ANNEX G

Early effects in man of high doses of radiation

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APPENDIX

ACUTE RADIATION EFFECTS IN VICTIMS OF THE CHERNOBYL NUCLEAR POWER PLANT ACCIDENT

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Introduction

1. A review of the early somatic effects of radiation in man was published in the UNSCEAR 1962 Report [U1]. This was supplemented in the UNSCEAR 1969 Report by two Annexes, one on radiation-induced chromosome aberrations, the other on the action of radiation on the nervous system [U2], and in the UNSCEAR 1972 Report [U3] by an Annex on the radiation response of the immunological system. The effects of high radiation doses in man were recently re-addressed in part in the UNSCEAR 1982 Report [U4]. Annex J, which dealt with non-stochastic effects resulting from localized irradiation of single organs or tissues.

2. In this Annex the Committee reviews data on the early effects of high doses of radiation delivered to the whole human body. There is continuing interest in the effects of whole-body irradiation because of the persistent possibilities of exposure in accidents or from acts of warfare. Whole-body irradiation is also being used in the treatment of disseminated malignancies. However, reliable quantitative data in this field are very limited. They are drawn essentially from isolated accidental exposures, from information gathered on the Japanese population exposed to radiation from the atomic bombs exploded in the Second World War, and from experience with groups of patients receiving whole-body irradiation for cancer or prior to the transplantation of organs.

3. This Annex reviews data on the effects occurring in man within 2-3 months of whole-body doses of more than approximately 1 Gy of low linear energy transfer (LET) radiation or biologically equivalent doses of other radiation types. However, it also includes mention, in some cases, of doses down to 0.5 Gy, of protracted exposures resulting in the same levels of effect as acute doses, and of exposure to internal emitters where the doses were sufficient to have serious effects within 2-3 months. Gaps in the knowledge for man are filled partially by information derived from experimental work with mammals, particularly those with a body size approaching that of man; in general, however, large-animal data are intended to be used for interpretation of responses rather than for extrapolation. Exposures of the whole body resulting in doses to different regions that vary by less than 10%, apply mainly to treatments in radiotherapy. In accidents or in acts of warfare, whole-body doses usually are highly non-uniform (for example unilateral), with the variation in dose from low-LET radiation by a factor of 2 to 3, and from neutrons up to a factor of 10 or more (see, for example, Figure XIX). In these cases, the dose at the midline of the body may bear little relationship to the signs of injury.

4. Many accidents and some oncological treatments involve irradiation of large regions of the body, for example the trunk or the chest. In these cases the doses to specific target organs will determine the response of the individual. The response may differ from that of the same organ exposed to the same dose from irradiation of the whole body, if there are contributions to the expression of injury in the organ from other irradiated tissues, for example granulocytopenia exacerbating intestinal injury.

5. Much information was gathered from the Japanese exposed to the atomic bombs in the Second World War. However, at distances from the hypocentre where doses received were a few Gy, there were also heat and mechanical injuries. Furthermore, the radiation doses received by these individuals remain somewhat uncertain, and recent calculations suggest that the contribution to the dose from neutrons was much less than considered in previous (T65D) estimates of dose. Other groups of individuals exposed to high doses of nuclear fallout radiation were the Marshall Islanders and 23 Japanese fishermen exposed to the nuclear explosions on Bikini Atoll in 1954. These groups received comparatively uniform external gamma-irradiation. beta-irradiation of the skin and internal irradiation. Groups of individuals irradiated with high doses to the whole body in accidents included those at Oak Ridge, United States (the group is widely referred to as "Y-12"), at Vinca, Yugoslavia, in 1958, in China in 1963, in Algeria in 1978, in Morocco in 1985, at Chernobyl, USSR, in 1986, and in Brazil in 1987.

6. When this Annex was approaching completion, important information on the subject became available in connection with the nuclear accident that occurred at the power plant in Chernobyl, USSR, where about 100 people were exposed to external and internal irradiation amounting to 1 Gy or more. The delegation from the USSR has made available especially to UNSCEAR a report on the data gathered in the wake of the accident. The Committee wishes to
acknowledge with gratitude this important contribution. Since time was too short for a definitive study of the data collected and for their incorporation into the text of this Annex, the Committee decided to present them as an Appendix.

7. Clinical data relate to the use of radiation delivered to the whole body to suppress the immune system prior to organ transplantation, to control multiple or systemic metastases from solid tumours, and to treat leukaemia. Although the radiation doses are known accurately for these patients, their responses to these treatments may be confounded to an uncertain extent by debility and disease, by the prior or concomitant use, in many cases, of cytotoxic or immunosuppressive drugs and by different degrees of medical treatment after irradiation.

8. Most of the doses quoted in the literature reviewed in this Annex were given in rad, or in terms of exposure, roentgen (R). As in the UNSCEAR 1982 Report [U4], 100 R of exposure will be taken to be equivalent to 1 Gy absorbed dose in the case of small animals. For larger animals, the doses at depth for equivalent surface doses become progressively less, and this depends on the radiation quality. Doses in the literature are quoted either as surface doses or, more commonly, as midline tissue doses. Conversions will be made where necessary to allow these doses to be expressed in terms of dose in the target tissue under consideration.

9. This Annex is intended to be a scientific compendium on the early effects of radiation in man. It is not meant to be a manual on the care and treatment of irradiated persons, although the information it contains is relevant to evaluating the radiological health consequences of accidents or acts of warfare and the effects of radiotherapy.

1. PATHOGENESIS AND DOSE-RESPONSE RELATIONSHIPS

A. CELLULAR EFFECTS

10. The cellular effects that are important in the response of tissues to irradiation have been described and discussed previously by the Committee [U4]. The severest injuries from radiation in most early-responding tissues are caused by a loss of cells. This results either from death of cells in interphase, as in the case of lymphocytes or, more commonly, from killing of progenitor cells at mitosis, which leads to a lack of replacement of mature cells lost through natural senescence and death. Most mature cells are radio-resistant because they divide only occasionally or not at all. In “flexible” type cell populations in tissues such as the liver, the low rate of division of the mature functional cells can be increased, e.g., by partial hepatectomy, and in this case the cells may appear radiosensitive. In the renewing “hierarchical” type tissues [P25] which are specifically discussed in this Annex, such as the bone marrow, gastrointestinal mucosa, epidermis and testis, the maturing and mature cells are resistant because they have, respectively, little or no mitotic potential. In contrast, their progenitor cells have the potential for many divisions and may die from mitotic death. The probability of mitotic death of a cell is a function of the dose and of the number of divisions a cell has undergone since irradiation. After doses up to 6 Gy, irradiated cells have a high probability of completing one division successfully, but a much lower probability of completing six divisions [H41]. Cells that successfully complete six divisions or more can form colonies of more than 50 cells and generally are capable of many more divisions if the cells remain undifferentiated. These colony-forming cells are vitally important for the repopulation of many early-responding tissues (see below).

11. The dose-response curve for the survival of these cells in some tissues (skin, intestine) shows a relatively low sensitivity to doses up to 1 or 2 Gy, followed by an increasing sensitivity at higher doses. The sensitivity to high doses can be approximated to an exponential curve, which is expected due to the stochastic nature of radiation action [18, T24, U4]. This is characterized by the parameter D₀, which is the dose required to reduce survival by a factor 1/e on the exponential portion of the survival curve. Other associated parameters are the size of the “shoulder” region, which is characterized by the intercept of the exponential survival curve on the linear dose axis, Dₐ, or on the logarithmic survival axis, n, of a semi-logarithmic plot. These are related by Dₐ = D₀ ln n. Survival parameters measured for various human clonogenic cells assayed in primary culture are given in Table 1. Cells that die by interphase death are often very radiosensitive, e.g., lymphocytes [W26], and this increases the overall range of sensitivities. Alternatively, the shape can be described by a continuously bending curve when log survival, S, is plotted against dose, D, where

\[ S = \exp(-aD + \beta D^2) \]

In this case a is the parameter describing the initial sensitivity, and the sensitivity increases at higher doses depending on the value of β and the dose. This formulation is generally considered to represent better the response of cells to fractionated exposures than formulations based on D₀ [T24].

12. The response of cells in vitro to single doses of radiation, in terms of their colony-forming ability, can be modified by a delay after radiation and before the cells are induced to proliferate. This time interval allows repair of potentially lethal injury to occur, such that more cells retain their colony-forming ability. This type of repair is likely to be important in the recovery of tissues after irradiation. The amount of repair in the tissues under consideration in this Annex will be smaller than in late-responding tissues, where the rates of cell division are lower and remain low for long periods of time after irradiation so that more repair can occur. In the normal tissues of rodents, where repair of potentially lethal damage has been investigated in vivo, the effect generally does not change the D₀ value but it increases all levels of survival on the exponential portion of the curve by factors of about 5 for mammary epithelium [G6], and
about 3 for thyroid epithelium [M24] and hepatocytes [15]. Other data for hepatocytes show an increase in $D_4$ [F11]. In bone marrow the opposite effect is observed; namely, a decrease in survival by a factor of 2, which could be due to radiation-induced differentiation [H11], specific for this cell type. The increase in survival observed for most tissues and attributable to repair of potentially lethal damage shows a peak in survival level by about 4 hours which remains unchanged at 24 hours. Studies using assays in vitro have revealed a time-related increase in $D_4$ for mouse lung cells and kidney cells [U4]. With the latter, the effect observed at 8 hours disappeared by 24 hours. The effects of protracted doses are discussed in chapter III.

13. The earliest effects on irradiated cells are not mediated through mitotic death but are connected usually with membrane integrity. Examples of such early phenomena are the effect on cells comprising the autonomic nervous system that leads to the symptoms and signs of the prodromal syndrome, the interphase cell death characteristic of certain lymphocytes [Y5] and salivary gland cells [S32] and blood vessel injury associated with acute erythema [P28]. When cells are not killed after low doses, membrane injury is generally recoverable. After high doses, these acute effects are often prognostic for later more serious injuries which develop as a consequence of subsequent cell death in other cell populations.

B. TISSUE EFFECTS

14. The majority of the tissues that respond early after irradiation are hierarchical in structure [P25]. In these, mature cells are replenished from proliferative cells by division, differentiation and maturation. The proliferative cells committed to differentiation are produced by very few ancestral stem cells, which are capable of self-renewal and of differentiation (Figure I). Under normal steady-state conditions, the rate of loss of mature cells is equal to the rate of their production.

15. Clinical signs of injury will occur when the loss of mature cells has reached a critical level in any particular tissue. The loss may be induced directly in the mature cell population, as in the case of lymphopenia. Alternatively, it may occur gradually at a rate governed by the natural lifetime of the mature cells when their numbers are not replenished because their precursors are sterilized, as in intestinal mucosa [M16, P25]. In the intestine, the rate of loss may be exacerbated by other factors, such as bacterial infection, which can modify the normal rate of turnover of the cells [M5]. Also, there may be a variable lag period between the time the critical level is reached and the time of failure of the tissue or death: an example is death due to bacteremia and electrolyte losses which follow cellular depletion in the intestinal mucosa.

16. Effects that are characterized by a threshold dose and by a severity that increases with increasing dose are called non-stochastic effects [9, U4]. Threshold doses for relatively minor effects are generally smaller than those for severe tissue injury. The time for the maximum effect is also usually dependent on the dose, occurring earlier after higher doses. When doses are relatively low and not all stem cells are killed, tissue injury is followed by recovery mediated through repopulation and differentiation of the precursor cells. The stem cells reproduce themselves and they also differentiate into precursor cells which divide and amplify the number of repopulating cells. After several or many divisions, these “transit” cells mature into the functional cells in the tissue. The time course of repopulation of the mature cells depends therefore on the rate of differentiation of the stem cells, the number of amplifying cell divisions and the cell cycle times [B16, M16, P25].

17. After doses higher than about 10 Gy, where virtually all cells in hierarchical tissues are sterilized, the time required for ablation of the mature and functional cell population is independent of dose, and in many cases it approximates the normal transit time
from one of the lesser differentiated precursor cells to maturity [M16, P8]. For the few non-hierarchical tissues that respond relatively early after irradiation, such as the lung, the latency interval from irradiation to failure may indeed be dependent on dose after fairly high doses before a plateau in latency is reached [M16].

18. After intermediate doses, where most cells in hierarchical tissues are sterilized, the small number of surviving cells in a given tissue type will vary markedly from one animal to another, for the same dose; this results from the stochastic nature of radiation in killing cells, which follows a Poisson distribution. It may be expected that in some cases the number of surviving cells necessary for regeneration of the tissue will have fallen below a critical number, and it may also be expected that the incidence of such cases is dose-dependent [H12, T24]. This allows the construction of dose-incidence curves for particular levels of effect in tissues, e.g., tissue or organ failure, or death of animals, as shown in Figure II.

19. The incidence of a given level of injury is usually related in a sigmoid fashion to the dose. Many empirical distributions have been tested for their goodness-of-fit to a large number of dose-incidence curves for marrow failure in various species, and overall the logistic and probit models were the best representations of the data [M48]. The probit model is based on the normal (Gaussian) distribution [U4, 18]. The 50% incidence level may be estimated most accurately. The slope of the curve, characterized by the standard deviation of the distribution (commonly called the probit width), is a measure of the variation in response among individuals in the population at risk. The dose for 50% incidence of lethality (LD_{50}) or other effects (ED_{50}) and the probit width (c) are the two parameters commonly used to describe the shape of the curve (Figure II; see also other examples in Figures XXI and XXII).

20. Three main sources of variation may contribute to the probit width [H12]. First, there is the Poisson distribution of lethal events among the critical cells at risk. The probit width generally is not less than the D_{50} value for the target cells (which may be in sensitive or resistant phases at the time of irradiation), and in those systems that the Poisson distribution adequately describes event frequencies, the probit width is empirically about 1.2 D_{50} [L3]. Second, there is the variation in sensitivity, 1/D_{50}, between cells in different individuals. Third, there is the variation in dose delivered to different individuals. This last source of variation may relate to the distance from the source or, in some situations, variations in the shielding of parts of the body. In cases where the first source of variation predominates, a Poisson model can be used to construct a dose-mortality relationship, and this is not markedly different in shape from a Gaussian curve over the range of mortalities measured from about 5% to 95% [L3]. Conversely, a lower limit to the sensitivity of the target cells can be deduced from a mathematical transformation of the mortality probabilities versus dose [G3].

C. THE RADIATION SYNDROMES

21. The lethal effects of radiation in animals reflect failure of particular organs. These fail after different periods of time, related to the underlying cell kinetics (see section 1.B). There is a latency period before the development of injury, and following the expression of injury there may be a recovery phase, depending on the dose. The temporal sequence of events is characterized by a combination of symptoms and signs (a syndrome). Radiation syndromes in man have been discussed in a number of publications [e.g., A16, B31, C36, C41, G26, L22, T23, U1, U4, U9, W13, Y7].

22. Different organs fail over different ranges of dose. The response of an organ is due primarily to the dose it receives, but this can be modified by effects in other irradiated organs: for example, granulocytopenia allows the development of bacterial invasion following epithelial loss in the irradiated gut. These additional features will change the incidence of mortality as a function of increasing dose by an amount that depends on the target tissue at risk and the particular confounding effects applicable.

23. In studies using groups of animals belonging to different mammalian species, the pattern of mortality versus acute dose can be delineated into a series of typical syndromes; namely, the bone marrow syndrome,
the gastrointestinal syndrome and the neurological (or neurovascular) syndrome. Representative data for animals are shown in Figure III. Doses (Gy) are quoted as approximate maximum tissue doses. With mice and monkeys, doses in the target tissues, i.e., marrow, intestine and CNS, probably are within 10% of these doses. With swine and goats, doses in the marrow and intestine may be less than the quoted doses by slightly more than 10%; for swine, this figure may be about 20% for bone marrow and could be up to 30-40% for the intestine if the dose in the middle of the abdomen is the most relevant dose. The percentage for goats is uncertain, as the irradiation was unilateral using mixed gamma rays and neutrons. Man is expected to conform to a similar pattern of response versus dose (dotted curve, Figure III). Figure III shows that in the interval of dose from roughly 2 to 10 Gy, where the bone marrow syndrome occurs, survival time decreases with increasing dose; survival time remains relatively constant between roughly 10 to 50 Gy, where the intestinal syndrome prevails; at still higher doses, the neurological syndrome becomes predominant and over this interval survival time again becomes very dependent on dose. It should, however, be emphasized that the syndromes are idealized clinical pictures, which are difficult to distinguish in practice, particularly when the inhomogeneities in dose are very pronounced and when injury from other causes is present [B57, W28, W29].

I. The prodromal phase

24. The prodromal phase comprises the symptoms and signs appearing in the first 48 hours post-irradiation [C36, G2]. After supralethal doses of several tens of Gy, all individuals begin to show all symptoms characteristic of this phase within five to 15 minutes. The reaction is mediated through the response of the autonomic nervous system and is expressed as gastrointestinal and neuromuscular symptoms. The former symptoms are anorexia, nausea, vomiting, diarrhoea, intestinal cramps, salivation and dehydration. The neuromuscular symptoms are fatigue, apathy, listlessness, sweating, fever, headache and hypotension, followed by hypotensive shock. The reaction after high doses is maximal within 30 minutes, then diminishing until it merges closely with the neurological syndrome or, later, with the gastrointestinal syndrome. Leukaemic patients given 10 Gy to the whole body at 0.05 Gy per minute in many cases had a fever, occasionally associated with chills at the end of irradiation, but they were usually afebrile by 24 hours [D17]. After lower doses, the symptoms are delayed, fewer and less severe, comprising mainly anorexia, nausea, vomiting and fatigue. Vomiting is infrequent after doses below 1 Gy [B32, D9, L8]. The responses can be produced by separate irradiation of the head, thorax or abdomen, the last being the most sensitive region [G2]. Also, the region below the umbilicus is less responsive than the region above it, as shown by prodromal responses in cancer patients receiving half-body irradiation at 3-10 Gy [F18]. In monkeys, vomiting is suppressed during incapacitation after high doses [M29].

25. Mechanisms of radiation-induced nausea and vomiting have been discussed [H34, Y3]. The neural control mechanism for emesis is located in two distinct regions of the medulla oblongata: the area postrema containing the chemoreceptor trigger zone
(CTZ) and the vomiting centre [B34]. The latter is the final pathway for emesis, whether the signal originates from the gastrointestinal tract or the CTZ. Ablation of the CTZ eliminates prodromal vomiting in the dog, monkey and man. Small peptides are implicated as mediators of emesis [C23]. Inflammatory processes could be involved in post-irradiation vomiting, as suggested by the success of anti-inflammatory agents in controlling emesis in animals [H30] and in patients receiving large-field or whole-body irradiation for radiotherapy [B32, S17].

26. Attempts have been made to define dose-response relationships for the various signs and symptoms of the prodromal phase. This has been done for casualties of the atomic bombs [O5], nuclear accident victims and cancer patients receiving therapeutic whole-body radiation [M18, L10]. The most comprehensive studies with cancer patients involved 504 individuals irradiated at various hospitals in the United States and Canada [L8]. The observations were corrected for the natural incidence of between 8% and 19% of non-radiologically induced symptoms. ED_{10} values (effective dose for a given response in 50% of the irradiated individuals) for various prodromal symptoms occurring within 48 hours are given in Table 2. Higher doses were required to elicit responses within 12 hours rather than within 48 hours, and after lethal doses the onset of vomiting in 100 patients was calculated to be greatest about two hours after irradiation [L4]. After very low doses, the peak incidence of nausea and/or vomiting, if these symptoms occurred, was calculated to be approximately 6 hours after exposure [G2]. An approximate relationship between the time of onset of prodromal symptoms and dose is shown in Figure IV. A comparison of ED_{10} values for patients not showing signs of illness before irradiation and ED_{10} values for all patients showed that the values for the former were only slightly greater than for the latter, suggesting that illness did not markedly predispose to greater responsiveness to prodromal symptoms. This was also indicated by the similarity in the dose-incidence relationship for vomiting, when the clinical data were compared with those for 45 healthy individuals who were separated into four average dose groups (label 2 in Figure V) [L4, U5]. The start of the prodromal reaction in people suffering from the bone marrow syndrome coincides satisfactorily with the data in Figure IV.

27. In relatively healthy Ewing's sarcoma patients treated with whole-body irradiation [M34, R6], prodromal symptoms were observed in all those receiving 3 Gy, but not in those receiving 0.5-2.2 Gy. With whole-body irradiation of leukaemic patients using 10 Gy to the midline delivered at 0.05 Gy per minute, nausea and vomiting began after 3-4 Gy had been given [T19, T20]. These patients were treated with high-dose cyclophosphamide during the week preceding irradiation, and they received sedation with barbiturates and chlorpromazine before irradiation. Vomiting after 3 Gy had been accumulated was also seen in another series of leukaemic patients given whole-body irradiation [B32]. Vomiting did not occur
followed by transient periods of depressed or enhanced motor activity leading to total incapacitation and death.

30. Histological studies on the brains of rhesus monkeys receiving 100 Gy showed perivascular infiltration, haemorrhages and oedema, reaching a peak at 8 hours after irradiation [V6]; necrosis of neurons was maximal at 24 hours, suggesting that vascular changes might be the initiating lesion in the brain.

31. A study of the brains of 49 casualties who died at various times greater than 6 days after the Hiroshima and Nagasaki bombings revealed pathological changes characteristic of perturbations in vascular permeability [S7]. In 10 patients surviving accidental gamma- and neutron-irradiation (average whole-body dose, 5-6 Gy; average head dose, 8-10 Gy), cerebral lesions (disturbances in the brain circulation of the blood and cerebrospinal fluid) were found soon after irradiation [K8]. In monkeys, irradiation of the head alone produces the CNS syndrome [C5]. One man receiving inhomogeneous whole-body irradiation, with a dose to the front of the head of about 100 Gy of mixed gamma and neutron radiation, died after 35 hours. The main neuropathological finding in the brain (mean dose of about 25 Gy) was severe oedema. The heart (dose of about 120 Gy) showed interstitial myocarditis, which was considered the primary cause of death in this particular case [S6]. The findings among the victims at Chernobyl, in connection with the neurological syndrome, are described in the Appendix.

32. High doses can result in severe cardiovascular dysfunction [H46]. For example, in two persons involved in criticality accidents, the inability to maintain systemic arterial blood pressure was considered the primary cause of death [S6, F17]. Also, in a study of cancer patients given half-body irradiation, two deaths were attributed to myocardial infarction after an acute hypertension episode during the first few hours postirradiation [S17].

33. Changes in sensory perceptions are also produced by high radiation doses. Reduction of tactile sensitivity and skin sensitivity has been reported in cases of accidental irradiation in the lethal range of doses [K8, S24].

3. The gastrointestinal syndrome

34. Animals receiving doses of between about 10 and 50 Gy die with signs of the gastrointestinal syndrome. The mean time to death after doses of about 50 Gy in various large species of animal varies between 3.5 and 9 days [B16]. The symptoms in man follow those of the prodomal phase, and include anorexia, increased lethargy, diarrhoea, infection, and loss of fluids and electrolytes. Other signs include weight loss, diminishing food and water intake, gastric retention and decreased intestinal absorption [B16, B56, G31]. The leucocyte count falls dramatically, and there may be haemorrhages and bacteraemia, which aggravate the injury and contribute to death after high doses and also after

earlier than 30 minutes after doses from 2.7 to 7.0 Gy. The effects were independent of dose rate above 0.06 Gy per minute.

28. Quite marked variations in responses are apparent between various small series of leukaemic patients irradiated similarly; this could be due to differences in the severity of their illnesses and in medications supplied. For example, only two out of eight patients with haematological malignancies vomited during irradiation with 10 Gy given at 0.05 Gy per minute. One of the two vomited after 5 Gy had been delivered and the other after 7 Gy had been delivered [C35]. Four out of seven ill cancer patients given about 1 Gy at 0.06 Gy per minute vomited, between 1 and 4.5 hours after irradiation, as did three out of four at 1.5-2.5 hours after about 1.3 Gy [L34]. Twenty-two out of 30 patients with various advanced cancers given 1.3 Gy at 0.02-0.05 Gy per minute experienced nausea but did not vomit [M18].

2. The neurological (neurovascular) syndrome

29. Doses higher than about 100 Gy to most mammalian species result in death from cerebrovascular injury within two days. Survival times are shorter for higher doses, and after 1,000 Gy most species survive only a few hours or less [B16]. The effects of radiation on the central nervous system (CNS) were reviewed in the UNSCEAR 1969 Report [U2]. The CNS syndrome is characterized by severe symptoms and signs of the prodomal syndrome,
lower doses where the gastrointestinal and bone marrow syndromes overlap.

35. The intestinal signs that follow the prodromal phase appear as a consequence of cell depletion of the intestinal lining, as described in detail in the UNSCEAR 1982 Report [U4]. The depletion is due to loss of reproductive capacity of the clonogenic cells in the crypts, so that the normal continuous flow of new cells on to the villi ceases. The hierarchy of cell populations in the intestinal mucosa is shown diagrammatically in Figure VI. The amount of cell sterilization is dependent on dose.

36. Histological specimens from individuals who died with signs of severe intestinal damage after irradiation from the atomic bombs in Japan revealed atypical epithelial cells, an oedematous and atrophic mucosa and petechiae, as well as ulcerative lesions after the seventh day [O5]. Similar histological findings were observed in monkeys dying 6-8 days after whole-body gamma-irradiation [W7]. In these monkeys the most prominent findings at necropsy were gastric and colonic ulcers, together with severe mucosal atrophy. The incidence of colonic ulceration was independent of dose over the range tested, 15-75 Gy, but the incidence of gastric ulceration increased with increasing dose. Gastric ulceration developed after the fourth day, predominantly in regions of the stomach richest in parietal cells.

37. The time course of events is almost independent of dose between 10 and 50 Gy but is very dependent on the species. The time course is correlated with the rate of loss of the intestinal cells covering the villi. For example, the development of the gastrointestinal syndrome is longer in germ-free than in conventionally housed mice, in which the villus transit time is shorter [M5, T26]. In man, the cell transit time on the villus is 3-4 days, as shown in Table 3, which summarizes kinetic data for the intestine. The time of death is also influenced by other concomitant factors, such as infection, haemorrhage and fluid loss. The dose range resulting in the gastrointestinal syndrome in man is unknown, but it is probably similar to that observed for large animals (see Figure III). Gastrointestinal signs were noted after whole-body irradiation of leukaemic patients prior to marrow transplantation, when the dose delivered at about 0.05 Gy per minute was increased to 12 Gy [D17].

38. The time to death can be deduced from the time course of the frequency of deaths following the atomic bombs in Japan. For a total of 757 documented deaths in Hiroshima and Nagasaki [O4], the time course of deaths showed two clear peaks in frequency, one between days 6 and 9 and the other between days 20 and 30 (Table 4). The first peak is attributed to the intestinal syndrome and the second to the bone marrow syndrome. One group of people dying at times around the first peak comprised 21 documented individuals who were in the Bankers Club in Hiroshima at the time of the explosion [O5]. Eight of them suffered radiation injury only and died at various times between 6 and 17 days after irradiation. On the fifth day after exposure, the leucocyte counts were below 500 per µl in five of the seven cases in the Bankers Club who died in the first week. The degree of anaemia was very variable. The sample in Table 4 is a very small proportion of the people that died after the bombing, and therefore selection procedures may have influenced the apparent distribution of deaths.

Figure VI. Diagrammatic representation of cell production in intestinal crypts, with new cells migrating on to the functional units, the villi.
(Adapted from [P29].)
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 [111]. 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 LD₅₀₅₀ 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 LD₅₀/₁⁰ or LD₅₀/₁₀₀ 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).

41. Animals die from marrow failure within 30 days after doses between about 2 Gy and 10 Gy, depending on the species. The LD₅₀/₁₀ 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 thrombocytopenia 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 LD₅₀ 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 LD₅₀ 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 LD₅₀/₁₀ and body weight for various mammals. (Modified from [U4, U5].)
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 foci 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 1). 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 4-11 10⁴ WBC/I for males and 4-9 for females; 4-6 10¹² RBC/I for males and 3.7-5 for females; 34-54% haematocrit for males and 33-48% for females; 130-176 g haemoglobin/I 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
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 values 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]](image-url)

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 [110] 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]](image-url)
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 concerned 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 ablative 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 radio-resistant 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 [TLL] 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 OKT8 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 [16, 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 S. 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]).

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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 x 10 cm² field on the median 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 cm² [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 D₀ = 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:

\[ Dose = k(\text{area})^{-0.16} \]
\[ Dose = k(\text{diameter})^{-0.33} \]

where \( k \) is a constant [C7, V8].

67. The extrapolation of the above formulae to areas greater than 400 cm² 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]](image-url)
penetrating electron beams for the treatment of diffuse diseases of the skin, and it is not known if these diseases predispose to increased radio-sensitivity. However, it has been concluded that there is little effect of changes in area for areas above 400 cm² [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 cm².

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 [16]. 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 cm² 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 lacrimation 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 6 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 [V6]. 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 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 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]
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 azoosperma at about 10 weeks after doses greater than 1.0 Gy (Table 10). Oligosperma 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].
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 pyknotic 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.

II. **DOSE-RESPONSE RELATIONSHIPS IN MAN**

A. **ACUTE DOSES**

1. The LD_{50/40}

90. For many purposes, particularly the planning of protection from accidental or other acute exposures to radiation, it is customary to think in terms of the probability of survival following a dose of radiation over the whole body. One would need to know the form of the dose-response relationship for death over a given time or, at least, the value of the 50% intercept of such a curve, which is most simply and reliably defined as the lethal dose for one half of the irradiated population (LD_{50}) over the given time; say, 30 days or 60 days (LD_{50/60} and LD_{50/30}, respectively). While the concept of LD_{50} is quite clear and widely applicable in experimental work, it is a difficult concept to apply in the context of human irradiation. For example, the final effects will always be modified to a greater or lesser extent, depending on the cause and the conditions of exposure by the nursing or therapeutic procedures applied after irradiation. These procedures will presumably increase the value of the LD_{50} relative to its value in the absence of such procedures. Also, the state of health of the irradiated human beings may not be representative of the average state of health in the population, at least not under all conditions of irradiation. For example, the exposure of patients will produce effects that may interact with the effects of the diseases requiring irradiation or with the effects of other forms of therapy, decreasing the value of the LD_{50} relative to its value for normal individuals. The exposure of nutritionally-deprived individuals, e.g., the Japanese in the Second World War, might also produce lower values of LD_{50}. Previous estimates of the LD_{50/40} are listed in Table 11, along with the factors that may increase or decrease it. Thus, when data from different groups are combined, the resulting values of the LD_{50} will, to different degrees, depart from the value obtained without complicating circumstances or treatments, and they will be affected by a variability larger than that applying theoretically to the LD_{50} of a normal human population. This variability will tend to lessen the slope of the overall dose-response curve.

91. Ideally, data on dose-mortality relationships should be derived from groups of individuals receiving doses homogeneous to within a few per cent. In practice, however, this condition is met only in the case of radiotherapy patients, and their response may be confounded by the underlying disease or by other cytotoxic treatments. In accidents, exposure is usually inhomogeneous, and this confounds the analysis of dose-effect relationships: for example, values of LD_{50/40} at the midline are 20% higher for unilateral than for bilateral irradiation of large animals. Most of the individuals irradiated by the atomic bombs in Japan received unilateral prompt exposure, accompanied by fallout irradiation, and some of them were partially shielded. The population of the Marshall Islands and the Japanese fishermen exposed in the 1954 nuclear test explosion received substantial but non-lethal doses of fallout irradiation, mainly in the first two days; they are probably the largest groups of healthy individuals exposed to near-homogeneous doses, albeit over a two-day period.

92. Doses quoted in the literature are usually those at the midline, and they depend to various extents on radiation quality. Some depth-dose curves for different types of radiation are given in Figure XIX. In that figure, the depth dose is shown as tissue/air ratio, which is defined for tissue dose versus kerma at the same point. It is, therefore, independent of the inverse-square law and dependent only on photon energy, depth in tissue and field size. The most relevant parameter for death following bone marrow failure is the marrow dose, and this is usually estimated as the mean dose in an annulus between 0 and 6 or 7 cm below the body surface. It corresponds to about 0.75-0.8 of the free-in-air tissue kerma for multilateral irradiation with 60Co or 137Cs gamma rays [15] (see Figure XX). The midline dose is about 10% less than the marrow dose for 60Co gamma rays, and the difference is greater for less penetrating radiations, e.g., for low-energy x-ray beams or neutrons (Figure XIX). Values of midline doses related to exposure for various radiation energies and species have been published [B6].

93. The form of the dose-mortality relationship for the LD_{50/40} in man is expected to follow approximately a normal (Gaussian) distribution. The relationship will be sigmoid on a linear plot of per cent mortality versus dose. There is a threshold region where doses