50} in mice is 12–14 Gy, depending on the strain. There is a marked effect of fractionation of x rays, such that data are fitted by $N^{0.39}$ up to 8 fractions and $N^{0.25}$ from 8 to 32 fractions (Figure V). Repair of sublethal damage

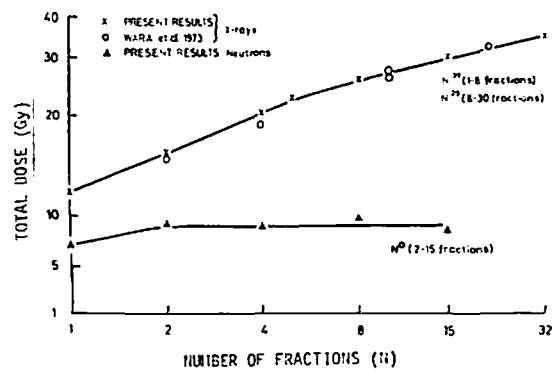

Figure V. Isoeffect curves of total dose versus number of fractions for lung LD_{50}. The upper curve is for x rays and the lower curve for neutrons. All data are corrected for an overall effective treatment time of 1 day [F17]

between two fractions occurs in a few hours as is the case for other cells and tissues [F3]. If lung damage is examined by the method of Dutreix et al. [D9], it is seen that repair of sublethal damage is considerable, perhaps greater than for other tissues. When the slope ratio is calculated for lung the ratio is very similar to values derived for skin with a ratio of 1 : 7 [F15].

111. With a constant number of fractions and a variable time between them, the T factor for lung may be derived. Two experimental series [W15, F12] showed that $T^{0.07}$ was a good fit to the data. This is smaller than that for skin owing to lack of repopulation in lung. Field and Hornsey [F8] showed that for neutrons there was no further effect of extending the treatment time beyond an hour, i.e., after repair of sublethal damage. Since repopulation is thought to be similar after x rays and fast neutrons, a slow repair process was suggested as the explanation for the x-ray result which is absent after neutrons. Repopulation between fractions has been excluded as the explanation by labelling experiments [C31] leaving slow repair as the explanation for the T factor.

112. In summary, lung is a highly complex organ comprising more than 40 cell types. The pathological changes following irradiation have been described, but the primary target or targets remain uncertain. Damage to type II cells or vascular damage are considered generally to account for the changes in elastic properties, pneumonitis and fibrosis that occur. Lung is a relatively sensitive tissue, probably because it lacks the rapid proliferative ability. However, lung has a large capacity for repair of sublethal damage which enables it to tolerate a high level of fractionated or presumably continuous irradiation.

F. LIVER

113. The liver performs a variety of essential functions. Its cells are normally not actively dividing and, therefore, radiation damage caused by moderate doses can only be demonstrated late after irradiation. As a result there has been a long debate as to whether liver is a radioresistant organ or not (see [L31] for details of post irradiation changes). Irradiation of the whole liver in laboratory animals is exceptionally difficult without causing severe damage to other more rapidly proliferating organs such as the intestine, irradiation of which can lead to early death. The liver has a very large reserve capacity and is able to maintain apparently normal function despite a large part of it having been damaged. In addition, the hepatocytes have an extraordinary capacity for regeneration. Should part of the liver be injured these cells will rapidly proliferate to maintain hepatic function.

114. The literature contains few animal experiments on liver and most of these are confined to studies of repopulation and regeneration. Results obtained also appear to be highly variable (see review [L12]) and it has been suggested that this is due to variations in the state of liver cells at the time of irradiation or subsequently. Any liver disturbance which elicits a proliferation response may seriously increase the reaction to irradiation, and most experiments have been performed in this way.

115. A technique for measuring liver damage was devised by Weinbren et al. [W16] in which latent damage was unmasked by stimulating the liver into division either by surgical removal of part of the organ or by using damaging chemicals, e.g., carbon tetrachloride. These experiments involved irradiation of two-thirds of the liver of rats (on exteriorization) to 50 Gy in a single dose. Major changes were not noticed unless partial hepatectomy was subsequently performed. Kinzie et al. [K7] reported fairly minor changes in rat liver after single doses of 15 Gy and Dettmer et al. [D16] showed very slight changes after total liver irradiation with 10 Gy but severe after 25 Gy. De Mignard et al. [D17] measured only a transient change in rats after 6 Gy, which had returned to normal by 6 weeks. Damage to the microsomal drug metabolizing enzyme system in the rat has been observed, but only after high doses of 7.5 Gy given daily. [Y3, N12]. Verga and Cali [V5] irradiated rats with 0.5 Gy per day for a total of 33 Gy before an abnormality was observed, i.e. hypertrophia of Kupfer cells. When 3 Gy per day for a total of 60 Gy was given to rats there was no reduction in the effect of detoxification.

116. Thus, liver is a slowly proliferating organ, but its cells can be stimulated into division by injury (including that from radiation) and thereby unmask latent radiation damage. Single doses of x rays of more than 10 Gy are needed for demonstrable permanent changes and this dose may be increased by a factor of 3–6 by extended fractionation.

G. URINARY SYSTEM

117. Under normal circumstances there is little cell proliferation and except for large radiation doses the effects of irradiation occur late. These late effects include proteinuria, hypertension and reduction in kidney function. It is possible to measure various aspects of kidney function, e.g., glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and tubular resorption rate (TM_{PAH}).

118. Human and animal kidneys show similar histopathological changes resulting from irradiation. These changes are reported to occur to varying degrees and at varying times but can be summarized as degeneration, necrosis or atrophy of the tubular epithelium; increased interstitial connective tissue; thickening of basement membranes; hyalinization of connective tissue; replacement fibrosis; degeneration necrosis; swelling or proliferation of endothelial cells; intimal vascular thickening; thickening of vessel walls and narrowing of lumina; degeneration, necrosis, or atrophy and scarring of glomeruli. Similar changes were described after irradiation of dog kidney by fast protons [F36]. A detailed review of the kidney pathology after irradiation has been made by Mostofi and Berdjis [M9].

119. It is by no means clear whether vascular or parenchymal damage in kidney is the more important. However, it is known that blood vessels become more sensitive to irradiation in conditions of hypertension [A3]. Animal experiments on kidneys have in general led to wide differences in interpretation. There is no consensus on the degree, extent or time of onset and progression of specific changes and considerable disagreement has resulted in interpreting the histological findings [M9].

120. The dog has been used by various experimenters. In some cases whole-body irradiation has been given, sometimes only the kidneys or one kidney has been treated and sometimes one kidney is removed and the other irradiated. Doses of 20 Gy or less cause profound changes. Mendelsohn and Caceres [M10] performed unilateral nephrectomy, allowed 15 weeks for compensatory hypertrophy of the remaining kidney and irradiated over 13 days. Kidney function tests indicated that tubular function was the most sensitive index but the authors suggested that the ultimate effect was through vascular damage.

121. Pospisil and Zaruba [P7] and Zaruba [Z1] measured kidney changes after whole body irradiation and found some with 6 Gy, but concluded that they were through indirect effect rather than direct damage to the kidney. Maier and Casarett [M11] irradiated dogs with a range of doses from 5 Gy. Physiological changes were measured during a 6 months period after irradiation. It was found that 5 Gy produced very little change but 10 Gy produced morphological and functional modifications at 6 months. In the neonate 3.3 Gy did produce changes in renal function later in life [L32].

122. In pigs, Hopewell and Berry [H12] measured physiological changes and observed thresholds for reduced function after approximately 10 Gy in a single dose or 40 Gy in 30 fractions in 6 weeks.

123. Rabbit kidney may be rather radioresistant [M9] but Caldwell et al. [C7] reported LD_{50} values at 6 months of 18 Gy in a single dose or 57 Gy in 24 fractions.

124. Effects in rats have been studied by Bennet et al. [B10] and Lamson et al. [L13] who observed hypertension with doses as low as 5 Gy. Hypertension was observed even if only one kidney was irradiated [W17]. Berdjis [B11] observed nephrosclerosis 1 year after 9 Gy to rat kidneys which was reduced but not eliminated if the rats had been given 5 Gy whole-body irradiation. Kärcher and Schulz [K8] observed functional and enzymatic changes if both kidneys were given 10 Gy, which were reversible if only 1 kidney was irradiated. Chauser et al. [C8] measured ERPF and collagen deposition at 18 weeks after irradiation of 1 kidney only in rat; 10 Gy had no effect on function and caused a very small increase in collagen; 20 Gy caused renal failure between 16 and 18 weeks, but the rats appeared normal.

125. Many authors irradiated mice over the whole body and estimated kidney changes. These occur at fairly low doses of about 5 Gy, but as stated previously, may not be direct effects on the kidney [B12, G1, C9]. Irradiation of only the kidneys by Glatstein [G2] demonstrated a threshold dose for impairment of renal blood flow of less than 10 Gy. Phillips and Ross [P8] estimated the LD_{50} to be 13 Gy at 16 months by unilateral nephrectomy and irradiation after hypertrophy of the remaining kidney. The threshold dose to cause death in these experiments was about 8 Gy. Donaldson et al. [D18] measured the inhibition of compensatory renal growth after unilateral nephrectomy in weaning mice. In this case the threshold for a permanent effect was 10–15 Gy. Geraci et al. [G3] measured decrease in kidney weight at 6 months and observed a threshold of about 10 Gy x rays and 7 Gy neutrons. Dogs irradiated with two doses of 3.5 Gy of fast protons and kept alive by shielding part of the bone marrow, showed a variety of changes after 6 months, including a decrease in secretory activity, proteinurea, hypertony and blood changes [N10]. Threshold doses from single dose experiments are summarized in Table 4.

126. Fractionation experiments have been performed on mouse kidney by Phillips and Ross [P8] and by Glatstein [G4] and on pigs by Hopewell and Wiernik [H13]. All series showed a marked reduction in the effect of irradiation with increasing fractionation. Recovery from sublethal damage was perhaps even greater than with skin but less than for lung [P8]. In general the Ellis formula provides a reasonable description of the fractionation effects on kidney.

127. The late foetal or neonatal kidney has been shown to be more sensitive than in the adult. For example, mice irradiated at birth showed far more intercapillary glomerulosclerosis than if irradiated at 12, 23 or 53 days of age [G1]. Guttman showed that 4.5 Gy given to mice at birth caused significant changes in the glomeruli followed by deposition of collagen. Phemester et al. [P29] observed beagle dogs which had received 2.7–4.4 Gy either at 55 days in utero or at 2 days old. The animals subsequently died with chronic renal failure.

128. Very few studies on the response of the urinary bladder to irradiation have been performed. However, recently a functional assay for damage to the mouse bladder has been developed [S73] and it has shown that beyond 5 months after single doses of irradiation the threshold for detectable changes is 15 Gy. Damage was to the epithelium with a loss of the specialized polyploid surface cells. Fibroses became apparent after one year. Compensatory proliferation occurred only when loss of function became apparent [S74].

129. In conclusion, a wide range of physiological measurements and histological changes have been reported for kidney. Data for threshold doses are relatively consistent between experimenters and for different species and are in the range 5–12 Gy. With extended fractionation these threshold doses would be increased by a factor of at least 3. Kidney is considerably more sensitive around the time of birth.

H. CENTRAL NERVOUS SYSTEM

130. Effects of radiation on the nervous system were comprehensively reviewed by the Committee in 1969 [U4]. The main findings were that the central nervous system is very sensitive whilst developing. Transient functional and behavioural changes can occur in animals with doses greater than 0.5 Gy and in some cases ionizing radiation can be detected at levels of a few tens of mGy, but there is no evidence of permanent injury at these dose levels. It was noted that workers exposed for many years within the recommended limits did not develop any consequence of note. This topic was reviewed by Maisin [M71]. It was pointed out [U4] that for permanent injury the nervous system of the adult was less sensitive than some other tissues and organs. During the subsequent years no new data have significantly altered these views. Additional information has been obtained, particularly on the role of the vascular system in the pathogenesis of radiation-induced neurological syndromes, although its exact role remains unclear since the vascular changes occurred more than one year after irradiation [R49].

1. Spinal cord

131. Irradiation of the spinal cord in animals and in man may result in myelopathy whose probability and time of onset are dose dependent. In some cases the time of onset both in rats and mice has been found to be inversely related to the dose of irradiation [C10, G5]. However, other experimenters observed after about 100 days acute ataxia and paralysis the probability of which was dose dependent [W6, V6]. In these experiments only a short segment of the cord was irradiated.

132. At the dose levels required to produce such late paralysis after irradiation of the cervical cord, necrosis was restricted to the white matter, but small haemorrhages were observed scattered throughout both the grey and white matter.

133. Using rats, White and Hornsey [W6] found that no paralysis occurred with single doses of less than 20 Gy. Van der Kogel [V7], also using rats, found that doses above 17 Gy caused paralysis. In these experiments paralysis occurring within 6 months was attributed to necrosis of white matter, i.e., neurological damage, whereas vascular injury appeared to cause later paralysis at 12–18 months at slightly lower dose levels. In mice, Geraci et al. [G5] observed a threshold of about 12.5 Gy x rays and Goffinet et al. [G6] observed only a small effect with the lowest dose used of 20 Gy.

134. The effects of dose fractionation on the spinal cord were carefully investigated by van der Kogel [V8] and by White and Hornsey [W6] on rats and by Geraci et al. [G7] and Goffinet et al. [G6] on mice. In all cases the dose to provide myelitis increased more rapidly with increasing the number of fractions than for most other tissue end-points, showing that the spinal cord has a relatively large capacity for accumulation and repair of sublethal damage. In both rat experiments the effect of varying the time between fractions was tested. There was initially no effect on LD_{50} of increasing the time separation, until 8–16 weeks [V1] or about 5 weeks [W6]. Both studies suggest that there is no slow repair in the spinal cord, but delayed repopulation. The repopulation gave a time factor of about $T^{0.03}$ and the dose fractionation an N factor of approximately $N^{0.4}$.

135. Goffinet et al. [G6] also tested the effects of irradiating different lengths of cord. They found that the tolerance for a single dose was reduced by about 20% when the irradiated length of mouse cord was increased from 6 mm to 12 mm.

2. Brain

136. Neuro-physiological methods to enable detection of effects of irradiation to the brain [L14] indicate that in some respects it is radiation sensitive. For example, Minamisawa et al. measured changes in evoked potentials recorded from the visual cortex of rabbits on photic stimulation and showed that this function gradually decreased over the lifetime of the animal after single doses of 1–3 Gy or 3–30 Gy fractionated [M44, M45, M72]. However, in general the organ was considered to be fairly radiation resistant. Doses greater than about 20 Gy are required to produce morphological changes and the latent period is shorter with increasing dose [Z2].

137. Russell, Wilson and Tansley [R6] investigated the response of rabbit brain. They estimated the minimal single dose to produce delayed necrosis to be between 20 and 24 Gy. Hopewell and Wright [H14] measured the latent period between irradiation and death in rats. In normal animals irradiated with 10 Gy to the head there was no weight loss, no neurological symptoms and their life span was not different from controls. However, 20 Gy did cause weight loss and the life span was reduced. Histologically there were three types of change: the earliest changes were in the subependymal plate, a region of mitotically active cells found around the anterior of the lateral ventricles; large areas of necrosis were observed later, mainly in the white matter; vascular lesions in particular hyaline thickening, fibrinoid necrosis of vessel walls and microaneurysms occurred still later.

138. The cells of the subependymal plate are the stem cells for neuroglia of the white substance [L15]. After irradiation with photons the number of these cells is depressed but recovers for doses of 10 Gy or less. With 15 Gy of photons there is total destruction of the subependymal layer [C11]. Even 5.5 Gy cause a persistent change in the glial cell balance [R52]. With fast neutrons there appears to be no recovery after doses as small as 1 Gy [C11].

139. Irradiation of rabbits with 1.5 Gy produced a decrease in intracranial pressure, while 10 Gy caused a transient increase in intracranial pressure persisting for 2 days [L26, L27].

140. An increasing amount of data supports the view that structural damage to neurones can occur after relatively low doses [A21, V14]. Fast protons (50–645 MeV) [K33] and gamma rays in the range 1–6 Gy produced degeneration in the rat brain cortex between

1 and 12 months after irradiation, leading to neural destruction. At 12 months after 2–4 Gy, 25–40% of the external granular layer of rat brain cortex was irreversibly altered. These degenerative changes were increasing with an increasing period of observation after irradiation, indicating that the nervous tissue cannot simply be regarded as radioresistant.

I. ENDOCRINE ORGANS

1. Thyroid

141. The parenchymal cells of the thyroid are not normally actively dividing and therefore do not exhibit early radiation-induced mitotic cell death. After doses of 50–100 Gy from ^{131}I interphase death occurs, detectable during the second week after irradiation [W43]. At later times there is no further radiation-induced cell death. However there is progressive atrophy of the parenchyma resulting in hypothyroidism [W44], due to prolonged impairment of cellular reproductive capacity, as demonstrated by reduced response to goitrogenic stimulation. Early radionecrosis of the gland, which is the result of damage to the fine vasculature, may appear but requires massive doses, well in excess of those which produce late changes resulting from damage to the epithelial cells. The pathogenesis of the thyroid changes associated with the development of hypothyroidism appears to involve primarily patchy degeneration and fibrosis of the fine vasculature and interfollicular stroma and secondarily degeneration of the follicular epithelium. In some of the less affected regions there may be hyperplastic reactions resulting in atrophic nodular structures containing little colloid [R1].

142. The time of onset of the late hypothyroidism is dose related, occurring earlier with larger doses. Using adult dogs, Michaelson et al. [M12] showed radiation-induced primary hypothyroidism occurring 3–4 years later with a threshold of about 10 Gy in a single dose. At these times the animals showed signs of thyroid malfunction, such as decreased activity, coarsening hair, increasing obesity and reduced body temperature. The uptake of ^{131}I by the thyroid was also reduced. The authors suggested that this radiation-induced chronic thyroiditis may involve an autoimmune mechanism through leakage of thyroglobulin and microsomal material, both of which have been shown to be antigenic.

143. Techniques to estimate epithelial cell survival have been developed. These are based on the fact that application of a goitrogenic stimulus, e.g., methylthiouracil, prevents hormone iodination and leads to a reduction in blood hormone level. As a result thyrotropic hormone level (TSH) is raised and the thyroid gland increases its weight by 3–5 times over a period of about a month. This weight increase is reduced by irradiation. With a single dose of 10 Gy the response is reduced by about 50% [M13]. Clearly the thyroid has a large reserve capacity. Not only can it tolerate a considerable loss of material, but it will also produce relatively more T_3 hormone at the expense of T_4, the former being by far more effective.

144. A transplantation technique was recently developed to assess thyroid cell survival. Irradiation was performed either in situ or in vitro after preparation of a cell suspension. In both cases the parameters of cell survival were found to be within the range for most mammalian cell types, although the D_0 of 19 Gy was rather higher than usually observed, indicating that thyroid cells could be rather more resistant than most [C22].

145. The thyroid is, in conclusion, a non-proliferating tissue in which radiation effects occur after many years. 10 Gy x rays in a single external treatment is required to cause signs of malfunction or a 50% reduction in epithelial cells.

2. Pituitary

146. In the adult the pituitary is regarded as a radioresistant organ. Its suppression results in a fall of gonadotrophin and in reduced function of other endocrine organs such as the thyroid and the adrenals [S34]. However, a fall in growth hormone may result from damage to the hypothalamus, as has been reported after radiotherapy, particularly in children [K52]. In the adult animal, very large doses of approximately 300 Gy are required to ablate the pituitary [R1]. In immature animals the organ is far more sensitive, for example, whole-body irradiation of 1 Gy caused weight loss in squirrels and 6 Gy caused stunting of growth in 2-day old rats [M46].

3. Adrenals

147. Evaluation of the response of the adrenals to irradiation is complicated. The adrenal responds to the stress from irradiation by an increase in weight and hormone production. It is therefore difficult to assess direct effects on the gland. As with the pituitary, the organ is resistant in the adult, but in immature animals it appears to be more sensitive. Six Gy to calves caused significant hypertrophy [R31] and 4 Gy to young rats prevented weight gain [W39]. Older animals are more resistant, although 9 Gy to rats caused medullary venous thrombosis and atrophy of the gland. In all the above experiments the animals died from intestinal injury a few days after irradiation and therefore the effects on the adrenals may not have been permanent, as was shown in experiments in which rats lived longer [S34]. Permanent changes to the adrenals require doses of 20 to 30 Gy [E18].

J. GONADS

1. Testis

148. Irradiation of the testes produces sterility, which may be permanent or temporary depending on the dose levels and dose rates employed. An understanding of the effects of irradiation on the testis requires a knowledge of the development of mature sperm from the testicular stem cells. The accepted model for this process is that described by Oakberg [O2, O3, O4] which has recently been re-examined by Meistrich et al. [M14]. The basic stem cell is an undifferentiated type A spermatogonium designated A_{is} which has an LD_{50} of 2–3 Gy [O5, E8, M42] and cycle times ranging from 2–9 days [O4, H15]. The developing spermatogonium is most sensitive when it is in the differentiated stages A_1 to B. There also exists an intermediate stage, designated A_{al}, with intermediate sensitivity between the stem cells A_{is} and the differentiated spermatogonia. Progression of differentiation continues through spermatocytes, spermatids to spermatozoa, the resistance to irradiation

increasing with further differentiation. The full cycle takes about 6 weeks in a mouse and about 10 weeks in man. Biochemical changes due to irradiation with x rays or protons have been investigated [S38, F37]. The topic has recently been reviewed by Kondratenko [K32].

149. From this description, it is clear that small doses will induce temporary sterility by killing the sensitive differentiating spermatogonia. Larger doses may also deplete the type A_{al} spermatogonia without inducing permanent sterility, since the stem cells are more resistant. If the stem cell compartment is seriously depleted, it will be initially restored by cell proliferation, after which it will begin to differentiate and ultimately produce sperm. About 20% of the normal spermatozoa count is required for conception.

150. Radiation doses to induce sterility have been measured by various workers. In mice, the Russells [R7, R8] observed recovery after single doses of 6 Gy and later after 10 Gy, but mutations were produced in the survivors. In rats, Shaver [S7, S8] measured single threshold doses of 5 Gy in adult and 3 Gy in immature animals. Erickson observed a threshold of about 4 Gy in the rat [E19]. In rabbits, single doses greater than 9.5 Gy were required [C12] and in bulls 8 Gy produced only reversible injury and not permanent sterility. With dogs, Casarett and Eddy [C13] demonstrated that even after 20 Gy some recovery occurred. In man single doses of about 5 Gy would appear to be around the threshold level [L16].

151. The response of the testis to fractionated and low dose rate radiation is different from most other tissues. The evidence suggests that there is no "dose sparing" by protracting the treatment as is normally the case but fractionated treatments may actually be more effective for a given total dose. Brown et al. [B13] reported that continuous irradiation at 0.02 Gy/day to rats and mice allowed reproduction for at least 10 generations although there was some evidence of life shortening [D19]. At dose rates slightly greater than 0.02 Gy/day, sterilization ultimately resulted. However, Stadler and Gowen [S9, S10] reported maintenance of the germ line in mice irradiated for 11 successive generations with daily doses of up to 0.03 Gy/day. A total dose of 15 Gy was accumulated without causing reduction in reproductivity or a change in the sex ratio. Oakberg and Clark [O6, O7, O8] reported a threshold of about 0.13 Gy/day in mice. Total doses accumulated at 0.014 Gy/day to 3 Gy caused the spermatogonial population to reach a new equilibrium ratio of 80% of the control.

152. Casarett and Eddy [C13] compared the effects of single and fractionated irradiation of testis in dogs using whole-body irradiation. Treatment at 0.03 Gy/day to a total of 3.75 Gy caused a greater degree of irreversible depression in sperm production than did a single exposure of 3.75 Gy. When 4.75 Gy was given at 0.03 Gy/day, all dogs became permanently aspermic. With life-long irradiation, 0.0012 Gy/day causes no deleterious effects, but 0.006 Gy/day ultimately caused permanent aspermia and sterility if total doses greater than 10 Gy were given. It is possible that recruitment of cells from an otherwise resting and resistant population into a more sensitive phase may be primarily responsible for this unusual and important effect of dose fractionation.

153. Fedorova and colleagues [F39, F40] irradiated dogs for 6 years at varying dose rates. There was no effect on sperm production below 0.0017 Gy/day, but 0.0034 Gy/day to a total of 7.5 Gy led to oligospermia. Giving 0.0017 Gy per day plus a single treatment of 0.42 Gy three times per year caused a still greater effect and after 2.5 years the ability for fertilization was lost, although recovery took place.

154. The hormonal secretory function of the testis is far more resistant to irradiation than spermatogenesis since 0.25–0.5 Gy/day to a total of 50–100 Gy in 25 weeks causes no reduction in secretory function [R32].

155. In summary, irradiation of the testes causes temporary sterility and with larger doses sterility may become permanent. The testis is unlike other normal tissues in that repair of sublethal damage does not occur. Moreover, fractionated or continuous irradiation renders the tissue more rather than less sensitive. In mice continuous life-long irradiation between 0.02 and 0.13 Gy/day is reported to cause permanent sterility. In dogs, the figure is lower, 0.006 Gy/day being sufficient but 0.0012 Gy/day insufficient to cause sterility.

2. Ovary

156. The most sensitive and critical component in the female reproductive system is the germ cell. In the ovary all cells in the oogonial stages progress to the oocytes in the embryo. Soon after birth all oocytes are in the resting phase with no further cell division and in the adult there are no stem cells but a finite number of follicles. These have been graded into categories related to their degree of maturity. In some species, e.g., mice, rats and rabbits, the primordial oocyte is more radiosensitive than the later stages of oocyte maturation [O7]. Such differences in sensitivity with stage of development have not, however, been observed in guinea pig, pig or cattle [E9, E10] or the trend in sensitivity is reversed, as in the monkey [B14].

157. There are great interspecies differences in the sensitivity of the ovary to irradiation. In mice 0.1 Gy in a single treatment was sufficient to destroy 50% of the primordial follicles [O9] and 1 Gy produced permanent sterility [R9]. Rat ovary is less sensitive, about 0.7 Gy being required to destroy 50% of the primordial follicles [M15], and more than 8 Gy to produce sterility [K9]. In monkey, the oocyte is little affected by 10 Gy [B14] and the minimum sterilizing dose is about 20 Gy [B15]. With the marmoset, more than 6 Gy is required to kill half the oocytes [L16]. Erickson has shown that the doses to kill half the oocytes in pigs and cows are 5 and 9 Gy, respectively. Single doses of 4 Gy or two doses of 3 Gy each, separated by 55 days, had little effect on the germ cell or follicular count, no effect in the production of ovarian abnormalities, and no change in fertility or quality of offspring [E11]. These differences in radiation sensitivity of ovarian follicles between species are discussed in chapter V of Annex I. They may simply reflect the existence of a sensitive stage, which may or may not be irradiated during the development of these species.

158. Andersen and Rosenblatt [A4] studied fertility after single or fractionated irradiation of female beagles. A single dose of 3 Gy had no noticeable effect, but 7.5 Gy given at 0.5 Gy per week caused total sterilization. Many authors [B2, S9, S10, G8, G9] reported maintenance of the germ line in mice given continuous irradiation for 11 successive generations with daily doses of less than 0.03 Gy. Mice accumulated 15 Gy at

these low dose rates, apparently without harm and with normal reproductivity and sex ratio, although at 0.02 Gy/day there was a progressive reduction in litter size [B2].

159. The developing oocyte is more sensitive. Afollicular ovaries and sterilization were produced by fractionated irradiations of 0.1 Gy/day to a total of 2 Gy in 2–4 day old dogs and 2.7 Gy in foetal monkeys [A5, A6]. In another experiment [A7], doses of 0.115 Gy given twice weekly to a total of 2 Gy severely damaged the ovaries of eight out of nine foetal bonnet monkeys and reduced follicle counts to less than 25% of normal, without causing damage to any other organ.

160. In conclusion, although there are considerable differences in sensitivity between species, the adult ovary is generally more resistant than the testis because the oogonial stages have progressed to the more resistant oocyte by the time of birth. However, the ovaries in foetal animals are severely damaged by much lower doses than those required to cause serious changes to the adult ovary. Fractionated treatments to a total of 2 Gy cause severe damage to the developing ovary in dog and monkey.

K. THE EYE

161. The eye is generally considered to be one of the more sensitive organs to irradiation. Damage to any part of the eye may occur, but for long term effects the most sensitive structure is thought to be the lens. Here, clinically significant progressive or irreversible changes can occur well into maturity, by radiation doses which evoke only transient reactions in other ocular structures, such as the cornea and conjunctiva.

162. Detectable changes in the normally transparent lens may vary from tiny flecks to almost complete opacification resulting in total blindness. Cataracts are most usually associated with old age or with abnormal metabolic disorder, chronic ocular infection, or trauma. The lens consists largely of fibre cells and is covered with an epithelium anteriorly. Dividing cells are limited to the anterior equatorial region, and the progeny of these dividing cells migrate posteriorly and then centrally to form the lens fibres. Cell division continues throughout life, and so the lens may be regarded as a self-renewing tissue. However, it is a cellular system that has no blood supply and no mechanism for cell removal. If dividing cells are injured by radiation, the resulting abnormal fibres are not removed from the lens but migrate toward the posterior pole and, because they are not translucent, they constitute the beginning of a cataract.

163. Many of the cells in the central portion of the lens are capable of proliferation but are in the resting stage G_0 [G10]. These cells may be stimulated into division, for example by injury. According to Bateman and Berdjic [B16], cataractogenesis can proceed either by germinal zone epithelial damage or by metabolic deficit of cortical fibres. They suggest that the former predominates at low radiation doses and the latter at higher doses.

164. Work on establishing the threshold doses in animals seems to fall into two groups. In all animals, including man, there is a finite probability of developing lens opacities during a life-time. In some laboratory animals this probability is very high. The threshold dose in these cases is defined as the dose to significantly increase the probability of opacification. The values obtained are very low indeed, ranging from a few hundredths of Gy depending on the type of damage [e.g., B16, U2].

165. In other animals, including man, the natural probability is very low. It was shown by Focht et al. [F18] that in this case increasing the dose causes a reduction in the latent period. In this type of response the threshold is much higher, for example, single doses of 5 Gy in mice at 1 year [R10], more than 3 Gy in rabbits at 4 years, and 5 Gy in rats at 2 years [U2].

166. Protons ranging from 25–645 MeV produced qualitatively similar effects to photons, at the same dose levels, independent of proton energy. The inverse relationship between dose and latent period was confirmed and it was shown that the probability of causing opacities decreased with decreasing dose rate or by giving the treatment in 2 fractions [K30, K31].

167. As with many other tissues, damage to the lens is reduced by protraction of irradiation. In experiments to test the time-dose relationships, mice were irradiated with 14 different schedules and followed for cataractous changes [S11]. The effects of number of fractions and overall treatment time were not separated and the slope of the "Strandqvist" isoeffect formula was calculated as 0.3. An analysis of earlier work [K10], also on mice, gave a similar figure. However, Merriam and Focht [M16] derived a factor of 0.17 from studies on rat and on man which represents a more pessimistic view of the sparing by fractionation.

168. It could be concluded that a minimum of 3–5 Gy are required to produce significant opacities in animals which are normally not prone to cataract development, as is the case for man. But in animals who are especially prone, very much lower doses increase the incidence. More dose is required when fractionated, but the dose sparing may be rather less than in other tissues.

L. HAEMATOPOIETIC TISSUES

169. Changes in all the elements of the haemopoietic tissues are observed after fairly low doses of radiation from the circulating blood cells, to bone marrow, spleen, thymus and lymph nodes (see [P10] and [M51] for reviews). These tissues have been extensively studied, partly because some elements are very radiosensitive and partly because relatively easy quantitative end-points are available.

170. Changes in peripheral blood counts have been well documented in both man and experimental animals (Figure VI). A differential count is considered to be a useful biological dosimeter in man but is too variable from animal to animal to be a good quantitative assay in rodents. In man, if the lymphocyte count falls below 1200 within 24–48 hours, the prognosis is serious and if it falls below 300, the patient is almost certain to die [D21, G30, A22].

171. Early experimental studies were mainly on organ weight loss and cellularity. After 4 Gy in mice there is a measurable weight loss in spleen, lymph nodes and thymus. The organs reach a minimum weight at 2–4 days, but are restored to normal at 2 weeks [B17]. In the bone marrow cell depletion is maximal at 3–4 days [B17] but later haemorrhage masks the hypocellularity

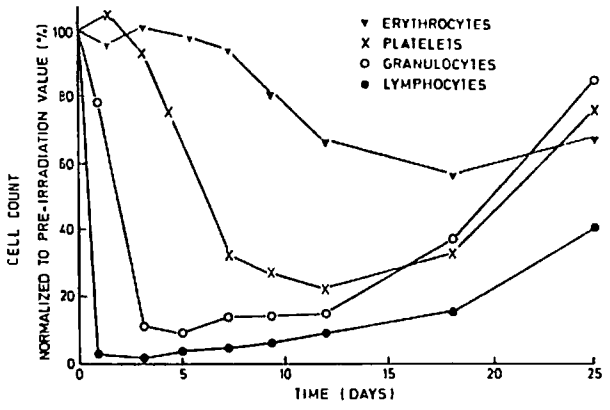

Figure VI. Peripheral blood counts of rats following 5 Gy whole-body radiation [D21]

[F19, N1]. Temporary changes in weight of these organs may be caused by very small doses, and as little as 0.4 Gy can be detected [K11, M17]. Changes in the bone marrow architecture (in excess of 20 Gy) cause permanent hypocellularity of the bone marrow, probably due to fibrosis [K12, K13, F19, S70].

172. Much effort has been directed towards the study of lethality from whole-body irradiation at 20–30 days caused by bone marrow depletion and resultant haemorrhage (from lack of platelets) and infection (from lack of lymphocytes and phagocytic cells). Table 5 shows some lethality results for a range of animal species. There appears to be a tendency towards lower LD_{50} values (higher radiosensitivity) in the larger species (Figure VII), but this may be partly a result of infestations with intestinal parasites [H6].

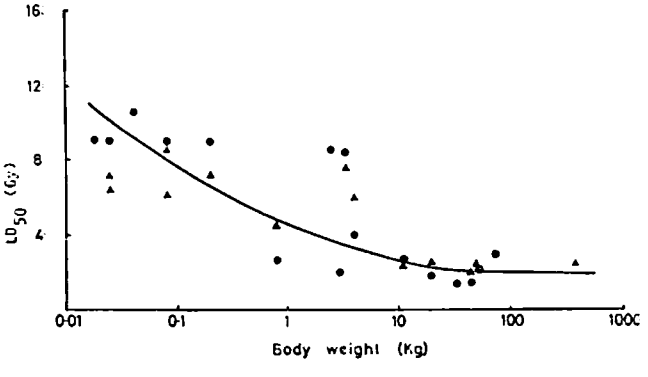

Figure VII. LD_{50} for bone marrow depletion as a function of animal weight [H6, B7]

173. If partial body irradiation is performed the LD_{50} increases. In rats the LD_{50} at 30 days was 11.5, 15.3 and 16 Gy for irradiation of the whole abdomen, front region and back region respectively [Z5]. LD_{50} was also shown to be related to the average area of individual endothelial cells from the aorta of different species [S37]. In mice it was 7.7, 14.7, 11.6 or 18.0 for irradiation of whole body, head, trunk or lower body, respectively [S71]. When mice were given 5 Gy of x rays either whole body or to the lower body, trunk or head only, the changes in leukocyte or platelet count were essentially similar. Loss of cells was greater, however, after whole-body than partial-body treatment [K47].

174. Among the more quantitative assays are those which test for the pluripotential stem cell, from which all blood cells are believed to derive. This cell is unidentifiable on morphological criteria, although the suggestion has been made that it resembles a small lymphocyte [Y2]. Survival of haemopoietic stem cells has been studied by a variety of tests. These include quantitative transplantation of bone marrow cells into lethally irradiated hosts with the subsequent assay of host survival [M18, S12], spleen colonies in the host for the estimation of colony-forming units (CFU) [T7, M19, B19], cell culture techniques [S35] or incorporation of ^{59}Fe to test for erythropoiesis [C14, H16]. Other tests include the response to exogenous erythroprotein in polycythaemic mice [J4], to endogenous erythroprotein in fasted and re-fed mice [P11], or scoring of granulocytes [H17]. Comparisons of functional assays of haemopoietic stem cells have been made [H54].

175. Belousova [B43] estimated the sensitivities of certain cells of the haemopoietic organs: 1–2 days after 4 Gy, depletion of lymphoid organs is at a maximum and 2 days after 7 Gy the same is true for bone marrow. All these studies indicate that the haemopoietic "stem cell" is a rather radiosensitive cell [S40, S41] with a D_o of 0.6–1.1 Gy and an extrapolation number of 1.2–2.7. A correction for various technical differences and for radiation quality brings most of the D_o estimates into the narrow range of 0.65–0.7 Gy [L18]. The bone marrow stem cell is therefore more sensitive than most other cell types.

176. If irradiation is not administered to the whole body, stem cells can migrate from unirradiated bone marrow and repopulate the irradiated areas [H63, R11, N2, S42, P27].

177. Fractionation studies have shown that the bone marrow has a rather small capacity to repair sublethal damage, consistent with the low values of extrapolation number (1.2–2.7) [T1]. Mole [M20] has even demonstrated an increased sensitivity with fractionation, which he attributes to recruitment of resting cells into the cell cycle.

178. When continuous irradiation is used there appears to be no sparing effect over the first 10–20 days [J5] with 2.4 Gy given as a single dose in 5 minutes or at 0.01 Gy/hour over 10 days, giving a similar reduction of CFU's to 40% of normal. However, a steady state of repopulation is then established, so that 38 Gy given over 160 days also depletes the CFU's to about 40% of normal. Fedotova [F42] observed mice given 0.025 Gy/hour showing a progressive reduction in stem cells up to 80 Gy. A similar but smaller reduction was found with 0.054 Gy/hour up to 60 Gy [M47, M48]. These experiments show that dose rate is of greater importance than the total dose, and this is due to compensatory proliferation.

179. Studies by Porteous and Lajtha [P12] at approximately 0.5 Gy/day showed a fall in CFU's to 10% by 20 days, with a rise by day 30 in spite of continued irradiation. The work of Lamerton and his colleagues [B1, L5] established that the erythropoietic system in rodents could tolerate continuous irradiation at 0.8–1 Gy/day. Other blood components are rather more sensitive but could tolerate 0.5 Gy/day [B1, L5, M49].

180. Differences in bone marrow response have been noted with different species. It was shown by Belousova that for mice irradiated at 0.5 Gy/day, after two weeks the level of bone marrow lymphoid cells sharply decreased. This was also the case for spleen and thymus. Granulocytes also decreased and after a total

of 40 Gy the number of erythroid cells also decreased. In rabbits and guinea pigs the same dose rate led to the development of a subacute form of radiation sickness with death occurring due to bone marrow failure at 45 Gy with rabbits and 20 Gy with guinea pigs [B43].

181. Very few late effects have been observed, apart from those reported after doses of 20–100 Gy given locally to a single limb [K12, K13] which are the result of local fibrosis. Late damage has been observed in the erythroid precursors in the rat bone marrow after 1.7 Gy, with an exponential return to normal, the half-life being 30 weeks [G11]. After doses higher than 40 Gy marrow undergoes delayed or lasting aplasia due to damage to the stroma. Recovery can only be effected by transplantation of healthy marrow into the marrow cavity [W44].

182. In summary, cells of the haemopoietic tissues, and in particular lymphocytes and bone marrow stem cells, appear to be very radiosensitive but they have a remarkable regenerative capacity and can show complete recovery, if the animal survives the initial cellular depopulation.

M. IMMUNE SYSTEM

183. An important effect of irradiation is impairment of the immune response. This may result in a decreased resistance to pathogens, development of auto-immune disorders and possibly increased probability of neoplasia. It is beyond the scope of this Annex to discuss changes in the immune response in detail. The topic was reviewed in the UNSCEAR 1972 report [U5], in which it was concluded that decreased resistance to immune challenge resulted from irradiation with more than approximately 2 Gy of photon irradiation, although short-term changes can be detected at lower doses. The radiosensitivity of immunologically competent cells have been reviewed by Anderson and Warner [A25] who concentrated on early changes, and more recently by Doria [D41] who points out the lack of knowledge to account satisfactorily for the changes in the immune system following irradiation. This is particularly true since the introduction of the network theory of the immune system [J25, U6]. Bazin [B80] has recently reviewed the effects of irradiation on subsequent infection, with emphasis on the gastrointestinal tract. A range of late changes in the immune system have been studied by Sado et al. [S47] on mice. They were unable to detect any significant effects up to 4.5 Gy x rays although all the immunological indices used showed changes at early times. Sado [S48] noted the paucity of studies of late effects, but also pointed out that in general few late changes have been observed in animals or humans surviving whole-body irradiation.

N. SUMMARY

184. The time at which radiation damage is maximal depends on the normal and post-irradiation proliferation kinetics of each tissue. Rapidly proliferating tissues such as the bone marrow exhibit the damage soon after treatment. Slowly proliferating tissues such as the connective and the vascular do not show serious changes until months or years after irradiation. With acute single exposures the bone marrow is a most critical tissue. For animals of similar size to man the LD_{50} is 2–3 Gy and there is no evidence that the human response would be very different. However, the bone marrow, as many other tissues, is capable of considerable repopulation between dose fractions or during low dose rate continuous irradiation. Observations on mice indicate that daily treatment with 5% of the LD_{50} dose can be tolerated for extended periods. Extrapolating to large animals, this would be 0.1 Gy/day. At this continuous dose level, the tissue likely to be the most affected is the testis or, in young females, the ovary. Continuous exposure to 0.006 Gy/day sterilized male dogs but 0.0012 Gy/day had no effect. Mouse testis is rather more resistant, 0.02 Gy/day being the lowest figure reported to cause permanent sterility. The pituitary is sensitive in the very young, 1 Gy causing weight loss in the squirrel. Doses of 2–5 Gy cause lens opacities if given in a single treatment, but more than 10 Gy are needed if the treatment is fractionated. Other tissues are more resistant and have significant repair capabilities so that they are able to tolerate still larger doses if fractionated or given continuously. Table 6 summarizes approximate values for threshold doses in experimental animals.

III. EFFECTS OF IONIZING RADIATION ON MAN

185. The effects of ionizing radiation on human tissues were first noticed by the early radiation pioneers. The first publication was in the "German Medical Weekly" in 1896 by a victim, an engineer, less than 6 months after Roentgen's discovery. A year or two later the dose required to produce dermatitis was being used to check the output of x-ray tubes. The early workers were unaware of the need for radiation protection and at least 336 fatalities were attributed to radiation exposure. Of these, 251 died as a result of skin cancer and 56 of blood dyscrasias, e.g., anaemia and leukaemia [H18]. When the importance of radiation protection was realized, the incidence of deliberate whole body exposure in humans fell sharply and most of the later information has been obtained from atomic bomb survivors, accidents with portable radiation sources, accidents in atomic energy establishments and patients treated with total-body irradiation. In some of these groups, treatments with pharmacological agents could alter the picture of radiation-induced changes.

186. Three different phases of injury are distinguishable in man as in other mammals. These are both dose and time related. After very high doses, damage to the central nervous system occurs which can be lethal within two days. After lower whole-body doses, death from gastrointestinal damage can occur between 1–2 weeks. Still lower doses may allow recovery from the gastrointestinal damage but death may result later from damage to various tissues, mainly to the bone marrow. A summary of the symptoms and injuries from Hiroshima and Nagasaki casualties is given in Table 7 [O16].

187. For whole-body exposure the threshold dose appears to be between 1 and 2 Gy for clinical symptoms. The LD_{50} is uncertain but probably within the range of 3 to 5 Gy [L17, B18]. If the exposure is only to a part of the body, the reactions may be much reduced. This is due to the regenerative capacity of stem cells from shielded areas (bone marrow) such that the level of dysfunction before repopulation is not sufficiently severe to cause death (e.g., by dehydration in the gastrointestinal syndrome). Partial-body exposure has been considered by Gregoriev and others who, on a

model basis, demonstrated that the dose may be increased as much as a factor of 5 to produce a given effect, depending on the dose distribution [G31, D37, D38].

188. Since the present document deals with localized exposure, it will consider only the results derived from radiotherapy. In radiotherapy of cancer normal tissues are unavoidably included in the treatment volume and it is the damaging effects on these tissues that limits the dose which can be tolerated. For each cancer site, a tolerance dose for a limited volume of normal tissue has been established empirically from years of practice. This dose is usually defined as the dose that will produce a small but detectable incidence of serious complications resulting from the radiation effect on the normal tissue. Each clinician has a slightly different level of morbidity that he considers acceptable, but often 5% of serious complications is considered reasonable. It should be emphasized that this tolerance dose is not the same as a threshold dose because it is concerned with serious long-term complications which may significantly alter the quality or duration of the patient's life. Transient early damage, or detectable but non-life-threatening damage are not normally considered to be dose limiting in radiotherapy. Threshold doses for a range of tissues are likely to be in the same hierarchy of sensitivity as serious complications although at lower dose levels.

189. Defining a threshold dose depends on the method of assaying the damage. Some tissues can withstand a high degree of cell depletion with no gross change; an example is the skin, for which the dose to produce signs of desquamation is equivalent to cell survival of about 0.1% on the basis of cell survival estimates (see paragraph 69). With a surviving fraction between 10% and 1% there is no gross visible damage, although changes are detectable histologically. The severity of damage that can be tolerated in a tissue or organ depends on a number of factors including: the level of cell depletion that causes tissue malfunctions; the time of expression of damage; the repair and recovery capacity of the tissue; the volume included in the field; the total dose administered; and the overall time and number of fractions into which the dose is subdivided.

190. Much clinical practice involves daily fractionation on 5 days per week with approximately 2 Gy per day, i.e., 10 Gy per week. In the following paragraphs this will be referred to as conventional fractionation treatment. In some cases the dose given will be converted to the Nominal Standard Dose (ret) according to the Ellis formula (see section I.F).

191. Nowadays, most treatments are given with supervoltage radiation, e.g., from a 4–20 MeV linear accelerator or from ^{60}Co source, both of which deposit their maximum dose several millimetres below the body surface, resulting in sparing of the skin. Treatments prior to 1950 utilized lower energy machines which deposited the maximum dose at the skin surface. Treatment planning has also progressed so that each daily fraction may be administered as 3–6 subfractions through different portals in order to maximize dose in the tumour and spread dose to the normal tissues.

192. In 1906, Bergonié and Tribondeau proposed their "law" relating radiosensitivity to the proliferation activity. Tissues with a high mitotic index showed a high "radiosensitivity" (i.e., severe early damage) whereas those with a low mitotic index showed a low "radiosensitivity" (i.e., little early damage or delayed expression of damage). Since radiation damage is mainly expressed at mitosis this concept of tissue sensitivity relates more to time of expression than to the dose that will cause a particular level of cell survival or a particular level of tissue dysfunction (see paragraph 59).

193. Rubin and Casarett [R1] have assessed their own clinical experiences and performed a major review of the literature. Their findings are summarized in Table 8 and Figure VIII, where the injury scored at 5 years and the threshold doses suggested as likely to give 1–5% or 25–50% complications is shown as an example. The amount of tissue included in the beam is also given. These data are also plotted in Figure VIII in order of increasing radiation resistance both in terms of actual dose administered, normally as 10 Gy per week at 2 Gy per day, and in terms of the Nominal Standard Dose in ret [E4].

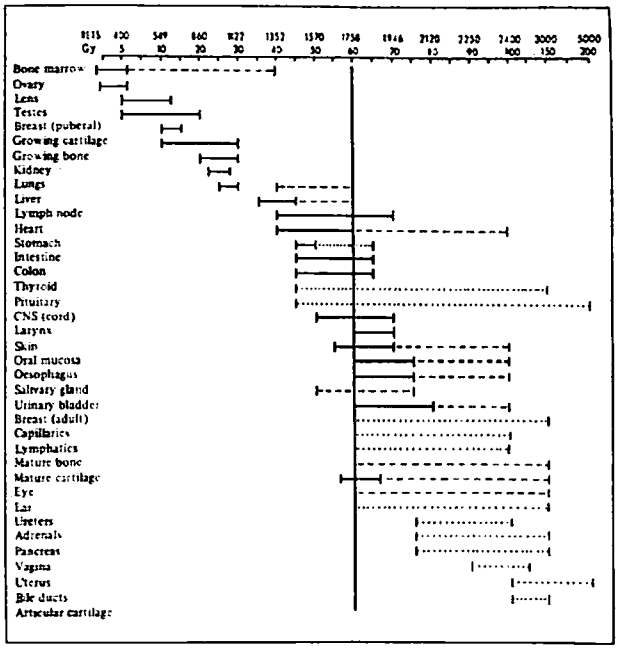

Figure VIII. Acceptable doses in radiotherapy. Both the total doses (conventional radiotherapy treatment) and doses in ret are given. The definition of "acceptable" is the personal view of the authors [R1]

194. Table 8 shows that there is a wide variation of acceptable doses from one tissue to another, the acceptable dose in radiotherapy being that for which side effects are reversible. This may result from a difference in inherent cellular radiosensitivity or may depend on critical levels of survival for limited subpopulations of cells. Some tissues react because of a primary response of the parenchymal cells, e.g., testis and ovary. Other tissues react by a delayed depletion of parenchymal cells, which may either be a late primary response to radiation or a secondary response to vascular damage resulting in a loss of nutrient supply. A third form of tissue failure results from radiation-induced fibrosis. The threshold doses are below the 1–5% acceptable doses. Both Figure VIII and Table 8 are summaries of the personal views of the authors [R1] and the doses quoted would vary somewhat if compiled by other radiotherapists, although for the purposes of this Annex the differences may not be considered large. Specific normal tissues are discussed in more detail below.

A. SKIN AND MUCOSA

195. Because the skin and the buccal mucosa are so readily accessible and because the early radiation sources delivered their maximum dose at the surface, these tissues have been more widely studied than any others in the body. Most of the clinical concepts of fractionation were originally based on clinical observations of skin reactions.

196. The threshold dose for the production of skin erythema is 6–8 Gy in a single treatment for fields greater than about 5 cm^2. This dose may cause a transient reaction a day or two after exposure with blood vessel congestion and subcutaneous oedema but without gross effect on the epidermis. The initial erythema may increase during the first week, but will fade after about 10 days. It is followed by the main erythematous reaction which reaches a maximum after about 2 weeks and lasts from 20 to 30 days. This reaction does involve the dermis and may, for larger doses, be followed by dry or moist desquamation or even necrosis. There may be several waves of reaction. With fractionated radiation the tolerance dose for the skin is considered to be 6–7 Gy/30F/6w (per 30 fractions given in 6 weeks).

197. The early phase of desquamation has usually healed by the end of a 6-week course of therapy by compensatory regeneration of the basal layer which is initiated when the skin function begins to fail. This compensation can even produce new cells more rapidly than they are being killed so that healing may occur before radiotherapy treatment is ended.

198. Late injury to the skin appears to result from damage to the tissue elements in the dermis, rather than the epidermis. It occurs at months to years after irradiation and can take several forms. Deep fibrosis and contraction of irradiated areas occurs with an increased deposition of collagen in a thick mat-like network. Progressive occlusion of blood vessels is seen, which may gradually lead to an undernourished atrophic epithelium with a greatly increased susceptibility to any external trauma. Cold, heat, friction or bruising can then lead to reversible or irreversible breakdown of tissue, in the worst instances resulting in ulceration and necrosis. Other late changes are depigmentation, depilation and telangiectasia. The term poikilodermia is also used to describe atrophy, telangiectasia and dislocation of pigment.

199. The degree of skin reaction and the tolerance dose are known to be influenced by a number of biological variables, including the age of the patient, the hormonal status, and the anatomical location [R1]. These factors may produce their effects as a result of differences in the thickness of the epidermis in different regions, the degree of friction to which it is normally exposed and thence the underlying cell proliferation kinetics. Anoxia of the skin is known to give radioprotection, whether it results from local pressure or from anaemia [R1]. Skin which has been recently grafted is more radiosensitive than normal but a successful graft gradually returns towards the sensitivity of undisturbed skin [R1].

200. The tolerance dose differs for different skin appendages, as was recognized by Borek [B20]. Detectable changes can be seen after 3–5 Gy to hair follicles when temporary depilation results and histological changes have been reported after 1–2 Gy [R1]. However, these are temporary or reversible changes of no serious consequence. It is common practice in radiotherapy for skin to receive 50–60 Gy in 30F over 6 weeks without severe consequences [F54]. However, in a study of functional changes in the skin of occupationally exposed workers, using capillary microscopic techniques, Leny et al. [L33] showed microscopic alterations of the capillaries without changes in the structure of the dermis after 10–30 Gy exposure during 8–25 years. Small fields have also been irradiated in experimental clinical studies of human skin prior to using neutrons in radiotherapy [M4, K29]. Dose-response curves for human skin are shown in Figure IX. The threshold single dose for x rays is about 7 Gy [J17].

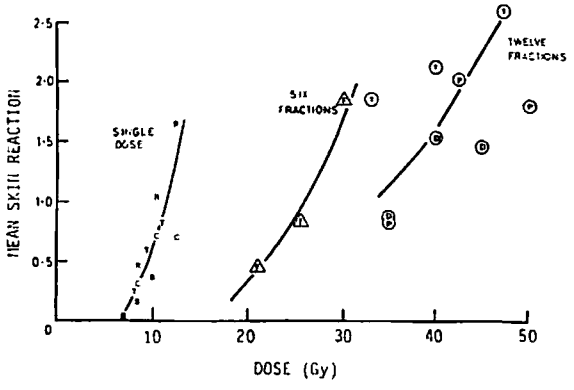

Figure IX. Dose-effect curves for human skin irradiated with x rays, obtained from average reaction between 5 and 80 days after treatment. A score of 1 represents a faint erythema. Each symbol represents a patient [F14]

201. The volume of tissue irradiated is critical, the damage being greater for greater areas or volumes. Cohen [C2] has reviewed this subject and suggests that the isoeffect dose is proportional to L^{-3}, where L is the average diameter of the irradiated field. Penetration of the radiation is also of great importance. For β rays, which do not penetrate through all the layers of the skin, less injury is produced with better recovery than for more penetrating radiation [O13]. This result has been confirmed by analysis of data resulting from occupational exposure [B44].

202. The relationships between total dose, number of fractions and total treatment time were considered in section I.F. These were mainly derived from data on skin and subcutaneous connective tissues, but the extrapolation to very large numbers of fractions over very long times is still the subject of some argument.

B. GASTROINTESTINAL TRACT

203. Damage to the intestinal tract leads to many acute and chronic symptoms ranging from diarrhoea and dyspepsia to ulcer, strictures and obstructions which can be life-threatening. There are, however, fairly wide variations in the radiosensitivity of the different parts of the gastrointestinal tract, the stomach, small intestine and colon being the most sensitive [F54].

204. The stomach will tolerate doses up to 40 Gy with conventional radiotherapy fractionation. Beyond this, the risk of ulceration or perforation increases rapidly with dose. This was discovered in a tragic series of treatments at the Walter Reed Hospital 40 years ago [A8, H19] where about one-quarter of 61 patients receiving 45–54 Gy developed ulcers, some with perforation.

205. The small intestine is also a radiosensitive organ commonly showing acute mucosal reactions after 30 Gy given in 3–4 weeks. These reactions are however reversible even after doses of 40 Gy. Higher doses than this will lead to chronic damage in the form of obstructions, constrictions and adhesions, unless a rest period is introduced during therapy to allow repopulation to take place. The incidence of intestinal complications is much higher after surgery if adhesions are already present, because these prevent the mobility of the intestine, which usually spares any region from accumulating the total dose. Gastrointestinal complications are much reduced by protracting the irradiation procedure [N13].

206. The colon has a similar or slightly lower radiosensitivity but because it is not mobile it is more likely to be exposed to the full dose. Early damage resulting in diarrhoea occurs at 1–2 months but this is not a good predictor of late damage due to fibrosis and vascular injury [R12].

207. The rectum is considerably more resistant than other portions of the gastrointestinal tract, although epithelial denudation causes transient symptoms after 30–40 Gy of fractionated treatments [R12]. The oesophagus is also a more radioresistant portion of the gastrointestinal tract and can withstand doses of 60 Gy. After higher doses fibrosis causes stricture which can lead to painful or even disastrous obstructions. After much lower doses of 20–30 Gy fractionated over 2–3 weeks, epithelial denudation leads to clinical symptoms of burning and dysphagia, but these are transient and recovery is rapid.

C. BONE AND CARTILAGE

208. Growing bone and cartilage are known to be much more sensitive to radiation than are these same tissues in the adult. A considerable body of data exists from children treated for abdominal tumours or for tumours of the limbs. In both situations growing cartilage and bones exposed to radiation show a dose-dependent retardation or even cessation of growth. Such growth disturbances were recognized in the 1930s [D22, S13] and 1940s [S14]. There are many descriptions of deformity of the spine caused by unequal irradiation of the vertebrae so that one side of each vertebral body grows more than the other, resulting in scoliosis. Varying degrees of radiologic change are observed in the vertebrae, depending upon the dose and the age of the child [N3]. Ten Gy (given in 6 daily doses/week) produced mild radiographic changes in a young patient, whilst 12–20 Gy produced moderate to severe changes in most of the children aged 0–6 years at irradiation. The younger the child, the more severe the degree of growth deformity. When fractionation results [T8] are transformed to NSD value it is found that the approximate threshold for producing detectable changes varies with age, being about 300 ret between 0 and 1 year, 800 ret at 1–2 years, and 1000 ret beyond 2 years.

209. Similar conclusions were drawn from 44 children treated with megavoltage radiation, using conventional fractionation, compared with 15 000 normal unirradiated children [P13]. Changes in both the sitting and standing heights were observed. In children treated with less than 25 Gy, there were differences, but very slight. Those treated with more than 35 Gy showed greater differences. The maximum depression of growth was seen in children whose bones were in active growth at the time of irradiation, i.e., up to the age of 6 years and during puberty (see also [G33, R36]).

210. Mature cartilage is known to be much more resistant to radiation damage and the doses to produce necrosis are high. For example, it has been noted that the elastic cartilage of the pinna will tolerate 60–65 Gy in 6–8 weeks of daily fractions. The tolerance levels for hyaline cartilage are similar. Laryngeal cartilage will tolerate 65–70 Gy over 2–8 weeks or more than 70 Gy in a more prolonged pattern of dosage over 10–12 weeks [B21]. With shorter overall treatment times there can be a marked increase in the incidence of necrosis as reported by Fletcher and Klein [F20] when they increased their dose from 48.5 to 55 Gy given in 20 fractions over 4 weeks.

211. In bone, the dose to produce necrosis is difficult to determine because the absorbed dose is dependent on the mineral content and changes markedly with the energy of the incident radiation [S15]. For 50 keV photons the local absorption in bone is 5 times that in water, at 200–5000 keV it is similar to that in water, and at higher energy it again becomes greater than water. Thus the doses quoted to produce osteonecrosis in the old literature may be in error by a significant amount, depending on the circumstances [P14]. At the higher energies used in modern radiotherapy bone necrosis is rare.

212. In general adult bone is considered to be fairly radioresistant, but it becomes susceptible to trauma and infection after irradiation and has a poor regenerative capacity. Osteonecrosis of the mandible occurs after irradiation of buccal tumours, but this is almost always associated with a break in the overlying mucosa, allowing infection to commence. Radionecrosis may occur between 2 months and 15 years after therapy [S16]: it is related to oral hygiene and precipitating trauma to a greater extent than to dose or fractionation scheme. A dose of 65 Gy given in 6–8 weeks does not normally lead to osteonecrosis, but may give a greater predisposition to fracture. This is site-dependent and is more common in the weight-bearing head of the femur than, for example, in the ribs [P14]. Another effect of radiation on bone is to delay the healing process of callus formation after fracture, and this is worse in adults [R13].

D. HEART

213. For many years the heart has been considered to be a radiation-resistant organ and only isolated examples of radiation-induced carditis had appeared in the literature. This was in part due to the limitation on thoracic irradiation resulting from the much greater sensitivity of the lungs. However, by the mid-1960s a large number of patients had survived more than 1 year after mantle irradiation for Hodgkin's disease and 25 cases of radiation-induced heart diseases were noted [S17]. This finding was subsequently confirmed by a more comprehensive study [S18, P19]. The changes observed in the heart all involve fibrosis, and may occur to varying degrees. Pericardial effusions may lead to clinical symptoms. After higher doses constrictive disease is seen, which may necessitate surgery, or may result in death. In general the pericardium is a more sensitive tissue than the myocardium, although transient early effects on the heart muscle have been noted. The dose-response curve is very steep, with a

threshold of 1350 ret. The dose to produce 5% mild complications is 1500 ret, and for 50% is 1650 ret. Stewart and Fajardo [S18] stress the high incidence of complications and severe damage after retreatment of patients suffering from Hodgkin's disease to a total dose in excess of 60 Gy.

214. If a smaller volume of heart is irradiated the same type of changes are observed, with diffuse fibrosis in the treated volume, but the tolerance dose for 5% mild complications is increased to 1850 ret [S18]. Other changes have been observed, e.g., in the electrophysiological patterns [T9] as reviewed by Berdjis [B22], but most of these have not been as carefully quantified in relation to dose as in the studies by Stewart and colleagues [S18].

E. LUNG

215. The lung is the most sensitive organ in the thorax. Although there is a large functional reserve in the pulmonary system, there is little capacity for regeneration and reformation of the elaborate structure after widespread cell depletion. A large literature exists on radiation responses in human lungs [V4]. In general, radiotherapists try to avoid including large lung volumes in a radiation field because the threshold dose for tolerance is low. Phillips and Margolis [P2] have estimated tolerance to be 900 ret for 5% complications and 1040 ret for 50% complication. A dose of 700 ret to the whole lung caused no measurable changes [C30]. The dose-response curve is however very steep [P2]. With total-body irradiation for treatment of leukaemia or aplastic anaemia, where reconstitution of bone marrow is performed, lung becomes the critical organ [T26]. Normally, single whole-body irradiation is given, lasting several hours, for which the accepted tolerance is in the region of 8 Gy. With non-uniform irradiation such as with ^{131}I for treatment of thyroid metastases in the lung, fibrosis has not been observed, in contrast with the effects of large fields of external irradiation.

216. Radiation pneumonitis may occur soon after irradiation, followed weeks to months later by radiation fibrosis. The reaction is complex, involving cell death, desquamation of epithelial cells, exudation into the alveolar space, thickening of the alveolar walls and finally collagenous changes, possibly with calcification or ossification [V4]. After irradiation of the chest wall in patients with cancer of the breast, pleural effusion leading to fibrosis has been reported [R1].

217. The main change discernible in irradiated patients is radiological evidence of fibrosis [T10, W20, D23]. This is evident after irradiation of large or small fields and is apparent even in the absence of any measurable functional impairment. Fibrosis is thought to be the end-result of a failed attempt to regenerate the complex units of normal alveoli. High doses to small fields may also lead to lung fibrosis [D39]. Functional changes that have been observed include reduced vital capacity and a reduced maximum exhalation volume. The volume irradiated is extremely important. Localized severe fibrosis can be well tolerated provided there is a considerable volume of unirradiated tissue.

218. There is much debate about the primary cause of radiation pneumonitis. Some authors postulate that the primary target is the endothelial cell and that this leads on to the occlusion of vessels, oedema and fibrosis [P2, P6]. Others favour the damage to the surfactant-producing alveolar epithelial cell, depletion of which would result in increased surface tension, fluid loss across the alveolar wall, haemorrhage and eventually fibrosis [V4].

F. LIVER

219. The liver, which was once considered to be a radioresistant organ is now known to tolerate doses of 40–50 Gy in 30 days to only part of the organ [K14]. The threshold for measurable effects to the whole liver seems to be 30 Gy conventionally fractionated [K14, I2, J6, K15]. The changes observed are both dose and time related [I2].

220. In the early literature, very few irradiated specimens had been studied. Lacassagne [L12] quotes only 30 livers at autopsy and about 12 studied by biopsy in which changes after external irradiation had been looked for. Most of the specimens were obtained within weeks to months after irradiation and showed lesions characteristic of non-specific venous occlusive changes. Endothelial cell sloughing, fibrosis and sclerosis are usually seen later. The most critical element in the liver appears to be the small central vein in each lobule. After irradiation of the whole abdomen for cancer of the ovary when the "strip technique" was used, liver necrosis was reported, increasing with increasing dose per fraction [D51].

G. URINARY SYSTEM

221. The urinary system, comprising kidney, ureter, bladder and urethra, shows a wide range of radiosensitivities. The kidney is the most sensitive element, the bladder has an intermediate sensitivity and the ureters are more resistant, although they seldom have their full length irradiated. For irradiation of abdominal tumours, kidney change is frequently a limiting factor and the kidneys are often shielded or the irradiation field shaped to avoid their exposure if possible. The kidney is a complex organ and a variety of functional disturbances are observed, including acute or chronic nephritis, hypertension and proteinuria [M21]. Stenosis of the ureters is a frequent complication of irradiation of the pelvis [F54].

222. Acute nephritis occurs within 6–12 months and can be lethal, or may lead to chronic nephritis. Some patients develop chronic nephritis without an early acute phase. The pathology of early nephritis is complex with glomerular, tubular and capsular changes. Chronic nephritis is characterized by sclerosis and fibrosis. Hypertension usually accompanies these changes. It appears earlier after higher doses, and depends upon the proportion of kidney that has been irradiated.

223. Less severe damage can be detected as changes in renal function. A fractionated dose of 20–24 Gy in 3–4 weeks usually produces between 10% and 60% reduction in renal plasma flow, with a reduction in glomerular filtration rate. The tolerance dose for the kidney is therefore normally set at about 23 Gy/5 weeks. Higher doses may be given if radioprotection is achieved by vasoconstriction with epinephrine. As with animals, renal injury is more severe in the young human. Urinary examination of children who were in utero during the atomic explosions at Hiroshima and

Nagasaki revealed proteinurea which was not found in adults [F43].

224. The bladder will tolerate 55–60 Gy given in 20 fractions over 4 weeks [M22]. It is usually exposed to a high dose when cervical cancer is treated with combined external beam and radium implants. The damage observed ranges from erythema to fibrosis, ulceration and contraction. A minor symptom is the frequency of urination but severe oedema of the ureteral orifices can lead to back-pressure on the kidneys resulting in hydronephrosis which may be fatal. Little information is available on the effects of radiation on the normal prostate. Late effects may include obstruction, incontinence, and, most frequently, impotence.

H. CENTRAL NERVOUS SYSTEM

225. The central nervous system was in early times regarded as a radio-resistant tissue. It has, however, negligible capacity for repopulation and there is now much evidence from physiological experiments and radiotherapy experience for it no longer to be regarded as resistant [L14, G24, G25, G26, B42, G44]. The lesions generally observed are consistent with the primary damage being to the vascular system and death or paralysis may result at times varying between 3 months and 9 years, although mostly between 1 and 3 years. Occasionally, an acute demyelinating process has been observed [R14, L19] after moderately high doses (in excess of approximately 60 Gy given in fractionated treatments), which may be transient or lethal. For a recent review see [G44].

226. It is believed that relatively few large fractions, or just excessively large total doses are the cause of most of the 57 cases of radiation-induced brain necroses that have been found in a review of the world literature [K16]. In this review only 1 case of dementia was reported [W21] although this symptom has been seen with higher frequency after fast neutron irradiations [C21]. This effect of size and number of fractions is observed also in the spinal cord and has been confirmed by animal studies (see paragraph 134) [G6, G7, V8, W6].

227. The tolerance dose for the whole brain is thought to be about 55 Gy fractionated over 5–6 weeks. An extra 10 Gy is sometimes given to a small area containing a tumour. For small parts of the brain 65 Gy fractionated over 6.5 weeks is considered safe. If these doses are exceeded, brain necrosis may result [K16, G27]. The threshold for morphological changes is approximately 40 Gy when fractionated [D40]. A recent review of the subject has been made by Franke and Lierse [F45].

228. For the spinal cord the tolerance doses are lower than for brain. The estimates of a safe dose for cervical, thoracic and lumbar cord vary from 35 Gy in 4 weeks [P16] to 50 Gy in 5 weeks [K16, P17]. The dorsal cord appears to tolerate a dose of 45 Gy in 4.5 weeks [K16]. Transient radiation myelopathy occurring 3–4 months after therapeutic irradiation (in the range of 26 Gy over 29 days to 56 Gy over 70 days) has been reported. This is described as similar to the perception of an electric shock when the spine is flexed [J23]. It is important that injury to the cord is inversely related to the length of cord irradiated [P18].

229. Months or years after irradiation (local or whole-body), diffuse demyelination and encephalitis may result [G26, B42, G25, G28]. After irradiation of the head with single doses mostly between 3 and 12 Gy (but up to a maximum of 30 Gy) acute radiation was followed between 3 and 10 years later with small degrees of demyelination and changes in brain circulation [G25, G27, G30]. In one individual who accidentally received 30 Gy to the head, brain necrosis had developed by 3 years [G30]. Thirty to 50 Gy given in fractionated radiotherapy at 2 Gy per fraction or single treatments between 3 and 10 Gy caused profound functional disturbances of the CNS, resulting in, for example, impairment of memory and weakness [G30, G28]. Functional changes after radiotherapy to the cranial axis region in children with medulloblastoma have been reported. Survivors for more than five years developed changes in character, impairment of memory and learning ability and even dementia and idiocy resulted if the age at exposure was less than 1.5 years. Severity of impairment was related to age at irradiation. Children with acute lymphatic leukaemia irradiated with 24 Gy over two weeks to the CNS developed loss of memory [B83].

I. GONADS

230. The ovary is a highly radiosensitive organ. It contains a limited number of germ cells which cannot be replaced if they are depleted. A loss of all the ova (approximately 400 000 in an adult human) results in total sterility. Table 9 shows some of the published observations on doses causing sterilization in women. Single doses of 1.7–6.4 Gy have been shown to cause temporary sterility, with higher doses required to produce the same effect when fractionated. Permanent sterility results from 3.2–10 Gy in a single dose, or higher fractionated doses. Doses in the range of 5.6 Gy almost invariably produce permanent sterility. Doll and Smith [D20] reviewed over 2000 women treated for menorrhagia by irradiation. A value of about 6 Gy given in 2–4 fractions was referred as the dose to ablate the human primordial oocyte population.

231. The radiosensitivity of the ovary depends on the degree of maturity [M24] being more resistant in young women, although the differences with age are hard to estimate [A24]. This is unlike other species of animal. Also, in women, unlike in rodents, the ova seem more resistant than the bone marrow.

232. Very small doses of radiation were used in the 1920s to 1940s to treat infertility. A treatment of three times 0.5–0.75 Gy in 3 weeks to the ovary was reported to increase the fertility of many women treated for amenorrhoea, resulting in normal pregnancies, normal children and normal grandchildren [K17]. There seems to be little or no evidence of an increase in malformed offspring resulting from conception after irradiation of the ovary or testis [L16].

233. The testis is also a sensitive organ, as indicated in Table 10. Doses as low as 0.1 to 0.15 Gy have been recorded as causing temporary sterility, although > 2 Gy and possibly about 6 Gy are needed to produce permanent aspermia. Type B spermatogonia seem to be exceptionally sensitive, with D_0 being about 0.2 Gy. The seminiferous epithelium in man requires many years before recovery of the spermatogonial series may be completed [L16]. Japanese fishermen exposed to fallout received doses of gamma rays estimated at about 1.4 to

6 Gy over 14 days, corresponding to approximately 0.7–3 Gy given as single doses. Their sperm counts were severely depressed, but began to increase by 2 years after exposure and most of these men produced healthy children [K51].

234. The testis is unusual in that fractionated treatment may be more effective than single doses, e.g., 20 doses of 0.25 Gy each cause a more rapid depletion and a slower recovery than after a single dose of 5 Gy [L16, H21]. This is attributed to the stimulation of relatively resistant type A spermatogonia into the much more sensitive type B compartment.

J. THE EYE

235. The eye was recognized as being vulnerable almost as soon as x rays were produced. It was also soon realized that the different components of the eye had different sensitivities, and that the lens was especially sensitive when uniformly irradiated. However, the threshold is greatly increased by non-uniform irradiation [B81]. Although epithelial tissues around the eye seem to have a sensitivity similar to that of skin, the human lens responds to doses of ~ 2 Gy in a single treatment, or ~ 4 Gy when fractionated, resulting in the formation of cataract [M25]. Table 11 indicates the sensitivity of different parts of the human eye.

236. The extent of cataract formation, as well as the incidence, is dose dependent. Higher doses yield more progressive cataracts with greater loss of vision. The latent period varies from 0.5 to 35 years, with an average of 2–3 years, although this latency is also dose dependent [F18]. Minimum stationary opacities have been observed after single doses of 1–2 Gy, but with 5 Gy more serious progressive cataracts occur. A single dose of 7.5 Gy causes some degree of cataract formation, with a probability of occurrence of 100%. The lens is spared by fractionation with the slope of Strandqvist curve perhaps slightly less than that for skin. Ten Gy over 3–12 weeks was shown to give 75% incidence of cataract and 14 Gy over the same period leads to 100% incidence [H25].

237. Occupational exposure during 10 or 20 years has also been shown to affect the eye. At between 0.5 and 2 Gy the optical density and staining properties of the lens were increased. For doses between 1.5 and 4 Gy the frequency of senile cataract was significantly increased together with changes in the vascular system [L28, L29]. With mixed gamma and neutron irradiation, doses of 0.7–1 Gy produced changes [L29]. Recent reviews [C23, B53, B35] suggest that the threshold for cataract for occupational exposure or lengthy fractionation is in the range of 6–14 Gy.

K. HAEMATOPOIETIC SYSTEM

238. The haematopoietic system is one of the more sensitive tissues in the body. Responses can be seen after 0.5–1 Gy of radiation, whether it is given as a single exposure [B7] or as a series of small fractions [T11]. The bone marrow is the source for most circulating cells, the lymphocytes, granulocytes, erythrocytes and platelets. The response of the peripheral elements depends upon their normal turnover time, except that the lymphocytes respond very rapidly. These cells are unusual in that they are generally believed to be differentiated end-cells yet are extremely radiosensitive, with a D_0 of 0.2–0.3 Gy [T11] and undergo interphase rather than mitotic death. There are also thought to be subpopulations of lymphocytes with different sensitivities [E20, S75]. A depletion of the lymphocytes is seen within hours after irradiation, whereas the fall in platelets and granulocytes is delayed for several days and the fall in erythrocytes occurs slowly, over weeks [B7]. The differential and total blood counts bear some relationship to dose received but the response of the lymphocytes is sufficiently dose dependent for it to be a useful dosimeter in some circumstances. The time at which the peripheral elements return to normal depends upon the level of dose and hence on depletion of the bone marrow. After higher doses, the rate of repopulation appears to be greater than after low doses which cause little depletion [B7].

239. Mitotic abnormalities are observed in the bone marrow cells from about a few hours to two weeks after irradiation [F21, P28] but no prolonged systematic study has been performed at much later times. In the bone marrow of Japanese fishermen exposed to radioactive fallout in 1954, chromosome aberrations of the stable type were found 15–25 years after exposure [K51].

240. If the depression in peripheral blood cells is too severe the patient may die from infection (due to loss of granulocytes) or haemorrhage (due to loss of platelets). The timing of death from the haemopoietic syndrome in man (at 3–6 weeks after exposure) coincides with the period of maximum depletion in these peripheral elements. In other species the maximum depletion and the "haemopoietic death" also coincide but usually occur at 10–30 days. The reason for this species difference in timing is not understood [B7]. The influence of radiation on the reticulo-endothelial phagocytes of the spleen and liver in maintaining the bloodstream free of bacteria is important, and the ability to resist infection may be reduced by doses smaller than those required to cause death [M26].

241. Long-term changes resulting from irradiation of bone marrow also occur. Evidence comes from three sources: local radiotherapy, systemic irradiation and atomic bomb survivors. Reduction in numbers of white cells was found up to 7 years after radiotherapy of mammary glands and adjacent tissues with doses of 50–150 Gy over 1–3 months [D39]. After localized irradiation at rather higher doses than can be tolerated by the whole body, long-term changes in the irradiated bone marrow have been observed, although the reserve capacity of the untreated bone marrow will maintain the peripheral blood count at a normal level. Local changes have been observed up to 3 years after fractionated treatments of 20–65 Gy delivered locally, and up to 18 months after 40–45 Gy to the sternum [S19]. Baisogolov and Pavlov [B50] investigated 45 cancer patients between 1 and 36 months after local radiotherapy. Persistence of bone marrow aplasia was dose-dependent with a threshold of 30 ± 5 Gy. Hirashima et al. [H68] showed that after local radiotherapy for uterine cancer to a total dose of 60 Gy in 1 month, the functional activity of T-lymphocytes was significantly impaired immediately and at one year after therapy, but had returned to normal by two years. In an analysis of nine patients who received non-uniform irradiation of bone marrow between 2 and 5 Gy, Sudovora et al. have shown that recovery is governed by the repopulation of individual areas,

indicating an absence of migration of human haematopoietic stem cells [S78]. In A-bomb survivors decreased white blood cell counts have been observed for up to 15 years, accompanied by changes in the bone marrow [W23]. Extra-corporeal irradiation of human blood for treatment of leukaemia has shown that red blood cells and platelets are very radiation resistant but lymphocytes are sensitive [C15].

242. Thus the effect of small doses of radiation to the haemopoietic tissues may produce a profound response, but unless the total bone marrow stem cells are depressed below a critical level, the numbers of peripheral blood cells will recover and the patient will survive. After acute, accidental exposure the LD_{50} for man is between 3 and 5 Gy [L17] but maintenance in sterile chambers, antibiotics and careful medical support, including transfusions and bone marrow transplants, have enabled accident victims to survive higher doses.

IV. EFFECTS OF RADIATION QUALITY

A. BIOPHYSICAL ASPECTS

243. Energy is deposited by radiation as discrete "events", with about 50–100 eV of energy absorbed per event [I10]. According to target theory only one or few such events are required to elicit a biological response, such as cell death. The quality of a radiation determines the biological response, the quality of two radiations being deemed the same if the biological effect per unit dose is the same. The quality of a radiation is thought to be primarily determined by the microscopic distribution of energy along the tracks of the particles. In the case of photons and neutrons these are secondary tracks, photons producing secondary electrons and neutrons secondary protons and other nuclei.

244. Specification of radiation quality is difficult. The most used parameter is Linear Energy Transfer (LET) where L_∞ = total stopping power of a particle in tissue. The width of the track core is often specified, e.g., L_{200} specifies energy transferred per unit length of track to electrons having initial energies of 200 eV or less. Electrons with greater range will be considered as producing separate tracks (δ rays) [I5].

245. The Relative Biological Effectiveness (RBE) is defined as the dose of a reference radiation (usually of low-LET x rays) divided by the dose of the radiation in question to produce a given level of damage. If the RBE is referred to ^{60}Co gamma rays or high-energy x rays, it is approximately 10–20% greater than if the reference radiation is 250-kVp x rays. However, this difference could be greater at very low doses [B82]. RBE is a relevant parameter only if the damage is qualitatively identical in the two cases. This is normally the case, but two examples of differences in response to photons and neutrons are the gut architecture [H29] and the disappearance of cells of the subependymal plate in the brain [C11].

246. It is known from experiments on cells, using the track segment technique, in which particles of a specific energy traverse a cell, that RBE increases with increasing LET to a maximum value and then decreases. For a neutron beam there is a spectrum of secondary charged particles and a mean LET may be calculated. This may be a "dose mean" or a "track length mean". However, for a number of reasons which have been discussed in detail by Bewley [B25] and Rossi [R17], LET, although a useful parameter for describing radiation quality, is by no means fully adequate [I5].

247. An alternative method of specifying radiation quality is based on the lineal energy, y, (the energy deposited in an event, divided by the mean chord length of the volume in which it occurs) and z (the energy deposited by one or more events, divided by the mass of the volume in which it occurs) as recommended by the ICRU [I3]. Spectra of y and z may be measured using small proportional counters filled with approximately tissue equivalent gas [R17] but as yet neither the experimental techniques nor biological knowledge are adequate to predict biological effects.

B. BASIC DIFFERENCES IN RESPONSE TO PHOTONS AND HIGH-LET IRRADIATIONS

1. Oxygen effect

248. With few exceptions throughout radiobiology, cells and tissues are more sensitive when irradiated in the presence of oxygen than in its absence. With increasing LET there is a constant decrease in the oxygen enhancement ratio (OER = ratio of doses with and without oxygen to produce a given level of damage) such that with mammalian cells the OER becomes 1 at a LET of about 180 keV/μm [B26]. Over a very wide range of neutron energies up to 50 MeV or probably greater, the OER is significantly reduced relative to photons, but to an approximately constant value, independent of energy, of about 1.5–1.8 [H22]. With lower energy neutrons (e.g., fission neutrons) the OER is rather less, between 1 and 1.5 [B27]. These values compare with 2.5–3.0 for photon irradiations. As a neutron beam penetrates into tissue, the OER is hardly altered [M27, B28, N5, B29].

2. Repair as a function of radiation quality

249. Differences in biological effectiveness of beams of varying quality are markedly affected by differences in the ability of the tissue to undergo the various repair processes. It is also important to establish whether or not the gross biological response of a tissue is similar after different qualities of radiation. If not, the concept of RBE is inapplicable.

250. *Repopulation* (see Section I.B.). It is necessary to establish whether or not repopulation is the same after comparable doses of x rays or fast neutrons for two reasons. One is that an analysis of RBE depends on there not being a difference and the second is to obtain knowledge of the effect of repopulation as a mode of repair during a protracted course of high-LET radiation. In general, it appears that there are no important differences in repopulation after x rays or fast neutrons [B30, B31, C16, D24, D25, F2, F14, F22, F23, F24, F25, H23, W24].

251. *Sublethal damage* (see Section I.B). With increasing LET the shoulder of a cell survival curve becomes reduced and repair between fractions is less. This difference is illustrated schematically for x rays and neutrons in Figure X. A major effect of this difference between neutrons and x rays is that the RBE is dose dependent, increasing with decreasing dose or dose per fraction. With fractionated irradiations, the RBE will primarily depend on the dose per fraction,

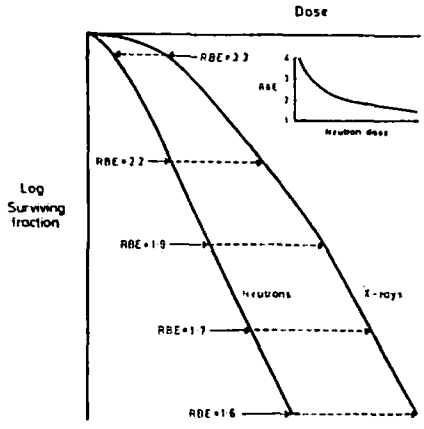

Figure X. Hypothetical survival curves for x rays and neutrons illustrating the smaller shoulder on the high-LET curve and the consequent increase in RBE with decreasing dose per fraction [F26]

providing any repopulation between fractions is indeed the same after the two types of radiation. Since the dose per fraction depends on the number of fractions, the RBE will also, but secondarily, depend on the fraction number. Tissues exhibit a considerable degree of sparing due to recovery from sublethal damage, usually far more than for cells in vitro. Therefore, at low doses per fraction, the RBE for tissues may have high values.

252. These RBE considerations were first tested in vivo using pig skin. It was shown that the RBE increased with increasing number of fractions (due to the decreasing dose per fraction [Figure X]). It was suggested that this increase in RBE might explain the severe reactions observed by Stone [S20] in an early trial of neutron therapy, since the original dose calculations were based on information from single treatments and various fractionated regimes were used in the clinical trial [F27, S21].

253. Recovery from sublethal damage may occur later for neutrons than for photons. There are some results consistent with this observation [F26, B32] but others which are not [H24, G16] and the question is not yet fully resolved.

254. *Potentially lethal damage (PLD)* (see Section I.B.).Whereas sublethal damage occurs during an interval between two dose fractions and manifests itself by repeating the shoulder region of the cell survival curve normally without a change in D_0, PLD does not require a second dose but only time before allowing further cell division to occur and is normally manifest by an increase in D_0. It appears that PLD is much reduced or absent after neutrons [H25, G16, S2].

255. *Slow repair* (see Section I.B.) It was shown [F8] that when two doses of x rays were given to mouse lung, there was an increase in LD_{50} due to pulmonary damage with increasing separation of the two treatments. During the first few hours after the initial dose this increase in LD_{50} is attributed to repair of sublethal damage between the two fractions, but the further increase was slow repair. In similar experiments with neutrons the initial repair of sublethal damage was observed (although, as expected, much reduced) but no further slow repair was observed. This phenomenon is thought not to be due to cell repopulation [C31]. It has also been shown by Curtis [C1] that there is a disappearance of chromosome aberrations in liver irradiated with x rays, but not with neutrons, which may also be a manifestation of slow repair.

256. The indications are therefore that with x-irradiation slow repair may occur in slowly dividing tissues, but is absent after neutrons. This has two consequences:

(a) The RBE for slowly dividing tissues would increase with increasing overall treatment time. Such an increase has been observed for skin damage with fractionation over 6 months compared with the same number of fractions in shorter time intervals [F9];
(b) There would be a greater degree of residual injury after neutrons than after x rays because of long term repair occurring after x-ray damage but not after neutron damage. Some evidence along these lines has been reported [D5, H8, F7].

257. As slow repair occurs after x rays then long fractionated regimes should spare slowly proliferating tissues which are presumed to be those involved in late radiation reactions. Such sparing of tissue damage would not occur with neutrons, so that the RBE would be higher for late than for early damage. This is a controversial issue and is not fully resolved at present.

C. RBE AS A FUNCTION OF NEUTRON ENERGY

258. In recent years a variety of neutron sources have been used for radiobiological experiments relevant to radiotherapy. These neutrons are generally in the range 6–50 MeV. In contrast, most work on lower energy neutrons was done earlier when the dosimetry was even less certain than it is today.

259. Hall et al. [H35] presented RBE as a function of the mean neutron energy for various in vitro and plant systems and showed that RBE was maximal at about 400 kV (Figure XI). In general, the RBE at 400 kV was 4 times that at 10 MeV. This result is in broad agreement with predictions based on the theory of dual radiation action [K20]. Fission neutrons would therefore have about twice the RBE of fast neutrons [D26, D28, S24].

260. With normal tissues, most comparisons of RBE with different energy neutrons have been obtained for jejunal crypt survival. Hendry and Greene [H36] have shown that the RBE of uncollimated monoenergetic neutrons (14 MeV d-T) is much smaller than for collimated beams [B36, H37] indicating that the dose from scattering material contributes an important element to neutron dose, at least with intestinal damage. RBE comparisons on both gut (clonal assay) and skin (average skin reactions) have been made for a variety of beams. The preliminary results are summarized in Figure XII [F29]. In this case neutrons were produced by deuterons of a given energy onto a beryllium target. The neutrons produced have a spectrum of energies, the mean being about 40% of the deuteron energy. It is clear that the RBE decreases with increasing energy and for neutrons of Ed = 16 MeV(Be)[1] it is 30–40% greater than for Ed = 50 MeV(Be).

[1] Ed = deuteron energy; e.g., 16 MeV(Be) = 16 MeV deuterons onto a beryllium target.

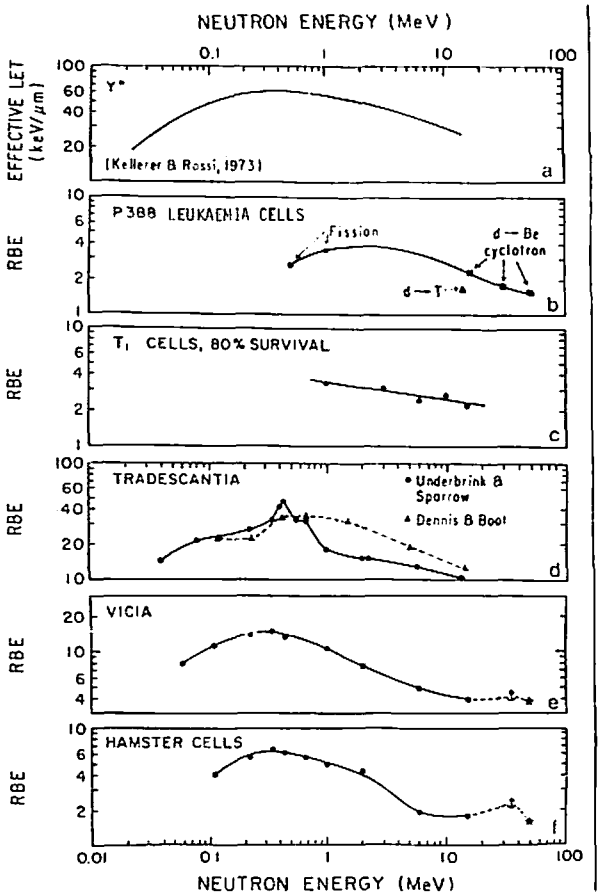

Figure XI. RBE as a function of neutron energy for plant and mammalian cells in culture. The top panel is a theoretical curve. The peak RBE at 0.3–0.4 MeV is clearly illustrated and it is a factor of 3 or 4 greater than the RBE for neutrons of energies in excess of about 10 MeV. The photon dose ranges were 2–12 Gy for the mammalian cells, 0.5–6 Gy for Vicia faba and 0.1–4 Gy for Tradescantia [H35]

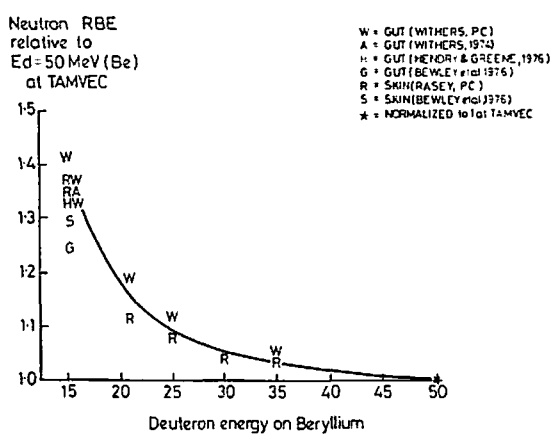

Figure XII. RBE for skin and intestine, as a function of neutron energies in the therapeutic range, i. e., mean energies from about 7 MeV upwards [F29]

D. NEUTRON FRACTIONATION

261. The two major factors governing the effects of fractionation of dose in radiotherapy are the number of fractions N and the overall treatment time T In the Ellis formula (section I.F.). Values for the exponents of N and T for damage to subcutaneous connective tissues are 0.24 and 0.11, respectively, for x rays. It is now clear from animal work that the exponents for N and T vary from tissue to tissue [A10, H28, H66, H67, W6, V1].

262. For clinical usage the Ellis formula has been adjusted, based on isoeffect curves for early skin damage, i.e. [F30]

$$TD = NSD_N N^{0.04} T^{0.11}$$

In the case of skin, the T factor is probably due to repopulation and was therefore specifically chosen to be the same for x rays and neutrons. The exponent of N is less because sublethal damage is less for neutrons. The formula was used successfully in the Neutron Therapy Clinic at Hammersmith Hospital when the routine neutron fractionation regime had to be altered.

263. Exponents of N and T for tissue damage, when measured for both x rays and neutrons, are given in Table 12. They are seen to vary from tissue to tissue but the factor for both N and T is small after high-LET radiation, indicating little or no sparing by fractionation. Small T factors indicate the lack of time-related repair after neutrons in slowly proliferating tissues. Small N factors may be a reflection of the highest LET component of the neutron dose playing the dominant role at low doses per fraction. Support for this interpretation is given by the reduction in OER observed with increase in fractionation of neutron dose [H33]. Domination of the low dose region of the neutron survival curve by the highest LET component of the beam implies that the initial region of a neutron survival curve would be exponential and with higher doses would bend downwards [H34, G20]. This would lead to the requirement for increasing the dose of neutrons to produce a given level of damage only on changing from a single dose to two or three fractions (i.e., on the bending part of the curve) without further increase with increasing number of fraction, as is seen to be the case with most tissues.

E. NEUTRON RBE FOR NORMAL TISSUES

264. There are two ways of examining the non-stochastic effects of neutrons. One is the direct examination of tissue response to the high-LET radiation; this is clearly the most desirable, but the information on it is rather limited. The second method is to study the RBE for various tissues, as a function of dose level. This is a less direct approach, but if RBE considerations can be generalized, as seems to be the case, then by using RBE as the conversion factor much of the available low-LET information can be extrapolated to neutrons or other high-LET radiation.

265. The relationship between RBE and dose/fraction for damage to a variety of normal tissues was analysed by Field [F28] who showed, as predicted from survival curves, that the RBE was high at low doses per fraction and decreased as the dose per fraction increased. The curve drawn through this data was used by Sheline et al. [S21] to calculate the appropriate RBE values and thus equivalent doses of x rays in a reassessment of Stone's first neutron therapy trial.

266. With the accumulation of more data it became apparent that the RBE was different for different tissues [H26]. This has been particularly clearly demonstrated with the Ed = 16 MeV(Be) beam from the Hammersmith cyclotron giving neutrons with a mean energy of about 7.5 MeV. More data exist from this beam than from any other. There are variations in RBE between different tissues of almost a factor of 2 (Figure XIII). Variation in RBE for normal tissue has also been

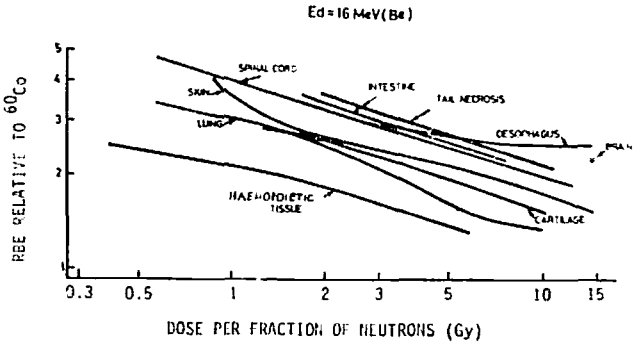

Figure XIII. RBE versus dose per fraction for neutrons produced by bombarding beryllium with 16 MeV deuterons. In all cases there is an increase in RBE with decreasing doses per fraction but there is an overall factor of about 2 in the range of tissues investigated

shown for other neutron beams [F29]. Differences in RBE have been mainly associated with differences in the degree of repair of sublethal damage [B33, H27] but slow repair may also play a role with some tissues.

1. Skin

267. More data are available for skin than for other tissues. The RBE for damage to skin of mouse, pig, rat, and man is shown in Figure XIV. The curve applies to damage leading to erythema, desquamation and regenerating clones of cells in the four species. The fact that the results from experimental animals and man fall on the same curve indicates that it is reasonable, at least for skin, to extrapolate results from animals to man. As predicted by theory [K20] over most of the dose range the RBE increases with decreasing dose, and the same is true for irradiation at low dose rates, for example, by ^{252}Cf [K29]. At the highest dose levels the RBE tends to increase with increasing dose, and this is due to hypoxia in the skin which will only be important with the largest doses. The above reactions observed in skin are primarily the result of damage to the basal epithelial layer. However, some observations on late damage (deformity in mice feet) also fall on the main curve in Figure XIV. This type of late damage has been shown to have a well-defined threshold which is higher than that for the production of an early reaction (as in the case with photons), after which there is a rapid increase in effect with increasing dose.

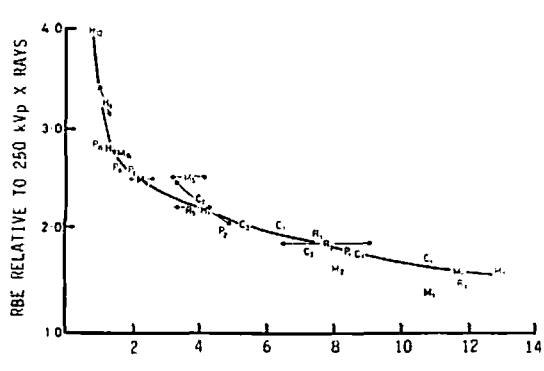

Figure XIV. RBE versus dose per fraction for the skin of four species. H, human; P, pig; R, rat; M and C, mouse. The subscripts indicate the number of fractions used. It is clear that the important factor is the dose per fraction, not the number of fractions

268. The relationship between early and late reactions was found to be similar for various treatments, both single and fractionated, photons or neutrons. It is, however, doubtful whether the late deformities seen in rodents are relevant to the human problem. In rodents these early and late reactions may stem from a common cause [F5, D6]. Rodent skin is very thin compared with that in larger animals and man and does not respond by producing extensive late subcutaneous fibrosis as is occasionally seen in patients following radiotherapy. Rodents may not therefore be suitable animals in which to study late skin damage relevant to that which occurs in man, despite the close correspondence with the early reactions.

269. In studies on pig skin, Withers et al. [W25] found, in a 6-week course of treatment, that gamma rays given twice weekly produced a worse late response than 5 times weekly, for the same early response. With neutrons (Ed = 50 MeV(BE)) they found no increase in sparing of late damage with an increase in neutron fractionation from twice weekly to four fractions weekly and both neutron regimes gave a more severe late response for a given early response than either of the gamma ray regimes. However, the authors suggest that this was probably associated with the increased absorption of neutrons in the subcutaneous fat. Human skin was irradiated with x rays and fast neutrons to establish RBE values for a neutron cancer trial [F14]. The results are quoted in Table 13.

270. Hendry et al. [H28] investigated necrosis in mouse tails. Necrosis seems to arise from an unhealed ulceration and closely follows the acute skin response. The RBE values both for skin damage and necrosis in tails are higher than those observed for other acute endpoints in skin [A10]. However, the tail acts as a temperature-regulating organ, and there is evidence of hypoxia in its skin which affects the sensitivity even at 16 fractions of 2–3 Gy x rays [H24]. This might increase the dose required to produce an effect and also be responsible for the high RBE values observed.

271. Retreatment of rodent skin a long time after a primary treatment with x rays or neutrons has shown more residual damage remaining after neutrons compared with x rays [H8, F7]. This implies that the skin tolerance dose for either x rays or neutrons (and possibly for other trauma) will be less after previous neutron treatment than after x rays.

272. In summary, the RBE for single doses of neutrons for production of skin damage is 1.5–2 and will depend on the neutron energy. The effect of fractionation with neutrons is much less than with x rays, and beyond two fractions the main contributing factor will be repopulation. A summary of threshold doses is given in Table 13.

2. Gastrointestinal system

273. RBE values for oesophageal damage in mice are rather higher than for most other tissues [H27, P20, G18]. The damage is primarily to the basal epithelial cells [P2, K5] which are of ectodermal origin, and one might therefore expect RBE values similar to those of skin rather than intestine. The histology of the mouse oesophagus is also similar to skin. However, hypoxia has been shown to influence the oesophageal sensitivity in anaesthetized mice, at least at high doses per fraction [H2]. Minimum single doses of neutrons required to

cause oesophageal death of mice are at least 8 Gy in a single treatment and 20 Gy in 10 fractions in 11 days [H2, P1].

274. RBE values for acute intestinal damage have only been derived for mice. In general the values obtained are slightly higher than those for skin (Figure XI) and this may be due to the greater reduction in sublethal damage compared with other tissues. For example, the fraction of recovery from sublethal damage after neutrons of 7.5 MeV mean energy compared with that after x rays was 0.2 for gut damage compared with 0.4–0.6 for skin damage [F23]. The minimum single dose of this energy neutrons to produce either a reduction in crypt count or animal death was close to 4 Gy in a single treatment.

275. When two fractions of neutron are given, there is a small degree of repair of sublethal damage. However, when the fraction number is increased above two, there is no further sparing of neutron dose [W2]. There will, however, be sparing due to cellular repopulation, just as with x rays.

276. The homeostatic control in the small intestine is such that although there may be rapid regeneration of stem cells in the crypt, the numbers of cells differentiating may be considerably depleted by cell death in fractionated regimes in therapy. This can be seen in a "stunting" of villus height [M5] which is first noted after doses greater than 1 Gy neutrons or in a change of the surface architecture seen with the scanning electron microscope [H29]. Differences in response for a given level of crypt loss were seen using these techniques for x rays and neutrons with single doses and these differences may be exacerbated with fractionation. The architectural changes may be more relevant in the case of long fractionation regimes but results are not yet availabile.

277. Late damage leading to fibrosis and narrowing of the lumen or adhesions and ulceration may occur. Geraci et al. [G17], following irradiation of a 4-cm segment of the ileum, have taken death within 6–90 days as a measure of such late intestinal complications which occur at higher doses than that for the early syndrome. These workers have suggested that the RBE is also greater than for acute intestinal damage but data from which conclusions may be drawn with any certainty are inadequate.

278. There is, in conclusion, no further effect of increasing the number of neutron fractions above 2, i.e., the exponent for N is zero, in contrast to the effects of x rays. There will, however, be considerable sparing during protracted irradiation by cellular repopulation. Single doses of neutrons greater than 4 Gy can cause a reduction in the number of crypts leading to animal death. Doses greater than 1 Gy cause architectural changes in the intestine.

3. Cartilage

279. The RBE for fast neutrons has been measured for growing cartilage, using two different methods. Kember [K19] counted surviving clones in the cartilage of 6-week old rats and obtained RBE values slightly higher than by the method of Dixon [D4, D27] who quantified stunting of growth in 7-day old rats. The average value for these measurements was similar to the RBE obtained for skin at the same level of dose per fraction. The results of Dixon [D27] indicate no threshold for neutron-induced stunting in the young rat. It was found that 1% stunting was caused by 0.13 Gy of fast neutrons. Kember [K19] measured a D_o for neutrons of approximately 0.8 Gy which is similar to that obtained in other tissues.

280. It has been suggested that cartilage in adults might contain a large fraction of hypoxic cells because the tissue is relatively avascular. Experiments by Dixon [D4] who varied the oxygen concentration in the air breathed by young rats showed that all the cells were slightly protected from x irradiation by hypoxia, but that the effect was insufficient to cause a large increase in RBE. Kember [K1] was unable to improve the oxygenation of the cartilage in young rats by the animals breathing hyperbaric oxygen. Whether these results may be extrapolated to man is not clear.

4. Lung

281. The RBE for lung damage to mice is lower than for skin and most other tissues, with the exception of the bone marrow (see subsection IV.E.5) although the differences are not great. Unlike skin but similar to intestine, there is no further sparing of damage by fractionation of neutrons beyond splitting the dose [F17]. This is in contrast to x irradiation, from which the sparing of damage to lung continues to increase with fractionation [H30]. This difference may be due to slow repair, which is important in lung (and possibly in other tissues which have a slow cell turnover) and which does not occur after neutrons [F8].

5. Nervous system

282. *Spinal cord.* The spinal cord shows considerable capacity to repair sublethal damage after x irradiation. The D_2-D_1 values for x rays are large ($\sim$ 9 Gy) and the slope of the isoeffect curve from 1–30 fractions is $\sim$ 0.4 [W6, V8]. Using 15 MeV D-T neutrons, van der Kogel and Barendsen [V6] have shown little recovery from sublethal damage after neutrons and the isoeffect curve is flat between 5 and 23 fractions. The RBE values obtained were similar to those for other normal tissues with this beam. Geraci et al. [G5], using neutrons with a mean energy of $\sim$ 8 MeV (Ed = 22 MeV(BE)) also obtained RBE values in mice similar to those for skin. The RBE pertaining to lumbar cord irradiated with single doses of neutrons from 16 MeV deuterons on beryllium is higher than that for skin: with fractionated irradiation preliminary results using doses to produce 10% myelopathy at one year post-irradiation also indicates a higher RBE than for skin [W37].

283. The RBE for spinal cord is similar to that for skin and several other tissues. Experiments have been performed with neutrons on the spinal cord of rats [W6, V6] and mice [G5, G7]. In mice, single doses of at least 6.8 Gy were required to cause paralysis and this was increased to approximately 10 Gy in 10 fractions. However, in fractionated experiments, renal failure also occurred at a similar threshold of 10 Gy [G7]. With rats, single doses of more than 10 Gy are required to cause a small probability of paralysis and they were increased to approximately 18.5 Gy in 23 fractions [V1, V8].

284. *Brain.* By counting cell numbers in the subependymal plate of the rat brain, Chauser et al. [C11] observed that with x-ray doses of less than about

15 Gy there was a loss in cells followed by a slow recovery in numbers. With neutrons, a dose as small as 1.2 Gy caused a steady fall in cells at least up to 6 months, with no sign of recovery. As the response after x rays or neutrons is so different, RBE varies with the time of observation. At late times the RBE is higher than for skin.

285. In the clinic Catterall reported that after neutron treatments of 15.6 Gy in 12 fractions over 4 weeks, gliomas in the brain were controlled but some patients suffered a slowly increasing dementia [C33]. Similar results were also reported by Parker from Seattle. The dementia is associated with the development of microscopic areas of demyelination throughout the treated volume. In Edinburgh, Duncan and Arnott, treating gliomas with 13 Gy of neutrons in 20 fractions over 4 weeks, observed cerebral oedema at about 6 weeks after completion of treatment, which is not normally seen after x irradiation, but dementia was not observed.

6. Thyroid

286. An assessment of the RBE for radiation damage to rat thyroid has been made by using the end-point of impairment of its proliferative potential. Using monoenergetic 14 MeV neutrons, Malone et al. [M29] derived the "survival curve", for which the D_o was 3.1 Gy. However, this value is very high, as is the value of D_o of about 4 Gy for x rays, owing to the unorthodox interpretation of the term "survival". The RBE at about 1 Gy of neutrons was 3.2 and at about 5 Gy of neutrons was 1.8. These values are in the range of those found for other tissues, indicating that the thyroid is not particularly sensitive to neutrons.

7. Testis

287. The RBE for damage to the testis has been obtained by two end-points; weight loss or spermatogonial stem cell survival. Weight loss of testis after irradiation is due to the killing of spermatogonia. The dose response curves obtained using this technique are biphasic with both x rays and neutrons, indicating a population of about half the total cells being more resistant [K18, H32]. With x rays there is no repair of sublethal damage in testis and the same is true for neutrons. When two doses of either radiation were given either 4 or 7 days apart, the dose-effect curves were not different from those obtained with single treatments [S22].

288. Hornsey et al. [H32], using neutrons of Ed = 16 MeV(Be) observed an RBE of 2.5 for neutron doses of less than 0.5 Gy and of 3.2 for larger doses. Geraci et al. [G19], using neutrons of Ed = 21 MeV(Be), obtained an RBE of 3.0 at low dose levels, but did not investigate at high doses. De Ruiter et al. [D26], using 1-MeV neutrons, obtained values at 5.5 and 4.1 at lower and higher levels, respectively. These results are consistent with the differences in neutron energies used (see section IV.C). Hornsey's results are therefore unusual in that over the dose range studied the RBE decreased with decreasing dose, which is the opposite of results found with other organized tissues (see Figure XIII). The reason for this difference is not clear.

8. The eye

289. The lens of the eye is avascular and, therefore, it may be concluded that it is also rather hypoxic. The RBE would, therefore, be expected to be about 1.5 times higher than for well-oxygenated cells and tissues, because of the reduced oxygen effect with high-LET radiations. Experimental RBE values have been determined by a variety of workers [B16, M25] and do seem to be higher than for other tissues at similar values of dose per fraction. For example, Merriam et al. [M28] obtained values of 4.5 at 1.8-MeV neutrons up to 9 at 0.43-MeV neutrons. The x-ray doses in their experiments were about 5 Gy.

290. Bateman et al. [B34] obtained much higher RBE values with 0.43-MeV neutrons, but these were for the comparatively low doses required to increase the probability of causing opacities in a highly susceptible mouse strain. Di Paola and others [D42] also measured high RBE values, increasing with decreasing dose per fraction from about 8 with 0.12–0.5 Gy of neutrons to about 20 with 0.01 Gy of neutrons. These values were also for increasing the probability of causing opacities, as in Bateman's experiments, but the RBE values were low. The RBE for 0.43-MeV neutrons would be expected to be higher than for other energies (see section IV.C).

291. The higher RBE for lens opacities generally found is borne out by the report of Abelson et al. [A11] that cyclotron workers exposed to neutrons over periods ranging from 10–250 weeks were observed to have lens changes with a mean dose of about 1 Gy of neutrons. In a trial of fast neutrons in radiotherapy, Roth et al. [R18] observed no changes with less than 0.8 Gy given as 12 fractions but slight permanent loss of vision with 2.2 Gy or more.

9. Haematopoietic tissues

292. The RBE for non-stochastic damage to stem cells of the haematopoietic system is low and varies little with dose per fraction [F28, B33, G19]. This is because there is little accumulation and repair of sublethal damage in these cells with x rays and virtually none with neutrons. RBE, therefore, mainly reflects differences in D_o, which are small.

293. There is also a dosimetric factor which will cause the neutron RBE to be low in bone marrow. Bone has a low hydrogen content so that the absorption of neutrons will be less than in other tissues because of the lower probability of collisions with protons. This is in contrast with an excess production of secondary electrons by photoelectric absorption of x rays because of the high mineral content in bone. However, Broerse and Barendsen [B33] conclude that although these dosimetric factors do play a significant role, there are indeed intrinsic differences between the biological response of cells of the bone marrow compared with many other tissues.

294. The lack of repair capacity is also seen in lymphocytes. The majority of untransformed lymphocytes are very radiosensitive, but the RBE values for killing unstimulated human lymphocytes, rat lymphocytes or white cells in mice are about 1 and for lowering the transformation index about 2 [G19, H31]. With photons, the haematopoietic tissues are more sensitive than the intestine, so animals which survive the early

intestinal syndrome may die later from the haematopoietic syndrome. This is not normally the case with neutrons, the intestine usually being the limiting factor in whole-body irradiation.

10. Blood vessels

295. The effects of radiation quality on the response of blood vessels has not been extensively studied. There are only a few studies with fast neutrons. In the intestine the RBE for leakage of albumin and PVP was estimated to be 3.4 ± 0.4 [T12] and 3.0 ± 0.5 [L10]. The RBE for capillary endothelium in subcutaneous tissues in the rat has been estimated by Broerse et al. [B35], using 14 MeV neutrons. For neutron doses between 2.5 and 5 Gy the RBE was 1.8–1.9. These values are similar to those found for skin and intestinal epithelium. The results of Aarnoudse and Lamberts [A12] suggest that the RBE for radiation-induced atheromatosis in hypercholesterolaemic rabbits depends on dose. A neutron dose of 5 Gy was more effective than the same dose of x rays, whereas for a dose of 10 Gy neutrons were less effective.

296. Stearner et al. [S23] conducted an electron microscopic study of changes in the microvasculature of the mouse ear between 12 and 20 months after sublethal whole-body fission neutron irradiation. There were degenerative changes in the smooth muscle of arterioles which are seldom seen after x irradiation. Although vascular damage was not sufficiently severe to be quantified, evaluations indicated more severe arteriolar degeneration after a total dose of 2.4 Gy of fission neutrons fractionated over 24 weeks than after the same single dose. This is the reverse of the normal fractionation effect.

F. MIXTURES OF NEUTRONS AND X RAYS

297. It is difficult from current knowledge to predict how a combination of low- and high-LET radiation will affect normal tissue tolerance and how the components of a mixed beam might add to produce a given degree of biological response. In principle, the treatments could either be simply additive or there might be some interaction between the different radiations to give enhanced damage. Information from cell studies in vitro is equivocal. Durand and Olive [D29] found that neutrons apparently caused a reduction in recovery from sublethal damage inflicted by x rays, whether given before or after x irradiation. They also found that the shoulder on the neutron cell survival curve did not represent recoverable sublethal damage. Others [R19, N6] found some interaction between the sublethal damage inflicted by x rays and neutrons when the two radiations immediately follow each other. It has been demonstrated in the stem cells of the intestinal epithelium that the rate of recovery from sublethal damage appears to be independent of its source [H24] and it has been suggested by Gragg et al. [G16] and by Hornsey et al. [H33] that recovery from sublethal damage with a neutron beam is simply due to its low-LET component. However, the presence of the high-LET part of the beam, which only inflicts lethal damage, will cause the total accumulation and repair of sublethal damage to appear less than with a photon beam. If the two radiations are separated by 24 hours, when recovery from sublethal damage is complete, then the effects are simply additive [H38].

298. There is little information on the effect of mixed treatments of neutrons and photons on either slow repair or potentially lethal damage, but there is evidence that tissues which have been treated with neutrons carry unrepaired damage for long periods. The tolerance to a subsequent course of x rays is less in a tissue previously treated with neutrons than in one previously treated to the same level of damage with x rays [H8, F9]. This observation may be particularly important for exposure to mixed beams for an extended period.

G. OTHER TYPES OF HIGH-LET RADIATION

299. Biological experiments have been performed with α particles, protons, negative π-mesons and with heavy ions. All of these particles have the property of increasing the LET with increasing penetration into tissue, before the particles are brought to rest. Fast protons in the range of 50–660 MeV have been shown in a wide range of biological materials to possess an RBE value close to unity. The same value would be expected to apply to man [R33]. For π-mesons the entrance particles have properties similar to those of sparsely ionizing radiations. This is also true for high energy protons and alpha particles. π-mesons have a "star region" of maximum dose deposition and maximum LET in which the oxygen effect is reduced and the RBE raised, but both to a rather lesser extent than with fast neutrons. In the peak region the increase in RBE is primarily the result of less sublethal relative to lethal damage after π-mesons relative to x rays [Y4]. The Bragg peak for alpha particles and protons is extremely sharp, and in this region of a millimetre or two the dose and LET are increased by a large factor relative to the entrance characteristics. Heavy ions also have a large peak dose and may reach LET values of about 1000 keV/μm for very short distances, just before the particles stop. These particles would then be expected to have high LET values: for example, a figure of approximately 10 was found for liver injury [R33].

H. SUMMARY

300. Throughout this section the emphasis has been on effects of fast neutrons. For single treatments sufficiently large to cause non-stochastic injury, neutron RBE values range between 1 and 5 compared with photons, depending on the neutron energy. Included within this range is a factor of about 2 in the variation of RBE for different tissues. Repair from sublethal damage is less with high-LET radiation, so that in some cases there is no further "dose sparing" by increasing fractionation beyond two fractions. Also the dose rate effect with high-LET radiation is small. This will cause an increase in RBE with decreasing dose per fraction (and thus with increasing number of fractions). Where cellular repopulation is important (skin or intestine) there is no reason to think that it will be dependent on the quality of the radiation and the sparing which occurs with x-irradiation will also apply to neutrons. For slowly dividing tissues, for which radiation damage occurs a long time after irradiation, repair by repopulation will be small for both x rays and neutrons. Since other repair processes after high-LET radiation are limited, the neutron dose which may be tolerated if given over a long period may not be significantly greater than that in a single acute exposure.

V. INTERNAL IRRADIATION BY RADIONUCLIDES

301. When a radionuclide is introduced into a living mammal, tissues absorb a proportion of the energy of transition to the stable nuclide. The energy per unit mass of tissue is largely delivered by radiations emitted by the radionuclide or its daughters during their decay, and constitutes a radiation dose. The biological effects of the deposition of energy in a tissue are usually reported in the literature in relation to the most accurate expression for the dose obtainable, which is often simply the activity introduced per unit weight of animal (Bq kg^{-1}). However, other derived or measured quantities are also given such as the tissue specific activity (Bq g^{-1}), the mean dose rate (Gy s^{-1}), and the mean cumulative dose (Gy). The latter might be thought to provide a useful quantity for comparison with the total dose delivered for the same effect by external irradiation, and forms the basis for the present recommended protection limits for internal exposure to radionuclides [11].

302. To interpret the results of studies in different species and to relate them to those involving external irradiation, it is necessary first to consider briefly the relationships between the various expressions of the dose from radionuclides. Then the factors which may influence the biological effects of a given dose will be discussed. Data obtained from studies in experimental animals together with the results of therapeutic, accidental and occupational exposures in man will be reviewed together in this chapter.

A. DOSE RELATIONSHIPS

303. Although the activity of a radionuclide introduced into an animal is of major importance in determining the dose to the tissues, it does not uniquely characterize it. Direct measurements of the dose are not often carried out owing to the technical difficulties involved in the use of dosimeters in vivo. Radiation doses and dose rates are therefore usually calculated and a recent ICRU report [19] has provided a review of the methods available, particularly with reference to the clinical use of radionuclides.

304. In this chapter some of the expressions occurring in dose calculations are discussed in order to illustrate the physical and biological factors which may be expected to influence the dose delivered to a tissue following the administration of a given activity of a radionuclide.

1. Mean dose rate

305. The mean dose rate $\overline{\dot{D}}$ (Gy s^{-1}) to a target tissue v in animal from activity A_r (Bq) of a radionuclide contained in a single source tissue r is given in general form by [19]

$$\dot{D}(v \leftarrow r) = A_r \sum_i \Delta_i \Phi_i (v \leftarrow r)$$

The summation is taken over all the i types of particle emission from the radionuclide, where particle is used in the sense defined by ICRU [19] for directly and indirectly ionizing particles. Δ_i (J) is the mean energy of the particles of type i emitted per nuclear transformation and is a constant determined entirely by the characteristics of the radionuclide. Φ_i (kg^{-1}) is called the specific absorbed fraction and is defined as the fraction of the energy of particles of type i emitted in the source tissue which is absorbed per unit mass of the target tissue. It depends on the nature and energy of the particles, the attenuating characteristics of the tissues and the geometry of the source and target regions.

306. The mean dose rate to a target tissue v from activity A_o contained in the whole animal is obtained by summation of the contributions given in the above equation for all the tissues in the body. This can be expressed as

$$\overline{\dot{D}} = \sum_r A_r \sum_i \Delta_i \Phi_i (v \leftarrow r)$$

where $\sum_r A_r = A_o$. The target tissue may be an organ or a region of microscopic dimensions. The mean dose rate is usually a function of time.

307. Calculation of the mean dose rate necessitates obtaining values of Φ_i and A_r, and these are usually calculated using physical or biological models to extend the applicability of the theoretical and experimental data which is available. Typical models are discussed in [19] and tabulations of useful data are appended to assist in such calculations.

308. It is clear from the above equation that the mean dose rate to a given tissue arising from a given total activity will be affected by the size of the organs contributing to the irradiation and in general will be dependent on the species as well as on normal individual variations. Alterations over a period of time may also be expected due to changes in the geometry of structures caused by radiation effects, disease, natural ageing or growth.

2. Mean cumulative dose

309. The cumulative dose $\overline{D}$ (Gy) averaged over a target tissue v for a time t (s) is given by the time integral of the mean dose rate $\overline{\dot{D}}$. When the geometry of the source and target regions remains constant, the above equation can be integrated to become

$$\overline{D} = \sum_r \tilde{A}_r \sum_i \Delta_i \Phi_i (v \leftarrow r)$$

where the quantity

$$\tilde{A}_r = \int_o^t A_r dt \qquad \text{(Bq s)}$$

is called the cumulative activity [19].

310. The cumulative activity is usually derived from measurements of the concentration of activity in an organ as a function of time after administration of the radionuclide and biological models are again used to extend the applicability of the data [19] to other tissues.

311. The many factors which influence the mean cumulative dose received by an organ following the administration of a given activity to an animal are those which affect the cumulated activities in the various tissues in addition to those already discussed affecting the specific absorbed fractions.

312. The cumulated activities in the body depend on the intake of activity, its transport, metabolism and re-utilization, as well as its excretion. These factors, in turn depend on: the characteristics of the material introduced, the nature of the radionuclide, its chemical

and physical form, the chemical and physical form of the carrier; the method of introduction of the activity, its distribution in time, route of entry, means of introduction; the animal species, weight, sex, age, condition, response to diet, etc.

313. Every element has its own characteristic metabolism in the body, although the presence of the carrier may affect it. The solubility of the carrier in body fluids, in particular, may determine the initial transport and excretion of the activity. The metabolism of an animal may be significantly altered if the activity incorporated is sufficiently high to produce radiation damage. After a period of continuous introduction of activity, the concentrations in the body may reach an equilibrium state, and the dose then delivered to tissues largely depends on the total time of irradiation, and may be relatively easy to determine. In general the distribution of the mean cumulative dose in the body tissues is not the same as the distribution of activity, but is related to it in a complex manner.

B. FACTORS INFLUENCING BIOLOGICAL EFFECTS

1. Temporal distribution of dose

314. The dose rate to a tissue is generally a function of time due to decay of the activity and metabolism or transport of the radionuclide in the body. For insoluble radionuclides in the gut, for example, the temporal distribution of dose to the gut wall is usually determined by the speed of passage of the gut contents. In most cases repair of sublethal damage will usually occur during exposure and the effectiveness of the mean cumulative dose will be much reduced over that from a single short exposure to external x-irradiation, although some damage will still occur.

315. A basis for relating the effects of radionuclides to fractionated radiotherapy has been suggested by Bigler [B59] using the time, dose and fractionation factor, TDF, concept of Orton and Ellis [O1]. However, the validity of these concepts has yet to be established. The dose rates involved are variable and considerably lower than those used in brachytherapy (> 0.3 Gy/h) for which the procedure was developed. In addition, the critical dose rates may not be represented by the mean dose rate to the organ but rather by the dose rate delivered to critical structures within it [B60].

2. Spatial distribution of dose

316. The biological effects of radionuclide decay are caused by one or several of the following processes [K40]: emitted radiation; chemical transmutation; nuclear recoil; change of atomic charge. The emitted radiation produces effects at distances depending on its penetration whereas the last three essentially produce effects within molecular dimensions close to the site of the disintegration.

317. Since the radiosensitive structures of cells are located at specific sites (for example, in the nuclear DNA) the biological effects of radiation depend on the microscopic distribution of energy along its path. Radionuclides emitting alpha particles causing dense ionization along their tracks, may be expected to be many times more effective than similar distributions of beta- or gamma-emitting radionuclides in producing tissue damage for the same absorbed dose.

318. The relationship of the sensitive site to the point of emission of the radiation is important. Radionuclides which emit a significant amount of energy in the form of Auger electrons may simulate the dense ionization produced by high-LET radiation. Figure XV shows results of calculations of the average energy deposition per disintegration in spheres of various diameters for ^{125}I and ^{3}H, in comparison with the mean energy transferred to the same volume by a 5 MeV alpha particle with a LET of 100 keV/μm [H56]. When the volume considered is sufficiently small, the energy deposited by the decay of ^{125}I is greater than that transferred by the alpha particle, whereas that deposited by the decay of ^{3}H is more than an order of magnitude smaller. The energy deposited in individual events is governed by stochastic processes and considerable variation about the mean values can be expected.

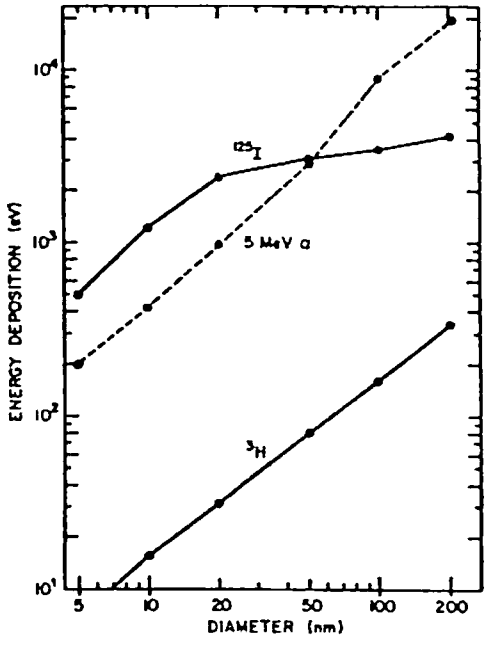

Figure XV. Average radiation energy deposited in spheres of various diameters by decaying ^{125}I and ^{3}H (solid lines), or by a 5 MeV alpha particle traversing the sphere (dashed line) [H56]

319. Experimental studies using labelled DNA precursors have shown [K40, F49] that the decay of ^{125}I located in the DNA of mammalian cells is 10–100 times more lethal per disintegration than ^{3}H in a similar molecular position. In comparing the doses to the cell nucleus in synchronized Chinese hamster cells [H56] ^{125}I-iododeoxyuridine was much more effective in causing cell death (LD_{50} : 0.45 Gy; D_o : 0.74 Gy) than either ^{3}H-thymidine (LD_{50} : 3.8 Gy; D_o : 0.74 Gy) or external x-irradiation (LD_{50} : 3.3 Gy; D_o : 2.3 Gy).

320. Radionuclides uniformly distributed in tissues or emitting particles with ranges which are large compared to cellular dimensions produce relatively uniform spatial distributions of dose. The biological effects are then determined by the temporal distribution of average tissue dose and the quality of the radiations emitted.

321. When radionuclides, particularly the alpha emitters, have heterogeneous concentrations within the tissues on a microscopic scale (i.e., a microdistribution)

and also emit particles with ranges comparable to cellular dimensions, their efficacy for producing a given effect is determined by the spatial relationship of the radionuclides as well as by the distribution of dose to the radiosensitive structures within the cells [F48]. If the localization of the radionuclide and the radiosensitive areas are congruent, the effectiveness of a given average tissue dose may be much enhanced both due to localized processes such as transmutation, which are associated with the disintegration, and to the particular microdistribution of dose.

322. The microdistribution of dose in tissues may also be important in comparing the relative efficiency of uniform and locally non-uniform distributions of activity [F48]. The dose microdistribution and other localized effects of radionuclide decay such as transmutation may be particularly important in considering the effects of radionuclides incorporated into specific vital molecules such as hormones or enzymes which control the metabolic functions of tissues and systemic processes.

C. EFFECTS ON TISSUES

323. The object of this section is to review information on non-stochastic effects of radionuclides which are likely to be of some significance for the health of contaminated individuals. The data are obtained from studies in experimental animals and reports of therapeutic, accidental and occupational exposures in man. Although one of the most important physical variables influencing the effects of radionuclides is the nature of the radionuclide itself, the emphasis of this Annex is on the radiobiology of individual tissues. Accordingly, the effects are here classified in relation to the tissue rather than the radionuclide.

324. The data on man are of most importance since species effects may be expected to be significant, not only because of inherent differences in the radiosensitivity of corresponding tissues, but also because of the differences in scale, morphology and metabolism, which determine the distributions of the dose delivered by a particular radionuclide. Often information concerning the radiation dose delivered for a given effect is not available, but even where it is, it should be remembered that the dose may be estimated to the time when the effects became evident, and the events producing the effect may have occurred at a much earlier time and for smaller dose. This concept of "wasted" dose has been reviewed by Mole [M52].

1. Gastrointestinal tract

325. Radiocolloids have been used in radiotherapy for the reduction of fluids accumulating in serosal cavities as a result of malignant disease. The colloid labelled with a suitable beta-emitting radionuclide (^{32}P, ^{198}Au, ^{90}Y) is introduced into the cavity and irradiates the tissue surfaces and disseminated neoplastic cells in the fluid while sparing deeper tissues. From autopsy data it has been estimated [H57] that 5550 MBq colloidal ^{198}Au in 400 ml saline injected into the peritoneal cavity resulted in total doses to the retroperitoneal lymph nodes, the omentum and the peritoneal serosa of about 77.5, 67.5 and 47.5 Gy, respectively. Mild radiation sickness and haematological complications have been recorded and sometimes persistent leukopaenia. Ileus and gastrointestinal complications have been seen up to ten years after treatment, at which time the serosa was found to be thickened and fibrosed. Adhesions and fragility of the bowel wall have been noted affecting the whole of the small intestine [H57].

326. When given in sufficient intraperitoneal amounts to mice both ^{32}P and ^{198}Au colloids can cause morbidity and death. Such effects were observed in a study using both radionuclides [H58]. After 15 days with 2–4 MBq of ^{32}P and 5.5–11 MBq of ^{198}Au there was marked blunting of the mucosal folds in both large and small intestines. Chronic inflammation was observed in the submucosa with slight fibrosis. Architectural changes in the myofibrils of the smooth muscle were also seen leading to early interstitial fibrosis and diffuse myofibrillar degeneration. However, since the distance from serosa to mucosa in mice is less than 1 mm (compared to more than 2 mm in humans) it is difficult to extrapolate these results to man.

327. Acute irradiation of the G.I. tract from injected insoluble beta emitters has been studied in rodents and dogs [S51]. The radiosensitive cells are in the crypts located beneath the mucosal surface at depths of some 0.2 mm in the large bowel of the rat and some 0.8 mm in that of the dog. The dose delivered to these cells depends on the energy of the beta radiations, the mass of the intestinal contents and the residence time of the radionuclide in any particular segment of the bowel.

328. In the rat, the LD_{50}s for suckling, weanling and adult animals for ^{106}Ru-^{106}Rh given by gavage were 55, 670 and 330 MBq/kg, respectively, and about 0.2 TBq/kg for ^{147}Pm in adults [S51]. In the neonatal animals the lower ileum showed the principal signs of damage and there was evidence that the ^{106}Ru-^{106}Rh pair, like ^{141}Ce [I6], ^{95}Nb [M53] and the actinides [S51] is absorbed into the epithelial cells of the mucosa in the immature small bowel. In the adults receiving a normal diet the main pathology was seen in the caecum and lower large bowel while the insensitivity of the weanlings was thought to be due to the relatively rapid transit of the gut contents in these segments of the young animal. Deaths occurred in the adults when 280 MBq/kg ^{106}Ru-^{106}Rh and 0.16 TBq/kg ^{147}Pm were exceeded, usually in the first or second week after treatment. Radiation doses to the target cells in the caecum were estimated to be similar for both radionuclides and suggested a $LD_{50/10}$ for ingested insoluble beta emitters in the rat of about 33 Gy [C26].

329. In dogs fed with ^{106}Ru- ^{106}Rh, the earliest death was at nine days after a dose of 130 MBq/kg but the survival time could not be closely related to the dose and one animal survived nearly 21 weeks after receiving 110 MBq/kg [S51]. Following ingestion of 92–150 MBq/kg the mucosa of the mid and lower colon were usually denuded at focal sites within eight days, and frequently the damage was irreparable. Animals surviving acute death had persistent diarrhoea until they were killed or died. The LD_{50} for acute death from ingested ^{106}Ru-^{106}Rh was estimated to be 130 MBq/kg and the $LD_{50/180}$ for delayed death, 100–110 MBq/kg [C26]. Direct measurements of the radiation dose carried out by means of thermoluminescent dosimeters sutured into the G.I. walls showed that the LD_{50} dose in the dog is about 40 Gy distributed over approximately 18 hours to critical tissue in the large bowel, regardless of the mode of death.

2. Bone and cartilage

330. Internal irradiation of bone has been investigated in various species following the administration of osteotropic radionuclides [V15]. It is convenient to divide these bone seeking radionuclides into two broad categories, volume and surface seekers, according to their basic metabolic behaviour [M55]. The alkaline earths, radium, calcium and strontium are volume seekers, distributing over a long period of time throughout the bone mineral by chemical exchange. From the blood stream they are rapidly transferred to accessible bone surfaces before concentrating in osteocytes involved in active mineralization and often ultimately being buried beneath new bone. Radium, unlike calcium or strontium, may remain for several days on the bone surfaces, particularly around the Haversian canals. Short-lived isotopes like ^{224}Ra may largely decay and irradiate these surfaces before they are incorporated into bone matrix. Plutonium and thorium are examples of the surface seekers which accumulate on the periosteal and endosteal surfaces, and may be resorbed or buried during growth or remodelling of bone. Plutonium is also concentrated in bone marrow, both as aggregates in macrophages and diffusely by a mechanism which is not understood.

331. Significant internal irradiation of bone in man has resulted from the deposition of isotopes of radium in the skeleton. ^{226}Ra and ^{228}Ra have been studied extensively since 1947 in groups of watch-dial painters, radium chemists and patients given radium therapeutically [A28, L36, S53]. Records in the United States have now been centralized at the Centre for Human Radiobiology at the Argonne National Laboratory, Chicago [R39]. ^{224}Ra was also given to about 2000 patients in the Federal Republic of Germany between 1944–1951 for the treatment of tuberculosis and ankylosing spondylitis [S54, S55]. ^{224}Ra at lower dosage is still used for treating ankylosing spondylitis in adults.

332. Severe bone dysplasia resulting in fractures especially of the long bones, vertebral collapse and severe bone pain has been associated with burdens of ^{226}Ra and ^{228}Ra [E24]. The effects of these isotopes cannot easily be distinguished in man [M56]. Hasterlik and colleagues [H59] have listed the following lesions seen on routine radiological examinations, often in subjects without symptoms: coarsening of the trabecular pattern; localized areas of bone resorption; patchy sclerosis; small and large bone infarcts; aseptic necrosis.

333. Some 20 years after the deposition of radium in the skeleton, characteristic punched-out areas alternating with areas of increased density are seen in the skull [L37]. The long and flat bones have a moth-eaten appearance. Increase in the number and severity of the lesions demonstrated over a period of years, occurs together with a progressive decrease in the body burden of radium. However, it has been concluded [H59] that body burdens in excess of 0.004 MBq ^{226}Ra are necessary before the radiographic lesions can be distinguished from those normally associated with ageing.

334. The microradiographic appearance of bone in subjects carrying radium burdens is similar to that found in dogs long after treatment with ^{226}Ra [J18] or ^{90}Sr [R40] and characteristic of vascular damage. Large numbers of Haversian canals are seen to be plugged with densely calcified material and the osteocyte lacunae may also be affected [H62, R40, L38]. In addition to complete plugging, a greater number of canals are found with highly calcified minor lamellae [H62] although large and bizarre resorption cavities are also present [J18].

335. Spiers has suggested [S56] that the skull lesions associated with radium burdens are related to the relatively high marrow dose to be expected in these areas. Measurements of mean path lengths in trabecular bone and in marrow cavities [S67] have enabled calculations to be made of the mean dose to the marrow spaces and to the endosteum, considered as a tissue layer of thickness 10 μm adjacent to trabecular surfaces [I1]. In the human skull the ratio of the mean path length in trabeculae relative to marrow spaces in the parietal bone was found to be 1.31 as compared to 0.16–0.30 for other bones, and the fraction of marrow irradiated was calculated to be some three times greater [S56]. However, on the assumption that a terminal radium burden of 0.37 MBq ^{226}Ra was evenly distributed through a 7 kg skeletal mass, the accumulated mean marrow dose would only be 5–10 Gy in 50 years whereas the dose to endosteal tissue would be 30–40 times greater. In parietal bone the marrow within range of the alpha particles would receive a dose 3–4 times greater. A quality factor of 20 would apply to all these doses [P60].

336. Radium-224 largely irradiates bone surfaces and sites of active mineralization at the time when the blood level is high. It has been estimated [S55] that the dose from ^{224}Ra to the endosteal surface in man is some nine times higher than the average skeletal dose whereas for ^{226}Ra it is less than two-thirds. Growth retardation, as measured by height, has been reported [S54] in 70% of children who had been injected with ^{224}Ra at 1–5 years, 44% injected at 6–14 and 12% injected at 15–20 years. Abnormal bone growths classified as osteochondromas were seen [M57] in 15% of the 204 juveniles receiving a mean skeletal dose of about 11 Gy from injections 0.85–1.7 MBq ^{224}Ra/kg over an average period of 11 months [S58]. These exostoses mostly developed in the long bones at sites where the metaphyses incorporated the activity; 73% were in males who have a natural preponderance of the hereditary tumours. Tooth breakage was also seen [M57] with maximum frequency of 15% in the 59 children injected between 16–20 years, although teeth are fully formed at this time. The tooth loss is characterized by resorption of the tooth near the gum line and breaking off of the crown. Similar changes have been induced in rats following the administration of ^{224}Ra and ^{226}Ra [R41] and in dogs with ^{239}Pu [T19].

337. Bone dysplasia in animals resulting from the administration of most bone seeking radionuclides has been widely reported. The early uptake of sufficient activity in epiphyseal growth cartilage, in the endosteal surface of the metaphysis and in the periosteal surface of the diaphysis, may rapidly destroy osteogenic tissue and damage the blood supply, causing a reduction in the rate and amount of growth. Irradiation to a high dose over a long period may result in bone fibrosis, necrosis and fractures at characteristic sites.

338. MacPherson and colleagues studied in great detail the inhibition of growth in weanling rabbits injected with 3.7 or 2.2 MBq/kg ^{90}Sr [M58]. Cellular damage was shown by an increase of disintegrating cell nuclei and decrease in mitosis in an area of high uptake in the metaphysis. A total dose of about 0.74 Gy received at a rate of about 0.08 Gy/h was sufficient to

cause a noticeable effect. The damage resulted in a thickening of the cartilage plate with failure of resorption. Damage to the blood supply, shown by leakage of red cells into the tissues, was noted after some 8 Gy at 3 days after injection, and in the animals receiving several tens of Gy the damage was so severe that the thickened cartilage plate became separated as a bar of dead bone. Fibrosis occupying marrow spaces between the trabeculae was seen after some 30 days and cumulative doses of 190 Gy. These animals had a marked reduction in tibial growth rate and ultimate shortening of the limb, whereas no difference in growth from control animals was seen for the animals receiving lower doses.

339. The incidence of radiation-induced bone fractures has been reported in the beagles at Utah [T19]. Radiation-induced fractures are unique in that they involve a minimum amount of pain and inflammatory response. Following single I.V. injections the fracture rate increased rapidly above 0.12 MBq/kg ^{226}Ra and ^{228}Ra, 0.033 MBq/kg ^{239}Pu and 0.0037 MBq/kg ^{228}Th [T20, T21]. Fractures due to ^{90}Sr were only seen in one animal who received 3.7 MBq/kg. The anatomical distribution depended on the radionuclide. Fracture healing was low in animals treated with ^{228}Th and ^{228}Ra but was high for ^{226}Ra and ^{239}Pu, 80% of the rib fractures induced by 0.11 MBq/kg ^{239}Pu being repaired in a satisfactory manner. The incidence and time of appearance of fractures is related to the average skeletal dose. Of the significant number produced in dogs by an activity level of 0.11 MBq/kg ^{239}Pu the earliest occurred approximately 390 days post-injection with an average skeletal dose of about 32 Gy [T19].

340. In beagles at Davis, California, kept on a regime of continuous intake of ^{90}Sr and ^{90}Y in the diet from mid-gestation to 1.5 years of age [M69], few fractures occurred at the highest levels of intake with maximum body burdens of 13.1 MBq ^{90}Sr delivering an average skeletal dose of 133 Gy over 2 years [M68]. The smallest dose from ^{90}Sr for which any radiographic bone damage was observed was about 70 Gy by 10 years of age, and occurred at an intake level of 0.44 MBq/d resulting in a maximum body burden of 1.7 MBq.

341. In the beagles given a total activity of 3.1 MBq ^{226}Ra in 8 semi-monthly intravenous injections starting at 14 months of age, 25% of the animals suffered fractures within six months of the last injection [M69]. In these cases the bone marrow had received an average dose of less than 50 Gy [M68]. Trabecular coarsening occurred in 100% and fractures in 50% of animals given a total activity of 1 MBq ^{226}Ra. The earliest fractures appeared soon after the last injection at 18 months, when, by extrapolation of the reported dosimetry, about 8 Gy would have been given on average to the skeleton.

342. Cartilage is inevitably irradiated during intra-articular injections of radioactive colloids for the radiotherapy of chronic synovitis. ^{198}Au-colloid was used initially [A27, M54] but its gamma-ray emission is more penetrating than is necessary to sterilize the cells of the synovium. In addition, the small size of the colloid particles results in substantial leakage of activity from the joint cavity and accumulation in the regional lymph nodes [T18]. The pure beta emitters ^{90}Y-silicate citrate and ^{32}P-chromic phosphate as colloids are currently used for the therapy of knee joints [R38]. For other joints such as in the hip, or the fingers, the less penetrating radiations from ^{186}Re-sulphide or ^{169}Er-citrate, respectively, may be used [I7]. The activities administered have been determined empirically to prevent cartilage necrosis or flexion deformities, while minimizing the failure rate of the radiation synovectomy. For the knee some 110–180 MBq ^{90}Y is commonly used and the dose delivered to the membrane is estimated as about 60–80 Gy [S52]. The dose falls rapidly beyond about 2 mm from the synovial surface [B61]. The colloid is phagocytosed into cells on the surface of the synovial membrane, although some is deposited on fibrin in the synovial fluid [W41]. Two cases of knee joint rupture have been reported, presumably arising from cartilage necrosis [D44].

3. Lung

343. The lungs of miners of uranium, fluorspar and other minerals are subject to internal irradiation from radon and its daughter products present in the air of mines in concentrations varying widely between $<10^3$ and 10^6 Bq per cubic metre of air. Radon diffuses rapidly through the body and the greater part is exhaled within its half-life of 3.5 days. Its immediate daughter products with a collective physical half-life of some 20 min become rapidly attached to the dust in the air of the mine and a high proportion of the activity breathed may be deposited in the respiratory tract. For a full discussion of these problems see Annex D. The induction of lung tumours in these workers and the possible influence of other ambient factors such as tobacco smoke on the induction of neoplastic and non-neoplastic diseases of the respiratory tract in man are also treated in Annex L.

344. In animals internal irradiation of the lung by radionuclides has been studied following the inhalation or intra-tracheal instillation of radioactive particles. The radiation dose delivered to tissues by a given radionuclide depends on its initial distribution of deposition and its rate of clearance from the lung.

345. Soluble materials may be cleared from the lung within a few days by rapid absorption into the blood and by transport to the oesophagus by mucociliary action followed by swallowing. They are then translocated throughout the body and may remain for long periods in the skeleton or in other tissues depending on their biochemical properties. Insoluble materials may remain in the lung for years, being cleared by local dissolution or transport (probably as intact particles) to the bronchial and tracheobronchial lymph nodes. The concentrations in regional lymph nodes may become many times those in the lung and in both tissues radioactive particles may form locations for the delivery of high radiation dose rates.

346. A comprehensive review of the radiation effects of radioactive particles deposited in the lungs of experimental animals has been published by the ICRP [I8]. Non-neoplastic pulmonary lesions resulting in early death occur when the activity is deposited in sufficiently high concentrations. Lower concentrations result in progressive fibrosis and may lead to death from pulmonary insufficiency. Data available from several animal species suggests that such non-stochastic processes might be expected to occur after an alveolar deposition of more than 0.37 kBq/g lung of alpha-emitting radionuclides [I8].

347. Rats receiving lung burdens of 0.22–0.74 MBq/g lung of relatively insoluble $^{238}PuO_2$ and $^{239}PuO_2$ died

within a few days from severe pulmonary oedema [S59]. Radiation pneumonitis caused early death in rats exposed to a cumulative dose of 98 Gy from a burden of about 0.15 MBq/g lung from relatively soluble $^{253}EsCl_3$ [B62]. In baboons, initial lung burdens of 3–10 kBq/g lung $^{239}PuO_2$ resulted in death at 1–6 months [M59]. The earliest deaths were due to alveolar oedema and vascular injuries, but after 2 months the alveolar septa were thickened and collagen deposits and progressive fibrosis led to respiratory insufficiency and death.

348. Deaths within 500 days due to radiation pneumonitis and pulmonary fibrosis were seen in dogs exposed to high concentrations of relatively insoluble forms of beta/gamma emitting radionuclides such as ^{90}Y, ^{91}Y, ^{144}Ce, and ^{90}Sr in fused aluminosilicate particles [M60, R42, B60, H60, S60, H61]. The alveolar septa were seen to be thickened with hypertrophic and hyperplastic alveolar lining cells. Frequently the alveoli were filled with protein material. Various degrees of fibrosis occurred, including fibrotic thickening of the pleura. The extent of fibrosis was increased in the longer surviving animals [J19].

349. The rate of dose delivery to lung is an important factor in determining the cumulative radiation dose and the time for death. ^{90}Y having a half-life of 64 h, requires a relatively low cumulative dose to produce a given effect and such effects will occur earlier; on the contrary, ^{90}Sr with a half-life of 28.8 a requires a higher cumulative dose and the effects are delayed. The smallest initial lung burdens to cause death in dogs within 500 days from radiation pneumonitis and pulmonary fibrosis ranged from 22 MBq/kg for ^{90}Y to 1.1 MBq/kg for ^{90}Sr [H60, S6O]. However, the cumulative dose delivered ranged from 93 Gy to 400 Gy and the minimum time to death from 7.5 days to 184 days, respectively.

350. A similar effect of dose rate may be seen for alpha emitters where the half-lives are long and the variable is chiefly the rate of clearance from lung. Death caused by respiratory insufficiency in beagle dogs resulting from pulmonary fibrosis occurred about 1600 days post-exposure to a lung burden of insoluble $^{239}PuO_2$ at levels >0.74 kBq/g lung [W42]. However, similar deaths were observed in less than 1000 days following exposure to the more soluble $^{238}PuO_2$ at levels >0.37 kBq/g lung [P30]. The greater solubility of $^{238}PuO_2$ than of $^{239}PuO_2$, attributed to the high specific activity of ^{238}Pu [F50, F51], was indicated by the faster clearance from lung and the ten times greater retention of ^{238}Pu in the skeleton at 70 months post-exposure [B64, P31]. Similarly, following exposure to the even more soluble ^{238}Pu nitrate at initial levels of about 0.37 kBq/g lung, death occurred in less than 300 days [P32].

351. In rats with initial lung burdens smaller than those necessary to produce acute effects, lungs are seen to have a smaller infiltration of serum proteins but an increasing deposition of fibrin and proliferation of bronchiolar epithelium and alveolar lining cells up to a year after exposure [S59]. Early hypoxaemia results in a compensatory increase in the blood mass and circulation time, although haemoglobin and erythrocyte concentrations are normal [K41]. A second phase of hypoxaemia appears at 8 months and at this time the total haemoglobin and erythrocyte mass remains unchanged. Early ultrastructural changes consist of an increase in the length of the air-blood pathway due to oedema [A32]. Later, proliferation of connective tissue cells increases the thickness of the basement membrane. The hypoxaemia is thus consistent with alveolar-capillary blockade.

352. In dogs quite small lung burdens (about 0.26 kBq/g lung $^{241}AmO_2$) produce local areas of dense pulmonary fibrosis and mineralization with bronchiolar and alveolar cell hypoplasia [T22, B65]. There may be marked fibrous pleural thickening and obliterative fibrosis of small arteries, together with some dense peribronchial fibrosis. Larger burdens produce functional changes such as increased respiration rate, decreased vital capacity and decreased partial pressure of oxygen and oxygen saturation [T22, B66]. In baboons lung burdens of 37–74 Bq/g lung $^{239}PuO_2$ lead to progressive fibrosis and respiratory insufficiency culminating in death 1–3 years later [M59].

353. A different sequence of events has been observed in the Syrian golden hamster following 15 weekly instillations of ^{210}Po with a half-life of 138 d [L40, A33]. Transient radiation pneumonitis and hyperplasia of the bronchiolar epithelium were observed together with a progressive epithelization of alveoli with a large variety of cell types. The latter became the dominant lesion at 30–180 days after the last instillation. This difference in pathology is presumably due to a species effect.

4. Liver

354. Internal irradiation of the liver for therapeutic purposes has been carried out in patients with colonic cancer using ^{32}P-phosphate colloid immediately following colonic resection [G34]. 550 MBq were injected in equal amounts into catheters located in the superior mesenteric and coeliac arteries. Previous trials in rats [N14] had shown that when the colloid was injected into the arterial supply of the gut, it became well mixed in the portal circulation and 70% of the activity was fairly uniformly distributed in the liver. A total cumulative dose of some 50 Gy given to the liver by this means has caused no significant tissue damage or functional changes, within the first year of follow-up, although a temporary radiation hepatitis was seen in one of the three patients one month after injection [G34].

355. In another much larger trial [A34], ^{90}Y-resin microspheres together with a chemotherapeutic agent, 5-fluorouracil, were injected into the hepatic artery to treat liver metastases in patients with primary cancer of the colon and rectum. 3700 MBq ^{90}Y was used, calculated to give a beta-radiation dose of some 100 Gy to the liver. No significant effects were associated with the internal irradiation in 25 patients surviving on average 26 months.

356. Following the injection of a pharmaceutical preparation containing soluble ^{224}Ra, irradiation of the liver arises both from the decay of the radionuclide during its initial deposition in soft tissues and from that of its daughter products with their own characteristic distributions in the body. ^{220}Rn is readily soluble in lipids and ^{212}Pb is bound to red cells as well as concentrating in the kidney and liver. In man chronic liver disease, usually cirrhosis, has been reported in 8% of 106 adult males injected with ^{224}Ra for the intended therapy of tuberculosis and in 3% of 329 patients treated for ankylosing spondylitis [S58]. The average activity of 0.84 MBq/kg given to male patients with

tuberculosis was more than double that administered for ankylosing spondylitis. The incidence was not significant in women and it was suggested that this might be related to the greater exposure of men to known liver toxins such as alcohol [S58]. Fifteen of the 18 cases were identified between 12 and 24 years after administration of the activity. The radiation dose to the liver has not been reported.

357. Many studies of patients receiving thorotrast as an intravascular contrast agent for angiography have shown an unusually high incidence of non-malignant liver disease [V17, D45, K42]. In 1237 patients traced in Portugal [D45], 2.7% of 931 deaths were attributed to liver cirrhosis or fibrosis. Some 25 ml of thorotrast was usually injected corresponding to an activity of about 0.022 MBq $^{232}ThO_2$ [K43]. The radiation dose delivered to tissues is difficult to estimate. However, the mean alpha dose to the liver of a 70 kg weighing man at 30 years after injection of 25 ml of thorotrast has been calculated to be 7.5 Gy [K43]. For nine Japanese patients who died of liver cirrhosis after a latent period of 21–41 years, the dose rates to liver were estimated to be between 0.17–0.53 Gy/a [K42] providing cumulative doses between 4.7–16.8 Gy [K42, K50].

358. Massive internal irradiation of the liver can produce liver cirrhosis in rats, rabbits and dogs [M61]. In rats injected with 38 MBq/kg ^{144}Ce and 0.25 MBq/kg ^{239}Pu nitrate liver cirrhosis was found in all the animals surviving beyond 200 days. The liver doses received were 160 and 57 Gy, respectively.

359. Hepatic changes induced by ^{239}Pu have been observed in the dogs at Utah [T23]. Following a single intravenous injection of 0.11 MBq/kg tetravalent ^{239}Pu the activity deposits in the hepatic cells and remains for 2–3 months before being transferred to the reticulo-endothelial cells lining the sinusoids. The evidence suggests that the transfer occurs on the death of the parenchymal cell and is related to dose. The lesions produced are principally hepatic cell necrosis followed by regenerative changes. Significant regeneration was seen at doses as low as 0.62 kBq/kg ^{239}Pu with mean cumulative liver doses of less than 0.8 Gy. Regeneration was sufficient to maintain normal liver weight, except for some dogs given the highest doses of 0.11 MBq/kg ^{239}Pu. In these cases liver atrophy was observed as early as 474 days from a dose of about 23 Gy. Based on the appearance of ascites, atrophy was probably significant as early as 350 days from doses of 15–17.5 Gy.

360. Decreased phagocytosis in liver was shown in mice after intravenous injection of polymeric ^{239}Pu (0.67 and 1.33 mBq/kg). At the time, when this effect became manifest, the accumulated liver dose was estimated to have been greater than 20 Gy. The depressed function coincided with the translocation of Pu from the liver to the lung and kidney [K49].

5. Kidney

361. Severe renal disease has been frequently found in patients who had received injections of ^{224}Ra [S58]. Kidney insufficiency and a wide range of renal disease were the recorded causes of death in nearly 13% of 222 patients. In both the living and dead subjects the incidence of recorded disease was 3.7% of 373 and 6.7% of 239 patients injected with a total activity grouped in the ranges of 0.015–0.52 and 0.53–2.4 MBq/kg, respectively. However, such evidence for a dose-related effect must be considered with some caution because the higher dose group contained larger numbers of patients originally affected by tuberculosis and the use of different drugs in the two groups may have affected the incidence of kidney disease.

362. A characteristic radiation nephritis together with a significantly increased serum phosphorus have been observed in beagles injected with 0.037–0.11 MBq ^{228}Th/kg [B79, C27]. ^{228}Th continually generates its daughter ^{224}Ra and some of this reaches the blood stream and is redeposited in the tissues with its own characteristic distribution. The average total dose to the kidneys contributed from ^{228}Th, ^{224}Ra and its daughters has been estimated as some 10–30% of the average skeletal dose [M62], less than approximately 3.6 Gy [S77].

6. Thyroid

363. The thyroid is regarded as a radioresistant organ from the point of view of cell death and failure of function. Results are available from irradiation in its unstimulated normal state in order to reduce metabolic rate and to control symptoms of angina in patients with cardiac insufficiency. At least 300 Gy is required to cause total ablation within a short time, e.g., 2 weeks. This can be achieved with single oral doses of 1850–3700 MBq of ^{131}I, resulting in an uptake of about 37 MBq/g in the thyroid [G12].

364. Unavoidable external irradiation of the thyroid sometimes occurs in the treatment of head and neck cancers. Several authors have observed hypothyroidism after normal fractionated therapy, e.g., [M23]. These authors reported five cases of myxoedema within 4–12 months after doses of about 25–49 Gy received by the thyroid. Rogoway et al. [R15] reported on patients treated for Hodgkin's disease developing myxoedema after irradiation of the thyroid to about 40 Gy in a fractionated treatment. Of these, 4% developed myxoedema after receiving both external radiation and lymphangiography, whereas no patients receiving either lymphangiography or the external radiotherapy alone were observed to develop hypothyroidism. This result was attributed to an increased radiosensitivity of the thyroid after stimulation into increased activity caused by the iodine present in the contrast medium used for lymphangiography.

365. There are numerous reports of reduced thyroid function caused by irradiation with ^{131}I or ^{125}I. About 90% of the radioactivity is concentrated in the colloid but the dose delivered by the relatively energetic beta/gamma emissions from ^{131}I is distributed fairly uniformly throughout the gland. Iodine-125, on the other hand, decays by electron capture and each disintegration is associated with a cascade of x rays and Auger electrons [D43]. A number of the latter have energies below 3 keV and about one-quarter of the radiation dose is delivered to the thyroid by electrons with a range of less than 0.4 μm in tissue. The sites of hormone synthesis, situated in the apices of the follicular cells close to the colloid-cell interface must therefore receive a significantly higher dose than the more distant cell nuclei. The mean dose to the gland from ^{125}I (in contrast to ^{131}I) is therefore somewhat higher than the dose to the nuclei of the parenchymal cells. Difficulties may be expected in extrapolating animal data to man owing to the difference in the scale and morphology of the cells in different species.

366. Several clinical trials of ^{125}I for the treatment of hyperthyroidism have been initiated on the basis that the reproductive capacity of the thyroid tissue is more radiosensitive than hormone secretion. Some estimates [G37, L42] have suggested that the microscopic dose delivered at the colloid-cell interface is about four times that at the nucleus, and about twice the dose averaged over the gland, although these factors depend on the gland mass and the colloid fraction.

367. As with other cell types and tissues, it appears that irradiation of the thyroid at low dose rate allows time for the repair of sublethal damage. In cell survival studies in rats [G35] a study on the effects of x rays, ^{131}I and ^{125}I gave D_os of 4.5, 55 and 94 Gy, respectively, when the mean dose to the gland was used for comparison. The extrapolation number for x rays was 1.7 whereas for radioiodine the survival curves were exponential from the origin. The difference between ^{131}I and ^{125}I was attributed to the relative sparing of parenchymal cell nuclei due to the inhomogeneous dose distribution from ^{125}I, particularly when it was noted that about 30% of the proliferating cells would be stromal and located at greater distances from the active colloid than the follicular cells.

368. Electron microscopic examination of thyroid tissue following irradiation has indicated that ^{131}I produces diffuse damage whereas ^{125}I produces localized effects at the colloid-cell interface [L41]. From experiments using rats, several workers have concluded that ^{131}I is less effective than ^{125}I in disturbing hormone synthesis than in affecting the response to TSH [G36, V18, L41]. However, Jongejan and van Putten found no such evidence and concluded that the ratio of $^{125}I/^{131}I$ activities necessary to produce similar effects on iodine uptake, serum T4 and damage to thyroid structure lay in the range of 11–17 [J20]. Gross et al. had calculated a ratio of 16 for both the mean radiation dose to the gland and the radiobiological effect as determined by radioiodine uptake suppression [G36].

369. A large body of data exists for treatment of hyperactive thyroid glands, usually by orally administered radioactive ^{131}I. In its hyperactive state the thyroid is more radioresponsive. Werner et al. [W22] observed a return to normal, or even hypothyroidism after fractionated doses of 1.5–3.7 MBq ^{131}I, giving estimated total doses of 2–8 Gy. A greater proportion of children than of adults responded, as has also been reported by Einhorn and Wikholm [E12]. Somewhat higher doses are normally used to reduce elevated function and if hypothyroidism results it is permanent rather than transient [F12]. The hypothyroidism develops slowly. In 7.5% of the cases it is apparent within the first year [W22, B23], and subsequently 3% per year of the patients develop symptoms up to 26% at 7 years [B23].

370. The total dose delivered to the gland depends on the uptake and rate of biological clearance. For diagnostic doses with a relatively long retention in the thyroid, the ratio of total doses delivered per unit activity of ^{131}I and ^{125}I, is as low as 1.6 for an uptake of 25% [M63]. However, ^{131}I delivers some seven times the initial mean dose rate to a 20 g thyroid compared with that from an equal activity of ^{125}I [S50].

371. Mean activity levels of ^{125}I were used for therapy in single and, where necessary, multiple doses ranging between 37 and 1480 MBq, corresponding to concentrations between 0.44 and 37 MBq/g thyroid [A35]. It is difficult to compare the frequency of induction of hypothyroidism between groups, because of variations in the populations treated and their diets. However, at least two centres [B67, S61] have abandoned trials because the results showed no improvement on those obtained with ^{131}I. A reduction in the dose necessary to reduce the incidence of hypothyroidism was accompanied by an unacceptable increase in the rate of persistent hyperthyroidism. Follow-up periods have been too short to indicate whether the rate of delayed hyperthyroidism from ^{125}I is lower than that following treatment with ^{131}I [B67]. Clinically, the loss of function in hypothyroid patients is not considered very serious and can be easily managed by administration of synthetic thyroid hormone, providing the late appearance and insidious nature of the symptoms are recognized.

372. In 1954 following a thermonuclear explosion at Bikini radioactive fallout was deposited on the Marshall Islands. Inhalation or ingestion of iodine radioisotopes (principally ^{131}I, ^{132}I, ^{133}I, ^{135}I) by the population resulted in exposure of the thyroid glands to significant internal, in addition to external, irradiation. Within nine years thyroid nodules were noted in children who had received the highest dose on Rongelap Atoll [L43]. In a subsequent follow up over the next 15 years [L43], 67% of individuals exposed at ages below 10 years and 15% of the remainder, developed nodules which have since been surgically removed. Doses to the thyroid were estimated to lie in the ranges 10.2–42.6 and 5–30 Gy, respectively.

373. Five children exposed at ages below 5 years showed some degree of growth retardation and two boys developed myxoedema [S62]. A recent study [L43] has shown that the population as sampled on Rongelap Atoll have a significantly impaired thyroid reserve as indicated by a smaller increase in T4 following TSH stimulation. Additional biochemical evidence such as basal and TRH induced serum TSH, and serum T4 concentrations suggests that at least four of 43 subjects have impaired thyroid function some 25 years after a thyroid dose from mixed radioiodine isotopes, estimated in three of these to be less than 3.5 Gy.

374. There is little data on the incidence of hypothyroidism in subjects receiving small radiation doses from radioiodine [H69, H70]. Preliminary results of a study of patients receiving ^{131}I for diagnostic uptake tests [U3] have indicated an incidence of 1.8% within an average follow-up period of 16 years. Hypothyroidism became evident in 2.0% of 146 patients and 3.3% of 151 patients who had received doses in the range of 0.31–0.80 and 0.81–19 Gy, respectively. However, in a study of 1378 children exposed to ^{131}I fallout, the incidence of overt hypothyroidism over a similar period of follow-up was not found to be significantly different from that in 3801 non-irradiated controls [R51].

375. Radiation-induced damage may not result primarily from effects on the thyroid parenchymal cells. In culture, these are rather radioresistant [D21] and they also appear unresponsive in the whole animal. Rather, the effects could be mediated via an autoimmune reaction, initiated by a large sensitizing dose of thyreoglobulin into the circulation [M23, B23, B13] or by radiation effects on the microvasculature, particularly after acute doses [R1]. Another possible explanation could be the impairment of long-term proliferative potential of epithelial cells.

7. Gonads

376. The effects of intramuscular injections of 0.048 MBq/g body weight ^{32}P on the ovary and testes of 30-day old mice have been studied at autopsy 30 days later [S63]. The ovaries showed severe damage with complete absence of normal oocytes or follicles. The seminiferous tubules of the testis were affected non-uniformly. Sperm cells were seen in considerably reduced numbers. Sertoli cells and interstitial cells were not affected.

377. Samuels studied the localization and oocyte survival in the ovaries of mice following intra-peritoneal injections of ^{210}Po which became localized in the follicular cells [S64]. Significant loss of oocytes occurred at four days after injections of 37 mBq/g body weight with an apparently non-threshold dose-effect relationship. There was no dependence on the age of the animal between 21–150 days. An activity of 3.7 Bq/g body weight destroyed oocytes at all stages of maturation within 30 days, at which time no pathological changes were seen in the uterus. In comparison with external ^{60}Co irradiation (see section IV.A.), the RBE appeared to depend on dose rather than dose rate and was thought to become as high as 50 from a mean dose of 110 μGy to the ovary resulting in a primary oocyte survival of 79%. For a cell survival of 2.7% at 30 days an RBE of 4.8 was calculated from a mean dose to the ovary of 54 μGy.

378. Activities of 0.18–0.74 MBq ^{90}Sr injected intravenously in female mice on the 11th day of pregnancy seriously affected the oocytes in the developing ovaries [R44]. After the maximum dose, the total number of oocytes relative to those in unirradiated controls was 21% at 56 days and 15% at 170 days post-partum. The reduction in cells at all stages of development was strongly dose-dependent but the naked oocytes and the young follicles appeared to be the most sensitive. Over a relatively short period of 100 days the irradiated mice produced litters of normal size and frequency, indicating that the pool of mature follicles was sufficiently large to compensate for the losses in young oocytes.

379. Further work by the same authors showed a strong relationship between the loss in oocytes and the time of administration of the activity [R45]. ^{90}Sr is more effective in the mouse the later it is injected between 8 and 19 days of the intra-uterine life. However, it has been shown using external irradiation [B68] that the sensitivity of the oocytes decreases markedly between the 15th and the 19th day, increasing only again at birth. It has therefore been suggested [R45] that some of the ^{90}Sr activity injected after the 15th day when the foetal skeleton has started to ossify, will be incorporated into it and together with ^{90}Y provide an additional source of irradiation to the ovary. In the foetal mouse the gonads are within the range of many of the beta rays originating in the skeleton. This might also account for the very marked effect of ^{90}Sr administered just before birth when the oocytes are in the radiation-sensitive dictyate stage. An activity of 0.011 MBq ^{90}Sr given to the mother at this time produced a significant reduction in naked oocytes at 56 days post-partum, [R46] even though the mean activity measured in the ovaries at 10 days post-partum was only 17 mBq kg^{-1} ^{90}Sr with 9.2 mBq kg^{-1} ^{90}Y (wet weight).

380. Tritium can be incorporated into all parts of the living animal, particularly as ^{3}HOH. The effects on the ovary have been studied [D46] in 14-day old mice following continuous administration of ^{3}HOH to the mothers in the drinking water during pregnancy and lactation. Oocyte survival decreased exponentially without threshold in the range of 3–410 kBq/ml body water, as measured in the urine. The LD_{50} was 74 kBq/ml, which would deliver a radiation dose of 0.0044 Gy/day. Continuous external γ-irradiation of the mice with ^{60}Co from conception to 14 days post-partum showed that the higher gamma dose rates were more effective in cell killing, but that the response was definitely smaller than that using ^{3}H, with an LD_{50} of about 0.01 Gy/day. The RBE therefore varied inversely with dose, ranging from 1.6 for 0.5 Gy of gamma rays to 1.9 for 0.25 Gy and up to 2.8 for the lowest exposures.

381. The effect on mice of ^{99m}Tc given as pertechnetate in daily intravenous doses to pregnant and lactating females has been investigated [L44]. The tissue distribution, and response to injected $NaClO_4$, of ^{99m}Tc in the foetus, was different from that in maternal tissue, and suggested the involvement of Tc in foetal metabolism. Significant effects on the body weight of mature mice were found extending into the third generation from doses as low as 185 kBq/d, giving about 10 mGy to the primary foetus during gestation. Hairlessness and sterility were observed in mice exposed to ^{99m}Tc in the milk secreted by lactating mothers given 1.8–18 MBq/d. However, it is difficult to distinguish radiation effects from the chemical toxicity of technetium since no stable isotope exists.

8. The eye

382. An increased incidence of cataract has been noted in patients who had received injections of Peteosthor containing ^{224}Ra, principally for the treatment of ankylosing spondylitis or tuberculosis [S58]. Periods of 7–26 years have intervened between therapy and cataract diagnosis. Since cataract is normally rare in young people, an incidence of 4% at ages between 14–46 years in 204 patients receiving ^{224}Ra as juveniles was particularly striking. In adults the incidence was 1% in 300 men receiving less than 0.53 MBq $^{224}Ra/kg$ and 4.5% in 155 of those receiving greater doses.

383. If radium isotopes are concentrated in the pigmented cells of the iris, as has been observed in dogs and rodents [T24], the emitted alpha radiation may well affect cell division in the lens and account for the induction of cataract. However it has not yet been determined if these lesions have a special character or are similar to those produced by uniform external irradiation. In addition, a possible association with any prolonged drug therapy or with the diseases originally affecting the patients cannot be excluded at this time.

384. Introduction of polymeric plutonium nitrate into dogs by inhalation has been found to result in an accumulation of about 0.01% of the total activity in the eye [S39]. The radiation dose received by the cornea was greater than that received by either the lens or the aqueous humour. No changes in the retina were observed for doses of less than 10 mGy, but local retinal dystrophy occurred in 75% of animals receiving doses of 1.7 Gy and 30% of those receiving 10–100 mGy.

9. Haematopoietic tissues

385. The late effects of chronic irradiation of the bone marrow by radium has been studied in female dial painters first employed before 1930. An analysis of the serum protein levels [P33] suggested a slight increase in α-2 globulin with age in those groups with the higher intakes of activity > 37 kBq/kg. There was little evidence for late effects of radium on white cell counts [P35]. A symptom-free but statistically significant reduction in haematocrit was found in the groups receiving the highest skeletal doses [P34], especially those with greater than 10 Gy, although these did not contain a higher frequency of low haematocrit values suggestive of anaemia. The dose rate to marrow within trabecular bone of a man with a 37 kBq burden of ^{226}Ra has been estimated to be about 16 mGy/year [M64].

386. The use of radioiodine to treat patients with metastatic thyroid cancer is generally limited by the dose to the bone marrow [B69]. In a large series in which the majority of patients had previously received a total surgical thyroidectomy, the activity of ^{131}I-sodium iodide administered was chosen to deliver 3 Gy to the blood. After nausea, depression of the bone marrow proved the most frequent serious complication.

387. Radiophosphorus, ^{32}P, has been widely used since 1939 in the treatment of patients with primary polycythaemia. Single or multiple doses are given until the patients red cells are reduced to acceptable levels. Spiers et al. [S65] have reviewed a series of patients given single doses of 144–222 mBq ^{32}P and showed that the dose rates to bone marrow follow a single exponential decay with a half-life of 6.7 d. The cumulative dose to the bone marrow was calculated to be 1.42 Gy per treatment or about 0.24 Gy/37 mBq injected. Late non-stochastic effects of such treatments have not been reported.

388. Following the demonstration of selective uptake of sulphur in chondrosarcoma [G38] and to a lesser extent in chordoma [W43], attempts have been made to treat these malignant tumours with ^{35}S injected as Na_2SO_4 [A36, B70, M65]. In a recent series [M65] doses of 185–222 mBq/kg were administered intravenously and the treatment repeated at intervals determined by the clinical and haematological response. A maximum of eight treatments were given over 88 weeks but in 13 patients the cumulative activity administered was in the range of 370–1780 mBq/kg. For an administered dose of 1110 mBq/kg it was calculated that the average radiation dose to normal cartilage and bone marrow was 40.5 and 9.9 Gy, respectively. From 70 to 90% of the activity was excreted in the urine over the first three days and most of the activity in the blood cleared with a biological half-life of 12 hours. In most patients the first dose had a minimal effect, but with each successive dose the prompt marrow depression increased and recovery became less complete. Thrombocytopaenia, leukopaenia and finally anaemia developed progressively and were dose-related. Only one patient with chondrosarcoma showed unequivocal improvement and all patients developed severe marrow hypoplasia, especially with respect to megakaryocytes and myelocytes.

389. Haematopoietic death has been described in the dogs at Utah given a series of single intravenous injections of various bone seeking radionuclides. Of those given 3.6 mBq/kg ^{90}Sr three died due to severe progressive thrombocytopaenia, leukopaenia and anaemia. Perivascular cuffing of central veins in the liver (which is characteristic of myeloid leukaemia) was also described together with myelofibrosis in some cases [D47]. The lowest average dose received one year before death was 38.4 Gy [M66] to the skeleton.

390. Following a single intravenous injection of 555 kBq/kg body weight of ^{239}Pu in mice, a moderate reduction in the apparent half-survival time of erythrocytes was measured [J24]. Polymeric plutonium entering the circulation is engulfed by the reticuloendothelial cells of the bone marrow, which are consequently subjected to continuous localized alpha-particle irradiation.

391. A single intravenous injection of 104 MBq ^{55}Fe in high specific activity (37 mBq/μg) causes early death in mice with severe depletion of haematopoietic cells in bone marrow and spleen, and atrophy of lymphoid tissues [L45]. Iron exists almost exclusively in intracellular form in the body and ^{55}Fe with a long half-life (2.7 a) is continually re-utilized. The radionuclide decays by electron capture depositing 75% of its decay energy within a range of 1 μm. The median survival time for animals given 52 MBq and 26 MBq ^{55}Fe was 117 and 439 days, respectively, in comparison with 847 days for controls. In these irradiated animals there was only slight atrophy of lymphoid tissues and nodular haematopoiesis of the regenerative type was sometimes seen in the spleen. However, they developed a dose-dependent pancytopaenia which was attributed to the inhability of the inactivated stem cells to replenish the loss from the various haematopoietic cell lines due to radiation damage. The effect was primarily seen in the erythroid series.

392. The chronic effects of ^{65}Zn have been studied in the rabbit [L46]. Zinc is a trace element influencing the activity of many enzymes and hormones and essential to the function of certain enzymes such as carbonic anhydrase. Following daily oral administration of ^{65}Zn as zinc chloride, the activity becomes very widely distributed in body tissues, reaching equilibrium within 3 months with a maximum concentration in the liver [A37]. ^{65}Zn decays mainly by K-capture associated with the emission of several short-range Auger electrons. The function of vital molecules into which the ^{65}Zn is incorporated would almost certainly be altered by transmutation of the radionuclide as it decays, in addition to any localized effects caused by the particles emitted and the radiation dose delivered.

393. The morphological changes observed in the blood-forming tissues are directly related to the level and duration of the continuous ^{65}Zn administration. In a group of animals given activity levels of 0.37 mBq/kg providing mean whole-body doses of 4.5 Gy/day, histological examinations after 3–5 months showed hyperplasia of the reticulo-endothelial elements in the spleen and lymph nodes, the appearance of foci of extramedullary haemopoiesis, and an increase in the number of cells of the white series in the bone marrow [G39]. Seven of the 20 rabbits in the group died during this period, 3 from bronchopneumonia with pleurisy and pericarditis and the remainder from a necrotic suppurative process spreading over the lymph nodes. Such inflammatory lesions of the lymph nodes may be considered characteristic of the chronic action of ^{65}Zn and have been attributed to the progressive formation of antibodies to proteins of the animals own tissues [F32]. Suppuration of cervical lymph nodes has been noted after 11–12 months in animals given activity

levels as low as 3.7 kBq/kg/d with corresponding mean whole-body doses 40 μGy/d [G39].

394. For sufficiently high levels of administered ^{65}Zn activity, erythopoiesis and lymphopoiesis are progressively depressed leading to the appearance of abnormal erythrocytes, reticulocytopaenia and lymphocytopaenia [B71]. At intermediate levels few such changes are seen, but at low activity levels [R47], providing mean whole-body doses of 40 μGy/d, there is an initial depression of erythropoiesis followed after 6–12 months by hyperplasia of the red and white series and marked reticulocytosis in the bone marrow. In the peripheral blood there is persistent reticulocytosis and transient increases in the number of lymphocytes, neutrophils and basophils. A similar apparently stimulating effect on haematopoiesis is observed for low dosage of other radionuclides such as ^{35}S [K44]. However, the granulocytic series seem to be particularly sensitive to exposure to ^{65}Zn [B72]. There is a gradual increase in the relative and absolute number of the young neutrophils in the bone marrow and an intensified release of rod nuclear neutrophils into the blood.

395. The haematological effects of inhaled radionuclides arise both from irradiation of haematopoietic tissue by activity translocated from the lung, and also by direct irradiation of the blood circulating in the lungs and the other tissues containing active deposits. The effects are therefore highly dependent on the solubility of the inhaled particles in the body fluids, and on the half-life and metabolism of the radionuclide.

396. The chlorides of the beta/gamma emitting radionuclides ^{90}Sr, ^{144}Ce, ^{91}Y are relatively soluble in the lung and are rapidly deposited in the skeleton. After their inhalation at high activity levels in dogs, deaths occurred in the following 12–44 days as a result of marrow hypoplasia, panleukocytopaenia, terminal haemorrhage and bacterial infection [M67]. The cumulative average beta dose to the skeleton to death ranged from 6–13 Gy arising from long-term retained burdens of 2.7–3.7 mBq ^{90}Sr/kg body weight, 5.2–11.8 mBq ^{144}Ce/kg body weight and 7.4–20 mBq ^{91}Y/kg body weight. For lower retained burdens, animals survived this acute phase and exhibited smaller depressions in the blood elements.

397. After inhalation of sufficient activities of the transuranic radionuclides in rodents and dogs, leukocytopaenia [B65, S59, B73] and depression of myelopoiesis have been observed [B66]. However, in dogs a dose-related lymphocytopaenia was the earliest and most consistent effect seen following inhalation of both transuranic radionuclides and insoluble particles containing beta/gamma radionuclides. Lymphocytopaenia has not been associated with either illness or premature death of the animals.

398. Lymphocytopaenia was observed in dogs within 2 weeks after exposure to high lung burdens of plutonium [W42, B74, P32, B73] and within 400 days following depositions of about 3.7 Bq/g lung $^{239}PuO_2$ with dose rates of more than 2.4 mGy/ day delivered to lungs and lymph nodes [Y5]. It was not seen in the 3–6 years following depositions of < 7.4 Bq/g lung [P36]. For lung burdens of 111–1480 Bq/g lung it became apparent after 1 year and persisted throughout life [P37]. From a review of the animal data it has been concluded that the magnitude and delay in onset of lymphocytopaenia depend on the dose of alpha-emitting radionuclides but can probably be detected after pulmonary depositions of ≥ 18.5 Bq/g lung [I4].

399. For beta/gamma emitters in fused alumino-silicate particles the lymphocyte response in dogs depended on the radionuclide [J21]. For short-lived ^{90}Y where the irradiation must have been largely confined to the lung, the maximum lymphocyte depression occurred 7–14 days after exposure with recovery to normal levels by 50 days. For ^{91}Y, depression occurred more slowly and by two years there were indications of recovery. For ^{144}Ce, the depression occurred during the first 200 days and was maintained over the remaining two years of observation. For ^{90}Sr the dose-related depression of lymphocytes was progressive over two years and was seen to persist for at least 2000 days [S66]. A reduced function in the surviving lymphocytes has also been demonstrated but it is not known whether T or B lymphocytes are primarily affected [B75].

400. Irradiation of the tracheobronchial, mediastinal or hepatic lymph nodes may also result from radionuclides translocated from the lungs. The mode of transfer of the activity from lungs to lymph nodes is unknown but for insoluble particles such as $^{239}PuO_2$ is probably mediated by macrophages. Concentrations of such particles can accumulate over a period of years to reach many times the levels in the lung, and retention of the activity in the nodes may be very prolonged.

401. Lesions of lymph nodes following the inhalation of alpha-emitting radionuclides and ^{144}Ce in fused alumino-silicate particles have been described in rodents and dogs [S59, D48, H61]. The primary lesions in nodes containing active deposits are characterized by lymphadenitis and fibrosis with some degree of depletion of the germinal centres. Lymphoid atrophy has also been observed following the administration of high levels of plutonium even in nodes without active deposits.

402. Following exposure to $^{239}PuO_2$ in dogs the histological changes observed in lymph nodes up to some 400 days proved to bear little relationship to the estimated cumulative radiation doses [Y5]. This was possibly due to variations in the rate of activity concentration and temporal distribution of the dose delivered to tissues. However, the changes correlated well with the mean dose rate, appearing to have a threshold at which no pathology was observed of some 50 mGy/ day to the lymph nodes from an initial deposition of about 1.1 kBq/g lung. At 400 days after depositions of more than about 3.7 kBq/g lung, lesions were apparent in nodes receiving mean dose rates of more than 70 mGy/day. Lymph node lesions have also been seen at much longer times after lung depositions of $^{239}PuO_2$ as low as 26 Bq/g lung [B76].

10. Vascular system

403. Vascular damage can lead to the development of sclerotic changes in internal organs following chronic irradiation. A form of nodular periarteritis affecting small and medium sized arteries was noted in 22%, 18% and 7.5% of rats surviving beyond 200 days from a single oral administration of 83 mBq/kg ^{106}Ru, 0.018–18 mBq/kg ^{144}Ce and 63 mBq/kg ^{137}Cs [M61].

404. Vascular changes were studied in the bones of the dogs from Utah contaminated with bone-seeking

radionuclides [J22]. The most sensitive measure of a vascular action was the length of vessels per unit area obtained from microphotographs. Table 14 shows the lowest values of injected activities, burden time and skeletal dose, where significant vascular reduction occurred in the compacta.

D. SUMMARY

405. Taking into account the difficulties of calculating the doses delivered to tissues from internal irradiation, this limited review of the data indicates that the effects of beta- or gamma-emitting radionuclides are not inconsistent with those expected from comparable mean tissue doses delivered at low dose rate by external x irradiation. The distribution of tissues affected is determined by the particular spatial and temporal distribution of the radionuclide in the body.

406. Alpha-, low-energy beta- and Auger-electron-emitting radionuclides produce microdistributions of energy around a disintegrating atom which sometimes coincides with a radiosensitive structure in the tissue, resulting in an enhanced effect. The enhancement with respect to external x irradiation may be expressed by an RBE factor which also takes account of effects due to the quality of the emitted radiation, the density of ionization and other results of decay, in particular the transmutation of the atom. RBE's as high as 50 for ^{210}Po and nearly 3 for ^{3}H have been reported for damage to oocytes in the mouse.

407. Another possible delayed effect of irradiation by radionuclides may be the indirect damage to tissues caused by alterations in metabolism or by autoimmunity. The low dose from iodine radioisotopes necessary to produce long-term impairment in thyroid function, as indicated by the data from the Marshall islanders, and also that from ^{65}Zn found to produce lymph node necrosis in rabbits call for further study.

VI. THE ROLE OF VASCULAR AND LYMPHATIC DAMAGE

408. Many factors other than direct effects on parenchymal cells may affect tissue response to irradiation, including hormonal changes, reactions mediated through the nervous system and modifications to the vascular system. Such changes have been considered in sections II. H and I, III. H and V. C, while the damage to vascular and lymphatic tissues is discussed in more detail in the present chapter in relation to the irradiation of organs and tissues. The role of vascular and connective tissue damage as a possible cause of generalized non-specific effects leading to life span shortening in whole-body irradiated animals is treated separately in Annex K.

409. Irradiated tissues frequently show vascular changes, particularly at late times after irradiation. For this reason, and because the turnover time of the endothelial cells is generally thought to be long, i.e., between 2 and 24 months (reviewed by Hirst et al. [H4]), it is often postulated that vascular damage is the common pathway for late radiation injury [R1]. This is the reason why radiation damage to blood vessels is discussed in a separate chapter. It should however be pointed out immediately that, owing to the intimate association of vascular and parenchymal elements, it is extremely difficult to decide whether long-term effects on parenchymal cells are the direct consequence of irradiation, or the indirect result of failure of the vascular or connective tissue elements.

410. After doses of radiation in the radiotherapy range, tissues which show no early reactions in parenchymal cells often show progressive vascular changes over a period of many months. Histological changes in blood vessels and interstitial fibrosis precede atrophy of parenchymal cells in liver [I2, R20], kidney [M10, C17], heart [F31] and lung [J3, M7, A13]. In general, changes in vascular function have been observed before severe late atrophy of tissues. Several authors have specifically noted that functional vascular changes precede damage to cells which are dependent on the vascular supply [G2, H39, K21, G21]. Increased vascular permeability is observed in the lung and in the mesentery before signs of fibrosis are apparent [T13].

411. These observations suggest that impaired vascular function may cause tissue atrophy at late times after irradiation. However, in the CNS, the situation is more complicated. At moderate doses (10–20 Gy) vascular lesions predominate after a long latent period, but higher doses (> 40 Gy) cause white matter necrosis at earlier times, in the absence of severe vascular lesions [H14, H41, V9]. This may be interpreted as an early response, which only occurs above a certain threshold for the glial elements [H42]. Sequential studies have also been performed in order to examine in which cells the damage is first expressed [P22]. Changes in lymphatics have been noted in the radiotherapy dose range. Alteration in lymphatic morphology occurs rather earlier than in blood vessels [A23, Z6, B47].

A. MORPHOLOGICAL CHANGES

412. Many descriptive studies of gross changes in blood vessels have been made, particularly for the skin. The time course of changes differs in different tissues, probably in relation to the death of surrounding parenchymal cells. The pattern of response also differs in different vascular elements, perhaps in relation to differences in the blood vessel walls. In capillaries and sinuses the endothelial cells are the main components of the vessel wall, whereas in venules, veins, arterioles and arteries, the thicker walls contain structural elements consisting of elastin, collagen, fibroblasts and smooth muscle cells. In the largest vessels the walls are sufficiently thick to require their own capillary network. Vascular damage can be roughly divided into early, intermediate and late changes.

413. Early changes occur roughly within minutes to days after irradiation. The earliest visible change is erythema, resulting from dilation of the capillaries. After very high doses of the order of 10 Gy this may occur within hours; after lower doses (1 Gy) erythema occurs after a few days. It has been postulated that histamine-like substances, released from dying epithelial cells, may cause this effect in skin [D30, E14]; however, capillary dilation has also been observed in the heart [F31] in which no early cell death occurs. Electron microscope studies have shown abnormalities in lung endothelial cells within 3 hours of exposure to 20 Gy [M30]. Vacuolation and lifting of endothelial cells has been observed within the first month after irradiation, preceding changes in the lung epithelial cells [P6]. In skin, vacuolation of endothelial cells has been observed within 10 days [Z3] but at this time many

epithelial cells have also died and the vascular changes may be a response to these dying cells.

414. Intermediate changes occur within approximately six months. Within each organ they show a patchy distribution with some areas being normal, whilst in others degenerative changes are apparent. In both lung [P6, M30] and heart [F31], electron micrographs show cytoplasmic swelling and endothelial cell sloughing. Thrombi sometimes obliterate capillaries. In some tissues, e.g., heart and kidney, endothelial changes precede changes in the parenchymal cells [P22]. Changes in the other components of larger vessel walls are seen at this time, e.g., effusion of plasma proteins leading to oedema, which is not drained by the lymphatics. It has been suggested that this protein leaking progresses to the hyalinization that characterizes large arteriolar lesions [Z3].

415. Late changes which are seen after about six months consist in degeneration of the walls of arteries, arterioles and capillaries. Endothelial proliferation at this time may lead to "sausage segments" by partially or completely obliterating the lumen [W26, M43]. Thickening of the basement membrane [P6, M31] and replacement of the lumen by collagen [P6, A13] also occur. Gross external changes, described as telangiectasis, are seen in many irradiated tissues [R21]. In the arteries and arterioles, tortuosities are also seen, with regions of dilation and constriction [H43, B37, L21]. Loss of endothelial and smooth muscle cells occurs and increased amounts of acellular material, including collagen, are deposited in vessel walls [R1, H40, Z3, W26, W27]. Changes in blood vessels and a reduction in their number can also be shown by computer analysis of microangiography results [E21].

B. FUNCTIONAL CHANGES

416. The function of the vasculature is to carry an adequate supply of nutrients to all parts of the body and to remove the waste products. Blood flow, vascular volume and vessel permeability have all been studied by means of radioactive tracer techniques.

417. In order to study blood flow, a radioactive tracer may be introduced into the blood (e.g., ^{42}K or ^{86}Rb) and the extraction in different tissues assessed from the incorporated radioactivity. Alternatively, the tracer may be introduced directly into the tissue (e.g., ^{22}Na, ^{99m}Te, ^{122}Xe) and its rate of clearance via the blood stream assessed. For the extraction studies the isotopes used must be taken up and retained by cells, whereas for the clearance assays the isotope must be freely diffusable [S25, K22, L22].

418. Early experiments to measure vascular permeability involved the intravascular injection of dyes which bind the plasma proteins and assessment of the degree of blueing of the tissue [R22, R23]. More recently large molecules have been used, labelled with radioactive isotopes, which would not normally diffuse across the vessel walls (e.g., albumin). Increased permeability leads to leakage of these molecules and to a greater accumulation of radioactivity in the tissues. The studies often require sequential sampling, or sampling at a fairly long time after intravenous administration of the labelled molecules. It is easier to interpret these permeability studies if an independent estimate of the blood volume can be made and this is often achieved concurrently by using radioactively labelled red blood cells (e.g., by ^{51}Cr), which do not cross even a leaky vessel wall [S26, J8].

419. These techniques have been used in studying a wide variety of irradiated tissues, after a range of different x-ray doses, and over different observation periods. Some of the studies are reviewed below.

1. Skin

420. This has been the most widely studied tissue in various species including rodents, dogs and pigs. In early studies using dyes in rabbit skin, waves of increased permeability were observed after 1–30 Gy. The exact timing varied in the different studies partly due to the different skin areas investigated [R24]. An early phase was seen almost immediately [P23, J9] with a second phase beginning at 20 minutes and lasting a few hours [E14, R24, J9]. Further waves of reaction were seen extending over the first month [J10, J11]. The threshold dose at which a measurable change was observed was about 1 Gy [J12].

421. Other studies were carried out on rabbits [M32], guinea pigs [S27], and rats [L23] using a variety of labelled proteins. Changes in permeability are observable for several weeks, but return to normal by 6 weeks after 10 Gy in rats. In general, rats and mice appear to be less sensitive to permeability changes than rabbits and guinea pigs [R25].

422. In dogs, the leakage of dextran molecules of varying size has been tested after 10–40 Gy. Some effect was observed at all doses with a peak at 2 weeks. With increasing dose the size of the dextran molecules that could leak out was increased [A14].

423. Blood flow changes are more variable than permeability changes, with both increases and decreases being reported at various times after irradiation. In general, changes are not observed until many months after irradiation. For example, no changes were observed in rat skin until 10 months after doses up to 40 Gy ([K21], Van de Mereck quoted by [D31]) after which time flow was reduced with a threshold dose of 15 Gy. In mouse foot skin flow was increased during the first 20 weeks after 10×4 Gy to 10×7 Gy [H44]. In tail skin, no change in resting blood flow was seen, but the hyperaemic response observed after releasing temporary occlusion was reduced, suggesting impairment of vascular function several months after irradiation [D32]. Glatstein [G2] could detect no changes up to 12 months after 15 Gy in mice but Hopewell [H45] observed increased blood flow and decreased vascular volume in hamster cheek pouches between 2 and 12 months after 20–30 Gy.

424. Pig skin has been investigated both by tracer techniques and by assessing the ability to vascularize a skin flap attached by a single pedicle. Above a threshold dose of 8 Gy more rapid flow was observed at 3 weeks, followed by a reduction at 12 weeks and a return to normal at 1 year. There may be a second decrease at 18 months [M33, H46]. Similar changes have been observed after 38 Gy/6 fractions/18 days, but after 80 Gy/30 fractions/39 days only slight changes were seen during the period 3–12 months [H46]. The skin flap assay of vascular function showed a progressive failure from 0–6 weeks after 20 Gy with no further change to 28 weeks [P24, W28]. Similar

changes were observed after 6 fractions/18 days or after 30 fractions/39 days [W28].

425. Human skin has been studied by thermography [W29] and by clearance of ^{22}Na [R26]. In the isotope studies, blood flow was measured up to 10 years after cumulative doses of 36–200 Gy. Of 37 patients studied, only one showed reduced clearance in the irradiated skin and 12 showed increased clearance despite the appearance of dense fibrosis, scarring and atrophy [R26]. A more recent analysis of this data suggests a trend towards reduced flow at later times after exposure [D31]. The thermography studies showed increased flow during early acute erythema (2–3 months) [W29]. Studies of blood vessels in patients developing radiation ulcers have been made using isotope techniques. After fractionated radiotherapy with doses between 40 and 120 Gy a reduction in circulation was noted together with sclerosis and fibrosis and an increase in the probability of blood clot formation. Blood and lymph vessel occlusion was observed which affected other tissues, e.g., nerves, bones and lungs. Disturbances in circulation sometimes led to swelling of the extremities [B46, B47, B48, B49]. There is little information about the response of blood vessels to vasoactive substances. The response to pharmacological mediators such as Compound 48/80 or carrageenan (all of which cause increased permeability) is not significantly affected by doses of 5–200 Gy of x rays to the rat foot [M34, V10].

426. Irradiation does affect the response to physiological agents involved in the regulation of blood flow to a tissue. The vessels of the rat foot show a reduced response to acetylcholine (vasodilation) at 24 hours and at 4–6 weeks after 30 Gy, but no change in the response to noradrenaline (vasoconstriction) [M34]. However, Lindop et al. [L21] found an increased response to adrenaline in the mouse ear between 1 and 55 weeks after exposure, with a threshold of 15 Gy. Indirect evidence suggests that blood vessels lose the capacity to respond to stress by vasodilation at late times after irradiation. The hyperaemic response of both the mouse foot [H44] and mouse tail [D32], which is normally observed on release of a temporary vascular occlusion, is reduced 4–6 months after exposure.

427. In conclusion, the lowest dose at which observable effects have been seen is 1 Gy for permeability changes in rabbit skin [J12] and 15 Gy or 8 Gy for blood flow measured in rats [K21] and in pigs [M33], respectively.

2. Intestine

428. Several authors have reported early changes in vascular permeability in the gastrointestinal tract after irradiation but it is difficult to say whether these could also be related to the early death of epithelial cells within the first 3 days. Willoughby [W30] found an increased capillary permeability in the vascular bed of the rat small intestine which began at about 18–24 hours and reached a maximum at 72 hours after 15 Gy of x rays to the abdomen. Turner and Fowler [T12] and Bromfield and Dykes [B38] measured ^{131}I-serum albumin leakage in the small intestine of rats after whole-body irradiation. Significant leakage occurred from the intestine at 3–5 days after doses of 5 Gy or more. Harris and Noonan [H47] observed two waves of increased permeability from intestinal blood vessels after whole-body irradiation. Doses of 7.5 or 15 Gy induced an initial peak at 3–4 hours and a second increase at 24 hours. Graham [G22] observed a biphasic increase in permeability after 8 Gy whole-body irradiation, with an early increase during the first hour and a second prolonged phase between 8 hours and 7 days. Vatistas and Hornsey [V3] also showed increased permeability, the extent of which was dose-dependent with a threshold of about 2.5 Gy. After whole abdomen irradiation of rats, Davies and Gamble [D33] observed increased permeability within 24 hours after 5–10 Gy.

429. Recently, changes have been studied in mesenteric vessels, in isolation from the ileum they supply, enabling the separate effects on vessels and parenchyma to be distinguished [H40]. In these experiments the vascular response was studied from 3 weeks to 24 months after 20, 30 or 45 Gy. Increased permeability was observed within 6 weeks after the two higher doses, with a maximum at 3 months and a return to normal by 12 months. A second phase was observed at 18 months. Very little change was observed after 20 Gy. Changes in blood volume and in vessel diameter were observed over the same period for single doses greater than 20 Gy. Thus, the dose required to cause changes in blood vessels could be greater when they are not in close contact with dying parenchymal cells, although the experiments referred to only involved larger blood vessels.

3. Cartilage and bone

430. Kember and Coggins [K25] investigated the effects of x rays on the epiphyseal blood supply to growing cartilage in young rats to test the hypothesis that the primary cause of damage would be to the blood vessels [M37]. After 9 Gy (soft tissue dose) there was a reduction in the number of blood vessels but those remaining seemed normal. Before the number of vessels was restored, damage to the cartilage plate was fully repaired. There was stunting in growth from this dose, but this was fully explicable on the basis of the parenchymal cell survival [K1]. It was concluded that damage to the vascular supply was not the primary cause of stunting.

431. Blood vessels in the vicinity of the cartilage plate pass through small channels (20 to 35 μm diameter) in the bony plate before reaching the cartilage space adjacent to it. Depending on the energy of the x rays used, the dose to the blood vessels may be increased by the presence of the bone. When this was accounted for, Kember and Coggins [K25] noted that even after doses of about 30 Gy in a single treatment to vessels passing through the bony plate, some vessels remained active. However, with doses of this magnitude, some clones of cells in the growth cartilage aborted at 5–6 weeks after irradiation. The possibility that this resulted from vascular injury at these higher dose levels could not be ruled out.

4. Lung

432. In spite of the numerous histological reports of oedema in irradiated lungs there are few studies of vascular permeability. Travis et al. [T13] observed increased vascular permeability in rat lung at 4 and 8 weeks, but not at 2 and 12 weeks, after 20 and 40 Gy to the hemithorax, while 5 Gy had no effect. In similar experiments on the mouse lung, Hornsey [H52] observed significant leakage at 4 weeks, which persisted

at 8–18 weeks. The effect was dose-dependent with a threshold at about 10 Gy. Maisin [M7] found an increased permeability at 30 minutes and at 3–7 days after 20 Gy to the mouse lung. Between 7 and 18 months there was a gradual decrease in permeability.

433. Long-term sequential studies of pulmonary blood flow in rats demonstrate reduced flow at 1–3 months after doses in excess of 10 Gy to one lung (Rana, quoted by Keyeux et al. [K21]). Blood flow returned to normal by 4–5 months after 10 Gy, but a prolonged depression of flow was observed after doses of 12.5 and 15 Gy. A dose of 20 Gy caused a complete arrest of the circulation within 6–12 months. Further experiments using ^{133}Xe injected intravenously, confirmed that there were two different phases of response [K21]. Clearance was allowed at 7–14 days, preceding the acute phase of radiation pneumonitis and the subsequent slowing of blood flow after 70 days coincided with the development of permanent histological lesions.

434. Glatstein [G2] used ^{86}Rb to measure vascular function after irradiation of one lung in the mouse. The uptake of ^{86}Rb decreased 3–4 months after single doses of 11 or 15 Gy, but subsequently returned to normal levels. Experiments in rats by Jovanovic et al. [J13] indicate that the volume of lung tissue irradiated is important. Following irradiation of one lung with 10–20 Gy, blood flow was reduced during the acute phase (up to 90 days) and also during the late phase (4–18 months). By contrast, irradiation of both lungs with doses of 5–15 Gy was followed by an increased blood flow during the acute phase. A reduced flow from poorly ventilated lung alveoli was observed during the later phases, but there was no significant change in the ventilated region.

5. Liver

435. In studies of liver circulation, the clearance from the blood of colloids which are taken up by Kupffer cells has been used as an index of hepatic blood flow. This is a reasonable method providing there is no accompanying change in the ability of Kupffer cells to function. Therefore, only the studies in which liver cell function has been assessed separately are discussed.

436. Fridrich and Schäfner [F32] observed decreased clearance of radiogold colloid, which was attributed to reduced blood flow, immediately after doses of 5 to 20 Gy to the livers of mice. The fact that uptake in spleen remained stable suggests that delayed clearance is not due to radiation damage to the reticulo-endothelial system, since if this were the case phagocytosis in the spleen would increase compensatorily. Impairment of the indocyanine green (ICG) clearance was reported by Paumgartner et al. [P25] at 2–11 days after local proton irradiation of the liver. Experiments with bromosulphtalein and labelled rose bengal ([K24, W32], Royer quoted by [D34]) indicate that the hepatic cell function is not affected during the first few weeks after irradiation so that clearance studies give a measure of blood flow at these times.

437. In an attempt to evaluate the function of both the hepatic cells and the vascular network, Keyeux et al. [K21] used colloidal gold to measure circulatory changes and labelled rose bengal to measure liver function in rats. A single dose of 15 Gy caused a transient marked reduction of liver blood flow index, but only a slight depression of hepatocyte function, during the first month. Between 2–28 months there was a gradual reduction in both blood flow index and liver function. A dose of 7 Gy caused no significant late changes but 15 and 30 Gy had comparable effects.

438. There is also one study of hepatic blood flow which does not depend on active uptake by liver cells. Using the ^{86}Rb extraction method, Glatstein [G2] showed no significant change in liver blood flow in mice after local single doses of 10 or 15 Gy up to 12 months after radiation exposure.

6. Kidney

439. The effective renal plasma flow (ERPF) may be estimated by measuring the disappearance of a tracer such as hippuran from the blood following a single intravenous injection, providing the tracer used is cleared by the kidneys. The disadvantage of this technique is that any impairment of the secretory function of the kidney tubules will also result in apparent reduction of the effective renal plasma flow. Although isotope clearance and extraction methods are not subject to this disadvantage, the ^{85}Rb extraction method has only been used in one study on mice.

440. The majority of experimental investigations into renal function have been in dogs. Mendelsohn and Caceres [M10] measured renal function after 20, 27.5 and 37 Gy, given in 13 days to the remaining kidney in unilaterally nephrectomized dogs. After 20 Gy there were no significant changes in renal blood flow. After the higher doses there was a temporary increase in both blood flow and tubular secretion during the first week, followed by a depression in function which reached a minimum at 9–11 weeks. This subsequently returned to normal by 36 weeks after 27.5 Gy but remained at 70% of the controls after the highest dose. Concannon et al. [C19] irradiated both kidneys of dogs with 19, 25 and 31 Gy in 12 fractions over 13 days. All doses caused persistent depression of renal blood flow from 10 to 60 weeks. Gup et al. [G21], using subcutaneous exteriorized kidneys, observed decreased renal plasma flow at 5–7 months after 5 and 10 Gy as single doses, and after 10 and 20 Gy in 10 fractions over 19 days. There were no histological signs of radiation-induced damage. Maier and Casarett [M36] used radiohippuran renograms to evaluate renal function in dogs. At 4–6 weeks excretion was reduced after 10 and 20 Gy but not after 5 Gy.

441. In pigs, the renal plasma flow is progressively reduced between 1–6 months after exposure [H12]. The single dose required to reduce function to 30–40% of normal at 6 months was 12.6 Gy. This was defined by the authors as the "tolerance dose". There was a further reduction in flow during 9–24 months, the tolerance dose falling to between 10.7–12.6 Gy [H48]. After fractionated treatments the maximum depression of plasma flow was observed at 6 months. There is good agreement between the data for pigs and dogs.

442. Estimation of renal function in rodents has been limited because of the small physical size of the animals. Smith and Boss [S28] measured renal function in exteriorized rat kidneys after single doses of x rays. No changes in renal blood flow were observed during the first 4 weeks after 25 and 30 Gy but 40 Gy caused a depression in flow at 28 days. Chauser et al. [C8] measured renal plasma flow in the rat at late times after

localized irradiation of a single kidney in situ. Doses of 10 Gy caused no effect by 20 weeks. Doses of 20 and 30 Gy caused total kidney failure by 12 and 20 weeks, respectively, with accompanying histological damage.

443. Thus, by the classical methods for measuring ERPF, there is a reduction in blood flow which is dose and time dependent. Similar results have been obtained using the ^{86}Rb extraction method in mice [G2]. Two months after irradiation of both kidneys with single doses of 11 to 19 Gy, blood flow had decreased and it continued to decline for at least one year. The effect was dose dependent and preceded fibrosis by several months.

444. An extensive study of renal function in man has been performed by Avioli et al. [A15]. They observed an early decrease in renal plasma flow during fractionated therapy as soon as a dose of 4.5 Gy had been accumulated. After completion of therapy there was a progressive fall in plasma flow which persisted for 12 months after cumulative doses of 20 and 24 Gy.

7. Central nervous system

445. Although the central nervous system is highly sensitive to slight decreases in oxygen and glucose supply and histological examination of irradiated brain and spinal cord indicate that there are radiation-induced lesions in blood vessels, there are few studies of vascular function in the CNS after local irradiation.

446. There is evidence that the blood-brain barrier is impaired by ionizing radiation. Permeability to protein, phosphorous, iodine, sodium and chloride can be increased [K23]. However, labelled proteins are probably the best agents with which to demonstrate gross permeability changes in the capillary endothelium [N7]. In rats, a dose of 100 Gy to the head caused no significant leakage of intravascular albumin between 1–96 hours [K23]. But, in the rabbit, permeability of the blood-brain barrier to albumin was increased at 24 hours after x-ray doses of only 8 Gy [W31]. Mogil'nitskiy and Brumshteyn (quoted by Keyeux [K23]) observed leakage of protein into the pericapillary spaces of brain vessels in dogs at 48 hours after 10–30 Gy and Clemente and Holst [C18] found that vascular permeability was increased in monkeys. The most severe changes in the blood-brain barrier were seen less than a day after doses of 45 and 60 Gy but 15 Gy also caused a detectable effect. Later effects have been studied in monkeys. No changes in the blood-brain barrier were seen before 28 weeks after 35 Gy but then increased permeability was observed until 40 weeks [T14].

447. Leith and Gaugl [L24] measured cerebral blood flow in the rabbit using an electromagnetic flow probe placed round the internal carotid artery. Doses of 100 Gy caused a transient decrease in flow at 1 hour and a further decline between 3–6 hours. However, Keyeux [K23] found that 200 Gy to the rat brain caused no change in blood flow at 48 hours, although blood volume was increased.

448. Delayed effects have been observed after lower doses. Keyeux et al. [K21] used local irradiation of the rat brain, and showed no change in blood volume at 8.5 months after 15 Gy, but blood flow was increased, with a threshold dose between 10 and 15 Gy. Moustafa and Hopewell [M35] observed modifications in vascular function after 20 and 30 Gy, but no changes after 5 or 10 Gy. The first change occurred 3 months after irradiation when there was a reduced blood flow. At 6 and 9 months blood flow was increased but by 12 months it had returned to normal.

449. Conflicting results have been obtained in the monkey, following localized irradiation of the right occipital lobe [T14]. Blood flow in both white and grey matter was reduced 28 weeks after a single dose of 35 Gy. At 40 weeks there was some recovery in the grey matter but not in the white. Changes in human brain haemodynamics have also been noted during acute radiation sickness [G27, T16, G29].

C. ENDOTHELIAL CELL SENSITIVITY

450. Since endothelial cells are present in all blood vessels, and since damage to these cells has been observed as one of the first pathological changes in many tissues [P22], several attempts have been made to measure their radiosensitivity. Because the turnover times for endothelial cells are very long, from 2 months to 3 years [H4, T3, S4, E15, S29], it is generally assumed that radiation-induced cell death would not occur for many months or years. However experiments on rats, rabbits and guinea pigs, in which the number of endothelial cells was counted in defined areas of the aorta, demonstrated a decrease in endothelial cell numbers at 5–11 days after irradiation. It was postulated that this was the result of interphase death. The dose required for 25% loss of cells was 4.9 Gy for guinea pig and 9 Gy for rabbit and rat. In these experiments the estimated values of D_q were 2.5 Gy for guinea pig, 8.3 Gy for rat and 8.8 Gy for rabbit [S43, S44]. More recent data [K4, H4] indicate that a small subpopulation of cells may exist with a cell cycle time of about 1 day. Therefore the kinetics of endothelial cells and their mode of death after irradiation are not known with sufficient certainty.

451. Other attempts to measure endothelial survival curve parameters have mostly involved stimuli to induce proliferation and to speed up expression of radiation damage. If the stimulus is applied before irradiation, the resulting survival curve refers to proliferating endothelial cells and may not be relevant to the normal slow turnover state. If the stimulus is applied after irradiation, the time of stimulation is found to be very important, owing presumably to repair of a slow type of potentially lethal injury [V2, R3].

452. Several studies have also been undertaken of endothelial cell survival in culture [N8, D35] but the survival characteristics of cells in vitro are mostly similar and not always the same as for cells in vivo. Essentially three methods have been employed in measuring in vivo endothelial survival parameters: (a) skin grafting, which stimulates growth of capillary loops linking host to graft; (b) stimulation of blood vessels in a subcutaneous air pouch by local application of agents such as croton oil or uric acid; (c) a technique of continuous labelling in utero which has been applied to the bone marrow [H64].

453. One of the earliest estimates of cell survival curve parameters was reported by Hopewell and Patterson [H49] in pigs. Three weeks after irradiation of a local area of skin, grafts of irradiated and unirradiated skin were transposed. Irradiated grafts on normal vascular

beds survived whereas normal grafts on irradiated beds sloughed off, indicating that the vascular bed was the important component. Capillary loops were visualized in the graft by injecting a dye at 48 hours after grafting and counting the number of loops linking host to graft. A dose-response curve with a D_0 of ~ 10 Gy and a D_q of ~ 3 Gy was derived from these data.

454. Reinhold [R27] obtained a D_0 of ~9 Gy after irradiating an area of a subcutaneous air pouch in the rat. Endothelial cell proliferation was stimulated by the local application of uric acid and the number of capillary sprouts was counted 5 days after stimulating division.

455. In later experiments, however, Reinhold and Buisman [R2] obtained a much lower value of D_0 by a modified version of the same system. These studies gave a survival curve with a D_0 of about 1.7 Gy, an extrapolation number of 7 and a D_q of about 3.4 Gy. Split dose experiments at 24 hours, using an initial dose of 5 Gy gave a D_2–D_1 value of about 3 Gy. The major difference between the two series [R27] and [R2] is that in the second experiment a longer period was allowed between proliferative stimulus and assay.

456. Van den Brenk [V11] has also used a longer follow-up period. Granuloma pouches were raised in the rat subcutis less than 5 minutes before irradiation by injecting air and croton oil beneath the panniculus carnosus. Both air pouch and adjacent tissue were irradiated. Thirteen days later, the air pouch was excised and opened. In unirradiated pouches a small confluent layer of granulation tissue formed. In irradiated pouches, discrete colonies of vasculature developed which could be counted, enabling endothelial cell survival curves to be plotted. These had a D_0 of 2.4 Gy, an extrapolation number of about 2 and a D_q of about 1.8 Gy. In later experiments, Van den Brenk et al. [V2] found no significant change in survival parameters if the radiation was given immediately before raising the air pouch. In these experiments, D_2–D_1 for the 24-hour interval was found to be 1.8 Gy after a first dose of 1.45 Gy.

457. It is not clear why the above investigations gave such widely different values for D_0. Cell survival parameters in vitro for a rapidly growing cell line of endothelial cell origin have been estimated to have $D_0 \simeq 2$ Gy, $N = 2.3$ [N8]. It seems that high values for D_0 (9–10 Gy) are obtained if the time interval between endothelial cell stimulation and assay is short [H49, R27]. It may be speculated that lethally-irradiated cells may perform one or two divisions before they die, maintaining functional integrity of the capillaries for a few days, whereas a later assay might detect the death of these cells and loss of the capillaries.

458. When the time between irradiation and subsequent stimulation is extended, repair of potentially lethal damage may occur before the damage is expressed. The three weeks between irradiation and grafting in the experiments of Hopewell and Patterson [H49] may have allowed repair of potentially lethal damage and this may account for the high D_0 observed. Van den Brenk et al. [V2] observed a dose sparing of 5–6 Gy when a 2–3-week gap was allowed between irradiation and the raising of the air pouch. Similarly, Reinhold and Buisman [R3] observed a repair phenomenon if the interval between irradiation and the uric acid stimulus was delayed for up to 60 days. The time course of the repair appeared to be exponential and had the effect of increasing the D_0 from 1.7 to 2.4 Gy for an interval of 16 days. This type of repair might be related to "slow repair" discussed earlier. In addition, repair of Elkind-type sublethal injury was observed in split-dose experiments, with a survival ratio of 5.

459. Gillette et al. [G23] studied the neovascularization after surgery on irradiated dogs' eyes. They suggested that cells stimulated before irradiation were more sensitive than cells stimulated after irradiation but their data are unconvincing. A split-dose increment D_2–D_1 of 3.5 Gy was obtained whether surgery was performed before or after irradiation.

460. Hirst et al. [H4, H40] measured depopulation and subsequent repopulation of endothelial cells in the mesenteric arterioles. A surprisingly early wave of depletion was observed, being more consistent with a short cycle time for 1–2% of the cells, than with a uniformly slow turnover of all cells. The subsequent repopulation was consistent with a D_2–D_1 of 7 Gy (as measured in split-dose experiments) and a D_0 in excess of 5 Gy. The rate of depopulation of the smooth muscle cells is, however, consistent with a generally slow turnover of all cells.

461. The above results suggest that the radiosensitivity of endothelial cells in vivo may be impossible to define because cells which attempt division soon after irradiation will be more sensitive than those that attempt division at later times when a significant amount of repair of potentially lethal damage may have occurred.

D. MECHANISMS UNDERLYING VASCULAR DAMAGE

462. A number of different mechanisms leading to the observed changes in vascular function have been postulated; they may be relevant at different times or after different doses in each of the tissues studied. The suggestions include widening of intra-endothelial cell gaps, changes in the amount of pinocytosis, changes in membrane permeability, depletion of cells, hyperplasia, leaking of proteins and development of fibrosis. The time course and extent of some of these individual changes are likely to be influenced by death of surrounding parenchymal cells. Hence the pattern of response must be considered separately for fast-recovering tissues such as intestine and skin, and for slow-turnover tissues such as lung and heart. In general, an early phase of dilation and increased permeability accompanies the early wave of desquamation which occurs in both intestine and skin. This has not been extensively investigated in slowly proliferating tissue. It is generally found that tissues show a gradual decrease in blood flow and an increase in permeability is seen at later times.

463. Gaps between endothelial cells have been observed in electron microscopic studies of skin within 10 days of irradiation [H50]. Maisin [M30], however, suggests that increased pinocytosis causes the increased permeability, although the correlation between these two is poor [M38].

464. Parenchymal cell death will produce chemical mediators (e.g., histamine or 5-hydroxytryptamine) increasing small vessel permeability [W33]. This has actually been postulated as the cause of the early changes observed [D30, V10]. The mediators in the late phase do not appear to be the same as those in the early

phase, and may involve release of lysosomal enzymes which cause the release of vasoactive polypeptides from plasma proteins [E14, M32, J14, J15, S30, E16].

465. At longer time intervals, e.g., 1–6 months after moderate doses, changes in endothelial morphology and in cell number are observed in rapidly and slowly proliferating tissues [P6, C17, A13, H40, Z3, W27, M39]. Vacuolation, sloughing and cell depletion have been observed in several tissues and this is probably the phase when direct damage to the endothelial cells is being expressed. At six weeks a good correlation has been shown between endothelial depletion in mesenteric arteries, and increased permeability, but not at later times [H40], probably because of other influences such as deposition of collagen.

466. At late times after irradiation, a reduction in blood flow with constriction and occlusion of blood vessels are seen. These changes have been attributed to localized proliferation of endothelial cells, which protrude into the lumen [M17, C17, H43] and have been related to the increased thymidine uptake seen in rabbit heart endothelium at 30–70 days [F33]. An alternative postulate relates to the insudation of the vessel walls by plasma proteins and their replacement by collagen leading to thickened walls, which limit the vessel diameters [Z3]. The processes are clearly complex and any or all of the changes which have been described may occur with time after irradiation.

E. COLLAGEN DEPOSITION

467. A characteristic of late radiation damage in tissues is an increase in the amount of acellular material. In particular, collagen is increased, although small foci of oedema and fibrin may also persist for many months or even years after treatment [R1, W34]. Moreover, the microscopic and biochemical appearances of collagen may be abnormal because the fibres tend to lose their orientation and take on a dense hyaline appearance [W34, G43].

468. Several authors have suggested that the increase in collagen is the final stage in the resolution of oedema fluid and fibrin which are observed at early and intermediate times after irradiation [R1, J3, L23, J16], and that fibrosis in vessel walls and intercellular spaces finally leads to parenchymal cell death. The sequence of changes observed in many irradiated tissues actually supports this view. Vascular changes and interstitial fibrosis precede atrophy of parenchymal cells in liver [I2, R20], kidney [M10, C17], heart [F31], lung [J3, M7, A13, J16] and brain [H14, P21]. On the contrary, other authors suggest that radiation has a direct lethal effect on parenchymal cells [H41, E17, C20, R28, Z4, M40], and that parenchymal cell death is followed by replacement fibrosis as a secondary effect when the cells cannot be regenerated [F34]. Therefore, collagen synthesis after irradiation is of interest.

469. In general, the concentration of collagen in adult tissue is maintained by a balance between synthesis and degradation. Radiation could upset this balance, either by altering the number of cells involved in synthesis or degradation, or by affecting the synthesis and degradation of collagen by surviving cells. Synthesis is measured by incorporation of labelled precursors (proline or glycine) after irradiation; degradation is measured by labelling before irradiation and following the subsequent loss of activity. In skin and in granuloma tissue, synthesis is depressed and degradation is increased for 3 weeks after 7.5–15 Gy locally, or 7.5–10 Gy whole-body irradiation [N9, A16, T15, K26, K27, O11]. Similar changes have been seen in muscle but not in tail tendon collagen [K26, K27]. With whole-body irradiation some effects may be secondary to starvation [K27], and after localized irradiation decreased degradation of collagen in granulation tissue has even been seen [R29, W35].

470. The depression of collagen synthesis taking place within 6 hours of irradiation is attributed to a direct effect on collagen biosynthesis, but the decrease at 2–3 weeks is attributed to reduced cell numbers available for synthesis [R29]. Collagen production per cell is increased, possibly because of less degradation, resulting in an accumulation of insoluble collagen.

471. The relevance of these early changes to the development of late radiation fibrosis is questionable. Degradation is inhibited only during the first three days after exposure [R29] whereas late radiation fibrosis develops over several months and gradual increases in the total collagen of adult rat skin have been measured between 4 and 12 months after irradiation [K28].

472. Radiation fibrosis may be the result of progressive organization of exudate from damaged blood vessels [R1, J3, L23, J16, R30]. An increase in the number of mononuclear cells, including fibroblasts, has been observed in irradiated tissues in which collagen also increases [J3, M7, R20, F31, D30, M39, R30]. This increase may persist, suggesting active collagen synthesis at months or even years after exposure [J3, R20, F31, M39, W34]. Increased collagen deposition has been observed after 36 weeks in mouse lung [L11] and at 20 weeks in mouse kidneys [C8] with a threshold between 10 and 20 Gy.

473. The collagen that is produced is less soluble than normal [O11, R29] but the detailed differences in chemical structure and cross linking are not known. External changes in pH may influence polymerization and thickness of collagen fibres and fibrin may be involved in collagen hyalinization [B39, W36].

F. CHANGES IN LYMPHATICS

474. Since the network of lymph vessels and lymph nodes forms an integral part of the vascular system, radiation effects on the dynamics and permeability of the blood vessels may result in reactive changes in the lymphatic system. In particular, the latter usually reacts to reduce circulatory disturbances caused by damage to the blood vessels, either through increasing drainage by lymph vessels or by opening of lymphatic-venous communications.

475. In general, the lymphatic vessels can withstand high doses of radiation before their function is impaired. Hodes and Griffith [H51] found no change in lymph flow in irradiated rats at 3–6 weeks after 22 Gy. In an extended study, Engeset [E18] also found no disturbances in lymph flow up to 1 year after 30 Gy to the rat limb. At later times lymph flow was not interrupted but was directed into newly formed vessels as fibrosis obstructed the original channels. Similar findings are reported in dogs by Sherman and O'Brien [S31]. Hind limb irradiation with 10–36 Gy did not affect lymph flow for 18 months after exposure.

476. The Sandison-Clark rabbit ear chamber was used by Van den Brenk [V12] as an experimental system for studying the effects of external radiation on lymphatics. A dose of 40 Gy did not induce endothelial swelling sufficient to cause blockage of lymphatic vessels up to 15 months after irradiation. Doses exceeding 50 Gy were required to cause destruction of lymphatic vessels. Lenzi and Bassani [L25] concluded that the threshold was even higher, i.e., 60 Gy in rabbit uteri. They described some dilations and varicosities which became progressively more pronounced after 80 Gy. The lymphatics were tortuous, varicose and rigid but patent in all cases.

477. Lymphangiography has often been used to estimate lymph flow in patients who have received therapeutic doses of radiation. In some early observations radiation to total fractionated doses of 20 Gy or greater did not appear to cause a reduction in flow up to 1 year after exposure [L25, P26, V13, A17, M41] although lymphatic vessels may appear rigid and flattened [L25] and lymph nodes may be reduced in size and increased in density [K34, Z6] or destroyed [A17, M41]. More recent work suggests doses in the lower limit of that range. In a study of 32 patients who developed skin ulcers between 6 months and 15 years after radiotherapy lymphatic changes were observed, including narrowing of the main vessels, anastomoses and the opening of vessels normally in reserve [B48, B47, Z6]. In some cases there may be leaking of contrast medium and the development of collateral lymphatic circulation [A18] but, in the majority of cases, lymphatic vessels did not undergo any marked changes in configuration [A17, M41].

478. Lymphangiography can only give a rather crude estimate of lymph flow rate but it can demonstrate cessation of flow either from intraluminal causes or from extravascular compression due to fibrosis. Results of lymphangiographic studies in man show that there is a progressive decrease in the size of irradiated lymph nodes reaching a minimum at 9–12 months after therapy. However, although lymph nodes become fibrotic the nodal sinuses remain patent. Irradiation per se does not cause obstruction of lymph vessels although perivascular fibrosis may cause a deviation of lymphatics.

479. In conclusion, lymphatic vessels in experimental animals and in man appear to be rather radioresistant. In most cases, large doses (single doses of 40 Gy to rats, fractionated dose of 75 Gy in 60 days to man) do not cause a change in lymph flow at 6–15 months after exposure. Any changes of lymph flow have frequently been found to be due to extravascular fibrosis, while irradiated lymphatics remain fully patent.

G. SUMMARY

480. After doses of radiation in the radiotherapy range, progressive morphological changes occur in all elements of the vasculature such that at late times after exposure vascular function is reduced. In general, changes in vascular function are observed before the occurrence of late atrophy of tissues, which suggests that vascular damage plays an important role in all late radiation injury after such relatively high doses.

481. Table 15 summarizes threshold doses for detectable changes in vascular function. Abnormal vascular permeability tends to occur at lower doses than marked reduction in blood flow. For any given species there is a wide variation between the threshold doses for different tissues, e.g., for the rat these range between 5 Gy in the mesentery to 15 Gy in the liver. These differences may of course reflect the different assay techniques used. However, it is also likely that they reflect intrinsic differences in various sections of the vascular system in different tissues. It should be recalled, finally, that the general response of a tissue depends on both the parenchymal and vascular components and that it may not be possible to view either in isolation.

VII. SUMMARY

482. Although the effects of irradiation on some body tissues were considered by the Committee in more recent specialized reviews, the whole field of morphological and functional changes in irradiated normal tissues of animals and man had not been systematically evaluated since 1962. A re-examination of the whole subject was therefore carried out with the main objective of identifying for each tissue and for various modalities of irradiation the effects and the doses that may become critical for the function of that tissue. As a secondary objective the Committee wished to analyse the main physical and biological factors which might modify these doses and effects. These objectives required a study of the dose-time relationships in each tissue, based on both animal data and on the observation of clinical effects in man.

483. The study was confined to the so-called non-stochastic or deterministic effects. Whereas the effects referred to as stochastic take place in one or a few cells and appear in an irradiated population as hereditary effects or tumours, the non-stochastic ones affect many cells and appear as tissue damage. In general, non-stochastic effects require that a minimum dose, called the threshold dose, be delivered before they can be detected. The clinical severity of the injury increases with increasing dose. The time of appearance of tissue damage is very variable as it may span from a few hours or days to many years after exposure, depending on the type of effect and on the characteristics of the particular tissue.

484. The concept of dose threshold is difficult to define and must be discussed in relation to each tissue and effect because it depends to a large extent on the sensitivity of the measuring technique. The loss of functional capacity of a given tissue, for example, may actually exhibit a much higher dose threshold than the appearance of subtle ultrastructural changes detectable only by sophisticated technology. Similarly, there is a need to distinguish between the threshold of appearance of clinical changes which have clear pathological connotations. While recognizing that these concepts have important practical implications, the Committee felt that a thorough discussion of tissue pathology was beyond the scope of this study which was primarily aimed at an assessment of the effects as reported, irrespective of their significance for practical purposes.

485. The amount of information that has accumulated on these subjects during the last twenty years is very large and an interpretative, rather than a comprehensive, treatment was therefore necessary. This was facilitated by the significant advancement in knowledge

of the basic mechanisms of cell and tissue response to irradiation. The premise of the Committee's review is that the non-stochastic response of a given tissue to radiation depends primarily on the level of killing of the component cells and that the degree of damage and its time of occurrence are related to the special way in which each given tissue is structured. Therefore an introductory treatment of the basic concepts of radiation effects on cells and tissues was required. In this part of the Annex the Committee discussed the mechanisms and the phenomenological characteristics of cell survival as a function of time and dose, repair phenomena, the normal mechanisms of cell proliferation in tissues and the changes induced by radiation thereupon. All this should be viewed as a unifying frame of reference for the specialized and systematic analysis of effects in various tissues.

486. Although the analysis of the Committee has considered separately the animal and the human data, the similarities between the observed effects warrant a common summary of the subject matter, with the necessary qualifications to point out major discrepancies.

487. In skin the early radiation reactions may increase from a temporary reddening through various degrees of severity to ulceration and necrosis. Late changes involve thinning of the skin, loss of hair, colour changes and dilatation of the blood vessels. In order to produce observable changes in animal skin by external irradiation, doses of the order of 7 to 10 Gy must normally be administered in acute exposures. However, this tissue has a very large capacity to repair radiation damage and thus, if radiation is delivered over a long time period, up to 5 times or more doses may be tolerated. Observations on radiotherapy patients generally confirm these findings. With single acute treatments temporary loss of hair results in man after 3–5 Gy and reversible changes cause no serious consequences. The area of skin irradiated is important, with more severe changes appearing for larger irradiated areas. A number of biological variables are known to influence the level of the threshold dose: among them the anatomical location of the skin, the age of the irradiated person, and the normal skin colour. Mucosae exhibit changes analogous to those seen in the skin at similar doses.

488. The blood and blood-forming cells appear to be particularly sensitive. The lymphocytes and the stem cells are inactivated by doses of a fraction of a Gy causing the disappearance of these cells from the bone marrow and the circulating blood. Blood forming organs have however a remarkable capacity for regeneration and may show complete recovery. In man, the haemopoietic system is also one of the most sensitive tissues. Responses may be observed after 0.5–1 Gy, whether given in a single exposure or as a series of small fractions. If depression of the peripheral blood cells is too severe death may occur, due to infection (loss of white cells) or to haemorrhage (loss of platelets) which are the major symptoms of the so-called haemopoietic syndrome. The LD_{50} for man lies in the range of 3–5 Gy.

489. External irradiation of the gastrointestinal system may lead to a variety of acute and chronic symptoms ranging from dyspepsia and diarrhoea with loss of fluid and blood, to localized ulcers and bowel strictures and obstructions. The review has treated separately the various sections of the gastrointestinal tract, since they are not uniformly sensitive. Considering the early forms of radiation injury, the stomach in man may tolerate up to 40 Gy of long-term fractionated treatment. The small intestine may also withstand fractionated doses of conventional radiotherapy of the order of 30–40 Gy. The large intestine is even more resistant and shows only transient symptoms at similar doses, while the oesophagus appears to tolerate up to 60 Gy. The late consequences of these large doses (particularly those given to large volumes) are little known and difficult to quantify. The liver is a very slowly proliferating organ, but its component cells may be stimulated into division by different types of injury including radiation: this could unmask latent damage that would not otherwise become apparent. In animals, single doses of over 10 Gy are necessary to induce permanent changes in liver and these doses may be increased up to six times upon extended fractionation. In man, liver is now known to tolerate 40–50 Gy in 30 days given to parts of the organ, the threshold for measurable effects being around 30 Gy of conventional fractionated radiotherapy.

490. The lung is regarded as being the most sensitive organ in the thorax and after moderate doses pneumonitis may develop which leads eventually, through a complex chain of pathological reactions, to fibrosis and loss of function. With whole-body irradiation and providing bone marrow function is maintained, the maximum dose which may be tolerated by lung is approximately 8 Gy, if given over several hours. The sensitivity of the lung with respect to long courses of irradiation is moderate. This is because it possesses a large capacity to repair intra-cellular damage, although it lacks the proliferative ability to reconstruct, by cellular repopulation, its elaborate structure. Doses of the order of 40 Gy in conventional radiotherapy (i.e., in 30 fractions) may lead to an appreciably increased incidence of complications. Among other thoracic organs, the heart is regarded, on the contrary, to be rather radioresistant in experimental animals where it shows only microscopic changes in the muscle cells and blood vessels after moderate doses. In man, a high incidence of cardiac complications consisting mainly of pericarditis and eventually fibrosis is seen after long fractionation courses to total doses in excess of 60 Gy.

491. The urinary system shows a wide range of sensitivities and among the various organs the kidney is believed to be the most vulnerable, followed by the bladder and the ureters. Acute and chronic nephritis followed by hypertension and proteinuria usually result from high radiation doses to the kidney. In experimental animals, morphological and physiopathological changes have been reported after single acute treatments with threshold doses between 5 and 12 Gy. With long-term fractionation these doses might be increased by a factor of at least 3. In man, 20–24 Gy in 3–4 weeks produce evident alterations in kidney function, so that the tolerance dose is normally regarded to be around 23 Gy in five weeks. In both man and animals the kidney appears to be more sensitive at around the time of birth. Doses of 55–60 Gy in 4 weeks are regarded as the tolerance doses for urinary bladder erythema, ulceration and eventually fibrosis.

492. The reproductive organs are particularly sensitive. Irradiation of the testis causes temporary sterility, which may become permanent after larger doses. The testis appears to be unique in that its component cells cannot undergo repair. Continuous

irradiation causes more, rather than less, damage than single acute treatments. In man, acute doses as low as 0.1 Gy have been reported to cause temporary sterility, although doses in excess of 2 Gy and possibly up to 6 Gy are needed to produce permanent aspermia. Many years may be necessary for complete recovery of the production of spermatogonial cells after severely damaging doses. The adult ovary is more resistant than the testis because, by the time of birth, the oogonial cells have all progressed to the more resistant oocytes. However, if irradiation is delivered to the developing ovary, fractionated treatments to a total of 2 Gy may cause severe damage in dogs and monkeys. Permanent sterility is caused in women by single doses in excess of about 3 Gy, or higher fractionated doses.

493. The threshold doses applying to the central nervous system differ for different structures. The lesions consist in alterations of the fibre structure, loss of myelin, encephalitis and necrosis. The damage is believed to result, at least in part, from primary lesions of the blood vessels and it is irreversible. The central nervous system, like the lung, has limited capacity for regeneration but a large capacity for repair of intracellular damage. An increasing amount of information in animals supports the view that structural damage to the nervous cells may occur after doses of 1–6 Gy. These doses may produce cellular degeneration of the brain some months after treatment with destruction of sections of the cortex. In man the tolerance dose for the whole brain is around 55 Gy delivered in 5–6 weeks, but morphological changes are seen after 10 Gy of fractionated treatment. Threshold doses for the spinal chord are lower, in the region of 35 Gy in 4 weeks.

494. Irradiation of growing cartilage leads essentially to disturbances in the process of bone formation, with resulting deformities. Growing cartilage is known to be one of the most sensitive tissues and the threshold dose to cause growth stunting is probably small and possibly zero. In the young animal, about 3% stunting per Gy has been reported. In children, total doses of 10 Gy or more given in daily fractions over a few weeks are sufficient to cause some degree of reduced growth. The younger the child, the more severe the degree of stunting. Mature cartilage, on the other hand, may tolerate up to 70 Gy in prolonged fractionation schemes. In general, adult bone is considered to be fairly resistant and doses of 65 Gy given in 6–8 weeks do not normally cause necrosis: there may be however predisposition to fracture, depending on the mechanical stress normally exerted on the bone.

495. Of the many tissues in the eye (lacrimal glands, conjunctiva, cornea, sclera, retina) the lens appears to be the most sensitive to radiation, with production of lens opacifications or clinical cataract. Initial effects are seen in man after 2 Gy of acute exposure. In animals which are particularly prone to the development of cataract, like the mouse, much lower doses are usually required to cause earlier cataract than normal. Fractionated irradiation may be rather less effective in increasing the threshold dose than in many other tissues. As to the endocrine organs, in the adult the pituitary is regarded as radioresistant. Adrenals respond to the stress of irradiation in such a way that it is difficult to assess the amount of direct effects on them. The thyroid is a slowly proliferating tissue in which radiation effects may become apparent after many years. Doses of the order of 10 Gy in a single treatment are necessary to cause morphological damage to cells and signs of malfunction.

496. The time sequence between changes in the blood vessels and parechymal tissue lesions suggests that vascular injury may play an important role in all radiation-induced disturbances appearing in tissues (cell loss, fibrosis). After high doses of radiation, such as those used in clinical radiotherapy, morphological damage is known to occur in blood vessels and long after exposure these changes may lead to disturbances of the vascular function. Threshold doses for relatively subtle changes, such as abnormal vascular permeability, tend to occur at lower doses (down to 5 Gy) than more marked functional injuries like the reduction in blood flow (10 Gy or more). A detailed study of available data suggests that blood vessels located in different tissues may have different thresholds of reaction and that the overall response of a given tissue may depend on the joint response of the parenchymal and vascular components, in such a way that it may not be possible to view the reaction of either component in isolation.

497. The Annex examined for each tissue the effects produced by radiations of different qualities (particularly by fast neutrons) that are known to produce, dose for dose, a higher degree of biological effects than x or gamma rays. For single acute doses sufficiently large to cause detectable non-stochastic injury, the relative biological effectiveness (RBE) of neutrons is in the range of 1–5 times that of x or gamma rays. The RBE increases in the course of fractionated treatments with the decrease of the dose per fraction or with the increase in the number of fractions. For tissues where post-irradiation repopulation is important (skin, intestine) there is every reason to expect that repopulation is independent of the quality of radiation; for slowly dividing tissues repopulation will be small with all radiations. However, since other modalities of repair are relatively less effective for neutrons, the doses of this radiation that could be tolerated if given over a long period of time will not be much greater than the doses for the same radiation given as acute exposures.

498. Consideration of the non-stochastic effects produced by beta- or gamma-emitting radionuclides administered internally showed that tissue injuries are usually consistent in type and degree with those caused by comparable mean tissue doses of external irradiation at low dose rate. The tissues affected by treatment with a given nuclide depend on the particular distribution of that nuclide in the body; the amount of injury depends on the radiation characteristics and on the temporal distribution of the energy delivered. Models to relate the temporal distribution of absorbed doses from a radionuclide to that of fractionated external irradiation on the basis of equal effects have not yet been fully explored. There are also uncertainties concerning the microdistribution of the energy delivered to the biological targets within the cells and they affect the assignment of precise RBE values to radionuclides emitting non-penetrating radiation, such as alpha particles and low-energy Auger electrons.

VIII. NEEDS FOR FUTURE RESEARCH

499. In general, this Annex has shown that non-stochastic damage is observed only with doses that are considerably greater than those producing stochastic injury. Nevertheless, further study of non-stochastic effects is important. The preceding chapters have repeatedly emphasized that the expression of non-stochastic injury is dependent on the proliferation kinetics of the tissue and on the relationship between the proliferating

cells and those responsible for the tissue-specific functions. There is generally a lack of information about the relationships between the various normal cell kinetic parameters and the timing and extent of injury. In addition, little is known of radiation-induced changes in proliferation kinetics during or after irradiation, particularly under chronic exposure conditions. Information is especially scarce for tissues with long turnover times in which the response is normally manifest a long time after irradiation.

500. Although a considerable body of data exists on tissue effects after single doses of irradiation or after a small number of dose fractions, there is a need for more information about effects of long term fractionation or continuous irradiation lasting over a significant portion of an animal's lifetime. Similarly, mathematical models which account for fractionation effects need to be extended to very long treatment times in order to confidently extrapolate existing data on man. Clearly the experimental and theoretical aspects of this problem need to be carefully related.

501. The translation of loss of clonogenic capacity of individual cells to impairment of tissue function is extremely complex and variable from tissue to tissue. In most cases the target cells of composite tissues and organs are not known: new techniques and much research on methodology are needed to gain information about them and the pathways of injury leading to functional impairment. The role of blood vessel damage and whether it is a primary or secondary effect of irradiation is unclear. Further studies are also needed on the pathogenesis of radiation induced fibrosis and sclerosis.

502. New and more sensitive and quantitative endpoints are needed to study effects of radiation in a range of tissues, including endocrine organs, reproductive organs, central nervous system, lung, liver, kidney, eye, haematopoietic tissues, etc. Of special interest are changes occurring late after irradiation. The existence of possible relationships between early and late responses would also be of importance for the quantification of long-term damage. Remote consequences of partial-body irradiation have as yet received scant attention. In recent years there have been great advances in knowledge of the immune system, but few comparable radiation studies have been made, particularly at low doses and dose rates. Also, in animal investigations little attention has been paid to alterations in response as a function of animal age or stage of development.

503. A reasonable body of data exists on RBE as a function of dose per fraction, but mainly for early effects and at doses greater than a few Gy. Below this dose level or at low dose rates little information exists. Data is also lacking on tissues which show damage late after irradiation. In complex organs the RBE may vary from one cell type to another so that the measured overall response of the organ may be qualitatively different with radiations of different LET. Such effects require careful examination.

504. Of fundamental importance in the response of tissues to long term irradiation is their capacity for repair. Intracellular repair mechanisms leading to repair of sublethal damage, potentially lethal damage and, in some tissues, slow repair are as yet not well understood and further knowledge of the mechanisms of cell killing and repair are required. Repair by regeneration is also an important factor, but after irradiation this may be incomplete and there may be replacement of functional parenchymal cells by fibrosis. Repair of all types requires further investigation after both low- and high-LET radiations for precise quantitative evaluations in all tissues.

505. The response of tissues to deposited radionuclides is often very difficult to evaluate owing to uncertainties in the dose distribution, together with variations in activity with time. This is particularly true where the decay scheme is complex. Efforts should be made to define the dosimetry more accurately. Studies are needed of effects of radionuclides emitting short range particles (e.g., Auger electrons), particularly where they are deposited in critical structures or molecules.

506. Quantitative results in man are urgently needed, but difficult to obtain. New methods to derive data from radiotherapy patients are required as is the continued careful monitoring of any situation of human exposure to doses resulting in stochastic damage to individual tissues or to the whole body. There are wide differences in the type and severity of the non-stochastic effects considered in this Annex. For practical applications it is important that attempts should be made to quantify this damage in terms of the degree of detriment.

Table 1

D_2-D_1 values for various tissues

Tissues	Species	Endpoint	D_2-D_1 (Gy)	Ref.
Skin	Pig	Radiodermatitis	5.0-7.0	[F1]
	Rat		8.9	[F2]
	Mouse		5.0	[D3]
	Mouse	Epidermal clones	3.5	[W4]
			5.7	[D3]
Oesophagus	Mouse	LD/50	5.6	[H2]
			8.5	[P1]
Gastrointestinal tract	Mouse	LD/50	4.5	[H3]
		Macrocolony assay	4.0	[W5]
Cartilage	Rat	Growth stunting	4.0	[D4]
			3.5	[K1]
Lung	Mouse	LD/50 (both lungs)	4.0-5.0	[F3]
			3.5	[P2]
Spinal cord	Rat	ED/50	9.5	[W6]
			6.0	[V1]
Testis	Mouse	Clonal assay	3.0[a/]	[W7]
Haemopoietic tissues	Mouse	Spleen nodules	1.0	[T1]
Endothelial cells	Rat	Stimulated dermal blood vessels	3.0	[R2]
		Colonies in granuloma pouch	1.8	[V2]
		Cell counts in mesentery	7.0	[H4]

a/ Decreases with increasing time between fractions.

Table 2

Changes in proliferation after irradiation of skin (Fractionation data) [D1]

Species	Fraction number	Overall time	Increment Gy/day	Doubling time (days)	Ref.
Pig	5	5-28	0.25	4	[F10]
Mouse	2	7-14	0.30	3.2	[D3]
		14-21	0.29	3.2	[D3]
Human	up to 25	up to 35	0.28-0.34	3	[C4]
Mouse	15	17-35	0.32	3	[D14]
Mouse	2	1-7	0.70	3.2	[C5]
Mouse	5	4-9	0.90	1	[F16]
Plucked skin					
Mouse	2	1-6	1.00	1	[W11]
Mouse	2	1-7	0.48	2	[E7]
		7-14	0.42	2.3	[E7]
		14-21	0.29	3.3	[E7]

Table 3

Threshold skin erythema doses for single doses of x rays

Species	Dose (Gy)	Area irradiated	Reference
Pig	10-15	Approximately 20 cm^2	[F10,W38]
Rat	10	Whole foot	[F2]
Mouse	10	Whole foot	[F12]

Table 4

"Threshold doses" for damage to kidney of various species

Species	Dose (Gy)	Type of injury	Ref.
Dog	< 20	Tubular function	[M10]
	6	Renal enzyme changes	[P7]
	6	Functional and enzymic changes	[Z1]
	5-10	Decrease in size and mass, histological and functional changes	[M11]
Pig	10	Function	[H12]
Rabbit	~ 12	Probability of lethality	[C7]
Rat	5	Hypertension	[L13]
	5	Nephrosclerosis	[B11]
	< 10	Functional and enzymic changes	[K8]
	10	Plasma flow and collogen deposition	[C8]
Mouse	5	Nephrosclerosis	[B12]
		Accelerated glomerulosclerosis	[G1,C9]
	< 10	Blood flow	[G2]
	8	Lethality after unilateral nephrectomy	[P8]
	10-15	Inhibition of growth	[D1]
	10	Decrease in weight	[G3]

Table 5

$LD_{50/30}$ (haemopoietic syndrome) for different species

Species	Approximate weight (gm)	LD_{50} a/ (Gy)	LD_{50} b/ (Gy)
Mouse	25	9.0	6.4,7.1
Desert mouse	30	15.2	
Gerbil	40	10.5	
Hamster	80	9.0	6.1,8.6
Rat	200	9.0	7.1
Guinea pig	800	2.6	4.5
Marmoset	3000	2.0	
Rabbit	3500	8.4	7.5
Monkey	4000	4.0	6.0
Dog	12000	2.7	2.5
Sheep	45000	1.6	2.1
Goat	50000	2.3	2.4
Man	70000	3.0 c/	3.0 d/
Swine	200000	2.0	2.5
Burro	400000		2.5

a/ [H6]
b/ [B7]
c/ [L17]
d/ [B18]

Table 6

Summary of threshold doses in experimental animals

Tissue	Endpoint	Single dose (Gy)	Multifractions or continuous irradiation (Gy)
Skin a/	Threshold erythema	~ 7	≥ 10
Oesophagus a/	LD/50	~ 20	50 in 10 F
GI tract	LD/50	8-15	2 Gy/day
Cartilage and bone a/	Stunting	1 Gy resulted in 3-5 % stunting	
Heart a/	Fibrosis, death	> 20	
Lungs a/	LD/50	≥ 10	50 in 30 F
Liver a/	Histological changes	> 10	30-60 in 10-20 F
Kidney a/	Various	5-15	Sparing by fractionation
Central nervous system a/	Neurophysiological changes	3	
	Paralysis	~ 15	~ 100 in 60 F
Thyroid a/	Malfunction	10	40-100 continuous
Pituitary	Weight loss of the animal	1-6 in the very young. Very large doses in adults	
Adrenals	Weight loss of glands	4-6	
	Permanent changes	~ 20	
Testis	Sterility	3-10	0.0012-0.006 Gy/day
Ovary	Reduction in cells and fertility	Very large species	~ 2 fractionated
Eye a/	Lens opacities	3-5	11-14 fractionated
Haemopoietic	LD/50		
	Cell depletion	2-15	~ 0.5 Gy/day

a/ These tissues have been specifically irradiated, as opposed to whole-body treatment.

Table 7

Atomic bomb survivors by clinical symptoms and signs of radiation injuries [016]

Degree of severity	First week	Second week	Third week	Approximate mortality and time of death in weeks
Very severe (Group I)	Nausea and vomiting (+++) Fever, apathy, delirium, diarrhoea (+++) Oropharyngeal lesions (+) a/ Leukopaenia (+++)	Fever (++) Emaciation Leukopaenia (+++) Anaemia Haemorrhagic diathesis (±) Epilation (±)		100 % first and second
Severe (Group II)	Nausea and vomiting (++) Anorexia Fatigue	Fever (++) Leukopaenia (+) Anaemia (±)	Anorexia, emaciation, fever, diarrhoea, epilation (+++) Oropharyngeal lesions (+++) Haemorrhagic diathesis (+++) Leukopaenia (++), anaemia (++)	50 % third to sixth
Moderately severe (Group III)	Gastrointestinal b/ syndrome (++)	Leukopaenia (+)	Anorexia, emaciation, fever, diarrhoea, epilation (± ~ ++) Oropharyngeal lesions (± ~ ++) Haemorrhagic diathesis (± ~ ++) Leukopaenia (++), anaemia (+)	Less than 10 % sixth or later
Mild (Group IV)	Gastrointestinal syndrome (±)	Leukopaenia (+)	Fever (±) Epilation (±) Oropharyngeal lesions (+) Haemorrhagic diathesis (±) Leukopaenia (±)	None

a/ These lesions (ulcerations) occurred on all mucous membrane surfaces but were more prevalent in lymphoid areas than elsewhere. The tonsil, pharynx, larynx, nasal passages, and tongue were frequently involved.

b/ Gastrointestinal syndrome includes nausea, vomiting, anorexia, and diarrhoea. (+++)(++)(+) and (±) connote grade of symptoms and signs in order of decreasing severity and frequency, such that ± indicates that the symptom was not always present. Approximate ranges of kerma are 4.5 to 6 Gy (or more) Group I; 2-4.5 Gy Group II; 2-3 Gy Group III; 1-2 Gy Group IV. Estimates of these doses are subject to change but it is anticipated that the modifications will not be large.

Table 8

Acceptable doses from conventional radiation therapy a/ [R1]

Structure irradiated	Injury after 5 years	1-5% Acceptable dose (Gy)	25-50% Acceptable dose (Gy)	Irradiation field
Skin	Ulcer, severe fibrosis	55	70	100 cm^2
Oral mucosa	Ulcer, severe fibrosis	60	75	50 cm^2
Oesophagus	Ulcer, stricture	60	75	75 cm^2
Stomach	Ulcer, perforation	45	50	100 cm^2
Intestine	Ulcer, stricture	45	65	100 cm^2
Colon	Ulcer, stricture	45	65	100 cm^2
Rectum	Ulcer, stricture	55	80	100 cm^2
Salivary glands	Xerostomia	50	70	50 cm^2
Liver	Liver failure, ascites	35	45	whole
Kidney	Nephrosclerosis	23	28	whole
Bladder	Ulcer, contracture	60	80	whole
Ureters	Stricture, obstructions	75	100	5-10 cm
Testes	Permanent sterilization	5-15	20	whole
Ovary	Permanent sterilization	2-3	6-12	whole
Uterus	Necrosis, perforation	<100	<200	whole
Vagina	Ulcer, fistula	90	<100	5 cm_3
Breast, child	No development	10	15	5 cm^3
adult	Atrophy and necrosis	<50	<100	whole
Lung	Pneumonitis, fibrosis	40	60	lobe
Capillaries	Telangiectasia, sclerosis	50-60	70-100	
Heart	Pericarditis, pancarditis	40	<100	$whole_2$
Bone, child	Arrested growth	20	30	10 cm^2
adult	Necrosis, fracture	60	150	10 cm^2
Cartilage, child	Arrested growth	10	30	whole
adult	Necrosis	60	100	whole
CNS (brain)	Necrosis	50	<60	whole
Spinal cord	Necrosis, transection	50	<60	5 cm^2
Eye	Panophthalmitis, haemorrhage	55	100	whole
Cornea	Keratitis	50	<60	whole
Lens	Cataract	5	12	whole
Ear (inner)	Deafness	<60		whole
Vestibular	Meniere's syndrome	60	100	whole
Thyroid	Hypothyroidism	45	150	whole
Adrenal	Hypoadrenalism	<60		whole
Pituitary	Hypopituitarism	45	200-300	whole
Muscle, child	No development	20-30	40-50	whole
adult	Atrophy	<100		whole
Bone marrow	Hypoplastic	2	5.5	whole
		20	40-50	localized
Lymph nodes	Atrophy	35-45	<70	
Lymphatics	Sclerosis	50	<80	
Foetus	Death	2	4.5	

a/ Usually the 1-5 % acceptable dose is considered reasonable in radiotherapy; 25-50 % is not.

Table 9

Doses causing temporary or permanent sterility of human ovary

Effect	Tolerance dose (Gy)	Ref.
Temporary or reduced sterility	1.5 fractionated a/	[T17]
	1.7	[G13]
	4	[P18]
	12 fractionated (3/day)	[R34,P18]
	174 (in 3 series/2.5 years)	[G14]
Permanent sterility	3.2	[G13]
	2.5-5 fractionated	[R34]
	4	[P18]
	6.25	[P19]
	8-10	[L20]
	2 (in 3 series/2 years)	[J71]
	6.25-12 fractionated (30F/6 week)	[R16]
	6-20 fractionated (30F/6 week)	[L16]
	3.6-7.2 fractionated (2-4F)	[D20]

Table 10

Doses causing temporary or permanent sterility of human testis

Effect	Tolerance dose (Gy)	Ref.
Temporary sterility	0.1-1.0 fractionated	[S45]
	1.5-3	[H20]
	1-2 fractionated	[H55,S46]
	2.5	[G13]
	4	[O10]
Permanent sterility	2-3 fractionated	[H55,S45]
	9.5	[C12]
	6	[H21]
	5-6	[G13]
	4.5-6 fractionated	[L16]

Table 11

Effects of radiation on the human eye [H25]

Tissue	Effect	Dose (Gy)	
		Single dose	Fractionated dose
Lid skin	Early erythema	4-6	6 x days$^{0.33}$
Lacrymal gland	Atrophy	20	50-60 30F/6 weeks
Conjunctiva	Late teleangiectasia		30-50 (3-5 weeks)
Cornea	Early oedema and keratitis	10	30-50
Sclera	Late atrophy		200-300
Retina	Early oedema		30-35
	Late degeneration		30-50
Lens	Cataract	2-10	4 x days$^{0.17}$

Table 12

N and T factors for neutrons compared with x rays

Tissue	Damage	Neutrons	x rays		Neutrons		Ref.
			N	T	N	T	
Subcutaneous	Fibrosis		0.24	0.11			[E4]
Skin	Erythema desquamation	16 MeVd/Be	0.26	0.11	0.04	0.11	[F30]
Tail	Necrosis	14 MeVd-T	0.39		0.00		[H28]
Tail	Erythema desquamation	16 MeVd/Be	0.39		0.03		[A10]
Lung	Pneumonitis	16 MeVd/Be	0.27	0.07	0.00	0.00	[F8,H30]
Spinal cord	Myelopathy	14 MeVd-T	0.44	0.03	0.00		[V1,V8]
Spinal cord	Myelopathy	16 MeVd/Be	0.38	0.00	0.00		[W6,H66]
Brain	Necrosis	16 MeVd/Be	0.38	0.00	0.00	0.00	[H67]
Small intestine	Crypt damage	16 MeVd/Be	0.29		0.00		[W2]
		50 MeVd/Be			0.00		

Table 13

Threshold skin erythema doses for fast neutrons

Species	Dose (Gy)	Area irradiated	Ref.
Pig	5	Approximately 20 cm^2	[B30]
Rat	4	Whole foot	[F2]
Mouse	5	Whole foot	[F26]
Man	2	Approximately 20 cm^2	[F14]

Table 14

Lowest injection, burden time, and skeletal dose where significant vascular reduction occurs after various radionuclides [J22]

Radionuclide (kBq/kg)		Days post injection	Skeletal dose (Gy)
41	^{226}Ra	1900 days	23
3.5	^{239}Pu	2200 days	3.5
6.3	^{228}Ra	2500 days	5
1.2	^{228}Th	1900 days	2.5
3700	^{90}Sr	1000 days	80

Table 15

Threshold doses for changes in vascular function (single treatments)

Tissue	Species	Functional study	Threshold dose (Gy)	Reference
Skin	Pig	Flow	8	[M33]
	Rabbit	Permeability	1	[J12]
	Rat	Permeability	20	[L23]
		Flow	15	[K21]
	Hamster	Flow	20	[H45]
Intestine	Rat	Permeability	5	[T12]
	Mouse	Permeability	2.5	[V3]
Mesentery	Rat	Permeability	5	[D33]
	Mouse	Permeability	20	[H40]
Lung	Rat	Permeability	20	[T13]
		Flow	10	[K21]
	Mouse	Permeability	10	[H53]
		Flow	11	[G2]
Brain	Monkey	Permeability	15	[C18]
	Dog	Permeability	10	[K23]
	Rabbit	Permeability	18	[N7]
	Rat	Flow	10	[K21]
Kidney	Man	Flow	4.5/3F	[A15]
	Pig	Flow	~ 12	[H12, H48]
	Dog	Flow	10	[M36]
	Rat	Flow	10-20	[C8]
	Mouse	Flow	11	[G2]
Liver	Rat	Flow	15	[K21]
	Mouse	Flow	5	[F32]
			> 15	[G2]

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