Also, there may have been a contribution from mechanical injuries. A more extensive analysis of mortality versus distance from the hypocentre and time after the bombing in Hiroshima was undertaken [I11]. This revealed a peak in mortality rate slightly before 10 days for individuals exposed at distances between 500 m and 999 m from the hypocentre, and a peak at about 20 days for individuals between 1000 m and 1499 m, after allowing for an estimated contribution to death from mechanical injuries. This is probably the best evidence available concerning time to death of people from the gastrointestinal and bone marrow syndromes.

39. Deaths at these times from accidental exposures have been rare, e.g., one person in the 1946 Los Alamos criticality accident died at day 9. The granulocyte count was below 500 per μl on day 6, and it remained low until death on day 9 [H9] (see also the Appendix for other cases of accidental exposure).

40. The gastrointestinal syndrome in all species occurs concomitantly with various degrees of fluid, protein and electrolyte loss, mucosal atrophy and ulceration, infection and haemorrhage [B16, B56, G31] In man, severe enteritis occurs from about day 4 after doses above 10 Gy and from about day 7 after 6-10 Gy (see Appendix). In animals, the incidence of intestinal death can be reduced by transfusions with balanced salt solutions and antibiotics; for example, the $LD_{50/5}$ for rats can be increased by a factor of 1.4 by the use of antibiotics [T1]. Fluid loss in the gastrointestinal syndrome can be counteracted by infusions of electrolyte solutions [F3] In most species, it has been stated in general that early mortality (3-6 days after exposure) after doses of 2-4 times the $LD_{50/30}$ or $LD_{50/60}$ can be reduced to zero if supportive care is employed [F3]. Such procedures, which involve fluid replacement, parenteral nutrition, antibiotic and blood-component transfusions, are effective in humans suffering from the gastrointestinal syndrome. However, no accurate assessment of their efficacy in man is available even following the experience in Chernobyl (see Appendix).

4. Haematological and immunological effects, and the bone marrow syndrome

41 Animals die from marrow failure within 30 days after doses between about 2 Gy and 10 Gy, depending on the species. The $LD_{50/30}$ is related to body weight, as shown in Figure VII. Death from bone marrow failure is associated variously among species with granulocytopenia, thrombocytopenia and lymphocytopenia [B16]. In most species, anaemia is less severe than neutropenia or thrombopenia and does not correlate well with time of death [B16]. This is due partly to the radioresistance and the long life span of red blood cells (109-127 days in man). The lack of a severe response indicates that haemorrhage is not a major problem after doses in the LD_{50} range, but it would become increasingly important with higher doses. Similarly, thrombocytopenia, occurring because of the sensitivity of megakaryocytes and the relatively short life time of platelets in the blood (8-9 days in man [L5, C17, B16]), would not be regarded as a major contributor to mortality in the LD_{50} range but would become increasingly important after high doses.

42. Regeneration of these mature populations of cells occurs from the surviving precursor cells after

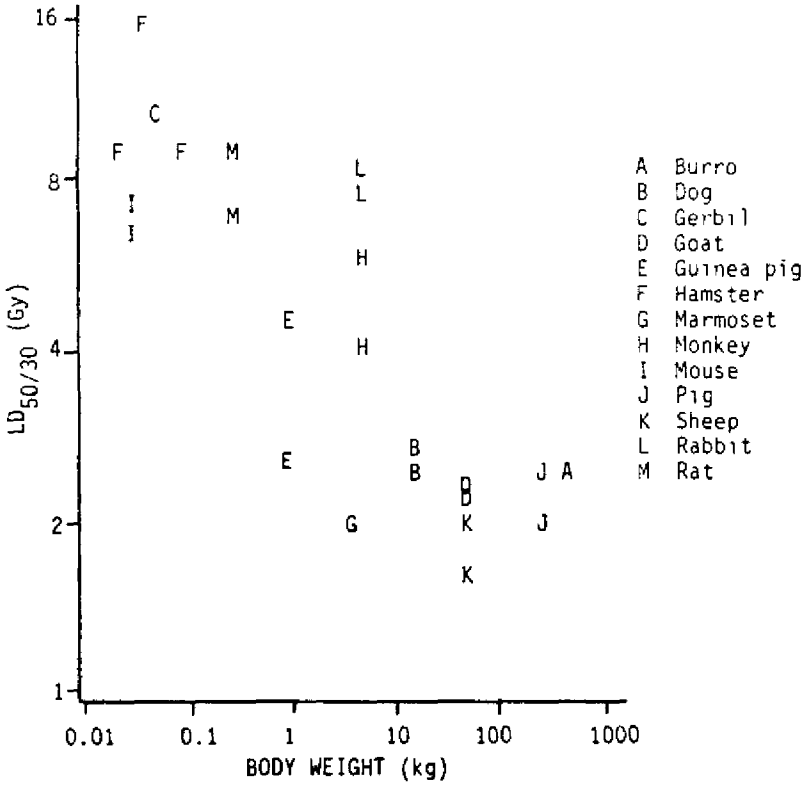

Figure VII. Relationship between $LD_{50/30}$ and body weight for various mammals. (Modified from [U4, U5].)

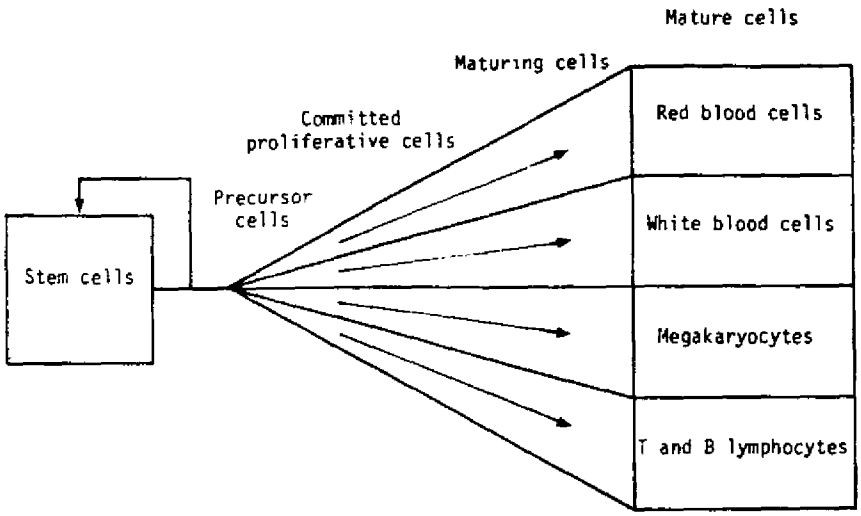

Figure VIII Simplified diagrammatic representation of the haemopoietic hierarchy, where mature cells are produced from proliferative precursor cells. Left arrow indicates renewal of stem cells, right arrows indicate differentiation and maturation down particular lineages.

irradiation; the hierarchy of haemopoietic cells is shown diagrammatically in Figure VIII The longer the animal survives, the greater will be the contribution to survival of cell progeny from primitive surviving precursor cells in the marrow Hence, in the short term, rescue of the animal will be assisted by survival of the more mature precursors, e.g., the granulocyte/macrophage colony-forming cells (GM-CFC); and, in the longer term, rescue will be dependent on the survival of multipotential stem cells. GM-CFC are assayed in vitro, and differences in radiosensitivity have been reported among species (reviewed in [H11]) GM-CFC in dogs are more sensitive than in mice or in man However, in view of the marked differences in apparent sensitivity of human GM-CFC measured using different culture conditions [B28], it is not clear whether the differences reported among species are artefactual or absolute.

43. The sensitivity of haemopoietic stem cells has been measured using the spleen colony technique in the mouse [T8] and in the rat [C8], but not in other animals. The possibility exists to measure the radiosensitivity of these cells in other species from the formation of foli of undifferentiated cells in irradiated bone marrow [H48, S47]. The precursor cell type that can be grown in vitro from different species and which is so far known to be nearest to the stem cell in the hierarchy is a cell that is capable of forming colonies in vitro comprising many haemopoietic cell types (Table I). The concentration of these cells in bone marrow is very low, as expected, so it is difficult to measure their intrinsic radiosensitivity. Their sensitivity has been measured in mouse and in man, but not in other species.

44. In human bone marrow, the total number of nucleated cells is reduced at day 1 by 10-20% after 1-2 Gy, by 25-30% after 3-4 Gy, by 50-60% after 5-7 Gy, and by a maximum of 80-85% after 8-10 Gy. Resistant cells remain, such as macrophages, stromal cells, vascular endothelium and some mature granulocytes and eosinophils [M25]. At day 1 after doses of a few Gy, resulting in the bone marrow syndrome, a relative trebling of macrophages and stromal elements has been reported [S21]. Bone marrow cellularity reaches a minimum value by days 3-4 after 5 Gy or above and by days 5-7 after 2-4 Gy. Regeneration can be detected in the marrow at days 4-6 by the presence of colonies of undifferentiated cells. The phase of pronounced aplasia is characterized in the marrow by oedema, a lack of adipose cells and a cellular composition of mainly lymphocytes, monocytes and plasma cells. When regeneration occurs, the number of undifferentiated cells increases to a maximum at days 14-20. It has been reported that after doses of up to 10 Gy cell regeneration in the marrow begins earlier than after lower doses [B38, V12].

45. Various attempts have been made to construct dose- and time-response curves for the changes in concentration of platelets, lymphocytes and neutrophils in the peripheral blood of healthy humans receiving whole-body exposures [A14, B31, C37, P13, W2]. A schematic picture of the smooth average time courses for the various blood cell types after different ranges of dose (Figure IX) was deduced from accidental human exposures [H9, C15, G9, H6, B29, J4, T5, B17, S6, C11]. The values in these idealized pictures are expressed as percentages of average levels in the normal population. Control ranges (± 2 SD) measured in five separate studies have been summarized [T29]. The extremes are 4-11 10^9 WBC/l for males and 4-9 for females, 4-6 10^{12} RBC/l for males and 3.7-5 for females; 34-54% haematocrit for males and 33-48% for females; 130-176 g haemoglobin/l for males and 113-162 for females.

46 The patients irradiated prior to kidney transplantation showed an earlier and more rapid decline in numbers of lymphocytes and granulocytes than the accident victims at Oak Ridge (Y-12) and Vinca irradiated with comparable doses. Also, in the patients the nadir levels (minimum values) were lower, but the regeneration of granulocytes began earlier and rose to higher levels. These differences would be compatible

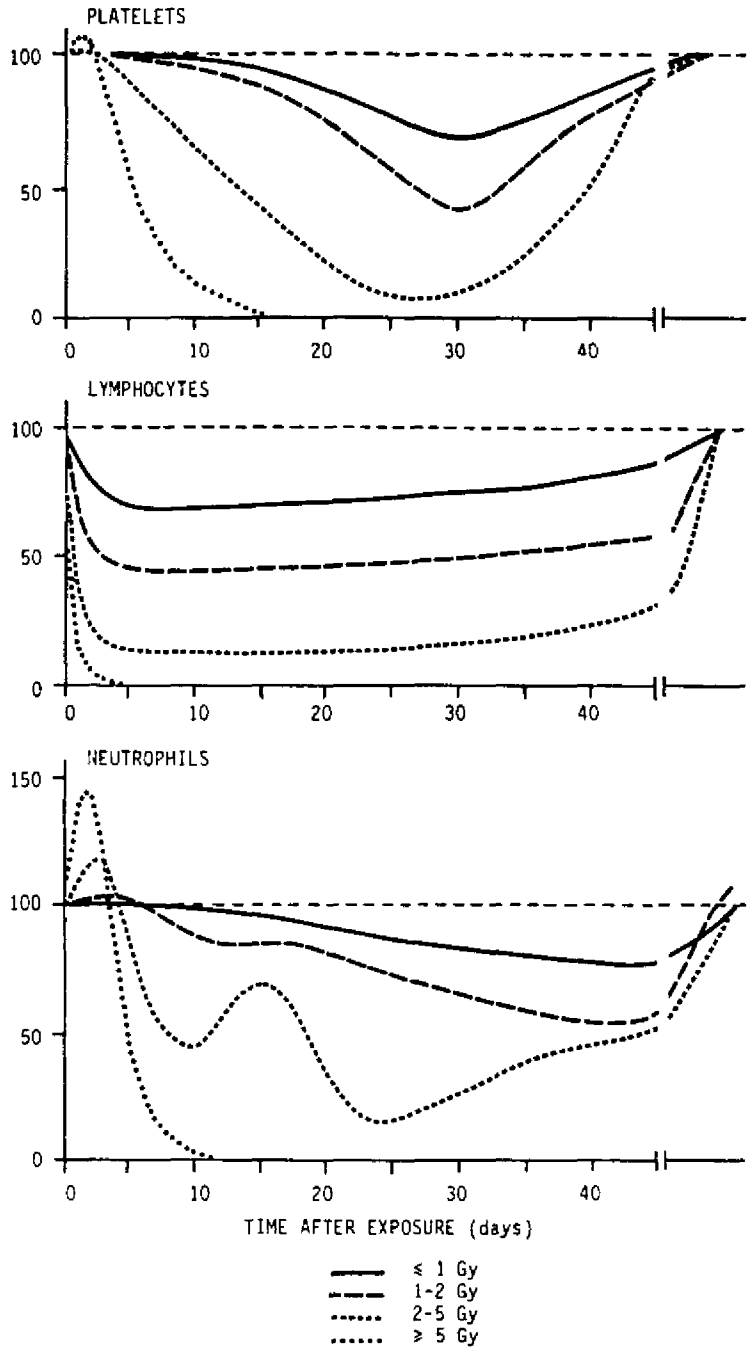

Figure IX. Schematic picture of average time courses for various cells in the blood, after various doses of radiation in man, derived from accident cases.
(Redrawn from [W2].)

with higher effective doses to the patients, because after the Y-12 accident the individuals receiving the higher doses, compared with those receiving low doses, had a greater fall in granulocytes but earlier regeneration reaching higher levels by day 60 [A2]. The greater response in the transplantation patients is difficult to explain, although it should be noted that many of the patients were anaemic and they had a short expectation of life. Different marrow doses, differences in the uniformity of dose, the contribution from neutrons in the accident cases and the confounding influence of concomitant disease have all been suggested as contributory factors [T10, T11, T12].

47. A greater-than-expected haematological response was also observed in patients with chronic granulocytic leukaemia [A1] exposed to 0.25 Gy and 0.5 Gy (midline doses) whole-body irradiation, in spite of the low exposure rate of 0.0012 to 0.0076 Gy per minute (at the midline). The rate of recovery of blood cell counts was slower than in the transplantation cases discussed above. These differences have been taken to indicate that data pertaining to irradiated patients suffering

from haematological diseases are not applicable to healthy individuals [A1] (except, perhaps, those data pertaining to patients in remission) [B41].

48 Figure IX shows that the lymphocyte count is the most sensitive index of radiation injury in the blood, in the sense that, for the same dose, nadir levels are reached earlier than for other cell types. Lymphocytes die in interphase, and doses of 1-2 Gy cause their numbers to decline to about 50% of normal by 48 hours. Decreases can also be observed during irradiation. For example, at the end of a 4-hour period during which 10 Gy was delivered to leukaemic patients in remission, the lymphocyte count was 50% of pre-irradiation levels, and it subsequently declined with a half-time of about 30 hours [D22]. A plateau was then reached which is dose-dependent, remained for about 45 days and was followed by a slow recovery over several months. The dose-dependence of the plateau level has been estimated in two reports from accident cases [W2, P13], and the results of the two reports are fairly consistent, one with another (Figure X and Figure A.II.b).

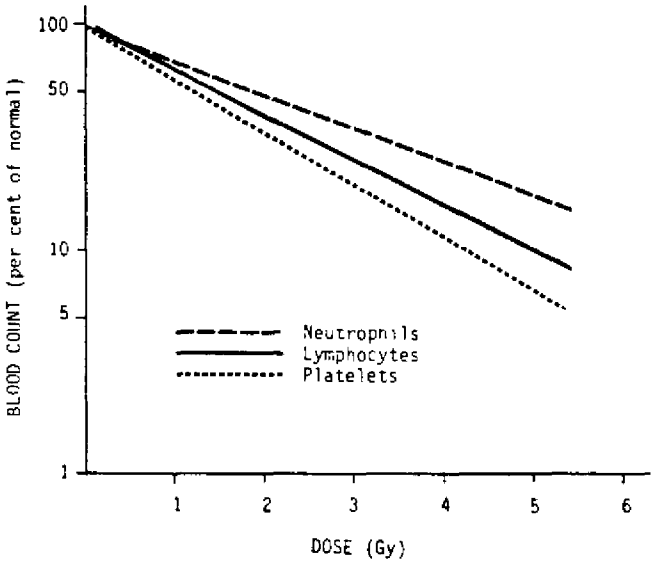

Figure X. Idealized average dose-response curves for nadir levels in blood cell counts.
[W2]

49 Neutrophils show an initial increase in number over the first few days after doses of 1-2 Gy or higher, and this "abortive rise" is greater after larger doses (Figure IX). Immediately after the delivery of 10 Gy in 4 hours to leukaemic patients in remission, the granulocyte count rose by a factor of 2-4 [D22]. A significant increase was noted as early as 10 minutes into the irradiation, when only 1.2 Gy had been given. The rise is probably due to a transient mobilization of cells from marrow and/or extramedullary sites and to accelerated maturation of precursor cells [B16]. This initial phase of granulocytosis is followed by a decline in the number of white cells, the rate and extent of which are dose-dependent. At day 10 after doses of 2-5 Gy there is the beginning of a second abortive rise, due to recovering haemopoiesis from precursor cell populations; this extends to about day 15 and is followed by a second decline to about day 25, due to a lack of recovery in the stem-cell population. The absence of a second rise in granulocytes is indicative of the failure of haemopoiesis to recover permanently [B16]. The second abortive rise is not seen after doses higher than 5 Gy (Figure A.V (left panel)).

50. With whole-body doses in excess of 6 Gy the critical level of neutrophils is reached in 7-9 days; after 4.2-6.3 Gy, it is reached in 10-20 days. With doses lower than 4 Gy, the critical level is generally reached after 20 days or more [U6]. The dose-dependence of the white cell count is shown in Figure A.V (left panel), which depicts the time to the minimum number of granulocytes; alternatively, Figure A.V (right panel) shows the time to reach the critical level of 500 granulocytes per μl (see below). From Figure A V (right panel) it can be seen that after about 6 Gy, the granulocyte level would be reduced to 10% (from 5,000 to 500 per μl) in 12-14 days. In Figure X, the nadir is also 10% after 6 Gy, but it is reached somewhat sooner, after about 7 days (Figure IX).

51. The times between days 20 and 30 are critical for fever and infections The period during which agranulocytosis is observed coincides with a period of fever both in animals [B17] and in man [T11, T12, Z2]. Studies of the correlation between granulocytopenia and the onset of fever showed that the latter was better correlated with the time of the minimum number of granulocytes (Figure XI [B37]) than with the absolute number of granulocytes at the start of the fever (Figures XII [B37]). Fever and granulocytopenia are also associated with intestinal injury [B31]

52. The degree and extent of leukocyte depression [J1] and bone marrow aplasia [I10] were shown to be correlated with mortality in the Japanese exposed to the atomic bombs. The chance of survival was very small in individuals having leukocyte counts of 1,000/μl

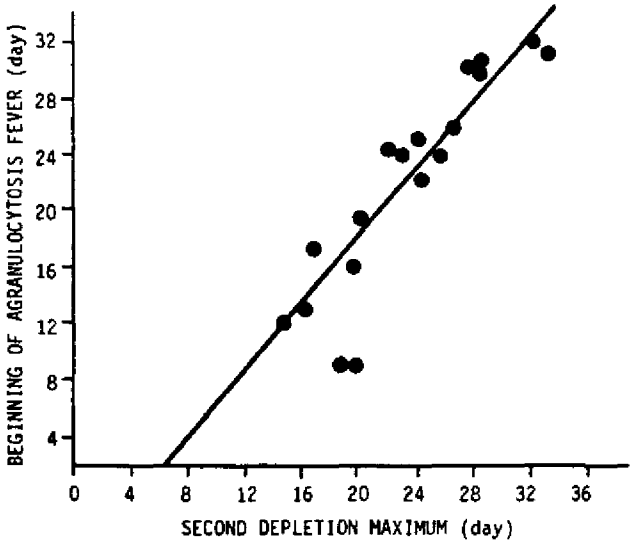

Figure XI. Time of the second depletion on the granulocyte count curve, corresponding to the beginning of agranulocytosis fever in man.
[B37]

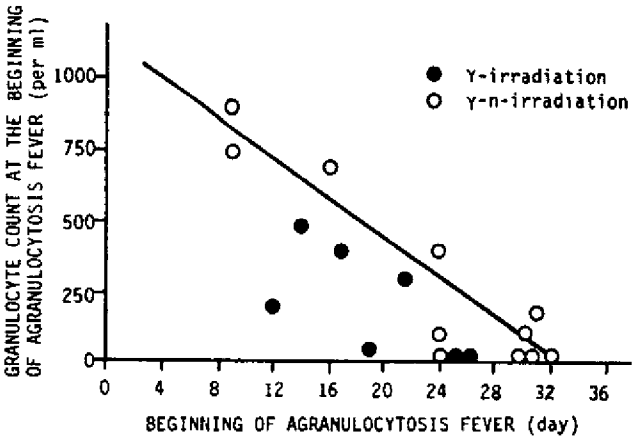

Figure XII. Granulocyte count at the beginning of agranulocytosis fever. [B37]

in the third and fourth weeks after exposure, and the correlation of leukocyte counts with survival was best in the third week. Counts of less than 3,000/μl were not so hazardous in the fourth and fifth week as in the third week. The studies also showed that mortality was greater in Hiroshima than in Nagasaki for equivalent blood count levels. A possible reason considered at the time related to the estimated greater contribution to dose from neutrons in Hiroshima, associated with injury in other tissues contributing to death; this explanation is now unlikely because revisions in dosimetry have markedly reduced estimates of the neutron components of that dose

53. The time course of the thrombocytopenia is broadly similar to that of granulocytopenia (Figure IX), but there is no second abortive rise. The dose-response relationship for the nadir of platelets shows a slightly more sensitive response than for that of lymphocytes (Figure X). After about 1 Gy, a decrease in platelets to 100,000 per μl is observed by day 30. The higher the dose, the earlier and greater is the reduction; after doses greater than 6 Gy, a minimum level of 10,000 per μl is observed by days 10-15. A thrombocytopenia below 30,000-50,000 per μl may be associated with bleeding, which can be prevented by transfusions of fresh platelets [F3]. Experience in treating patients suffering from bone marrow syndrome indicates that the critical level of thrombocytes requiring platelet transfusion is 20,000 per μl (see Appendix). Haemorrhages are also associated with the development of infections [J4, O5]. Owing to the long lifetime of the radioresistant red blood cells, anaemia is observed acutely only when bleeding has been substantial [B16].

54. The effects of radiation upon the immune response were reviewed by UNSCEAR in 1972 [U3]. As noted above, lymphocytes are especially susceptible to the acute effects of irradiation. Since this cell type is an integral part of the immune system, profound abnormalities of immune function would be expected as a consequence of whole-body exposure. This appears to be the case, although data pertinent to man are limited [C48, V19, M53]. The paucity of information is due in part to the fact that most of the relevant observations were made before many of the concepts that underlie current thinking on cellular immunology had been developed, in particular the concept that lymphocytes are heterogeneous in terms of structure and function. The situation is further complicated by differences in the radiosensitivities of those subpopulations of cells whose co-operative activities result in an immune response [A19, A21, A33, M53, M54, W26].

55. An increased susceptibility to infection has been well documented in persons exposed accidentally and therapeutically to doses in the low- to mid-lethal range [A3]. These infections may be caused by either endogenous (normal flora) or exogenous organisms. However, when assessing the role of an altered immune response in the presence of these infections, it is important to keep the following points in mind: (a) radiation at these dose levels may cause an increase in permeability of the vasculature, which may allow the normal bacterial flora to enter the circulation, and (b) when employed therapeutically, whole-body irradiation is generally administered to persons with haematological disorders, often in conjunction with high-dose chemotherapy and bone marrow transplantation. Even with bone marrow from an identical twin, the confounding effects of the primary disease (often leukaemia or aplastic anaemia) and other therapies on the immune response are considerable. Despite these cautions, however, there can be little doubt that whole-body irradiation causes marked acute alterations in the immune response of man.

56. Support for the above statement comes from several sources, the first of which is the whole-body irradiation of experimental animals, especially mice, whose immune response is remarkably similar to that of man. The consequences of such exposure in mice are profound, even with whole-body doses of less than 1 Gy [A19]. The effects on the immunological system are dose-dependent and may result in an augmented or a suppressed response to the same antigen, depending on the dose and the time between irradiation and the introduction of the antigen [A20]. This discrepancy in response appears to relate to differences in the radiosensitivity of effector and suppressor cells. Suppressor T cells ($CD8^+$) are more radiosensitive than helper T cells ($CD4^+$), and B cells have an intermediate sensitivity [A21, S47] In addition, whole-body irradiation with doses as low as 0 5 Gy results in marked impairment of the normal recirculation of lymphocytes [A22, S22].

57. The second source of evidence is the results of graded doses of radiation administered in vitro. With some antigens, it is possible to evaluate the response of immuno-competent cells completely in vitro. These in vitro responses are strikingly similar to the corresponding in vivo reaction. Irradiation of one or several of the component T- and B-cell populations prior to introduction of the antigen results in dose-related abnormalities in function, abnormalities that by and large would have been predicted from complementary experiments in laboratory animals [A19, A23].

58. A third source of information is the results of partial-body exposures administered therapeutically.

Extensive immunological assessment has been carried out in persons given total lymphoid irradiation [TLI] for Hodgkin's disease [M53, V19] and in other persons irradiated regionally. Although the extent and the character of these changes appear to depend on the region of the body that is irradiated [B39], the results in general correspond to what would have been predicted from experimental animals. One of the best-studied groups of patients receiving regional irradiation are women who have received local radiation therapy for carcinoma of the breast. These and related studies support the notion that lymphocyte subpopulations differ in their depletion and repopulation after irradiation [P15, W3]. The following abnormalities were noted in individuals who had received 45 Gy regional irradiation over five weeks before or after mastectomy, in comparison with individuals treated by surgery alone [R16, W17]: (a) surface markers. there was a significant reduction in the total lymphocyte count, which returned to a suboptimal plateau by seven months after irradiation. The plateau persisted for at least 10-11 years after radiotherapy. The reduced recovery level was due primarily to a reduction in T-cells (lymphocytes binding to sheep erythrocytes and reacting with the monoclonal antibody Leu-1 (CD5)). There was a significant reduction in T-cells of the helper/inducer phenotype (detected by anti-Leu-3a (CD4)), and this persisted at one year and 10 years after irradiation Normal numbers of T-cells of the suppressor/cytotoxic phenotype (stainable with anti-Leu-2a (CD8)) were found between one year and 10 years after irradiation. Induced IgG and IgM synthesis was also reduced after irradiation, with later recovery. In a related experiment, Job et al. [J9] showed a reduction in the helper/suppressor ratio in patients receiving adjuvant radiation therapy for primary breast cancer and in patients receiving brachytherapy and external beam radiation therapy for carcinoma of the cervix or corpus uteri. This change began during therapy and was due to a decrement in helper T cells detected by the OKTB monoclonal antibody These alterations persisted for at least 18 weeks after irradiation. Similar observations have been made in patients receiving total lymphoid irradiation for rheumatoid arthritis [K10]; (b) mitogen and antigen responses· no significant changes in response of T-lymphocytes to PHA were found, but the reactivity to PPD tuberculin was markedly decreased after irradiation and gradually restored during the subsequent six months The reactivity to allogenic lymphocytes (MLC reaction) was also reduced, but had reconstituted three months later; (c) cytotoxic functions: lectin-dependent cytotoxicity was unaffected by irradiation, but antibody-dependent cytotoxicity was reduced after irradiation, recovering by three years. Natural killer cell activity was unaffected when tested against one tumour cell type, but affected with another. The latter decrease was restored by three months.

D. EFFECTS ON OTHER TISSUES

1. Skin

59. Effects in skin are important. Because they are dose-dependent and because they are readily detected by eye, they can provide an approximate measure of injury with prognostic value. Attention must be paid, however, to the type of radiation used, because with higher photon energies, there is a build-up of dose in the surface layers and the maximum dose may be delivered to the dermis or deeper. In these cases, estimates of dose in deeper tissues derived from effects in the epidermis could be underestimated.

60. The thickness of human epidermis ranges from 40-50 μm on the trunk to 370 μm on the fingertips [I6, K15]. The average time for all basal cells to reach the stratum corneum was measured to be 17.7 ± 4 2 (SD) days [E6]. A review of these times at different sites in the body gave 32-36 days for the palm of the hand, 17 days for the upper limbs and 29-30 days for the lower limbs [R10]. The transit time through the stratum corneum is between six and 21 days, depending on the body site [B1]. A summary of cell kinetic data for human epidermis, averaged over various sites in the body, is given in Table 5. The hierarchy of cell population types in the epidermis is shown diagrammatically in Figure XIII.

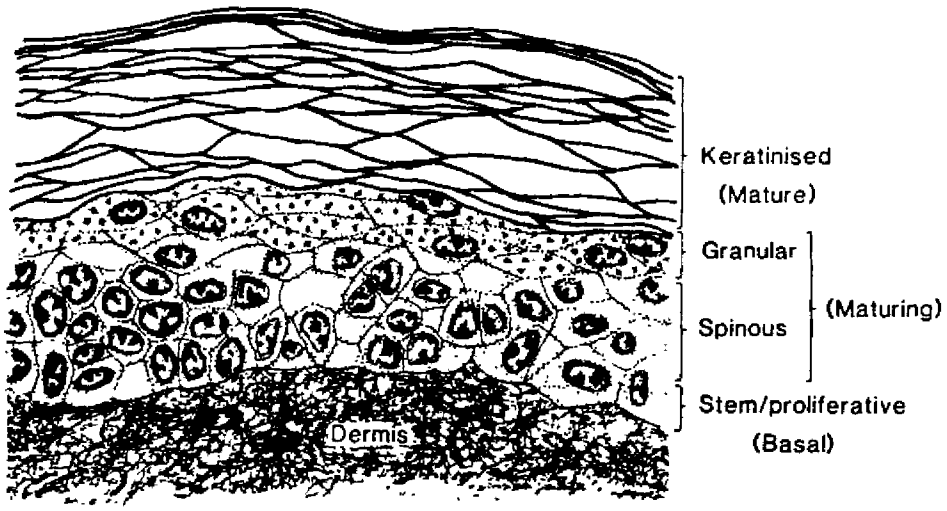

Figure XIII. Diagrammatic representation of the hierarchy of cell population types in the epidermis, drawn from a vertical section through normal human epidermis. (Adapted from [P28].)

61. The effects in skin are very dependent on the dose and on the area of skin irradiated (e.g., [A34, E12, H19, P28]). Erythema proceeds in waves. After doses greater than 10 Gy, there may be an initial phase, which reaches a peak around day 1, followed by a second wave between one and four weeks. Higher doses produce erythema of increasing severity, and the latency interval is shorter. After very high doses, erythema can appear and disappear several times. Erythema was used as a biological dosimeter in the early days of radiotherapy, and the "threshold erythema dose" varied with energy, dose rate and field size [E12]. Erythema is less easily recognized in pigmented skin and in exposed skin areas. The dose resulting in a visible erythema reaction within four weeks in 50% of individuals (not the initial transient erythema appearing within hours) after an acute single exposure with 200 kVp x rays over a 10×10 cm^2 field on the medial surface of the forearm is about 5.7 Gy [D6, L4].

62. In patients given radiotherapy to a 3 cm diameter area of the scalp with 100 kVp x rays the percentage of abnormal hairs increased between days 4 and 10 [V4] The incidence of abnormal hairs rose above 10% only after doses to the hair roots of 0.75 Gy or more. The incidence was about 50% on day 10 after 1.5 Gy, and doses above 2.5 Gy resulted in abnormality in 100% of hairs [V4]. Temporary epilation is produced after doses of 3-5 Gy and is most severe in the second and third weeks [D2], as noted, for example, in patients receiving whole-body irradiation prior to kidney transplantation [T11, T12]. Similar time courses were observed in the survivors of the atomic bombs, and if regrowth of hair occurred it was observed by 12-14 weeks after irradiation [O5]. Epilation may be permanent after doses greater than about 7 Gy. Hair on the scalp is more sensitive than the beard or body hair.

63. Desquamation reactions appear following marked erythema, after acute radiation doses greater than about 12 Gy. The severity of the reaction depends on the anatomical location, the vascularity and oxygenation of the skin, and the genetic background, age and hormonal status of the exposed individual [R12]. Dose-time and dose-incidence relationships have been studied in radiotherapy patients receiving doses to relatively small fields. Moist desquamation is produced in 2-3 weeks in 50% of individuals after a dose of about 20 Gy to areas of 35-80 cm^2 [A4, E2, J6, L4, P2] The maximum reaction occurs at about three weeks. After whole-body irradiation with such doses, the individual will have died from the intestinal syndrome before the desquamation reactions occur, except when the irradiation is poorly penetrating, as in the treatment of skin diseases or in direct skin exposure to short-range fallout radiation.

64. Desquamation reactions in skin are due primarily to the killing of cells in the basal layer of the epidermis and its associated appendages [P11, P28]. Measurements of the sensitivity of epidermal clonogenic cells in situ in man have been made after fractionated doses [A5] but not after single doses. However, the sensitivity has been assessed using human skin samples irradiated and assayed in vitro [D10]. The survival parameters were $D_0 = 0.7$-0.9 Gy, $n = 10$-16 (Table 1). The keratinocytes were more sensitive than epidermal clonogenic cells assayed in situ in mice or in pigs.

65. The time to full depletion of the epidermis after high doses corresponds to the transit time from the least-differentiated committed progenitor cell in the basal layer to the surface in unirradiated epidermis [P8]. This was deduced using a model applied to different types of epithelia, in which it was assumed that the clonogenic stem cells were sterilized after high doses, and also that the few divisions of committed proliferative cells, together with the processes of differentiation, maturation, and migration, were very radioresistant and hence unaffected. The normal turnover time of the epidermis would be expected to be longer than the above transit time by an amount equal to the lifetime of the stem cells in the basal layer. The time to full depletion of the epidermis after irradiation would be shortened where there is an acceleration of cell depletion as it proceeds after irradiation [P8, P28].

66. The degree of skin desquamation is markedly dependent on the area of skin irradiated. This has been studied in radiotherapy patients [C6, E2, J6, J7, M1, P2, V8], and some of these findings are summarized in Figure XIV and in Table 6. Some investigations were confounded by the use of various degrees of reaction acceptable as "tolerance" in different field sizes, e g. [J6], as discussed in [H19]. In general, the effect of field size is similar for single or fractionated doses and can be described by either of the formulas:

$$\text{Dose} = k(\text{area})^{-0.16}$$

$$\text{Dose} = k(\text{diameter})^{-0.33}$$

where k is a constant [C7, V8].

67. The extrapolation of the above formulae to areas greater than 400 cm^2 is uncertain, because evidence for very large areas relates only to the use of lightly

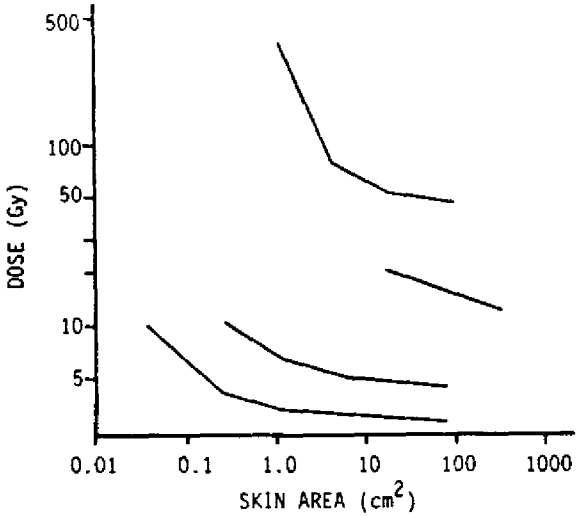

Figure XIV. Relationship between iso-effect dose for skin tolerance and field area using single doses (bottom two curves) or fractionated doses (top two curves) in man. [H19]

penetrating electron beams for the treatment of diffuse diseases of the skin, and it is not known if these diseases predispose to increased radiosensitivity. However, it has been concluded that there is little effect of changes in area for areas above 400 cm^2 [S15]. The 50% erythema dose was estimated to be about 3 Gy for a single dose of electron radiation to the total body surface [S15, W6], corresponding to about half the dose required for areas of 100 cm^2.

68. It is the dose to the basal layer of the epidermis that determines the degree of early skin desquamation, and concomitant doses to the dermis have little influence. This was shown by experiments in pigs [M21], where various isotopes were used to irradiate to different depths a 1 cm diameter circle of skin. Surface doses to produce transient desquamation varied enormously with the energy of the radiation from the isotope but the relative doses to the basal layer, at a maximum depth of 90 mm, were much more similar (Table 7). Further experiments have been carried out with pigs, comparing irradiation by strontium-90 and thulium-170 [P32]. The percentage of the dose reaching the epidermal basal layer was similar for the two isotopes, but only about 10% of the surface dose reached the base of the dermis using thulium-170, compared with about 50% using strontium-90. These studies concluded that there was no effect of field size for epidermal reactions with thulium for areas between 5 and 19 mm in diameter, but a marked effect of field size was observed with strontium. This was considered to be due to the contribution to repopulation from hair follicles, spared more by thulium than by strontium.

69. The severity of desquamatory skin reactions may be decreased by post-irradiation treatments using corticosteroids, but erythema is not decreased [H26]. Standard procedures of cleanliness during the healing period will prevent infection. Skin haemorrhages (petechiae) in monkeys can be prevented by antibiotic treatment [S3], suggesting that infection may be involved in their initiation. However, once petechiae have appeared, their development continues because of thrombocytopenia.

70. The effects of cell depletion in the dermis are manifested later than in the epidermis and in the epidermal-associated hair follicles, primarily because there is a slower rate of cell turnover in the constituent cell types of the dermis. The dermis contains connective tissue, sebaceous glands, muscle fibres, nerve plexuses and nerve fibres, sweat glands and blood vessels. The thickness of the dermis varies markedly over the body, but is generally 1-2 mm [I6]. The effects on the blood vessels after high doses are observed initially as erythema and later as haemorrhages. Haemorrhages on the skin appear as small (petechiae) or larger (purpura) lesions. Purpura can appear as early as day 3, but the peak onset occurs in the third or fourth week after irradiation, predominantly on the upper half of the body [O5]. The duration of purpura varies according to the severity of the injury, and in fatal cases the lesions remain until death. Purpura occurs concomitantly with epilation in many cases, and it has been described in nearly all people who died 3-6 weeks after the atomic bombings [O5]. Hence, although the dose-incidence curve is not accurately known, the effect is produced by doses of 4-6 Gy.

71. Irradiation of the dermis with high doses produces a second wave of erythema (at 10-16 weeks in the pig and the rat). This is dusky red/mauve in colour and is considered to be due to damage to the deep dermal plexus of blood vessels [H18]. It is followed by dermal necrosis, ulceration and sloughing of the dermis.

72. Pain is an important feature of the exposure of skin to high doses of radiation, particularly in the case of deep lesions after exposure of the extremities. Pain is experienced during the first few days, it lasts several hours per day and it may persist for long periods [N1]. The period of maximum pain corresponds to the appearance of vascular lesions.

73. Effects on sebaceous glands were observed when treating facial acne with superficial x rays [S13]. There are 400-900 glands per cm^2 on the head. After 3 Gy, glands are reduced in size by 20% at two weeks. After 4 Gy, the glands are reduced in size by 25-50% at two weeks, with recovery by four weeks. After 8 Gy, the gland size is 50% of normal at one week, with further reduction at two and three weeks, and recovery to normal size by six weeks. After 15 Gy to a 2 cm circle, the glands are severely atrophied by two weeks, and there are only a few small glands present up to two months later [S13].

74. Interesting clinical information about the skin reaction after beta-irradiation is contained in reports on the Japanese fishermen irradiated on board the Lucky Dragon [K4] or on people irradiated in the Marshall Islands [C16]. The frequency and intensity of skin reaction were highest in individuals on the island of Rongelap, where radioactive fallout was also highest. The period of appearance of skin lesions and epilation in these people is described in [C16]. The skin reactions to beta-irradiation observed during the accident at Chernobyl are described in the Appendix.

2. Oral mucosa

75. Information relating to the effects of radiation on oral mucosa comes from observations on atomic bomb survivors [O5] and from radiotherapeutic treatments [P12, U9]. With the former, who received whole-body irradiation, oropharyngeal lesions occurred on all mucous membranes but were more prevalent on lymphoid areas than elsewhere [O5]. The tonsils, pharynx, nasal passages and tongue were frequently involved. The lesions were concomitant in many cases with epilation and purpura. The time of onset varied from a few days to five weeks, with a peak in the fourth week and a mean of 22 days. The initial symptoms were pain in the throat or gums associated with swelling and inflammation. This rapidly progressed to bleeding, ulceration and, in many cases necrosis. Ten per cent of survivors had severe ulceration. Healing was generally completed in 2-3 weeks,

with the lymphoid areas being the last to heal. Antibiotics greatly assisted healing [O5]. Necrotic gingivitis occurred in 10% of the 20-day survivors with oropharyngeal lesions in Hiroshima and in 6% in Nagasaki [O5]. This was characterized by redness, swelling and haemorrhage, and there was ulceration of the gums in fatal cases. Healing occurred slowly by re-epithelialization. The doses needed to precipitate these lesions are not accurately known, but are approximately in the range that cause epilation, purpura and some deaths, i.e., 3-5 Gy.

76. Injury to the mucosa of the mouth and throat is greatest in the cheeks, soft palate and hypoglossal area; it is less in the gums, hard palate, nose, posterior wall of the throat and tongue. Other areas, including the larynx, are less responsive [P12]. After local irradiation, accidental or radiotherapeutic, with doses of 5-10 Gy, hyperemia appears on day 1 and spreads to nearly all sections of the oral and nasal cavities. By day 4-5 there is oedema in the posterior wall of the throat, in the soft palate and the mucosa of the cheeks and nose, with pain in the mouth. These effects become more marked by day 10-15 and spread to the gums, tongue, and the hard palate. If there is necrosis, it appears at 8-12 days, followed by re-epithelialization. Recovery of the mucosal surfaces after doses up to 10 Gy occurs by 2-3 weeks after irradiation. After doses of 10-20 Gy, erythema extends to the larynx, there is virtually no latent period, there is pain and oedema in the mouth, and extensive mucosal necrosis begins on day 4-5. The recovery of the mucosa is slow and lasts for 1.5-2 months. Infectious complications occur together with local haemorrhages, and the effects are severe if there is also leukopenia [B36, G14, K7, K8, V13, V14]. Oral mucositis was noted at 5-7 days after whole-body irradiation of leukaemic patients (about 10 Gy, 0.05 Gy per minute) [D17].

77. Salivary glands are very responsive to irradiation, but recovery is possible even after high (fractionated) doses. Parotitis was observed after the Chernobyl accident, predominantly in those individuals receiving more than 6 Gy (see Appendix). This was coupled with an inability to salivate and a high level of amylase in the blood from day 1 to day 4 after irradiation. Studies in monkeys have shown that these effects in salivary glands are due largely to the high sensitivity of the serous cells, which undergo rapid interphase death after irradiation [S32]. In man there is also a loss of taste, experienced after doses as low as 2.4-4.0 Gy [C49]. In patients given daily radiotherapy, a 50% reduction in parotid gland secretion was noted at 24 hours after the first dose of 2.25 Gy, and the secretion was at negligible levels 24 hours after a second dose of the same amount [S45]. This effect was coupled with a transient tenderness and swelling of the glands, which was more severe after high doses. Doses of 15-28 Gy produced a dry mouth at 2.5 hours, on average, and pain and tenderness at 4.5 hours, reaching a maximum between 12 and 24 hours [K20]. The symptoms disappeared by seven days. In leukaemic patients treated with whole-body doses of 6-10 Gy, parotitis occurred in many cases about eight hours after the start of irradiation, and it persisted to 2-3 days [B32, D17].

3. Eye

78. The effects of low-LET radiation on the eyes of various species of mammal, including man, were reviewed by Merriam [M15] Information concerning early effects in man derive mainly from the treatment of eye tumours by radiotherapy, and they are summarized in Table 8. For the superficial ocular tissues (particularly the conjunctiva and cornea), 10-15 kVp x rays were used; in other cases, 120-250 kVp x rays were used. Eyelid skin appears to be more responsive to irradiation than skin at other sites, the minimal erythema dose for eyelid skin was quoted as about 2 Gy, with hyperemia of the skin observed after 12-15 hours. Single doses of 3 Gy produced slight hyperpigmentation, and doses of 4-6 Gy gave marked hyperpigmentation in a few weeks. A dose of 4-6 Gy led to hyperemia after 6-8 hours, oedema and haemorrhages on day 2 and erythema by 2-4 weeks in about 50% of cases. Partial epilation of the eyebrows and eyelashes can occur [Z1]. After 6-10 Gy there may be erythema after 1-3 hours, together with oedema and pain. Partial epilation of eyebrows and eyelashes may persist for a few weeks, the eyelid skin becomes dry and atrophic, and telangiectasia develops. Necrotic changes in the eyelid skin and underlying tissues occur at doses above 10 Gy. After 4-10 Gy, keratitis is observed at days 20-40 in the upper epithelial layer of the conjunctiva. After 15-20 Gy, there is lacrymation and pain in the eyes, with irritation of the cornea and the iris. In the absence of infections these may last for three to four months.

79. A decrease in tear production was noted in leukaemic patients following whole-body irradiation (about 10 Gy, 0.05 Gy per minute) [D17]. The Japanese fishermen who received whole-body doses of 2-7 Gy and much higher surface doses from radioactive ash after the nuclear test explosion at Bikini developed acute keratoconjunctivitis by two weeks after irradiation [K4].

4. Lung

80. The pathogenesis of radiation injury to the lungs has been described by several authors [W4, V1, P5], and the radiobiology of the lungs has been discussed in [T32, U4]. The target cell population responsible for pneumonitis after irradiation remains unknown, but type-2 alveolar cells are implicated and vascular injury may be contributory [D26, T27].

81. After the thymus, the lung is the most radiosensitive organ in the thorax Because lung tissue has a lower density than other soft tissue, a nominal 8 Gy corresponds to doses 8-15% higher to lung tissue using cobalt-60 gamma rays and 5-8% higher using 8 MV x rays [M9]. Hence 8 Gy becomes 8.6-9.2 Gy (cobalt-60) or 8.4-8.6 Gy (8 MV). The earliest signs of radiation injury in the lungs are oedema and changes in blood circulation followed by pneumonitis, which appears after a latent period of 1-3 months after doses greater than about 8 Gy. After whole-body irradiation with such doses, marrow failure may intervene before severe signs of lung injury appear, unless successful

marrow transplantation is performed. In some of the Chernobyl accident cases receiving the highest whole-body doses, the terminal period was characterized by the development of pneumonitis and pronounced respiratory insufficiency [U6]. Also, lung injury develops after high doses when the lower half of the body is shielded, as in the half-body treatment of lung metastases by radiotherapy [F12, V3].

82. Threshold doses and dose-incidence relationships for pneumonitis can be deduced from whole-body radiotherapy treatments of leukaemia prior to marrow transplantation, or half-body treatments for metastases. The effects are variously confounded by the concomitant use of cytotoxic drugs, e.g., cyclophosphamide. A survey was made of 15 centres in Europe giving whole-body irradiation before marrow transplantation to a total of about 400 patients [B32]. The dose rates ranged from 0.025 to 0.35 Gy per minute, and the lung doses from 6 to 10.5 Gy. The incidence of pneumonitis increased above 8 Gy and was dependent on the dose rate. Included in this survey were patients from the Royal Marsden Hospital in London, and a separate report described 107 of these patients with acute leukaemia given whole-body irradiation resulting in 9.1-10.5 Gy to the lungs at a dose rate of 0.025 Gy per minute. Eleven (10.3%) developed interstitial pneumonitis and five (5%) died of it [B49]. Sixty of them were irradiated and received a bone marrow transplant when they were in their first remission, and they were considered to be in a good clinical condition.

83. Irradiation to the upper half of the body was given to 245 patients for the palliation of disseminated cancer [F12]. The dose rates ranged from 0.5 to 4.0 Gy per minute. The results of these treatments, together with those given to a further 58 patients, were analysed subsequently in terms of corrected doses to the lung. Patients with significant previous and subsequent lung irradiation, with previous lung disease or with known tumour masses in the lung were excluded

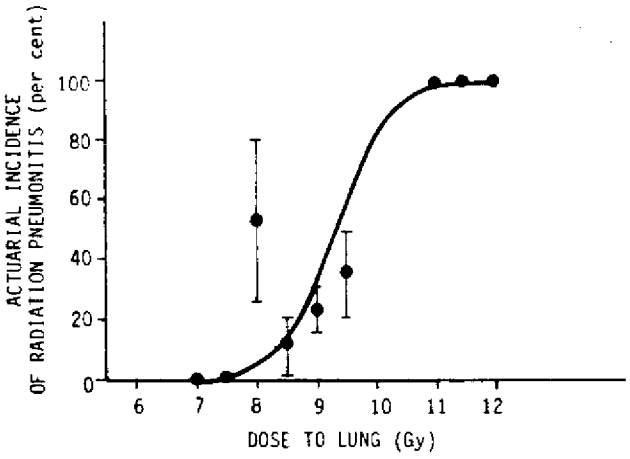

Figure XV. Incidence of pneumonitis versus dose to lung in man. Best fit sigmoidal complication curve using probit regression analysis. The point to the left of the curve was based on only four patients and hence has a large uncertainty. Based on patients excluding significant additional irradiation, previous lung disease, carcinoma in lung. Standard deviations do not apply for 0% or 100% incidence.
[V3]

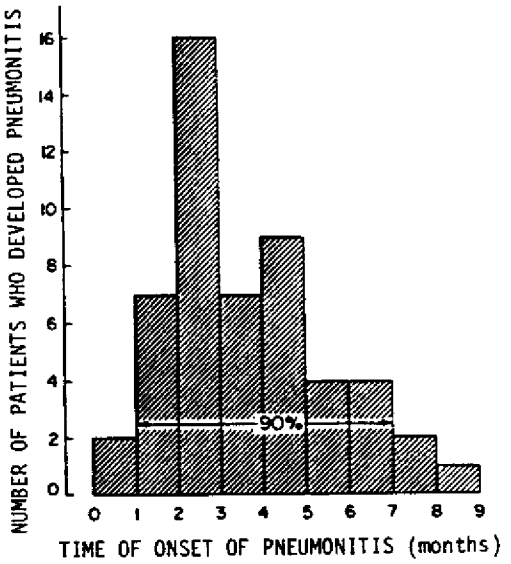

Figure XVI. The frequency distribution of the time of onset of radiation pneumonitis for 52 patients who developed the complication.
[V3]

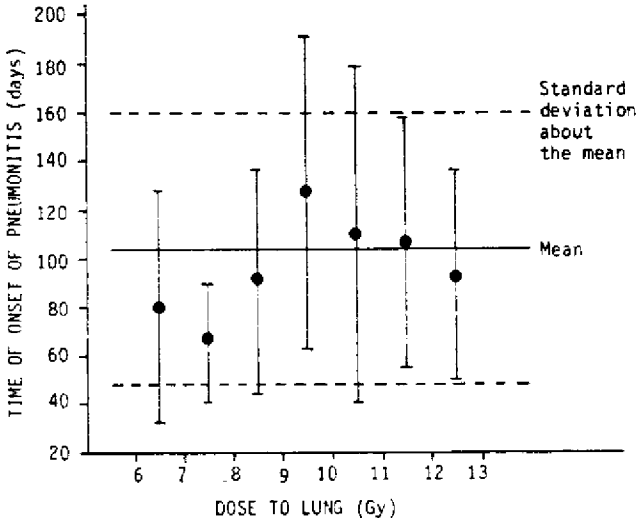

Figure XVII. Time of onset of radiation pneumonitis versus dose to the lung for 52 patients who developed radiation pneumonitis. Error bars represent standard deviations.
[V3]

from the analysis. A dose-incidence relationship for pneumonitis was presented by Van Dyk et al. [V3]. The doses to lung tissue needed to produce pneumonitis in 5% and 50%, respectively, of the cases were about 8.2 Gy and 9.5 Gy (Figure XV). The steepness of the dose-response curve could be interpreted by a D_0 value of ~ 0.6 Gy for the unknown target cells responsible for pneumonitis [T32]. The dose-incidence data are in agreement with other data for upper half-body irradiation [S17], where an incidence of pneumonitis of 10-20% was observed after lung doses estimated to have averaged 8.8 Gy [V3]. The frequency distribution of the time of onset of pneumonitis in 52 patients who developed the signs is shown in

Figure XVI: in about 90% of these patients pneumonitis appeared between one and seven months. Figure XVII shows that the time of onset was not significantly dose-dependent between 6.5 and 12.5 Gy, but this may reflect the limited sample size. Other data for humans [S17] and dogs [M40] indicate a decrease in latency interval with an increase in the dose. Lung fibrosis begins to develop at the end of the pneumonitis phase after high doses.

5. Testis

84 The kinetics of spermatogenesis in different species have been described by Bianchi [B11], and the information available on the kinetics of spermatogenesis in unirradiated man is summarized in Table 9. The testis is very responsive to radiation because the early differentiating forms of spermatogonia are extremely radiosensitive [B11, U4]. Spermatogonial cell necrosis can be detected in man at 4-6 hours after local testicular irradiation, with loss of these cells by 12 hours [H8]. The more mature cells composing the second and third phases of spermatogenesis (from preleptotene spermatocytes through meiosis and including the spermatids) are unaffected by doses below 3 Gy. These cells mature normally after such doses, and they therefore maintain the normal sperm count for about 46 days, which is the time of development from preleptotene spermatocyte to spermatozoa. The sperm count begins to drop after 46 days, approaching azoospermia at about 10 weeks after doses greater than 1.0 Gy (Table 10) Oligospermia is induced by lower doses down to 0.15 Gy The sperm count drops earlier after doses between 1 and 4 Gy, when the spermatids also become affected. Below 3 Gy, there are no morphological alterations in the spermatozoa. Changes in sperm count at various times after different x-ray doses are shown in Figure XVIII [H8].

85. Concomitantly with the histological changes, changes in testicular hormone levels are also observed. Plasma and urinary levels of follicle-stimulating hormone increase after doses to the testis of greater than 0.1 Gy [R11], and the increase after 0.75-6 Gy may be as much as four times over the control level. Plasma levels, but not urinary levels, of luteinizing hormone are elevated after doses greater than 0.2 Gy, and the levels may be two times higher than the pre-irradiation value after 6 Gy. The levels of urinary oestrogen, urinary testosterone and plasma testosterone are not changed significantly.

86. In mice, there is a correlation between the level of stem cell killing, the sperm count at a fixed time of recovery after irradiation, the final plateau level of recovery and the length of the infertile period [M46]. In man also, the spermatogonial stem cell is considered to be the target for long-term sterility [M46]. Doses inducing temporary or prolonged sterility in men have been reviewed by UNSCEAR [U4] and ICRP [I9]. Acute doses of up to about 4 Gy cause temporary or prolonged sterility in some men [G4, H27, H29, O1]. Higher doses may cause permanent sterility, and the dose inducing permanent sterility in 100% of men is greater than 6 Gy (Table 10). After 6 Gy, long-term histological recovery has been reported at 7.5 months, with sperm appearing in seminal fluid at 24 months [R11] The number of Leydig cells increased 90 days after 6 Gy [R11].

87. The few data for accidental exposures of the testis are consistent with the above controlled study by Rowley et al. [R11]. The acute accidents include two men who received estimated doses of 1.7 Gy and 1.8 Gy [H6]; one man who received about 3.9 Gy of mixed neutrons and gamma rays [O1]; one man who received 0.6-1.0 Gy to the testis from iridium-192 gamma rays [R7]; and 23 Japanese fishermen who received doses of 2-7 Gy over two weeks (1.5-4.5 Gy in the first day) after the nuclear explosion on Bikini Atoll in 1954 [K4].

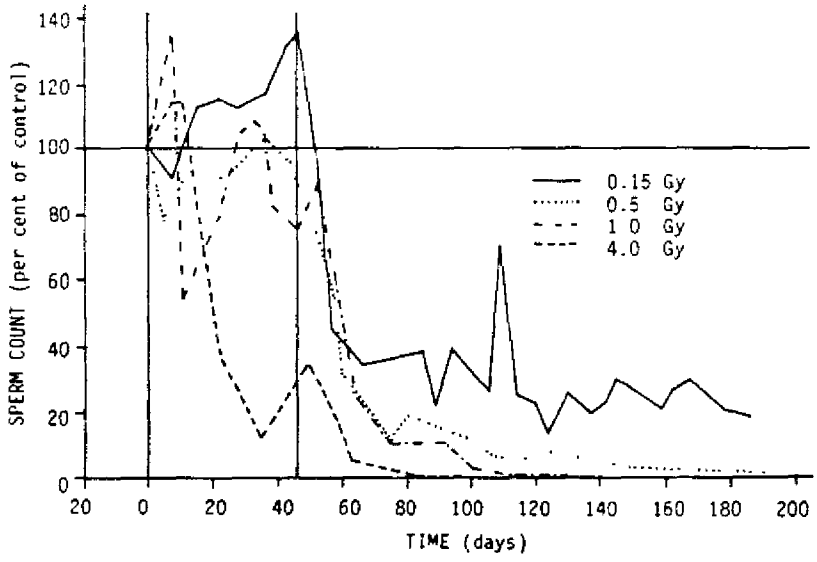

Figure XVIII. Time course of sperm-counts of normal men following exposure to various doses of 190 kVp x rays.
[H8]

6. Ovary

88 There are a total of about 2 million germ cells in the human ovary at birth, of which 50% are atretic (degenerating) [B2, B4, K3]. The mean number of follicles declines from an average of 382,000 at age 12-16 years, to 150,000 at 18-24 years, 59,000 at 25-31 years and 8,300 at 40-44 years [B14]. This decline is due to atresia since only about 400 oocytes are ovulated during a reproductive lifetime of about 35 years [B4]. Germ cells killed by radiation become pycnotic and are removed by phagocytosis within a few days. Primordial oocytes are more resistant than oocytes in growing follicles [B3]. The germ-cell content and the radiosensitivity of the ovary in different species were reviewed in the UNSCEAR 1982 Report [U4] and by Bianchi [B11].

89. Observations on ovaries and ovarian functions come from patients treated locally in the past with low doses of radiation to the ovaries to treat infertility, higher doses to induce an artificial menopause, and doses delivered incidentally during the treatment of abdominal tumours. Doses inducing temporary or permanent sterility in women were reviewed by UNSCEAR [U4] and ICRP [I9] Acute doses of up to about 4 Gy cause temporary sterility in some women, and doses of 3 Gy up to 10 Gy cause permanent sterility in an increasing proportion of women [G4, L1, P2, P3]. Older women are more susceptible, probably because the number of follicles decreases with age.