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 obtained, 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 \( \overline{D} \) (Gy s⁻¹) to a target tissue \( r \) in animal from activity \( A_r \) (Bq) of a radionuclide contained in a single source tissue \( i \) is given in general form by [19]

\[
\overline{D} (v \rightarrow r) = A_r \sum_i \Delta_i \Phi_i (v \rightarrow r)
\]

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. \( \Delta_i \) (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, \( \Phi_i \) (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 \( A_v \) 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

\[
\overline{D} = \sum_r A_r \sum_i \Delta_i \Phi_i (v \rightarrow r)
\]

where \( \sum_r A_r = A_v \). 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 \( \Phi_i \) 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 \( D \) (Gy) averaged over a target tissue \( v \) for a time \( t \) (s) is given by the time integral of the mean dose rate \( \overline{D} \). When the geometry of the source and target regions remains constant, the above equation can be integrated to become

\[
D = \sum_r \overline{A}_r \sum_i \Delta_i \Phi_i (v \rightarrow r)
\]

where the quantity

\[
\overline{A}_r = \int_0^t A_r dt \quad \text{(Bq s)}
\]

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 cumulative activities in the various tissues in addition to those already discussed affecting the specific absorbed fractions.

312. The cumulative 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](image)

Figure XV. Average radiation energy deposited in spheres of various diameters by decaying $^{125}$I and $^3$H (solid lines), as well as 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; $D_{0}$: 0.74 Gy) than either $^3$H-thymidine ($LD_{50}$: 3.8 Gy; $D_{0}$: 0.74 Gy) or external x-irradiation ($LD_{50}$: 3.3 Gy; $D_{0}$: 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 (32P, 99mTc, 198Au) 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 5500 MBq colloidal 198Au 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 leucopenia. 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 32P and 198Au 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 32P and 5.5–11 MBq of 198Au 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 fibers 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 mucous membrane of 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 LD50s for suckling, weanling and adult animals for 106Ru-106Rh given by gavage were 55, 670 and 330 MBq/kg, respectively, and about 0.2 TBq/kg for 147Pm in 147Pm in adults [S51]. In the neonatal animals the lower ileum showed the principal signs of damage and there was evidence that the 106Ru-106Rh pair, like 141Ce [I6], 95Nb [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 of 106Ru-106Rh and 0.16 TBq/kg of 147Pm 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 LD50/10 for ingested insoluble beta emitters in the rat of about 33 Gy [C26].

329. In dogs fed with 106Ru-106Rh, 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 irreversible. Animals surviving acute death had persistent diarrhoea until they were killed or died. The LD50 for acute death from ingested 106Ru-106Rh was estimated to be 130 MBq/kg and the LD50/180 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 LD50 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-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 microangiographic 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 marrow dose to the marrow spaces and to the endosteum, considered as a tissue layer of thickness 10 μm adjacent to trabecular surfaces [11]. 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 breakdown 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 narrow 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 to 0.12 MBq/kg 226Ra and 228Ra, 0.033 MBq/kg 239Pu and 0.0037 MBq/kg 232Th [T20, T21]. Fractures due to 90Sr 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 232Th and 228Ra but was high for 226Ra and 239Pu. 80% of the rib fractures induced by 0.11 MBq/kg 239Pu 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 an activity level of 0.11 MBq/kg 239Pu 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 90Sr and 90Y 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 90Sr delivering an average skeletal dose of 133 Gy over 2 years [M68]. The smallest dose from 90Sr 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 226Ra 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 226Ra. 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. 199Au-colloids were 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 90Y-silicate citrate and 32P-chronic 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 166Er-sulphide or 169Er-citrate, respectively, may be used [T7]. 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 90Y 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, fluor spar 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 by 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 [18]. 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 [18].

347. Rats receiving lung burdens of 0.22–0.74 MBq/g lung of relatively insoluble 238PuO2 and 239PuO2 died
within a few days from severe pulmonary oedema [SS9]. 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 $^{235}$EsCl$_2$ [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, $^{131}$I, $^{90}$Sr, and $^{239}$Pu 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, S60]. 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 the 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 $^{239}$PuO$_2$ at levels >0.37 kBq/g lung [P30]. The greater solubility of $^{239}$PuO$_2$ than of $^{239}$PuO$_2$, attributed to the high specific activity of $^{239}$Pu [F50, F51], was indicated by the faster clearance from lung and the ten times greater retention of $^{239}$Pu in the skeleton at 70 months post-exposure [B64, P31]. Similarly, following exposure to the even more soluble $^{239}$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 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 [SS9]. 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 hyperplasia [T22, 166]. There may be marked fibrous pleural thickening and obliterated 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 days [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 $^{228}$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 adults injected with $^{228}$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 thoronast 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 thoronast was usually injected corresponding to an activity of about 0.022 MBq 228ThO2 [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 thoronast 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 144Ce and 0.25 MBq/kg 239Pu 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 239Pu have been observed in the dogs at Utah [T23]. Following a single intravenous injection of 0.11 MBq/kg tetravalent 239Pu the activity deposits in the hepatic cells and remains for 2–3 months before being transferred to the reticuloendothelial cells lining the sinuses. 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 239Pu 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 239Pu. In these cases liver atrophy was observed as early as 47 days from doses 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 239Pu (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 224Ra [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 228Th/kg [B79, C27]. 228Th continually generates its daughter 224Ra 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 228Th, 224Ra 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 radiosensitive 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 131I, 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. Rogoyaw 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 131I or 131I. About 90% of the radioactivity is concentrated in the colloid but the dose delivered by the relatively energetic beta/gamma emissions from 131I 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 smaller 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 131I (in contrast to 125I) 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 125I 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 to 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, 131I, and 125I gave D50 of 4.5, 5.5 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 radiiodine the survival curves were exponential from the origin. The difference between 131I and 125I was attributed to the relative sparing of parenchymal cell nuclei due to the inhomogeneous dose distribution from 125I, 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 131I produces diffuse damage whereas 125I produces localized effects at the colloid-cell interface [L41]. From experiments using rats, several workers have concluded that 131I is less effective than 125I 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 125I/131I 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 radiiodine uptake suppression [G36].

369. A large body of data exists for treatment of hyperactive thyroid glands, usually by orally administered radioactive 131I. In its hyperactive state the thyroid is more radiosensitive. Werner et al. [W22] observed a return to normal, or even hypothyroidism after fractionated doses of 1.5–3.7 MBq 131I, 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 Wilkom [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 dose delivered per unit activity of 131I and 125I is about 1.6 for an uptake of 25% [M63]. However, 131I delivers some seven times the initial mean dose rate to a 20 g thyroid compared with that from an equal activity of 125I [S50].

371. Mean activity levels of 125I 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 131I. 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 hypothyroidism from 125I is lower than that following treatment with 131I [H67]. 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 131I, 132I, 133I, 135I) 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 radiiodide 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 radiiodine [H69, H70]. Preliminary results of a study of patients receiving 131I 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 131I 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 radiosensitive [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 thyroglobulin 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 32P 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 testes 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 210Po 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 60Co irradiation (see section IV.A), the RBE appeared to depend on dose rather than dose rate and was thought to become as high as 30 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 90Sr injected intra-vaginally 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]. 90Sr 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 [R68] 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 90Sr activity injected after the 15th day when the foetal skeleton has started to ossify, will be incorporated into it and together with 90Y provide an additional source of irradiation to the ovary. In the female 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 90Sr administered just before birth when the oocytes are in the radiation-sensitive diacylate stage. An activity of 0.011 MBq 90Sr 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\(^{-1}\) 90Sr with 9.2 mBq kg\(^{-1}\) 90Y (wet weight).

380. Tritium can be incorporated into all parts of the living animal, particularly as HHO. The effects on the ovary have been studied [D46] in 14-day old mice following continuous administration of HHO 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 LD50 was 74 kBq/ml, which would deliver a radiation dose of 0.0044 Gy/day. Continuous external y-irradiation of the mice with 60Co 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 3H, with an LD50 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 99mTc given as pertechnetate in daily intravenous doses to pregnant and lactating females has been investigated [L44]. The tissue distribution, and response to injected NaClO4 of 99mTc 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 99mTc in the milk secreted by lactating mothers given 1.8-18 MBq/kg. 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 Pectoschor containing 224Ra, principally for the treatment ofankylosing 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 224Ra as juveniles was particularly striking. In adults the incidence was 1% in 300 men receiving less than 0.53 MBq 224Ra/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 α2 globulin with age in those groups with the higher intake 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 226Ra 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 131I-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, 32P, has been widely used since 1939 in the treatment of patients with primary polychythaemia. 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 32P 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 35S injected as Na2SO4 [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. Thrombocytopenia, leukopenia 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 90Sr three died due to progressive thrombocytopenia, leukopenia 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 239Pu in mice, a moderate reduction in the number of half-surviving leukocytes 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 55Fe 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 most exclusively in intracellular form in the body and 55Fe 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 55Fe 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 pancytopenia which was attributed to the inability 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 65Zn 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 65Zn 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]. 65Zn decays mainly by K-capture associated with the emission of several short-range Auger electrons. The function of vital molecules into which the 65Zn 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 65Zn 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 reticuloendothelial elements in the spleen and lymph nodes. The appearance of foci of extramedullary haemopoiesis, and an increase in the number 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 suppurrative process spreading over the lymph nodes. Such inflammatory lesions of the lymph nodes may be considered characteristic of the chronic action of 65Zn 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 62Zn activity, erythropoiesis and lymphopoiesis are progressively depressed leading to the appearance of abnormal erythrocytes, reticulocytopenia and lymphocytopenia [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 by 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 35S [K44]. However, the granulocytic series seem to be particularly sensitive to exposure to 62Zn [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 red 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 90Sr, 144Ce, 91Y 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, panleukocytopenia, 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 μCi 90Sr/kg body weight, 5.2–11.8 μCi 144Ce/kg body weight and 7.4–20 μCi 91Y/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, leukocytopenia [B65, S59, B73] and depression of myelopoiesis have been observed [B66]. However, in dogs a dose-related lymphocytopenia was the earliest and most consistent effect seen following inhalation of both transuranic radionuclides and insoluble particles containing beta/gamma radionuclides. Lymphocytopenia has not been associated with either illness or premature death of the animals.

398. Lymphocytopenia 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 239PuO2 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 lymphocytopenia depend on the dose of alpha-emitting radionuclides but can probably be detected after pulmonary depositions of >18.5 Bq/g lung [14].

399. For beta/gamma emitters in fused alumino-silicate particles the lymphocyte response in dogs depended on the radionuclide [J21]. For short-lived 90Y 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 91Y, depression occurred more slowly and by two years there were indications of recovery. For 144Ce, the depression occurred during the first 200 days and was maintained over the remaining two years of observation. For 90Sr 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 with 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 239PuO2 is probably mediated by macrophages. Concentrations of such particles can accumulate to 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 144Ce 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 239PuO2 in dogs the historical 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, approaching 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 239PuO2 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 106Ru, 0.018–15 mBq/kg 144Ce and 63 mBq/kg 137Cs [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 210Po and nearly 3 for 3H 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 65Zn 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 cellular changes over a period of many months. Histological changes in blood vessels and interstitial fibrosis precede atrophy of parenchymal cells in liver [J2, 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 [T12].

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]. Vasculature and lifting of endothelial cells has been observed within the first month after irradiation, preceding changes in the lung epithelial cells [B6]. In skin, vasculature and lifting 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, M33] 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 [Z5].

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 telangiectasia, are seen in many irradiated tissues [R21]. In the arterioles and capillaries, tortuous vessels [R21] are also seen. 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., 42K or 88Rb) and the extraction in different tissues assessed from the incorporated radioactivity. Alternatively, the tracer may be introduced directly into the tissue (e.g., 22Na, 99mTe, 125Xe) 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 diffusible [S25, K22, L22].

418. Early experiments to measure vascular permeability involved the intravenous 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 51Cr), 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 Meerick 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 10–40 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].

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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 22Na [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 vascular active 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 53 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 hyperemic 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 [T12] 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. Williams [W10] 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 131I-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. Vaitius and Horsey [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, Horsey [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 133Xe 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 86Rb to measure vascular function after irradiation of one lung in the mouse. The uptake of 86Rb 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 Schäffer [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 bromo-sulphalein 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 86Rb 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 86Rb 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. Maior and Casarett [M36] used radiophipuran 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 in 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 ERG, there is a reduction in blood flow which is dose and time dependent. Similar results have been obtained using the 86Rb 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 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'niksky and Brumshyeyn (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 D4 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 subpopulation. 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 Dₐ of ~ 10 Gy and a Dₐ of ~ 3 Gy was derived from these data.

454. Reinhold [R27] obtained a Dₐ 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 Buismans [R2] obtained a much lower value of Dₐ by a modified version of the same system. These studies gave a survival curve with a Dₐ of about 1.7 Gy, an extrapolation number of 7 and a Dₐ of about 3.4 Gy. Split dose experiments at 24 hours, using an initial dose of 5 Gy gave a Dₐ-Dₐ 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 cotton 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 confluently formed 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 Dₐ of 2.4 Gy, an extrapolation number of about 3 and a Dₐ 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, Dₐ-Dₐ 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 differing values for Dₐ. Cell survival parameters in vitro for a rapidly growing cell line of endothelial cell origin have been estimated to have Dₐ ~ 2 Gy [N6]. It seems that high values for Dₐ (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 Dₐ observed. Van den Brenk et al. [V2] observed a dose sparing of 3–6 Gy when a 2–3-week gap was allowed between irradiation and the raising of the air pouch. Similarly, Reinhold and Buismans [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 Dₐ 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 dog's eyes. They suggested that cells stimulated by irradiation were more sensitive than cells stimulated after irradiation but their data are unconvincing. A split-dose increment Dₐ-Dₐ 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 depopulation 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 Dₐ-Dₐ of 7 Gy (as measured in split-dose experiments) and a Dₐ 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 preceed 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 the amount of collagen are not yet 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 Griffin [H51] found that a 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 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].

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.

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 include a variety of the skin, loss of hair, changes of 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 haemo poetic 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, possibly, tumour regression, 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 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 aspermatia. 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 fully resistant to doses of 60 Gy. Even doses of 60 Gy 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 parenchymal 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 both in the 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 longer 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 at the given amount of injury. The RBE 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 inves-

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 time 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_{2-3} values for various tissues

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Species</th>
<th>Endpoint</th>
<th>D_{2-3} (Gy)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Pig</td>
<td>Radiodermatitis</td>
<td>5.0-7.0</td>
<td>[F1]</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td></td>
<td>8.9</td>
<td>[F2]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td></td>
<td>5.0</td>
<td>[D3]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Epidermal clones</td>
<td>3.5</td>
<td>[W4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.7</td>
<td>[D3]</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Mouse</td>
<td>LD/50</td>
<td>5.6</td>
<td>[H2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.5</td>
<td>[P1]</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Mouse</td>
<td>LD/50</td>
<td>4.5</td>
<td>[H3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macroculture assay</td>
<td>4.0</td>
<td>[W5]</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Rat</td>
<td>Growth stunting</td>
<td>4.0</td>
<td>[D4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5</td>
<td>[K1]</td>
</tr>
<tr>
<td>Lung</td>
<td>Mouse</td>
<td>LD/50 (both lungs)</td>
<td>4.0-5.0</td>
<td>[F3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5</td>
<td>[P2]</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Rat</td>
<td>ED/50</td>
<td>9.5</td>
<td>[W6]</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>6.0</td>
<td>[V1]</td>
</tr>
<tr>
<td>Testis</td>
<td>Mouse</td>
<td>Clonal assay</td>
<td>3.0a/</td>
<td>[W7]</td>
</tr>
<tr>
<td>Haemopoietic tissues</td>
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<td>Spleen nodules</td>
<td>1.0</td>
<td>[T1]</td>
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<tr>
<td>Endothelial cells</td>
<td>Rat</td>
<td>Stimulated dermal blood vessels colonies in granuloma pouch Cell counts in mesentery</td>
<td>3.0</td>
<td>[R2]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.8</td>
<td>[V2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.0</td>
<td>[H4]</td>
</tr>
</tbody>
</table>

a/ Decreases with increasing time between fractions.

### Table 2

Changes in proliferation after irradiation of skin

(Fractionation data)'01

<table>
<thead>
<tr>
<th>Species</th>
<th>Fraction number</th>
<th>Overall time</th>
<th>Increment Gy/day</th>
<th>Doubling time (days)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig</td>
<td>5</td>
<td>5-28</td>
<td>0.25</td>
<td>4</td>
<td>[F10]</td>
</tr>
<tr>
<td>Mouse</td>
<td>2</td>
<td>7-14</td>
<td>0.30</td>
<td>3.2</td>
<td>[D3]</td>
</tr>
<tr>
<td>Human</td>
<td>up to 25</td>
<td>up to 35</td>
<td>0.28-0.34</td>
<td>3</td>
<td>[D4]</td>
</tr>
<tr>
<td>Mouse</td>
<td>15</td>
<td>17-35</td>
<td>0.32</td>
<td>3</td>
<td>[H14]</td>
</tr>
<tr>
<td>Mouse</td>
<td>2</td>
<td>1-7</td>
<td>0.70</td>
<td>3.2</td>
<td>[C5]</td>
</tr>
<tr>
<td>Mouse</td>
<td>5</td>
<td>4-9</td>
<td>0.90</td>
<td>1</td>
<td>[F16]</td>
</tr>
<tr>
<td>Plucked skin</td>
<td>Mouse</td>
<td>2</td>
<td>1-5</td>
<td>1</td>
<td>[W11]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>2</td>
<td>1-7</td>
<td>0.48</td>
<td>[E7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7-14</td>
<td>0.42</td>
<td>[E7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14-21</td>
<td>0.29</td>
<td>[E7]</td>
</tr>
</tbody>
</table>

### Table 3

Threshold skin erythema doses

for single doses of x-rays

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (Gy)</th>
<th>Area irradiated</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig</td>
<td>10-15</td>
<td>Approximately 20 cm²</td>
<td>[F10, W38]</td>
</tr>
<tr>
<td>Rat</td>
<td>10</td>
<td>Whole foot</td>
<td>[F2]</td>
</tr>
<tr>
<td>Mouse</td>
<td>10</td>
<td>Whole foot</td>
<td>[F12]</td>
</tr>
</tbody>
</table>
### Table 4
"Threshold doses" for damage to kidney of various species

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (Gy)</th>
<th>Type of injury</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>&lt; 20</td>
<td>Tubular function</td>
<td>[M10]</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Renal enzyme changes</td>
<td>[P7]</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Functional and enzymic changes</td>
<td>[Z1]</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>Decrease in size and mass, histological and functional changes</td>
<td>[H11]</td>
</tr>
<tr>
<td>Pig</td>
<td>10</td>
<td>Function</td>
<td>[H12]</td>
</tr>
<tr>
<td>Rabbit</td>
<td>~12</td>
<td>Probability of lethality</td>
<td>[C7]</td>
</tr>
<tr>
<td>Rat</td>
<td>5</td>
<td>Hypertension</td>
<td>[L13]</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Nephrosclerosis</td>
<td>[B11]</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>Functional and enzymic changes</td>
<td>[X8]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Plasma flow and collagen deposition</td>
<td>[C8]</td>
</tr>
<tr>
<td>Mouse</td>
<td>5</td>
<td>Nephrosclerosis</td>
<td>[B12]</td>
</tr>
<tr>
<td></td>
<td>&lt; 10</td>
<td>Accelerated glomerulosclerosis</td>
<td>[G1,C9]</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Blood flow</td>
<td>[G2]</td>
</tr>
<tr>
<td></td>
<td>10-15</td>
<td>Lethality after unilateral nephrectomy</td>
<td>[P8]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Decrease in weight</td>
<td>[G3]</td>
</tr>
</tbody>
</table>

### Table 5
LD$_{50/30}$ (haemopoietic syndrome) for different species

<table>
<thead>
<tr>
<th>Species</th>
<th>Approximate weight (gm)</th>
<th>LD$_{50}$ a/ (Gy)</th>
<th>LD$_{50}$ b/ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>25</td>
<td>9.0</td>
<td>6.4, 7.1</td>
</tr>
<tr>
<td>Desert mouse</td>
<td>30</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>Gerbil</td>
<td>40</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Hamster</td>
<td>80</td>
<td>9.0</td>
<td>6.1, 8.6</td>
</tr>
<tr>
<td>Rat</td>
<td>200</td>
<td>9.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>800</td>
<td>2.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Harmoset</td>
<td>3000</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>3500</td>
<td>8.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Monkey</td>
<td>4000</td>
<td>4.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Dog</td>
<td>12000</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Sheep</td>
<td>45000</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Goat</td>
<td>50000</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Man</td>
<td>70000</td>
<td>3.0 c/</td>
<td>3.0 d/</td>
</tr>
<tr>
<td>Swine</td>
<td>200000</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Burro</td>
<td>400000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a/ [H67];
b/ [B7];
c/ [L17];
d/ [B18];
**Table 6**

*Summary of threshold doses in experimental animals*

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

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 [018]*

<table>
<thead>
<tr>
<th>Degree of severity</th>
<th>First week</th>
<th>Second week</th>
<th>Third week</th>
<th>Approximate mortality and time of death in weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very severe (Group I)</td>
<td>Nausea and vomiting (++)</td>
<td>Fever (+++)</td>
<td>Multifractions or continuous irradiation (Gy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever, apathy, delirium, diarrhoea (++)</td>
<td>Emaciation</td>
<td>Leukopaenia (+++)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal lesions (+) /</td>
<td></td>
<td>Anaemia (++)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukopaenia (++)</td>
<td></td>
<td>Haemorrhagic diathesis (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilation (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (Group II)</td>
<td>Nausea and vomiting (++)</td>
<td>Fever (+++)</td>
<td></td>
<td>100 % first and second</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately severe (Group III)</td>
<td>Gastrointestinal b/</td>
<td>Leukopaenia (+)</td>
<td></td>
<td>Less than</td>
</tr>
<tr>
<td>Syndrome (++)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (Group IV)</td>
<td>Gastrointestinal syndrome (+)</td>
<td>Leukopaenia (+)</td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Effect</th>
<th>Tolerance dose (Gy)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary or reduced sterility</td>
<td>1.5 fractionated &lt;sup&gt;a/&lt;/sup&gt;</td>
<td>[T17]</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>[G13]</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>[P18]</td>
</tr>
<tr>
<td></td>
<td>12 fractionated (3/day)</td>
<td>[R34, P16]</td>
</tr>
<tr>
<td></td>
<td>174 (in 3 series/2.5 years)</td>
<td>[G14]</td>
</tr>
<tr>
<td>Permanent sterility</td>
<td>[G13]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5-5 fractionated</td>
<td>[R34]</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>[P18]</td>
</tr>
<tr>
<td></td>
<td>6.25</td>
<td>[P19]</td>
</tr>
<tr>
<td></td>
<td>8-10</td>
<td>[L20]</td>
</tr>
<tr>
<td></td>
<td>(in 3 series/2 years)</td>
<td>[J1]</td>
</tr>
<tr>
<td></td>
<td>6.25-12 fractionated (30F/6 week)</td>
<td>[R16]</td>
</tr>
<tr>
<td></td>
<td>6-20</td>
<td>[L16]</td>
</tr>
<tr>
<td></td>
<td>3.6-7.2 fractionated (2-4F)</td>
<td>[D20]</td>
</tr>
</tbody>
</table>

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### Table 10

Doses causing temporary or permanent sterility of human testis

<table>
<thead>
<tr>
<th>Effect</th>
<th>Tolerance dose (Gy)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary sterility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1-1.0 fractionated</td>
<td>[S95]</td>
<td></td>
</tr>
<tr>
<td>1.5-3</td>
<td>[N20]</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>[H55, S46]</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>[G13]</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>[D10]</td>
<td></td>
</tr>
<tr>
<td>Permanent sterility</td>
<td>2-3 fractionated</td>
<td>[H55, S45]</td>
</tr>
<tr>
<td>9.5</td>
<td>[C12]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>[H21]</td>
<td></td>
</tr>
<tr>
<td>5-6</td>
<td>[G13]</td>
<td></td>
</tr>
<tr>
<td>4.5-6</td>
<td>fractionated</td>
<td>[L16]</td>
</tr>
</tbody>
</table>

### Table 11

Effects of radiation on the human eye [H25]

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Effect</th>
<th>Dose (Gy)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lid skin</td>
<td>Early erythema</td>
<td>4-6</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 x days</td>
<td></td>
</tr>
<tr>
<td>Lacrymal gland</td>
<td>Atrophy</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-60 30F/6 weeks</td>
<td></td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>Late teleangiectasia</td>
<td>30-50 (3-5 weeks)</td>
<td></td>
</tr>
<tr>
<td>Cornea</td>
<td>Early oedema and keratitis</td>
<td>10</td>
<td>30-50</td>
</tr>
<tr>
<td>Sclera</td>
<td>Late atrophy</td>
<td>200-300</td>
<td></td>
</tr>
<tr>
<td>Retina</td>
<td>Early oedema</td>
<td>30-35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late degeneration</td>
<td>30-50</td>
<td></td>
</tr>
<tr>
<td>Lens</td>
<td>Cataract</td>
<td>2-10</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 x days</td>
<td></td>
</tr>
</tbody>
</table>

### Table 12

N and T factors for neutrons compared with x rays

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Damage</th>
<th>Neutrons</th>
<th>x rays</th>
<th>Neutrons</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Fibrosis</td>
<td>0.24</td>
<td>0.11</td>
<td></td>
<td>[E4]</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>0.26</td>
<td>0.11</td>
<td>0.04</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>desquamation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tail</td>
<td>Necrosis</td>
<td>14 MeVd/Be</td>
<td>0.39</td>
<td>0.00</td>
<td>[H28]</td>
</tr>
<tr>
<td></td>
<td>Erythema desquamation</td>
<td>16 MeVd/Be</td>
<td>0.39</td>
<td>0.03</td>
<td>[A10]</td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonitis</td>
<td>16 MeVd/Be</td>
<td>0.27</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Myelopathy</td>
<td>14 MeVd/Be</td>
<td>0.44</td>
<td>0.03</td>
<td>0.00</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Myelopathy</td>
<td>16 MeVd/Be</td>
<td>0.38</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Brain</td>
<td>Necrosis</td>
<td>16 MeVd/Be</td>
<td>0.38</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Crypt damage</td>
<td>16 MeVd/Be</td>
<td>0.29</td>
<td>0.00</td>
<td>[W2]</td>
</tr>
<tr>
<td></td>
<td>50 MeVd/Be</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 13

Threshold skin erythema doses for fast neutrons

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (Gy)</th>
<th>Area irradiated</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig</td>
<td>5</td>
<td>Approximately 20 cm²</td>
<td>[F30]</td>
</tr>
<tr>
<td>Rat</td>
<td>4</td>
<td>Whole foot</td>
<td>[F2]</td>
</tr>
<tr>
<td>Mouse</td>
<td>5</td>
<td>Whole foot</td>
<td>[F26]</td>
</tr>
<tr>
<td>Man</td>
<td>2</td>
<td>Approximately 20 cm²</td>
<td>[F14]</td>
</tr>
</tbody>
</table>

Table 14

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

<table>
<thead>
<tr>
<th>Radionuclide (kBq/kg)</th>
<th>Days post injection</th>
<th>Skeletal dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 ²²⁸Ra</td>
<td>1900 days</td>
<td>23</td>
</tr>
<tr>
<td>3.5 ²³⁹Pu</td>
<td>2200 days</td>
<td>3.5</td>
</tr>
<tr>
<td>6.3 ²²⁸Ra</td>
<td>2500 days</td>
<td>5</td>
</tr>
<tr>
<td>1.2 ²²⁸Th</td>
<td>1900 days</td>
<td>2.5</td>
</tr>
<tr>
<td>3700 ⁹⁰Sr</td>
<td>1000 days</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 15

Threshold doses for changes in vascular function (single treatments)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Species</th>
<th>Functional study</th>
<th>Threshold dose (Gy)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Pig</td>
<td>Flow</td>
<td>8</td>
<td>[M33]</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>Permeability</td>
<td>1</td>
<td>[J12]</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>Permeability</td>
<td>20</td>
<td>[L23]</td>
</tr>
<tr>
<td></td>
<td>Hamster</td>
<td>Flow</td>
<td>15</td>
<td>[K21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow</td>
<td>20</td>
<td>[M45]</td>
</tr>
<tr>
<td>Intestine</td>
<td>Rat</td>
<td>Permeability</td>
<td>5</td>
<td>[T12]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Permeability</td>
<td>2.5</td>
<td>[V3]</td>
</tr>
<tr>
<td>Mesentery</td>
<td>Rat</td>
<td>Permeability</td>
<td>6</td>
<td>[D33]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Permeability</td>
<td>20</td>
<td>[H40]</td>
</tr>
<tr>
<td>Lung</td>
<td>Rat</td>
<td>Permeability</td>
<td>20</td>
<td>[T12]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Permeability</td>
<td>10</td>
<td>[K21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow</td>
<td>10</td>
<td>[H53]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow</td>
<td>11</td>
<td>[G2]</td>
</tr>
<tr>
<td>Brain</td>
<td>Monkey</td>
<td>Permeability</td>
<td>15</td>
<td>[C18]</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>Permeability</td>
<td>10</td>
<td>[K23]</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>Permeability</td>
<td>18</td>
<td>[N7]</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>Flow</td>
<td>10</td>
<td>[K21]</td>
</tr>
<tr>
<td>Kidney</td>
<td>Man</td>
<td>Flow</td>
<td>4.5/3F</td>
<td>[A15]</td>
</tr>
<tr>
<td></td>
<td>Pig</td>
<td>Flow</td>
<td>~ 12</td>
<td>[M12, H48]</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>Flow</td>
<td>10</td>
<td>[H36]</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>Flow</td>
<td>10-20</td>
<td>[S8]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Flow</td>
<td>11</td>
<td>[G2]</td>
</tr>
<tr>
<td>Liver</td>
<td>Rat</td>
<td>Flow</td>
<td>15</td>
<td>[K21]</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Flow</td>
<td>5</td>
<td>[F2]</td>
</tr>
</tbody>
</table>

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