SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

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NOTE

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ANNEX G

Early effects in man of high doses of radiation

CONTENTS

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.

I. 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 radioresistant 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 [I8, T24, U4]. This is characterized by the parameter D_0, 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, D_q, or on the logarithmic survival axis, n, of a semi-logarithmic plot. These are related by $D_q = D_0 \ln n$. 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

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

In this case α 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 D_0 [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 D_0 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 [J5]. Other data for hepatocytes show an increase in D_0 [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_0 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 bacteraemia 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 [I9, 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

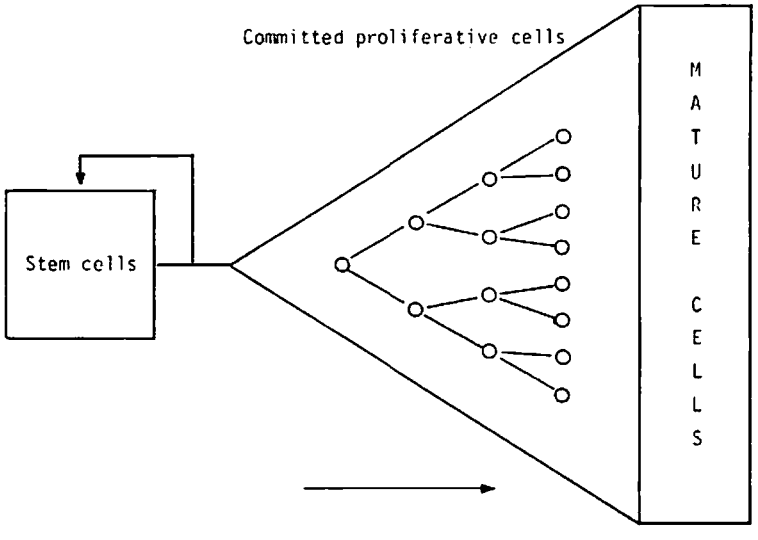


Figure I. Diagrammatic representation of cell population hierarchy where mature cells are produced from proliferative cells. The ancestors of the lineage are the stem cells which renew themselves (left arrow) and which also differentiate into various maturing cell lineages (right arrow).

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

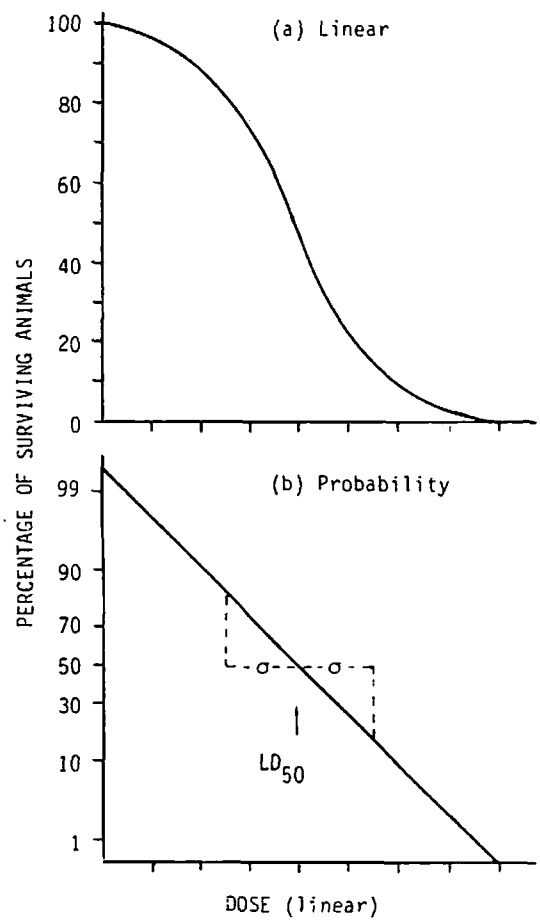


Figure II. Diagrammatic representation of a typical dose-survival curve for irradiated animals, using a linear ordinate or a probability ordinate. The LD_{50} is the dose for 50% incidence, and the slope is characterized by the standard deviation (σ) of the distribution.

representations of the data [M48]. The probit model is based on the normal (Gaussian) distribution [U4, I8]. 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 (σ) 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_0 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_0 [L3]. Second, there is the variation in sensitivity, $1/D_0$, 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 I.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,

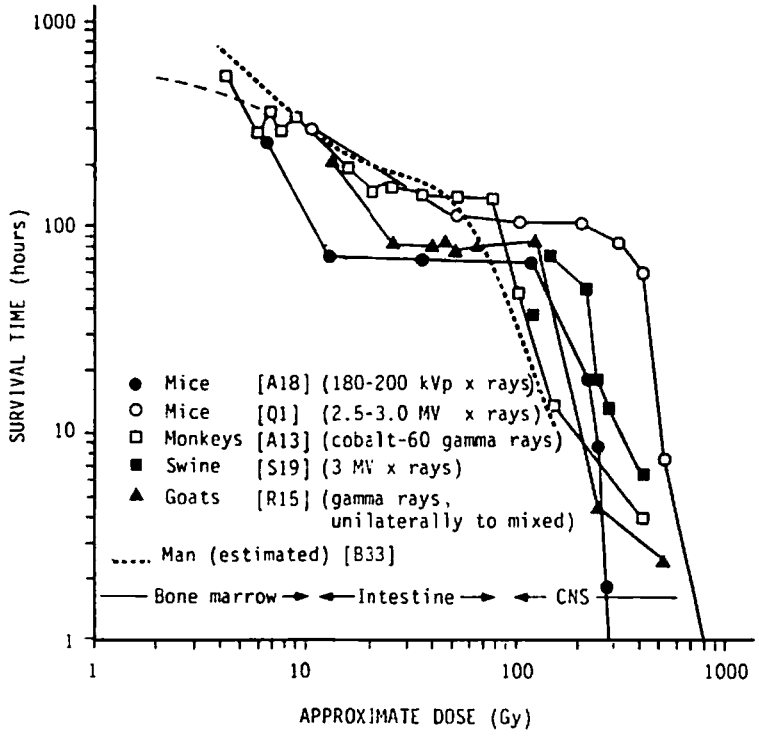


Figure III. Survival time of several mammalian species after various whole-body doses (doses are quoted as approximate maximum tissue doses).
[B16, T24]

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].

1. 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 irradiation [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_{50} 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 chloropromazine 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

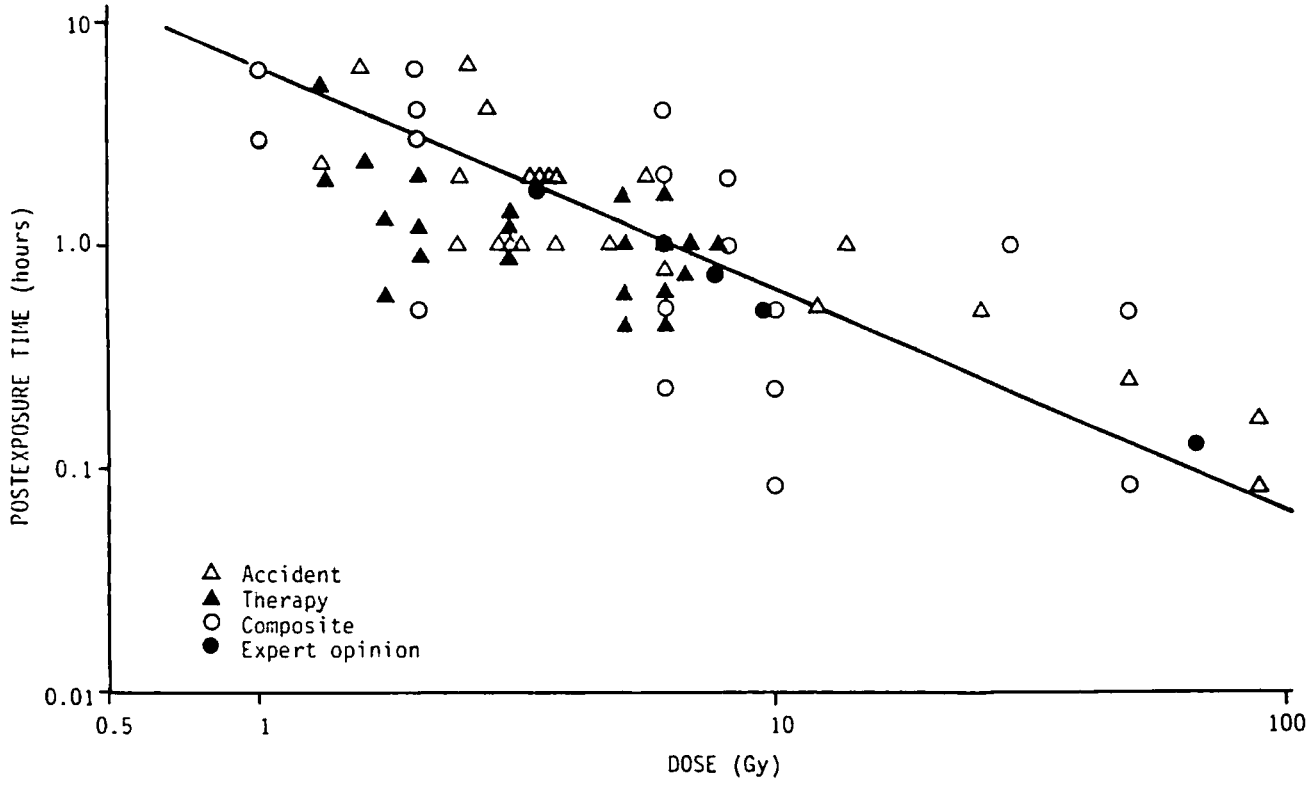


Figure IV. Relationship between time of onset of prodromal symptoms and dose in man. Dose rates ranged from very high (accident cases) down to 0.3 Gy per minute (radiotherapy patients). Approximate midline doses are quoted. (Modified from [B33].)

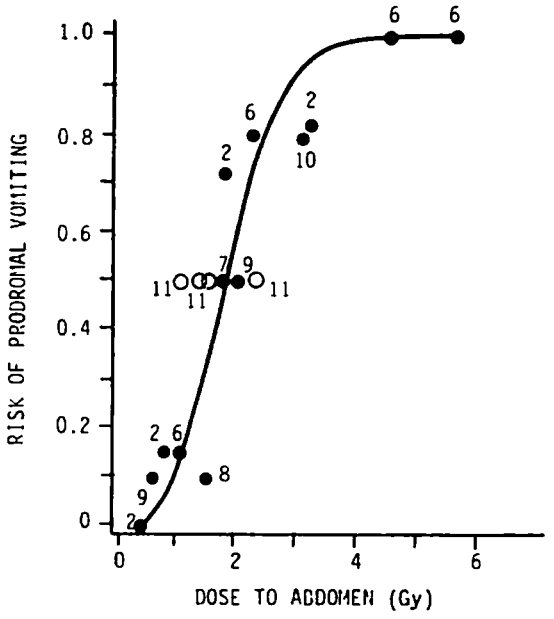


Figure V. Dose-effect relationship for prodromal vomiting within two days in man.
[U5]
2 — accident cases [L4]; 6 — accident cases [T5]; 7 — therapy patients [T17]; 8 — Rongelap natives exposed to fallout radiation [L4]; 9 — midway between the normal arithmetical and log-normal values in the analysis given by Langham [L4]; 10 — Toronto-therapy cases (11/14) with Gravol pretreatment; 11 — doses calculated for a risk of 0.5 of, respectively, anorexia, nausea, fatigue and vomiting (same as symbol 7) and diarrhoea (from left to right in figure) in 163 therapy cases [L9]. Doses are original estimates in the cases of accidents.

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 prodromal syndrome, 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]; pycnosis 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 post-irradiation [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 prodromal 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

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.

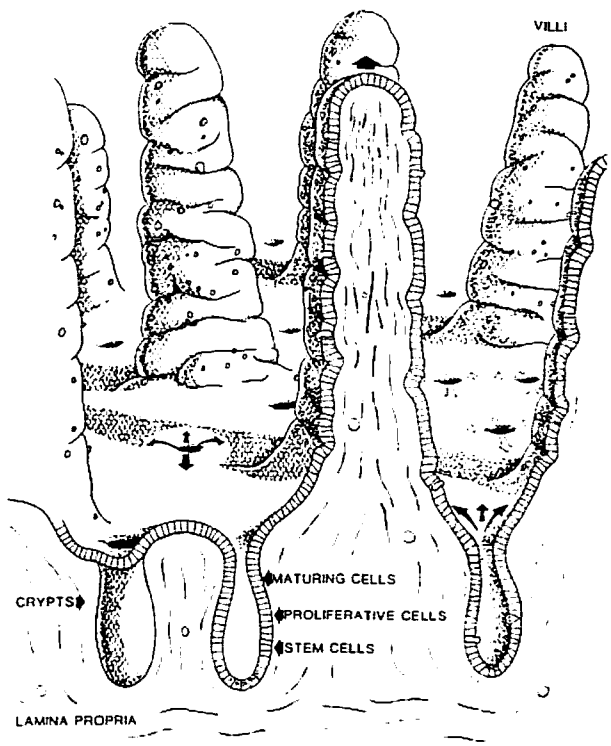


Figure VI. Diagrammatic representation of cell production in intestinal crypts, with new cells migrating on to the functional units, the villi.
(Adapted from [P29].)

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 [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

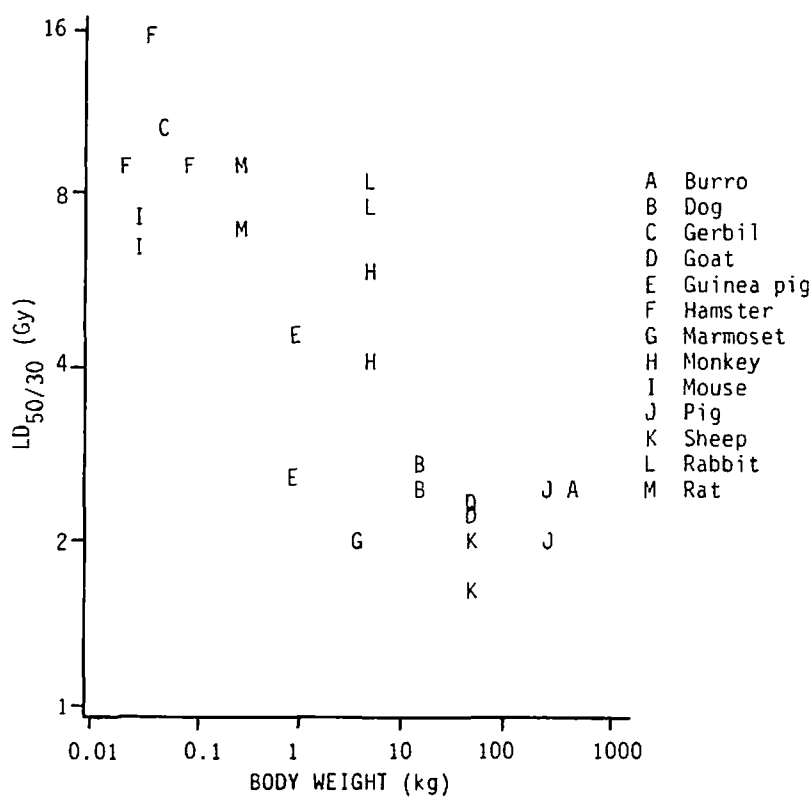


Figure VII. Relationship between $LD_{50/30}$ and body weight for various mammals. (Modified from [U4, U5].)

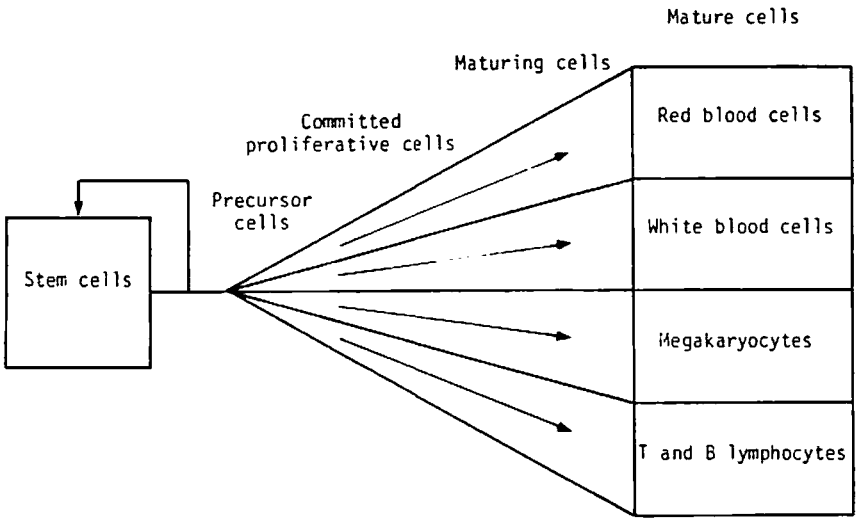


Figure VIII. Simplified diagrammatic representation of the haemopoietic hierarchy, where mature cells are produced from proliferative precursor cells. Left arrow indicates renewal of stem cells, right arrows indicate differentiation and maturation down particular lineages.

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 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 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

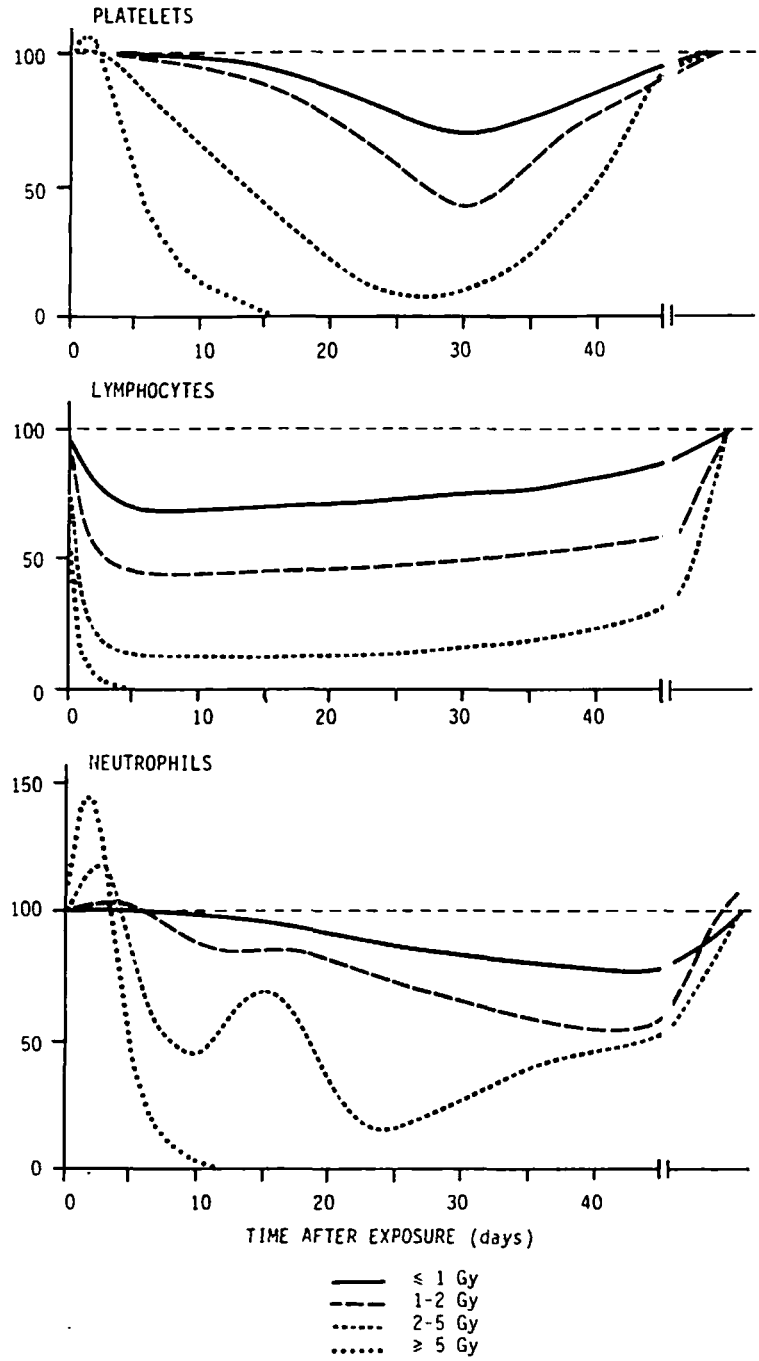


Figure IX. Schematic picture of average time courses for various cells in the blood, after various doses of radiation in man, derived from accident cases.
(Redrawn from [W2].)

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).

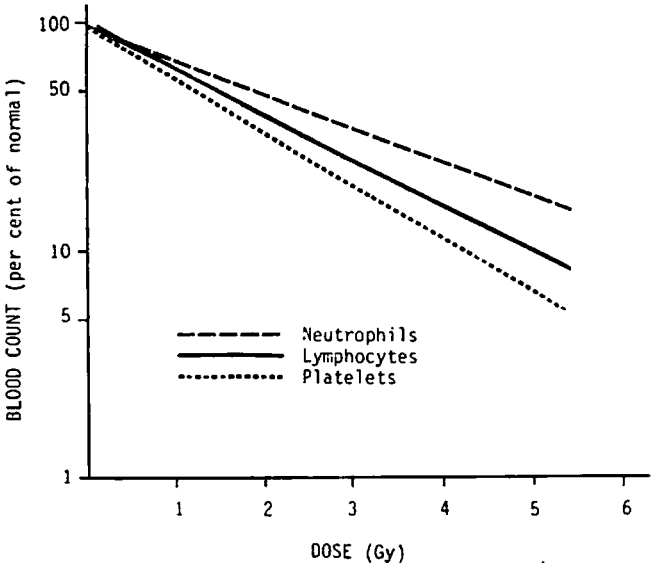


Figure X. Idealized average dose-response curves for nadir levels in blood cell counts.
[W2]

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

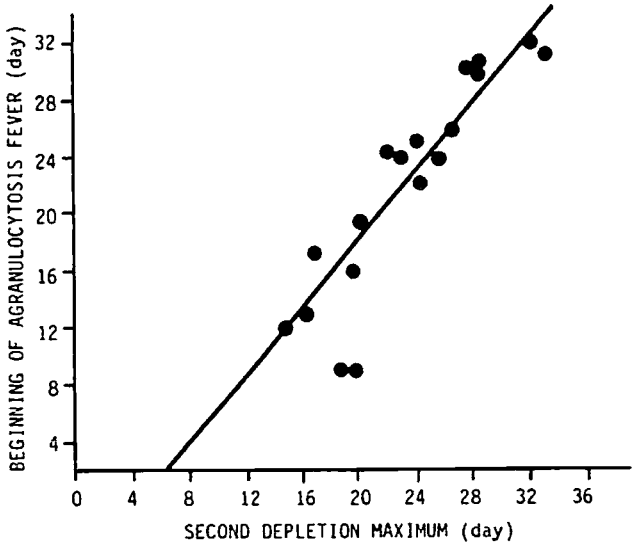


Figure XI. Time of the second depletion on the granulocyte count curve, corresponding to the beginning of agranulocytosis fever in man.
[B37]

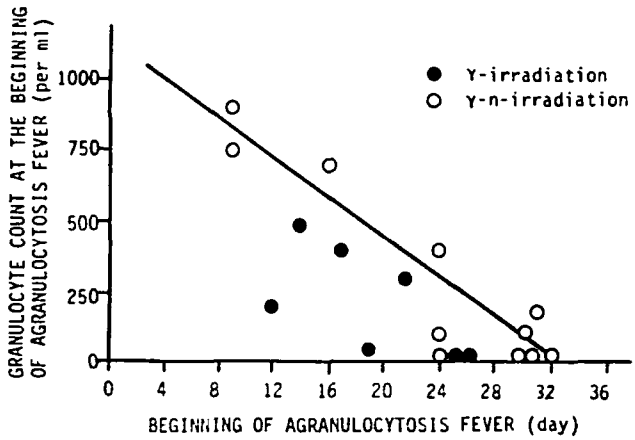


Figure XII. Granulocyte count at the beginning of agranulocytosis fever.
[B37]

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.

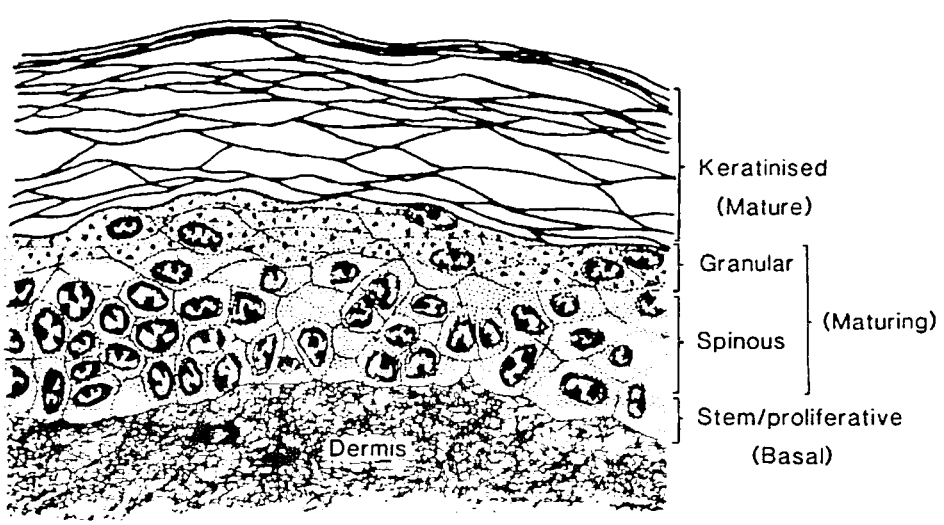


Figure XIII. Diagrammatic representation of the hierarchy of cell population types in the epidermis, drawn from a vertical section through normal human epidermis. (Adapted from [P28].)

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

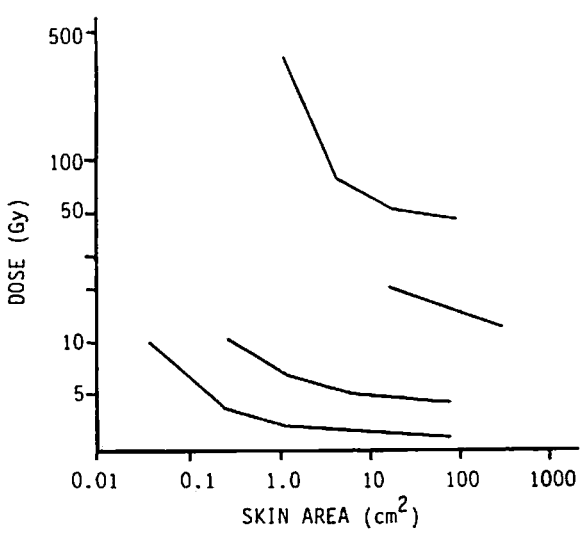


Figure XIV. Relationship between iso-effect dose for skin tolerance and field area using single doses (bottom two curves) or fractionated doses (top two curves) in man.
[H19]

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

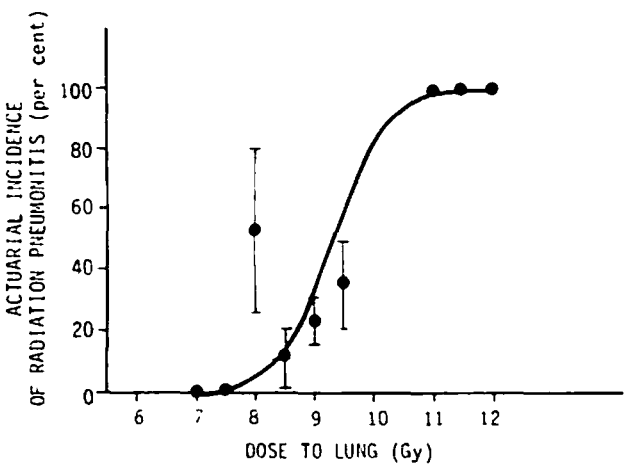


Figure XV. Incidence of pneumonitis versus dose to lung in man. Best fit sigmoidal complication curve using probit regression analysis. The point to the left of the curve was based on only four patients and hence has a large uncertainty. Based on patients excluding significant additional irradiation,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

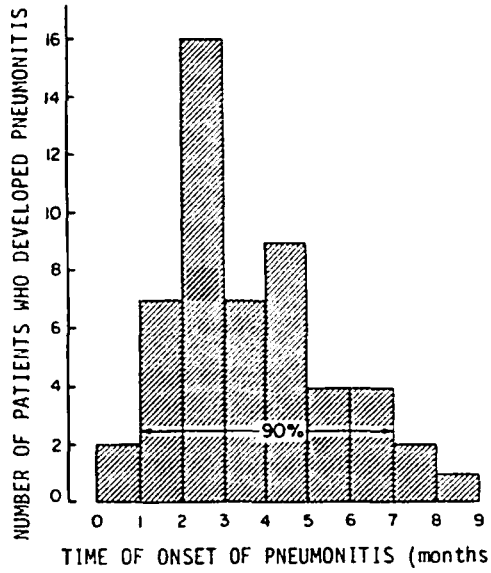


Figure XVI. The frequency distribution of the time of onset of radiation pneumonitis for 52 patients who developed the complication.
[V3]

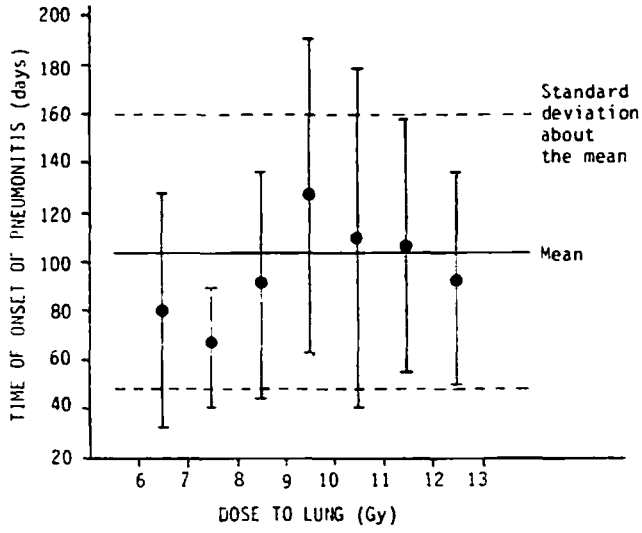


Figure XVII. Time of onset of radiation pneumonitis versus dose to the lung for 52 patients who developed radiation pneumonitis. Error bars represent standard deviations.
[V3]

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].

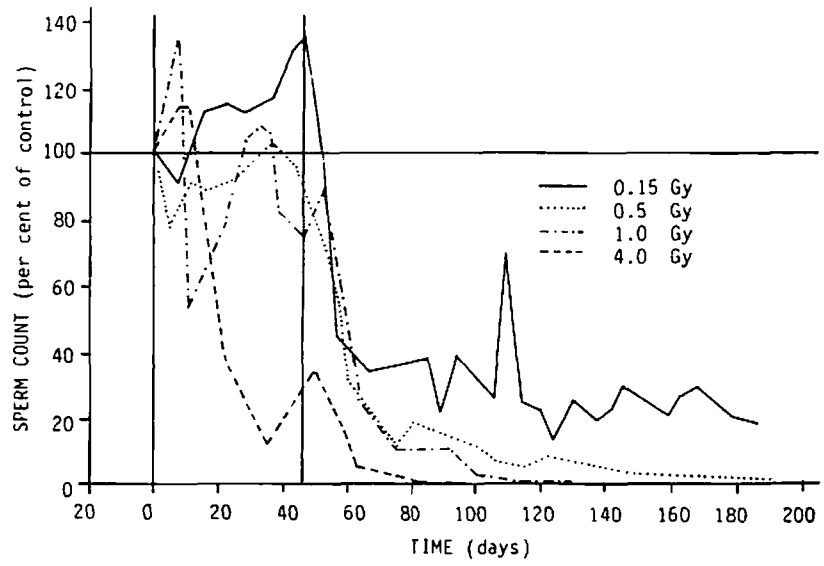


Figure XVIII. Time course of sperm-counts of normal men following exposure to various doses of 190 kVp x rays.
[H8]

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.

II. DOSE-RESPONSE RELATIONSHIPS IN MAN

A. ACUTE DOSES

1. The $LD_{50/60}$

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 ($LD_{50/30}$ and $LD_{50/60}$, respectively). While the concept of LD_{50} is quite clear and widely applicable in experimental work, it is a difficult concept to appiy 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 $LD_{50/60}$ 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 $LD_{50/30}$ 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 ^{60}Co or ^{137}Cs gamma rays [I5] (see Figure XX). The midline dose is about 10% less than the marrow dose for ^{60}Co 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 $LD_{50/60}$ 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

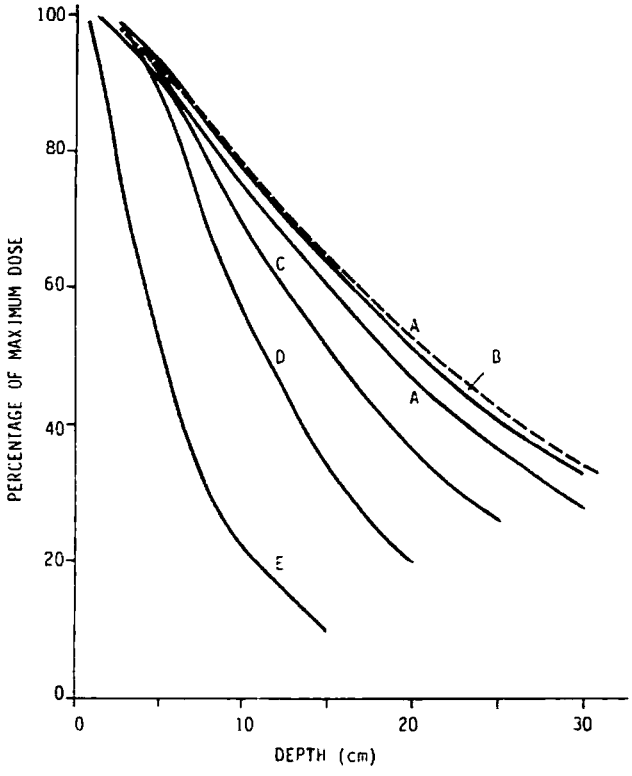


Figure XIX. Depth-dose curves for different radiation qualities. [B20, S4.] Data are tissue-air ratios (corrected for the inverse-square law) expressed as a per cent of the maximum dose:

	Radiation type	*SSD (cm)*	*Field size (cm × cm)*
Curve A	^{60}Co γ rays	80	20 × 20 and 35 × 35
Curve B	4 MV x rays	Infinite	20 × 20 or 35 × 35
Curve C	^{137}Cs γ rays	40	20 × 20
Curve D	230 kVp x rays	50	20 × 20
Curve E	^{235}U fission neutrons	500	6 × 8

cause no mortality, followed by a sharp increase in mortality with progressively higher doses, reaching a plateau at 100% mortality after still higher doses. Doses causing very little mortality are generally quoted in the range LD_{1-10}, and those causing high mortality in the range LD_{90-99}. To estimate these doses directly would require analysing large groups of individuals exposed homogeneously to the same dose. For example, with 100 individuals, the accuracy of estimates for 10% and 90% mortality would be, respectively, 3% and 30% of the mean (binomial standard sampling error). With 1,000 individuals, the accuracies would be 1% and 19%, respectively. Since there is no experience with such large groups, the doses must be estimated from dose-response relationships, where the most accurate parameter that can be calculated is the $LD_{50/60}$. These doses apply to the average individual in a population and not to a specific individual, who may have a response different from the average. The $LD_{50/60}$ will be considered first. As has already been noted, previous estimates of $LD_{50/60}$ reported in the literature are given in Table 11.

94. The $LD_{50/60}$ has been estimated from the data on mortality following the atomic bombings of Japan in the Second World War. A value for $LD_{50/60}$ of 1.5 Gy (marrow dose) has been deduced for people exposed inside Japanese-style houses at Hiroshima [R20]. This was calculated by first ascertaining the distance from the hypocentre at which there had been 50% mortality, and then converting this distance into dose. The distance was deduced to be 892 ± 11 m from a survey of 201 documented individuals who died between one day and two months after the explosion. This distance was given later as 887 m [H44]. At the distance of 892 m, revised estimates of free-in-air tissue kerma were used [K16], together with shielding factors [E9], to calculate a cumulative marrow dose of 1.5 Gy from gamma rays and neutrons. Similar calculations of dose at other distances enabled a dose-mortality curve to be deduced. The revised dosimetry (DS86) has caused the estimate to be increased from 1.5 Gy to 1.8 Gy [F15]. Further, a total dose of 2.4 Gy at 892 m was quoted in an analysis using individual transmission factors [F15]. A recent re-assessment of such data [F15] concerning deaths versus distance at exposure has produced a value for $LD_{50/60}$ in the range 2.7-3.1 Gy (see Table 11 and Figure XXI).

95. The mortality in known numbers of individuals exposed to the bomb irradiation at particular places is being further studied [e.g., F15]. For example, a

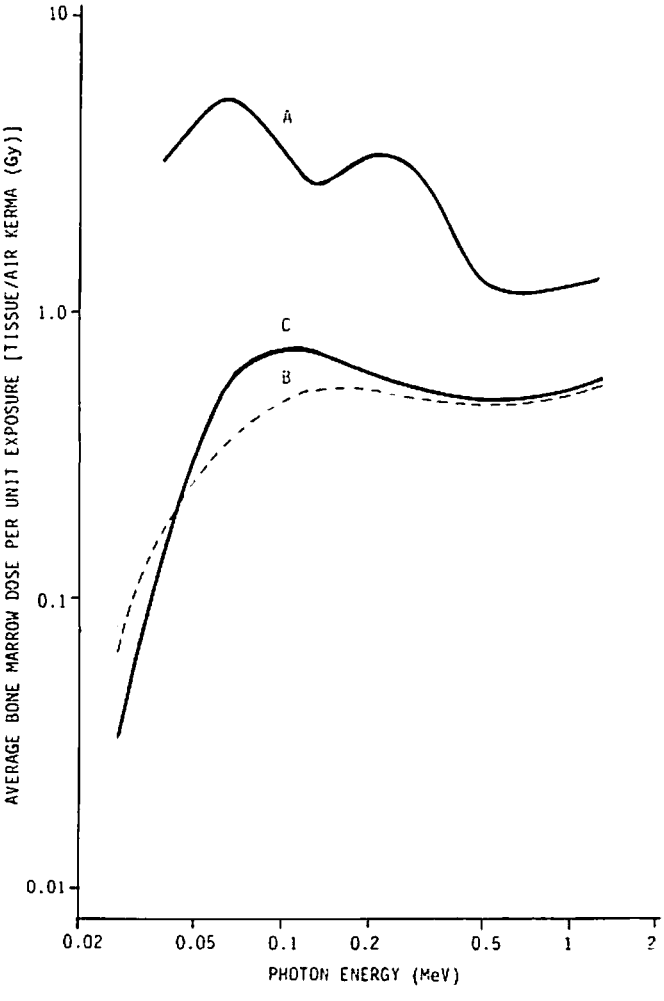


Figure XX. Average dose in bone marrow per unit exposure measured by a personal dosimeter on the front of the trunk (curves A and B) and per unit exposure measured in free air at the position of the centre of the body (curve C). Curve A: irradiation from the back only. Curve B: irradiation from the front only. Curve C: rotation during exposure, simulating irradiation from all sides.
[15]

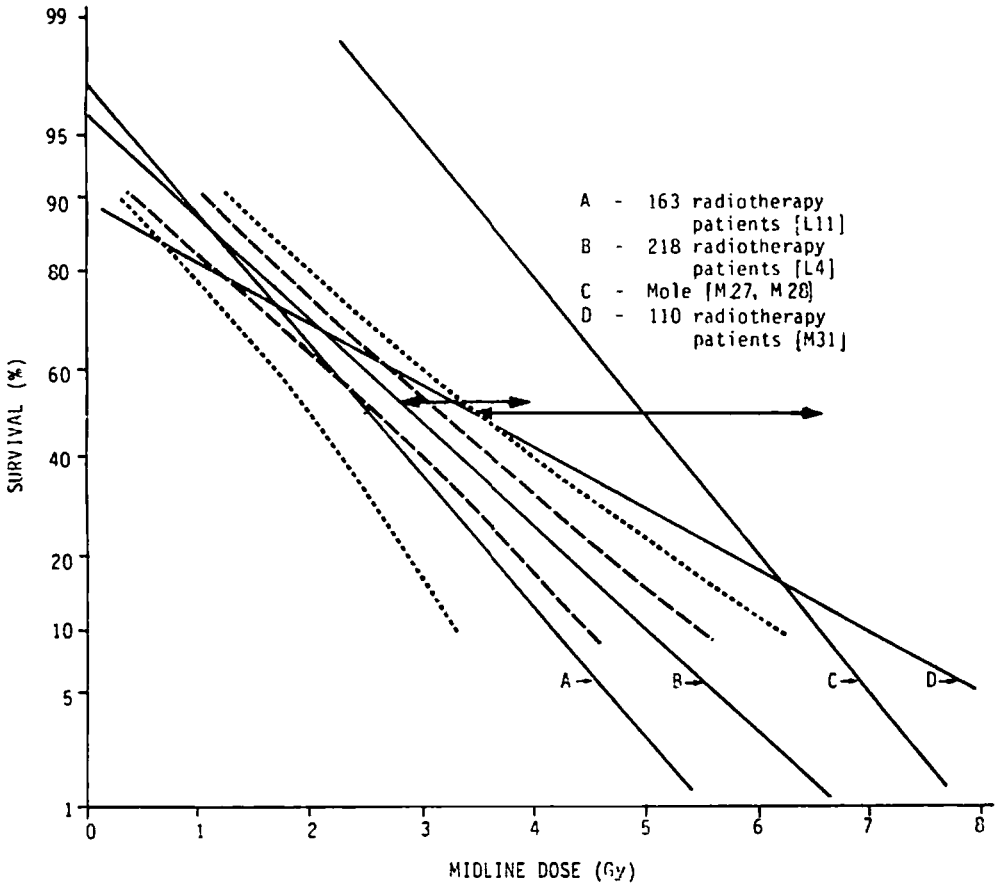


Figure XXI. Estimates of dose-survival curves for man, at 60 days. Curves A and B: Standard error limits (dotted curves at both sides of curve A, dashed curves at both sides of curve B) calculated using probit analysis; Curve C: The line is drawn assuming a coefficient of variation of 0.24, derived using several species of large animal [M28]. The left arrow extends to approximately the LD_{50} calculated using lower levels of survival at the 90% Poisson probability level, and the right arrow is included speculatively for completeness. Curve D: Arrows denote standard error limits. The dose-survival curve estimated from the population in Hiroshima receiving atomic bomb irradiation is expected to lie in the range between curves A and B.
[L4, L11, M27, M28, M31, R20]

group of 159 labourers were exposed when shielded by wooden buildings about 1,000 m from the hypocentre at Hiroshima, and of these 58.5% died between day 20 and 38 [O5]. Using the revised doses, as in the preceding paragraph, the tissue kerma of about 2.4 Gy multiplied by a factor of 0.79 gives marrow doses of 1.9 Gy, and possibly 2.1 Gy if prompt and delayed radiation components are considered separately [F15]. Also, of 193 workmen exposed unshielded at 1,000 m from the hypocentre, only 10 survived a marrow dose currently estimated to have been about 3.3 Gy [F15].

96. Other groups of individuals were exposed inside concrete buildings. Ninety 15-year-old girls were exposed in the Central Telephone Office of Hiroshima at 550 m from the hypocentre. Of the 59 who survived to 24 hours, 29 (49%) died between one and ten weeks after exposure. The majority (20) died in the fourth, fifth and sixth weeks. From measurements made years later of chromosomal aberrations in the T-lymphocytes in the survivors [F15], the dose was estimated to have been 6.5 Gy. Although this is similar to the value of 6.0 Gy according to the T65D estimates, the revised estimates of dose are lower, perhaps as low as 4 Gy [F15]. None the less, the survival rate of these girls was higher than that of adults irradiated in other buildings who had apparently lower doses.

97. A recent detailed analysis of weighted data concerning deaths versus distance from the hypocentre, including those occurring on the first day after exposure, has given a value for $LD_{50/60}$ of 2.1-2.5 Gy marrow dose, the value depending on the mathematical model used to fit the data. A probit fitting of the data gave a value for $LD_{50/60}$ of 2.2 Gy, and for $LD_{95/60}$ of 5.8 Gy [F15]. It was considered that the value of $LD_{50/60}$ may be too low by up to 17% because of the contributions to mortality estimates from deaths on the first day and of the severely injured. This was estimated in a separate smaller study of 184 individuals, 84 of whom died on the first day, where the $LD_{50/60}$ was calculated using probit analysis to be 3.2 Gy or 2.6 Gy marrow dose when the above early deaths were respectively excluded or included. Hence the true value of $LD_{50/60}$ may be around 2.5 Gy or higher. The true value of $LD_{05/60}$ is even more uncertain. It may also be higher, or lower down to 4.5 Gy [F15]. In view of these uncertainties, it is concluded that the dose-survival curve for the Japanese exposed to atomic bomb radiation in Hiroshima is

likely to be similar to curves deduced for ill radiotherapy patients receiving whole-body irradiation (in the range of curves A and B, Figure XXI).

98. There have been many radiation accidents involving single individuals or a few individuals, often with very inhomogeneous doses from gamma rays or x rays, or mixed radiation, including a neutron component. These accidents have been summarized by several authors [B7, B31, D24, D25, L12, M19, U4]. The most comprehensive listing is probably the REAC/TS Radiation Accident Register [L12]. Between 1944 and October 1983, 188 accidents were recorded involving 928 persons, 22 of whom died from acute effects [F10]. One hundred and forty-four individuals received whole-body doses greater than about 0.25 Gy, and eight of these died; 46 received, in addition, local irradiation with doses greater than 6 Gy, and eight of them died; 62 received high internal doses, and four of them died; 110 Marshall Islanders received both internal and external irradiation, and one of them died. In March 1987 these numbers were updated to 284 accidents involving 1,358 persons, 33 of whom died from acute effects (excluding Chernobyl) [L38].

99. Before the accident at Chernobyl ([U6] and the Appendix), the accidents involving the largest number of individuals, and therefore the most useful for analysis, were those in 1958 at Oak Ridge, United States [O2, H23] and at Vinca, Yugoslavia [H22, I1, J4, M49]. The doses received by these individuals are still a matter for debate; some recent estimates are reported in Table 12. The various estimates depend on the assumptions about the position and orientation of the individuals, and the dose and RBE of the neutron component. None the less, there was only one death, individual V at Vinca, who received a marrow dose estimated recently to have been approximately equivalent to 4.5 Gy of low-LET radiation (Table 12). Although he had marked haematological responses, these were not the primary causes of death. Two of the individuals irradiated at Oak Ridge received antibiotic treatment for respiratory infections, whereas the Vinca cases had barrier nursing, and a series of antibiotics, platelet and red cell concentrates, and later marrow cells. In one report, recalculation of the doses broadened the possible ranges of dose so that they overlap, depending on the uncertain aspect of exposure, particularly at Oak Ridge, i.e., from the side or from the front [B7]. Another report concluded that the data from Oak Ridge were more reliable than those from Vinca, because in the latter accident the exposures may have been more inhomogeneous [M19]. From a re-analysis of the measurements of sodium activation, it has been suggested that the doses at Oak Ridge should be increased by about 10% and at Vinca, by about 30% (column 8, Table 12) [M26]. This could remove the apparent difference in clinical effect for estimated equivalent doses in the two accidents in earlier reports.

100. In the accident at Chernobyl, described in the Appendix, 115 persons received doses ranging from approximately 1 to 16 Gy (Table A.3). In most cases the individuals received antibiotics and were hospitalized, if necessary under aseptic conditions, and platelet and red-cell infusions were administered when considered necessary. Thirteen patients received allogeneic marrow transplants and six received embryonic liver transplants. In the lowest dose group, 31 individuals received relatively uniform bone marrow doses of gamma-irradiation of approximately 1 to 2 Gy. In the second dose group, 43 individuals received marrow doses between 2 and 4 Gy; in many cases higher doses to the skin from beta-irradiation were also received. None of the patients of this group died up to 60 days after irradiation, but one died at day 96. A further 21 persons received marrow doses between 4 and 6 Gy. Seven of them died between 16 and 48 days after irradiation, and six of these seven had severe skin injuries, which contributed greatly to their death. In the highest dose group, 20 individuals received doses between 6 and 16 Gy. One person died at day 10 after irradiation, 17 died between 14 and 48 days, and two died at days 86 and 91, respectively. The individuals in this dose group had severe skin injuries to 40-90% of the body that were probably lethal, as well as severe signs of radiation sickness (Table A.7). These observations, in particular the survival of 43 individuals in the dose group 2 to 4 Gy surviving more than 60 days, suggest that the $LD_{50/60}$ for this irradiated population was at least 4 Gy.

101. Various groups of cancer patients have been given acute whole-body irradiation. Some were relatively ill people with advanced disseminated cancer and others were relatively healthy individuals irradiated while in remission or when bearing metastasizing solid tumours. A group of 19 children and adolescents with Ewing's sarcoma and one with leukaemic infiltration of bone received 3.0 Gy from whole-body irradiation with cobalt-60 gamma rays given in 15 minutes (dose homogeneity to within ± 10%) [R6]. None of these 20 individuals died within one year. They were given antibiotics when infection arose, blood infusions at about day 30 to replace haemoglobin, and barrier nursing during the phase of pancytopenia. According to Poisson statistics, zero deaths in a sample of 20 individuals might be observed 1 in 20 times (i.e., a 5% probability) if the true number of deaths on average among many such samples was 3.7; that is, if the true mortality was 3.7/20 = 19%. Hence it is possible that, although no mortality was observed in this particular sample, the average mortality level characteristic of this 3.0 Gy dose could be as high as 19%, but not as high as 50%.

102. An attempt was made to extend this type of analysis to a total of 27 individuals, by including subjects A, C and D in the Y-12 accident, and subjects V, M, D and G in the Vinca accident [M28]. Estimates of the total (n + γ) marrow doses that were used ranged from 2.8 to 3.3 Gy (column 7, Table 12). The one death (case V at Vinca) was attributed to marrow failure for this exercise, in order to provide a maximum value to the observed mortality. Using these 27 individuals, the statistical exercise in the preceding paragraph gives virtually the same result, with the possible average mortality being 21%. A further point is that if the true average mortality was 50% at these estimated doses of about 3 Gy, as is suggested by an analysis of mortality in radiotherapy patients (see the

next paragraph), or more (column 8, Table 12), there would be a 5% probability of as few as six deaths out of a random sample of 27 individuals, in contrast with only one death observed. Hence the data for the Ewing's sarcoma patients, with or without the inclusion of these accident cases, are inconsistent with an $LD_{50/60}$ as low as 3 Gy. The revisions in the dosimetry for the accident cases that increase their respective doses [M26] strengthens this conclusion, as does the survival to 60 days of all 43 individuals receiving doses estimated to be between 2 and 4 Gy in the Chernobyl accident (Table A.3).

103. One group of 163 relatively ill cancer patients was irradiated to the whole body with acute doses of low-LET radiation [L11]. The estimated dose (with its standard error) giving 50% deaths within 60 days was 2.5 (+0.98 −0.51) Gy, calculated using a normal distribution, and 2.35 (+5.06 −0.87) Gy using a log-normal distribution. The data were corrected for a death rate of 4% in unirradiated patients, and average doses were given for a 26 cm diameter sphere in the epigastric region. A similar analysis of 218 patients irradiated within an overall period of one day, gave an $LD_{50/60}$ of 2.86 ± 0.25 Gy [L4]. These two calculated dose-mortality curves (A and B) are shown in Figure XXI.

104. An analysis of 110 patients receiving whole-body irradiation from 1 to 10 Gy, either for various cancers and leukaemia or prior to kidney transplantation, indicated an $LD_{50/60}$ of about 4.0 Gy [M31]. The Committee's probit analysis of these data produced an $LD_{50/60}$ of 3.4 ± 0.5 Gy (curve D, Figure XXI). The data for the patients with malignancies were not significantly different from the data for the (fewer) patients with kidney debilities.

105. Smaller groups of patients have also been given whole-body doses of up to 3 Gy, without bone marrow transplantation. For example, one patient with metastatic bronchogenic carcinoma given about 3.8 Gy (midline dose) using ^{60}Co died on day 20 after irradiation, and one with generalized neuroblastoma given about 2.6 Gy survived to 4 months after irradiation [K18]. Of seven patients with advanced colon and lung cancer irradiated with 2.0 Gy (midline dose) using ^{60}Co, two died within 60 days (at 28 and 56 days) [S27]. Three patients, in a series of 18, in remission from acute leukaemia were given 3 Gy midline dose using ^{137}Cs, and they survived more than 60 days [K23]. They received antibiotic therapy and transfusions of platelets and red cells when considered necessary.

106. Since the $LD_{50/60}$ for ill cancer patients is confounded by their disease and other concomitant treatment, it may be lower than the $LD_{50/60}$ for healthy people. The data in the last three paragraphs suggest that for ill cancer patients treated with conservative supportive medications and blood-cell infusions when necessary, the $LD_{50/60}$ is about 3.0-3.5 Gy (marrow dose).

107. The cancer patients considered relatively healthy at the time of irradiation were those with Ewing's sarcoma. Whole-body irradiation was given to these children and adolescents to sterilize the metastases. Three patients with localized disease given 3 Gy (midline dose) survived more than 60 days without needing supportive medications [M34]. Ten patients with localized disease given 3.0 Gy (midline dose) survived more than 60 days [J17]. A larger series of 20 patients was described, one of whom was diagnosed subsequently to have had instead a leukaemic infiltration of bone [R6]. All 20 survived more than 60 days. This indicates that the $LD_{50/60}$ of relatively healthy people is greater than 3.0 Gy, although it is not known if these young people were more resilient to irradiation than adults. The apparently high doses tolerated by the schoolgirls irradiated by the atomic bombs [K17] would support this idea.

108. Attempts have been made to use experiments with animals in order to predict the dose-mortality relationship for man. Two similar approaches have been described. The first approach [L4, M28] relies on the similarity of the coefficient of variation (CV) of the LD_{50} [i.e., the inverse slope (probit width) divided by the mean] among different species of large animals. The CV for irradiated cancer patients was 0.58, which is much larger than the CVs calculated for dogs (0.15) and monkeys (0.21) [L4]. This greater variability was attributed to the marked heterogeneity of responses among patients. The mean CV for dogs and monkeys (0.18) was applied to the data for 218 irradiated cancer patients [L4], where the $LD_{50/60}$ was 2.86 ± 0.25 Gy, to calculate the doses for 10% mortality (2.2 Gy) and 90% mortality (3.5 Gy). Mole [M27, M28] calculated the weighted mean CV for five different species of large animal (dog, sheep, goat, pig, donkey) to be 0.24. This value was used, together with pertinent but sparse information for mortality in "healthy" humans, to deduce a value for the LD_{50} in man of about 5 Gy (Figure XXI). The information just referred to came from the 27 individuals described in paragraph 102 [M28].

109. The second approach was to take the ratio of the doses that produced measurable, very low or very high mortalities [B6]. The ratio of LD_{95}/LD_5 or LD_{90}/LD_{10} from 34 experiments in six species of large animal was close to 2.0. This ratio was used, together with the data for the Ewing's sarcoma patients, to consider the LD_{90} or LD_{95} for man. The two approaches are consistent with one another, and they suggest that the dose that would kill "few" healthy humans is about 3.0 Gy, the dose that would kill "most" is about 6.0 Gy [B6] and the LD_{50} is 4.5-5.0 Gy [M27, M28].

110. Estimates of dose-survival curves for various animal species are given in Figure XXII. Data from many published experiments were reviewed by Baverstock [B6], and were re-analysed to obtain a mean curve for each species [T24]. Doses in each experiment for a given species were multiplied by the ratio of the LD_{50} for that experiment and the mean LD_{50} for all experiments. This assumed that variations between experiments were due to dose-modifying influences, e.g., to changes in dose rate or LET. The data for mice were reviewed and analysed separately [H32].

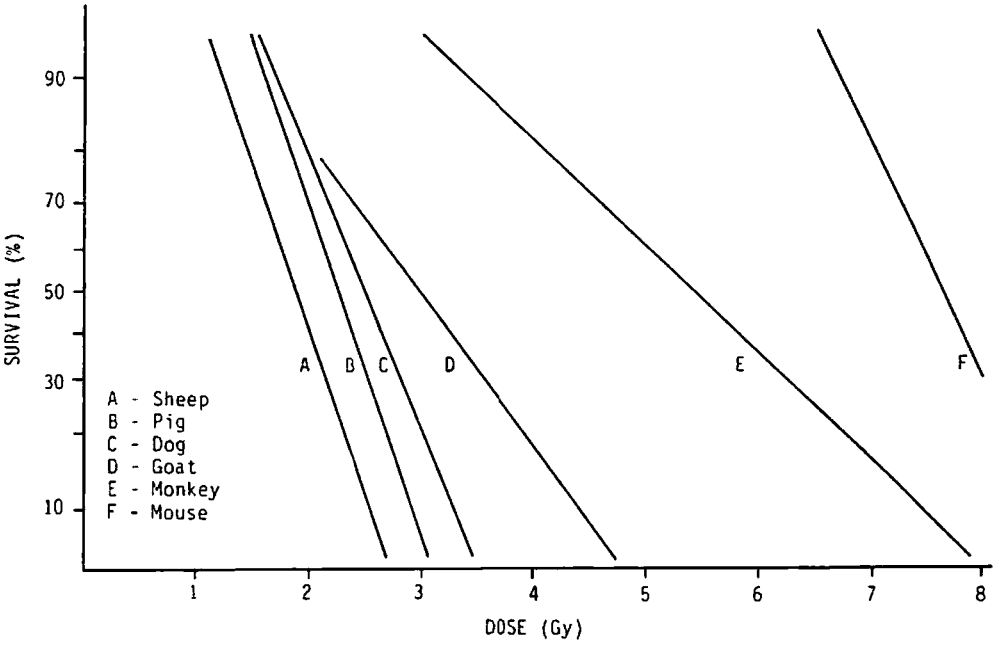


Figure XXII. Midline dose-survival curves calculated from various published experiments using different species of animal irradiated bilaterally.
[T24]

111. In the data for large animals reviewed by Baverstock [B6], lower slopes correspond with higher values of LD_{50} (see curves for goat and monkey in Figure XXII). This indicates that heterogeneity in the irradiated population is greater for species showing a higher LD_{50}, possibly because variations between individuals are greater in species with a high LD_{50} or because the sensitivity of their target cells is less. Evidence for the latter possibility is that the D_0 for granulocyte-macrophage colony-forming cells is generally reported to be much lower in dogs (~ 0.7 Gy) than in mice (~ 1.8 Gy) or in humans (~ 1.5 Gy) [H11]. Data are not available for other species.

112. It is concluded from the preceding discussion that the $LD_{50/60}$ for acute irradiation is likely to be around 3.0 Gy marrow dose in the case of humans receiving no or little medical treatment, as deduced from recent analyses of the results of the atomic bombings in Japan. A similar value pertains to some groups of ill cancer patients receiving good medical care. The $LD_{50/60}$ for healthy humans receiving good supportive medical treatment after irradiation (e.g., barrier nursing, antibiotics symptomatically and blood cell infusions) is likely to approach or equal 5.0 Gy, in particular for children. This is deduced from the lack of mortality in the young and relatively healthy Ewing's sarcoma patients given 3.0 Gy marrow dose, the presence of only one death out of the seven individuals receiving the highest doses in the Vinca and Y-12 accidents; the survival of all 53 individuals receiving doses of 2-4 Gy and of 14 out of 21 individuals receiving 4.2-6.3 Gy in the Chernobyl accident; and the data on dose-response relationships available for other large animals. It should be noted that the $LD_{50/60}$ can be further increased markedly by successful marrow transplantation, probably up to about 9 Gy acute single dose. After these higher doses there may be some cases of pneumonitis occurring in the second month, unless the lungs are shielded. At even higher doses (>10 Gy) acute gastrointestinal injury will become more prevalent.

113. A summary of the effects and their time courses after whole-body irradiation of man, prepared by the Committee, is given in Table 13. The Table lists possible therapies for the responses. More detailed summary tables of symptoms and signs after various ranges of dose are available, for 0.5-1.0 Gy, 1.0-2.0 Gy (Table 14), 2.0-3.5 Gy (Table 15), 3.5-5.5 Gy (Table 16) and higher doses [Y7].

2. Doses for very low and very high mortality in man

114. The dose-mortality curves for ill cancer patients are shown in Figure XXI, together with a curve for healthy humans described by an $LD_{50/60}$ of 5.0 Gy and a coefficient of variation of 0.24 [M27, M28]. The slope of the latter curve is consistent with the conclusion of Baverstock [B6], using data for various species of large animals, that the ratio of doses (LD_{90}/LD_{10}) or (LD_{95}/LD_5) was about 2. Also, the probit width, for this curve, of 1.20 Gy (i.e., 5.0 × 0.24 Gy) would correspond to a D_0 value for the bone marrow target (stem) cells of 1.20/1.2, or 1.0 Gy, using the Poisson model described by Gilbert [G3]. From Figure XXI it may be seen that a dose of 2 Gy would be unlikely to kill more than about 1% of a healthy population (curve C). This is compatible with the Chernobyl experience (Table A.3) but not with the atomic bomb data [F15]. By contrast, a dose of 2 Gy could kill up to 30-40% of a population of very ill cancer patients (curves A, B and D). Similarly, a dose of 7 Gy would probably kill about 95% of healthy people (curve C) but 5-6 Gy to ill cancer patients could probably achieve the same level of mortality (curves A and B).

3. Geometry of exposure and depth-dose distributions

115. Large animals irradiated unilaterally exhibit greater LD_{50} values than those irradiated bilaterally, by about 20% for dog, sheep, pig and goat [M28] (Table 17). Further information on the effect of exposure geometry is that the LD_{50} for goats irradiated dorsally is 0.63 of the value for ventral irradiation [B7]. Also, higher values for the LD_{50} of goats are obtained when parts of the vertebrae are specifically shielded from direct dorsal irradiation [B7]. Similar effects would be expected for man, but no data exist on this subject.

116. The interpretation of the differences in LD_{50} with the direction of exposure relates to the exponential relationship between cell survival and dose. Irradiation of a cell population with a non-uniform dose is always less effective than a homogeneous irradiation with the average dose of the distribution [B18]. In the case of bone marrow, the effects depend on the depth-dose curve for the particular radiation used and the distribution of active bone marrow along such a depth-dose curve. Models for these effects have been described [B18, B19, T3].

117. Depth-dose distributions are shown in Figure XIX for a variety of radiation qualities [B20, S4]. These are expressed as percentages of maximum tissue-air ratios, independent of the inverse-square law, and measured for large radiotherapy fields (> 20 cm $\times$ 20 cm) and source-to-surface distances (SSD) greater than or equal to 40 cm. No ideal comparison exists wherein a full range of radiation qualities has been used with the same large field size and the same SSD. Hence the curves shown in Figure XIX would change slightly, depending on the particular irradiation set-up. For 4 MV x rays, the highest energy considered, the surface dose for well-collimated beams and short SSD is between 40% and 50% of the maximum dose. For low energies and non-collimated beams, the surface dose is a greater percentage of the maximum dose. With non-collimated beams and very long SSD, the surface dose may be equal to the maximum dose. For fission neutrons, a significant build-up effect would be unlikely.

118. The average dose in bone marrow per unit exposure is shown in Figure XX [15]. These curves were obtained by calculation and measurement using a phantom. Similar curves are available for the average doses in the intestine and the gonads [J10].

119. With low-energy x rays there is an additional dose at bone surfaces due to the greater photoelectric effect with the high-atomic-number elements (e.g., calcium and phosphorus) in bone. The greater dose depends on the x-ray energy and on the thickness of the bone, and the effect decays within a few hundred microns of the bone surface. The increase in dose is as great as 50% on the bone surface using 250 kVp x rays [E5], and on average about 20% for a single layer of cells situated against the bone surface. This effect in the mouse would increase the dose to the marrow on average by about 9% compared to the dose in soft tissue remote from bone, and it should be reflected in the $LD_{50/30}$ if the concentration of marrow cells critical for survival is constant in all regions of active haemopoietic tissue. Since higher concentrations (about twice as high) of critical stem cells have been detected close to bone surfaces in the mouse [L7], the above figure of 9% may be slightly higher. No information is available on the measurement of such effects in large animals, apart from the lower concentration of granulocyte-macrophage precursor cells close to bone surfaces in human ribs [T33].

4. Dose inhomogeneity, shielding and bone marrow distributions

120. The effect of dose inhomogeneity on the haematological response and survival in rodents and dogs has been reported in papers submitted by the delegation of the USSR [D28]. In mice, the $LD_{50/30}$ was about 5.5 Gy for whole-body irradiation, about 14.5 Gy when only the front half of the body was irradiated and about 8 Gy when only the rear half was irradiated. The corresponding values for dogs were about 2.8 Gy and 3.8 Gy. Different critical organs were probably responsible for death after these types of irradiation. Thus, for both mice and dogs, larger average doses to the body could be tolerated when only the front half was irradiated, and smaller average doses when only the rear half was irradiated, compared to uniform irradiation. Also, these average dose differences were reduced when both halves of the body were irradiated.

121. When small portions of the body containing active marrow are shielded during irradiation, the LD_{50} can be markedly increased. This would also apply to some degree in the case of non-uniform irradiation. Shielding the right legs of mice increased the $LD_{50/30}$ from slightly less than 7 Gy without shielding (7 Gy gave 70% mortality) to about 12 Gy [C2]. Shielding the right leg below the hip joint gave 73% survival at 30 days after 10.5 Gy, in contrast to 0% without such shielding [D1]. Shielding the leg only below the knee joint, or below the tibia, did not cause survival to drop below 70% [D1]. These phenomena are due partly to the migration to and repopulation of irradiated marrow by progenitor cells from the shielded marrow and partly to the ability of the shielded marrow to increase its normal rate of producing maturing haemopoietic cells. In mice, a persistently reduced complement of only 10-20% of stem cells remaining during chronic irradiation [L2] or after repeated irradiation [H14] can maintain a normal output of mature haemopoietic cells into the blood for many months.

122. In dogs, shielding the skull reduced lethality after 4-5 Gy from 100% to 20%, and shielding sternum, pelvis or skull doubled the LD_{50} [A31]. Also, shielding, separately, the head and neck, chest, abdomen or pelvis gave no deaths in separate groups of 20 dogs each given 6 Gy, a 100% lethal dose if given to the whole body [L31]. Shielding smaller volumes of marrow in dogs has also been shown to markedly increase survival [D28]. Shielding one or two vertebrae was found sufficient to protect dogs from an otherwise fatal exposure to radiation [S41]. Shielding the limb

epicondyle resulted in 100% survival after doses three times the $LD_{50/60}$, but shielding only the third and fourth ribs was insufficient [C34].

123. The above data suggest that in man, the shielding of perhaps as little as 10% of the active marrow, while the remainder of the body receives a dose close to the $LD_{50/60}$, may reduce the number of deaths to zero. The efficacy of shielding different parts of the body in man depends on the distribution of active bone marrow.

124. Various estimates of the percentage of active marrow residing in the different bones of man have been calculated from histological measurements using ^{59}Fe uptake. The values for humans aged around 40 are compared with those for other species in Table 18. Some of the values for humans were calculated from the absolute weights of total marrow in the bones of 11 cadavers [M12]. These weights separately for each cadaver were multiplied by the proportion of marrow that was active. This proportion has been estimated by various investigators on the basis of marrow cellularity and uptake of ^{59}Fe, and the values given by Cristy [C12] for humans aged around 40 were used by Woodard [W8]. The absolute weight of active marrow in a given bone was expressed as a percentage of the total weight of active marrow. Finally, the average of these percentages was calculated over the six males and five females investigated. The averages differ in many cases from the values presented by Ellis [E4], as used by ICRP [16] for reference man. The largest differences are evident in the values of 3.9% for the sternum (3.6% in females), given as 2.3% by Ellis [E4], and 7.7% for the sacrum (7.4% in females), given as 13.9% by Ellis [E4]. Also, the percentage of active marrow in the total marrow, 27.5% (28.5% in females), was given as 50% by ICRP [16]. The values from Woodard [W8] probably apply quite well for ages above 20 years but not so well for younger people, because the skull has a higher proportion of active marrow than other regions of the skeleton [C12]. In diseased patients there may be significant extramedullary haemopoiesis, which would modify the normal distribution.

125. The distribution of active marrow in Japanese adults was measured by weighing the marrow in each bone of seven male and three female cadavers, aged between 26 and 41 years [M30]. The red-marrow component of the mean weight of marrow in each bone was assessed histologically. The values are given in Table 18. These values are the mean for each bone, an approach similar to that used by Ellis [E4], rather than the mean of the proportions for each individual, the approach preferred by Woodard [W8].

126. The less-detailed distributions in man measured using ^{59}Fe uptake and scanning techniques [S43, A32] are in broad agreement with an anatomically derived distribution [M30]. A particular difference between these distributions and others based on earlier anatomical assessments [W8] is the significant amount of active marrow in the lower limbs (as is found in other species, Table 18); 8.7% [S43], 7.9% [A32] and 10.6% [M30], versus 0% [W8].

5. Radiation quality

127. Most accidental human whole-body exposures to high-LET radiation have involved both fission-spectrum neutrons and gamma rays. Exposures from the atomic bombings also involved gamma rays and fission neutrons, but the revisions in dosimetry [K16] have reduced the estimate of the neutron component, particularly at Hiroshima (Figure XXIII). For example, at 890 m from the hypocentre in Hiroshima, where about 50% of individuals irradiated inside Japanese-style houses have been considered to have died from marrow failure, the contribution to the dose from neutrons has been calculated to be only about 2% of the total marrow dose [R20]. Thus the contribution from doses of neutrons to early effects in the population at Hiroshima is now considered to be much less than had previously been thought and approaches the level calculated for Nagasaki.

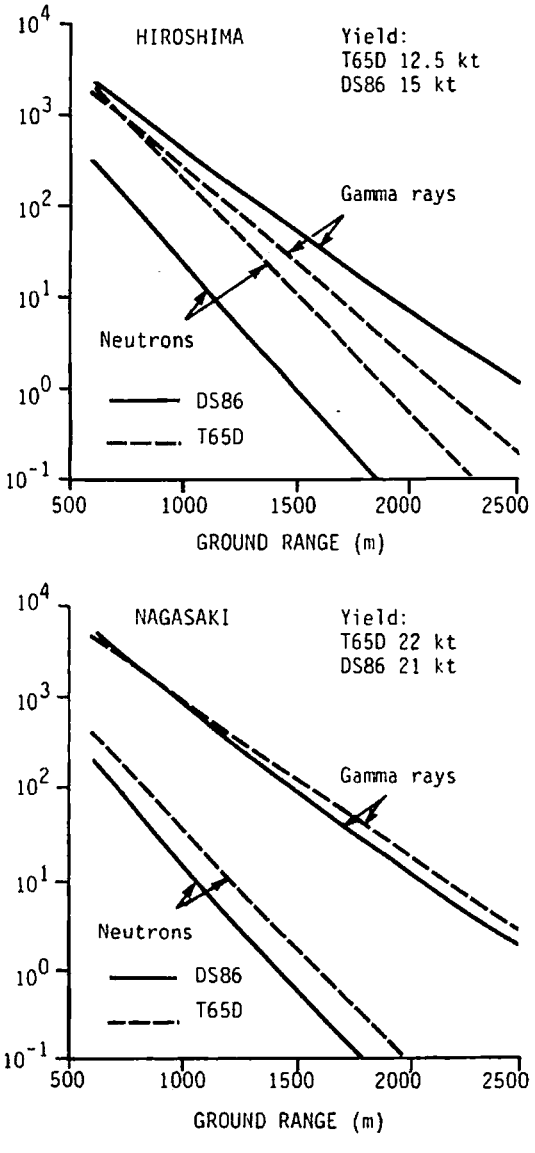


Figure XXIII. Comparison of 1965 estimates (T65D) and revised 1986 dosimetry (DS86) for initial nuclear radiation in Hiroshima and Nagasaki.
[K16]

128. RBE values for fission neutrons are 2-3 for $LD_{50/30}$ in small rodents, e.g., 2.0 for guinea pigs [B5] and 2.7 for mice [G1]. Similar values are obtained for haemopoietic stem-cell survival [C1]. Although in general RBE is a function of dose, RBE values for haemopoietic stem cells are not markedly dependent on the dose in the range under consideration for components of dose in the $LD_{50/30}$ [C1, C3]. Also, it has been considered valid to assume that there is no interaction between doses of neutrons and doses of gamma rays, so that the effects of combined simultaneous exposures to neutrons and gamma rays can be calculated on the basis of the estimated separate components of dose and RBE values measured at high doses, as, for example, in the accident data reviewed by Mole [M28]. There is, however, some evidence that doses from various components do interact, giving greater effects than expected for cells in vitro [H16, M11], and also for haemopoietic stem cells when the neutron component of dose is small [C3].

129. The RBE for exposures with fission neutrons appears to decrease with an increase in body size. For example, the RBE for LD_{50} in bilaterally-irradiated pigs has been reported to be 0.4-0.54 [W9, B25], 0.73 for $LD_{50/30}$ in goats and 0.83 for sheep [E1]. There are several reasons for this apparent reduction in RBE with an increase in body size. First, neutrons are attenuated more rapidly in tissue than are gamma rays, so the dose at greater depths is less and is due increasingly to gamma rays. Second, in small animals, a large part of the dose from neutrons is from charged particles, whereas with large body masses neutron capture reactions dilute the dose from charged particles with dose from knock-on protons. Third, the dose from neutrons in and near bone is less than in soft tissue remote from bone. The dose from neutrons to a one-cell-thick layer on the bone surface can be up to 20% less as a consequence of this effect [B22]. When the doses in the experiments with sheep were expressed as average doses in a 7-cm-thick outer annulus, the RBE value increased to 3, as expected for haemopoietic failure [E1].

130. The doses to the individuals in the Oak Ridge and Vinca accidents are calculated generally by summing the three components: (a) gamma ray dose due to emission from the source; (b) gamma ray dose from neutron capture in a 6 cm annulus of a 30 cm cylinder; and (c) first-collision, charged-particle dose multiplied by an RBE factor of 0.8-1.0 [M28]. All of these components have uncertainties, in particular the RBE. None the less, when the calculations are performed and doses are estimated for the various individuals (Table 12), the low mortality in this small number of exposed individuals is consistent with that in the Ewing's sarcoma patients irradiated with similar doses of low-LET radiation [M28, B7].

131. With small animals, the RBE of neutrons for the gastrointestinal syndrome is often higher than for the bone marrow syndrome [B22], and the ranges of dose resulting in the two syndromes often overlap. Thus, interpretation of the appropriate RBE values must take into account the times of death characteristic of each of the syndromes. With an increase in body size, the RBE for the gastrointestinal syndrome does not decrease as it appears to do for the bone marrow syndrome, but remains at 2.5-3, as shown for dogs [A10, A11] and for sheep [A12]. This is partly due to the confounding influences on the marrow dose of the precise distribution of active marrow and of target cells within the active marrow, and the effect of the presence of bone, which influences do not apply to the intestine. However, in the case of the intestine, a high dose to a small segment may be sufficient to lead to death (this is not true in the case of marrow). Also, because of the greater RBE values for the intestine, the contribution of gastrointestinal injury, i.e., haemorrhages and infections, to the bone marrow syndrome is greater with neutrons than with low-LET radiation, particularly after doses slightly above the $LD_{50/30}$ [E1, B23, B24]. With unilateral irradiation, severe injury to the skin can contribute to deaths after neutron doses slightly higher than the $LD_{50/30}$ [B25].

6. Modification of the $LD_{50/60}$ by post-irradiation treatments

132. The management of persons after irradiation or combined injuries has been discussed in a number of publications (e.g., [B57, C50, C51, W28, W29]). However, the value of routine medical treatments after irradiation in man is uncertain because there are no suitable groups, treated or untreated, with which the treated groups can be compared. The populations in Hiroshima and Nagasaki received minimal medical treatment owing to the destruction of the already sparse supplies and facilities [O5]. The Y-12 subjects at Oak Ridge were treated conservatively, and were admitted to hospital two hours after the accident [B29]. Prophylactic antibiotic treatment was not given, nor were bone marrow transplants. Antibiotic treatment was given to two patients for mild oropharyngeal infections. The subjects at Vinca were treated more extensively [J2]. They received antibiotics on the day of the accident and thereafter when necessary. They were barrier-nursed and given injections of packed red cells and transfusions of platelets when necessary. The patient who later died had received a transfusion of foetal and later adult haemopoietic tissue. The other four subjects apparently showed a favourable response to the transplants, with parallel changes in the blood and bone marrow and clinical condition. However, because the haemopoietic cells were given at 27-36 days after irradiation, when endogenous recovery would be expected to have begun, it is difficult to judge the degree of efficacy of the transplants. The radiotherapy cases [R6] were barrier-nursed, with antibiotics given for febrile infections. Platelet transfusions were given on two occasions. The Appendix describes the extensive treatment, including marrow transplants, given to the victims of the accident at Chernobyl.

133. The use of antibiotics is reported to have been beneficial in large animals. Monkeys, whose $LD_{50/30}$ is 6.0 ± 0.2 Gy without the use of antibiotics, were given doses of 8.2 Gy, which would normally result in less than 5% survival [B30]. Antibiotics given between 1.5 days before and 14 days after irradiation increased the survival rate to 28% (7/25), and the addition of

typhoid vaccine to the treatment protocol to hasten marrow regeneration gave a survival rate of 36% (5/14). The estimated $LD_{50/30}$ was increased to 7.5 Gy, i.e., by a factor of 1.25. The medications prevented most of the diarrhoea and anorexia observed in the monkeys who had been irradiated but not treated. These latter animals died between days 10 and 13 of septicaemia due to enteric organisms.

134. Other studies with animals have combined antibiotics with other supportive treatments such as fluid replacement and blood or marrow transfusions. In dogs, platelet transfusions, together with antibiotics, were successful in overcoming the critical period of haemopoietic failure between day 10 and day 20 after doses near the LD_{50} [S9, P4]. Mortality after three dose levels, where the mean survival times were about 14 days, was decreased from 9/10, 5/5, and 5/5 to 2/10, 2/5, and 1/5, respectively [P4]. Six of 12 monkeys, irradiated with lethal doses of 8-8.9 Gy and treated with autologous marrow and routinely with antibiotics, survived to seven weeks, and five of these survived to at least one year [S2]. All seven monkeys receiving the autologous marrow but antibiotics only symptomatically died between days 7 and 23. Also, six monkeys irradiated with 8.5-9.5 Gy then treated by autologous marrow 2.2-12.9 10^6 cells survived over 50 days, in contrast with a mean survival time of 14.5 days for six irradiated monkeys that had not received the graft [C19]. Only three of 18 monkeys similarly irradiated but receiving 8 10^5 homologous bone marrow cells survived to 30 days. All of these monkeys developed graft-versus-host disease; 14 out of 18 showed recovery of haemopoiesis from the donor cells, but only two survived to 30 days. Another series of experiments with monkeys showed that the $LD_{50/30}$ could be increased by a factor of about 1.8 using injections of 2-4 10^8 autologous bone marrow cells per kilogram body weight, and thrombocyte concentrates, erythrocytes and prophylactic antibiotics when necessary [B23].

135. From the limited evidence available, the efficacy of post-irradiation treatments after neutrons appears to be similar to their efficacy after low-LET radiation. The increase, by a factor of about 1.8, in $LD_{50/30}$ for monkeys, brought about by injecting 2-4 10^8 autologous marrow cells per kilogram body weight after irradiation, was found for both x rays and fission-spectrum neutrons [B23].

136. When the platelet level falls markedly below 20,000 per μl of blood, transfusion of platelets will help prevent bleeding. Infusions of granulocytes would be expected to help combat infections, but the short half-life of these cells (6.7 ± 1.4 hours in man [M6, A9, B16]) makes this procedure difficult to realize in practice.

137. The studies with large animals described above demonstrate that conventional supportive medications and transfusions of blood elements after irradiation can increase the $LD_{50/30}$ by as much as 1 Gy [B30, P4, S9]. Although this dose increment may appear small, the corresponding survival rate would increase quite markedly because of the steepness of the dose-response curve (Figure XXI).

138. Clinical data on the efficacy of bone marrow transplantation after irradiation refer mainly to the treatment of leukaemia; the results are confounded by the disease itself, concomitant cytotoxic treatment and other supportive measures. By extrapolating to man the relationship between body weight and the number of injected autologous marrow cells required for rescue of 50% of animals after LD_{100}, a value of 2 10^7 cells per kg was deduced for man [V11]. For 100% rescue, 4 10^7 cells per kg was estimated. The minimum cell dose for rescue after lethal whole-body doses to leukaemic patients using HLA identical allogeneic bone marrow cells is approximately 1 10^8 per kg body weight [T6]. This is compatible with the above extrapolations for healthy individuals, because in mice and dogs approximately four times as many allogeneic as autologous marrow cells are required for rescue [V9, V10]. Foetal liver is also an important source of haemopoietic stem cells for transplantation purposes, e.g., [W30]. The experience with bone marrow and foetal liver transplantation to the victims of the Chernobyl accident is described in the Appendix.

B. EFFECTS OF DOSE PROTRACTION

139. Protracted or fractionated doses are usually less injurious than are single doses, for two main reasons. First, cells are capable of repairing sublethal radiation damage. This process is complete in six to eight hours, and the attending increase in survival is generally greater after higher doses than after lower doses. Repair of sublethal damage can also be described by an increase in the total dose required to achieve a given level of cell killing or tissue injury. The sparing effects of protracted or fractionated irradiation are much less important after high-LET radiation, because such radiation produces much more irreparable damage than low-LET radiation.

140. Second, repopulation of cells may take place during the overall time of irradiation. The time of onset of compensatory proliferation is specific to a given tissue. It occurs once depletion of the normal complement of mature cells has been recognized. In the intestine, repopulation usually commences within a few days of the beginning of irradiation and in skin it commences after about two weeks. The doubling time of regenerating clonogenic cells is usually about one day, and may be less. The doubling time is longer than the cell cycle time because of concomitant differentiation of the clonogenic cells and hence their loss from the precursor cell pool. The cycle time during regeneration is much shorter than before irradiation, and there can be an increased number of divisions in the amplifying proliferative populations, leading to a transient overshoot in the mature cell populations. Low dose rates, 0.4-2.7 Gy per hour, can block cells in the cycle and prevent cell division [M36].

141. Of the main tissue responses described in this Annex and occurring within a few months of irradiation, the lung shows a greater sparing effect of dose protraction or fractionation over a week or two than the intestine or skin [T24, U4] (the marrow shows a lesser effect). Empirical formulae have been devised to

describe the increase in dose that is tolerated with protraction or fractionation in radiotherapy. With dose protraction, the increase in iso-effective dose with increasing irradiation time, T, can be described by the formula

$$\text{Dose} = \text{Constant} \times T^{m}$$

where m is the exposure-time coefficient. Alternatively, $D = \text{constant} \times R^{m/(m-1)}$, where R is the dose rate. The formula is applicable over a limited range of exposure times, which, like the value of the coefficient, varies between tissues [T24]. For human skin tolerance, m is about 0.29.

142. The most widely used description of fractionation effects is the Ellis formula [E3], in which the number of fractions and the overall time are variables. According to Ellis,

$$\text{Total dose} = \text{NSD} \times N^{0.24} \times T^{0.11}$$

where NSD is the nominal standard dose and the exponents 0.24 and 0.11 apply to early skin reactions. The formula is generally considered valid for between 4 and about 30 fractions, and it is recognized that different exponents apply to different tissues [T24]. Variations on the formula that consider partial tolerance, time-dose factors and cumulative radiation effects (CRE) have been described [T24, U4].

143. An alternative to these power-law relationships has been described more recently; the linear-quadratic relationship [D20]. It is considered to be more representative than the Ellis formula of the relationship between total dose and fraction size over a larger number of fractions, when the overall time is less than a few weeks and does not influence the dose required for a given effect [F4]. The effect E in a tissue of a series of n fractions each of dose d is given by:

$$E = n(\alpha d + \beta d^{2})$$

where α (Gy^{-1}) and β (Gy^{-2}) are constants. When n and d are changed from n_1 and d_1 to n_2 and d_2, total doses D_1 and D_2 resulting in the same effect E are related by

$$D_2/D_1 = n_2d_2/n_1d_1 = (\alpha/\beta + d_1)/(\alpha/\beta + d_2)$$

The ratio α/β is tissue specific. Lower values indicate a greater sparing effect of fractionation, e.g., $\alpha/\beta \sim$ 2-4 Gy for pneumonitis, and higher values indicate less of a fractionation effect, e.g., $\alpha/\beta \sim$ 10-20 Gy for early skin reactions [T24].

1. Prodromal responses

144. Comparatively little is known about the effects of dose rate or fractionation on prodromal responses, but there is some decreased effect due to dose protraction. The information comes mainly from radiotherapy treatments, and different centres have used different dose rates. Even when the same dose rate is used, the severity of prodromal symptoms after a given dose has differed between centres. For example, only two out of eight patients with haematological malignancies given 10 Gy (0.05 Gy per minute) had nausea during irradiation, with vomiting after 5-7 Gy [C35]. In contrast, all seven patients with a similar condition treated by Thomas et al. [T17] developed nausea, and six out of seven vomited towards the end of irradiation. Prodromal symptoms were more severe when the dose rate used to give 3 Gy to patients with Ewing's sarcoma was 0.3 Gy per minute [R6], compared to 0.03 Gy per minute [M34]. With whole-body irradiation prior to marrow transplantation, it was noted that the onset of nausea and vomiting was related to total dose, but not to the rate at which the dose was given, except possibly in the case of dose rates of less than 0.06 Gy per minute [B32]. The incidence of vomiting was about 10% in the 64 Rongelap natives exposed to fallout doses estimated to have been about 1.75 Gy, where the dose rate decreased from about 0.055 Gy per hour at the start of irradiation to about 0.016 Gy per hour after 50 hours [C16]; vomiting appeared in slightly less than 40% of accident cases and radiotherapy patients after estimated acute doses of similar magnitude (Figure V). There is no accurate information concerning high-LET radiation.

145. In monkeys, the latent period to retching or vomiting after 4.5 Gy was increased by a factor of 3 (from 30 to 90 minutes) when the dose rate was reduced from 1.2 to 0.07 Gy per minute [H35, H36]. Most of the increase occurred between 0.5 and 0.15 Gy per minute. In dogs, routine emesis during irradiation with 18 Gy could be avoided by reducing the dose rate from 0.18 to 0.05 Gy per minute [H38].

146. In the radiation accident in Mexico City in 1962, the individual receiving the highest dose delivered at 3.0 Gy per day for seven days and 0.25 Gy per day for a further 17 days, had anorexia and vomiting only after the seven days of exposure at the higher dose rate [M3]. In the individual receiving the lowest dose of about 1 Gy over 106 days of exposure at 0.09-0.16 Gy per day, fatigue was reported on day 36, but there were no intestinal symptoms.

147. An extensive series of studies was performed on patients receiving abdominal radiotherapy with 45-55 Gy (midline dose) given in 2 Gy fractions, five per week [B56]. Nausea and vomiting appeared after the first few sessions. These symptoms were highly variable in severity and they lasted for about a week. The effects were more frequent and intense after either the upper half of the abdomen or the epigastric region had been irradiated. Diarrhoea occurred during the third week when the total accumulated dose had reached 25-30 Gy, particularly in women where the field included the lower abdomen. Gastric pain was experienced by men irradiated in the epigastric region, but only rarely did diarrhoea occur in those who received irradiation to the lower abdomen and pelvis. The apparent sex differences may reflect technical differences in the irradiations.

148. Retrospective studies on 2,000 patients receiving whole-body irradiation showed increases in ED_{50} values when doses were protracted over eight days or more (Figure XXIV) [L9]. In 1,085 patients given small, daily whole-body exposures, 20-30 R (about 0.15-0.20 Gy to the stomach) per day for 30 days or

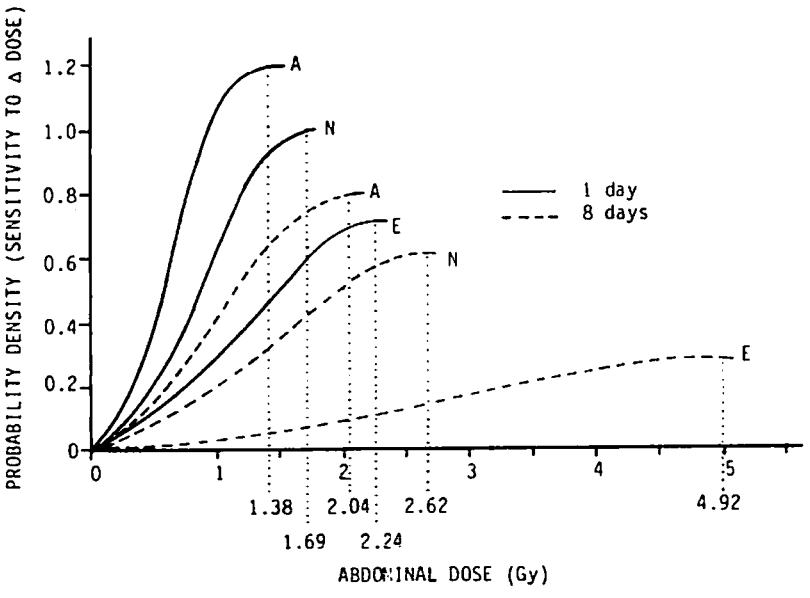


Figure XXIV. Changes in incidence of prodromal symptoms for fractionated doses in man. Fractionation of total body dose over eight days increases the doses required to produce the same incidence of various prodromal symptoms in the exposed population of patients by 1.5 for anorexia (A), 1.6 for nausea (N) and 2.2 for emesis (E).
[L9]

more were required to cause prodromal symptoms. Exposures from 10-20 R (about 0.075-0.15 Gy to the stomach) per day produced nausea infrequently, even when these exposures were delivered rapidly at approximately daily intervals for 3-4 weeks, and exposures of 5-6 R (about 0.04 Gy to the stomach) per day produced no symptoms [L9]. Patients irradiated at very low rates (less than 1.5 R, about 0.01 Gy per hour to the stomach) and receiving less than 30 R (about 0.20 Gy to the stomach) per day also showed a lack of prodromal symptoms, except fatigue [R5].

2. Intestinal responses

149. Studies of human intestinal mucosa have been made during and after x-ray therapy, using serial biopsies from patients irradiated to the abdomen for malignant disease [T9]. Exposures of 2,000-3,300 R (15-20 Gy to the intestine) delivered in daily fractions of about 1-2 Gy produced during the treatment a decreased mitotic activity in the crypts, a decrease in the absorptive surface area of the bowel, and an increased infiltration of the lamina propria by inflammatory cells and plasma cells, with occasional crypt abscess formation. Both the mitotic activity in the crypts and the mucosal surface recovered by two weeks after the end of treatment. Gastrointestinal malabsorption was reported in patients during irradiation to the abdomen with daily fractions of 1-1.5 Gy, to a total of about 30-40 Gy in five weeks [P1], or fractions of 2 Gy to a total of 45-55 Gy [B5]. Biopsies of rectal mucosa taken from radiotherapy patients receiving a total dose of 42.5 Gy in 10 fractions for bladder and cervix cancer showed a depression in total cells per crypt during treatment, with recovery to control values by day 70 after the last fraction [W10]. The number of fibroblasts in the crypt sheath was depressed by the end of the fractionation schedule; this was followed by recovery, but there was a subsequent depression at days 360 to 800 after irradiation.

150. Low-dose rate or multifractionated radiation spares the intestine in all species quite substantially [U4]. With radiotherapy treatments, tolerable fractionated doses are in the middle of the range accepted for all tissues in the body [R12]. The small intestine, rectum, colon and stomach, in this order, are the most responsive regions [F2] and will tolerate not more than 40 Gy delivered over four weeks to large volumes of tissue. Dose-mortality relationships for man due to protracted intestinal irradiation in man are unknown.

3. Haematological responses

151. Protracted irradiation is generally less efficient than acute irradiation in reducing the number of blood neutrophils. However, this effect was not detected when the overall exposure time was relatively short, as in the case of the Marshall Islanders given 1.75 Gy over 50 hours, where the haematological responses were those expected after a similar dose delivered acutely [C15, C13]. With further protraction, there is less effect per unit dose. For example, in the Mexican accident [M3], the one survivor received between 9.8 and 17 Gy over 106 days, and his lowest recorded blood cell counts were 2,000 white cells per μl and 70,000 platelets per μl.

152. The dependence of the nadir in WBC count on total dose and exposure time was described by Yuhas et al. [Y2], who analysed data for 121 patients with non-

haematological malignancies receiving fractionated whole-body irradiation over various periods of time. The relationship was:

$$\text{Per cent WBC} = K \times 100 \times D^{-b_1} \times T^{b_2}$$

where K is a constant, required for extrapolation to the ordinate at zero dose because no effect was seen below 25 R (about 0.15 Gy to the marrow); D/0.0075 is the total marrow dose in Gy; b_1 is the slope of per cent WBC on D/0.0075; T is the time of protraction in days; and b_2 is the slope of per cent WBC on T. For the patients with non-haemopoietic malignancies and with normal initial levels of WBC, $b_1 = 1.04$, $b_2 = 0.63$. The contribution to the observed effect from the diseases of these patients is unknown.

153. The recovery of marrow in irradiated leukaemic patients was slower than in patients with non-haematological malignancies [Y2]. This was deduced from 2,000 case histories where fractionated treatments had been given. Values of the coefficient b_2 were markedly different from the value of 0.63 for patients with non-haematological diseases, being 0.392 for patients with chronic myeloid leukaemia (CML), 0.221 for chronic lymphocytic leukaemia (CLL) and 0.231 for lymphosarcoma (LS). The values of b_1 were not markedly different from one another, being 0.999 (CML), 0.91 (CLL) and 1.119 (LS). The analysis indicated that the greater sensitivity of WBC levels in leukaemic than in non-leukaemic individuals was associated more with dose protraction and recovery phenomena than with total dose.

154. A study was made of patients in remission receiving fractionated whole-body irradiation over four days prior to cyclophosphamide and bone marrow transplantation for acute lymphocytic and non-lymphocytic leukaemia and chronic myeloid leukaemia [S5]. From blood samples taken during the fractionated course of irradiation, an effective D_0 of 3.7-5.4 Gy was deduced for lymphocytes and about 10 Gy for granulocytes. This confirmed that the greater radiosensitivity of lymphocytes (relative to granulocytes) applies also to fractionated doses. The values of sensitivity refer to cell numbers measured within a few hours of a dose fraction and not to the later nadir levels. In a similar study using 11 fractions of 1.2 Gy given over four days, the decline in lymphocyte numbers during irradiation was characterized by $D_0 = 1.2$ Gy [D22]. Further, the decline was similar for B- and T-cells and for the OKT4 and OKT8 lymphocyte subsets. Low whole-body doses of 0.1-0.15 Gy, given twice weekly to a total dose of 1-1.5 Gy for the treatment of generalized lymphocytic lymphoma and lymphosarcoma, produced a drop in the white cell and platelet counts, both of which reached a nadir at 4-5 weeks after completion of the irradiation [J20, J21].

155. A continuing decrease in granulocyte/macrophage colony-forming cells (GM-CFC) in bone marrow and blood during irradiation, followed by regeneration after irradiation, was reported in patients treated for malignant lymphomas using whole-body doses of 0.1 Gy delivered three times per week to a total of 1.1 Gy [L19]. In contrast, studies of the concentration of GM-CFC in the blood of five patients receiving whole-body irradiation (1.5 Gy in 15 days) for various metastatic cancers showed an increase around day 10 during the irradiation [T18].

156. GM-CFC have also been measured in patients receiving fractionated partial-body irradiation. After irradiation of 16%-30% of the total marrow in patients with various malignancies (carcinomas of the cervix, lung and rectum), a significant decrease in GM-CFC per millilitre of blood took place between days 5 and 14 after the start of treatment, by which time the cumulative doses were between 4 and 14 Gy [B48]. Between days 15 and 24 after termination of therapy delivered over several weeks, the GM-CFC per millilitre of blood were about 12% of normal and thereafter increased slowly to 24% on day 45. After doses of 30-40 Gy (five 2-Gy doses per week) delivered to 25-45% of the marrow of patients with Hodgkin's disease or non-Hodgkin's lymphomas, the ablated marrow repopulated slowly over a period of months (the repopulation was faster in larger irradiated volumes) [D16, M37].

4. $LD_{50/60}$ in man

157. There have been few instances where the number of individuals exposed to near-homogeneous protracted irradiation has been sufficient to allow an estimate of the change in $LD_{50/60}$ with dose protraction. The only information relates to a few accidents, from groups of individuals receiving irradiation from atomic bomb tests, and to radiotherapy patients receiving low-dose-rate or fractionated whole-body irradiation. Some examples of protracted whole-body exposures are given in Table 19. The 64 individuals exposed to doses of about 1.75 Gy from fallout radiation received most of their dose in the first few hours. The average exposure rate over 50 hours was about 0.03 Gy per hour, decreasing according to $t^{-1.2}$. The haematological responses were those expected for similar doses given at high dose rate, and hence any dose rate effect was small [C15, C13]. The other individuals in Table 19 received exposures over 5-115 days.

158. An accident occurred in Goiania, Brazil in 1987 [123] which resulted in initial acute whole-body external exposures followed by low dose rate chronic whole-body exposure from internally deposited ^{137}Cs chloride (from a damaged teletherapy source). In addition, many persons received acute localized radiation injuries (beta/gamma) to the skin and deeper tissues. Twenty-one persons required intensive medical care. Ten persons were critical with dose estimates (cytogenetic dosimetry) ranging from 3-7 Gy. Four persons died as a result of their exposures. In addition to good nursing care, antibiotics and platelet transfusions, the experimental drug granulocyte-macrophage colony-stimulating factor (GM-CSF) was administered to eight patients suffering from the acute radiation syndrome. Four of the patients who received GM-CSF subsequently died as a result of their radiation insult. The efficacy of using GM-CSF was not demonstrated.

159. Several formulae have been proposed to calculate equivalent doses for mortality when the dose is protracted, and these are empirical guides to changes in dose. One of the first to be proposed involved the equivalent residual dose (ERD), which was the dose required to cause equivalent injury in an unexposed individual.

$$ERD = D_1[f + (1 - f)e^{-t/r}]$$

where D_1 is the dose delivered in a single exposure, f is the fraction of the total injury that is irreparable, t is the time in days that has elapsed since exposure and r is a constant equal to the repair half-time in days divided by 0.693 [L4]. The ERD during protracted exposure at a constant dose rate is calculated as

$$ERD = D_d[ft + r(1 - f)(1 - e^{-t/r})]$$

where D_d is the dose rate and t is the exposure time in days [L33, N12]. The recovery half-time in man was postulated to be 15-35 days and f to be 10%, on the basis of sparse clinical results and extrapolation from animal data [L4, N12].

160. A power function was proposed [L9]:

$$\text{Iso-effective (fractionated) } LD_{50} = LD_{50}\text{(1 week exposure)} \times t^{0.26}$$

where t (in weeks) is longer than one week. This formula was deduced from the whole-body irradiation of cancer patients, where the LD_{50} (one-week exposure) was taken to be 3.45 Gy. It was suggested that the exponent 0.26 might be 2 or 3 times higher for healthy people.

161. Another formula has been proposed more recently for calculating accumulated iso-effective doses up to 10 Gy [B10, B21, M19] and up to 100 days exposure [M2, H47]. The operational equivalent dose (OED) for acute exposures is expressed by the formula

$$\text{OED (Gy)} = \text{total accumulated marrow dose (Gy)} - 1.5 - 0.1\,t\text{ (days)}$$

The formula was deduced from a large number of dose rate and fractionation experiments in various animal species including mice, guinea pigs, sheep and swine [M19]. The dose of 1.5 Gy in the formula represents the average amount of dose recovered in the first day among all species, and thereafter an extra dose per day (dependent on species) is required to counteract repopulation. A dose of 0.1 Gy per day is assumed for man. In view of the differences in the values of the constants between species, the formula is considered suitable only as a guide and not as an accurate assessment [M13]. It is intended for application in circumstances where a large initial dose is given. The maximum value of OED is transformed into the expected mortality using the dose-mortality curve for an acute exposure. Negative values have no meaning. Also, the relationship applies only to mortality from marrow damage.

162. The above formulae are consistent with the data for single and fractionated exposures in man (Tables 11 and 19), but they should be taken as only a very rough guide.

5. Skin

163. Information on the response of skin to fractionated doses of irradiation comes mostly from radiotherapeutic experience. This information was reviewed in detail in the UNSCEAR 1982 Report [U4], and is summarized here, together with more recent information.

164. Dose-incidence curves for erythema using fractionated doses (Figure XXV) have been measured using reflectance spectrophotometry [T21]. The measurements were made on patients irradiated using two parasternal fields, each 5 × 12 cm.

165. A dose-survival curve for epidermal clonogenic cells in situ was measured in patients receiving fractionated radiotherapy to an area 22-24 cm × 15-18 cm on the chest wall [A5]. The total doses ranged between 63 and 72 Gy and were given in 34 to 48 fractions. Cell sensitivity was characterized by $D_0 = 4.9 \pm 1.5$ Gy for these fractionated doses, a value compatible with predictions from extensive information in mice.

166. Data obtained by various radiotherapists since about 1930 were reviewed and analysed by Cohen [C7, C21], and these data formed the basis for the Ellis formula [E3]. The nominal standard dose (NSD) is about 18 Gy for skin tolerance when areas of 35-100 cm^2 are irradiated. The exponents of N (number of fractions) and T (overall time) also apply if the end-point is erythema, because the slopes of the iso-effect curves are similar, but the doses are lower. Also, the same exponents apply for different field sizes, where the values of NSD differ according to the formula given in section I.D.1.

167. For early skin reactions, the α/β ratio is generally considered to be in the range 10-20 Gy. For erythema on the chest wall, ratios of 8.4 Gy, 21.9 Gy and 21.5 Gy were determined at incidences of erythema of, respectively, 16, 50 and 84% [T21].

168. The influence of dose rate on skin reactions is known from the results of radiotherapy. Curves relating total dose and dose rate to produce "tolerable"

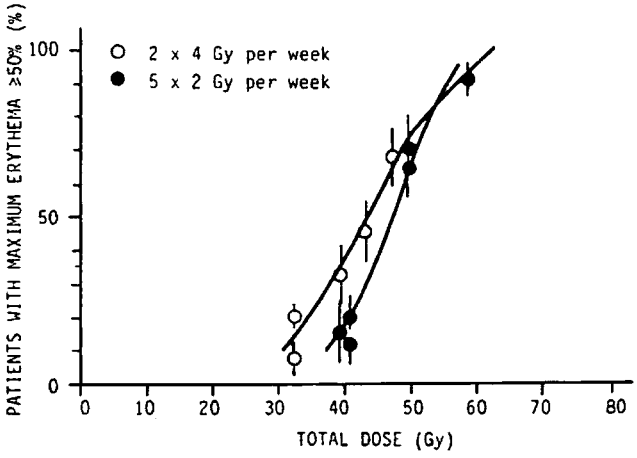


Figure XXV. Dose-incidence curves for human skin erythema. [T21]

reactions, mainly in skin, were presented by Hall [H1]. An equation describing the shape of these curves [O3] has the form

$$T = 2.1 \times 10^4 \times r^{-1.35}$$

where T is the treatment time in hours using dose rate r (Gy per hour × 0.01).

169. The time course of skin reactions is similar after neutrons or after x rays [F1]. The RBE value for single doses of neutrons (16-MeV D on Be) producing erythema on 5 cm × 4 cm areas of thigh skin is about 3.0, with reference to 8-MeV x rays [F1]. Earlier work using 200-kVp x rays as the reference radiation [S11, S12] also gave a value of about 3.0 when the original "doses" were converted to Gy [B15] and 3.5 when using (8-MeV D on Be) neutrons. For fast neutrons, the exponent of N is reduced to 0.03 [F1].

170. Radiation-induced skin injury was evident in 19 patients involved in the Goiania accident (1987). Lesions were present on hands, feet, legs, armpits and numerous small areas on chest, abdomen, face, arms and the anterior medical aspects of the legs. Skin injury was due to beta radiation from contamination (external) and to deeper underlying tissues from penetrating gamma radiation. Beta injuries healed within 3 months after exposure followed by expression of gamma injuries to deeper tissues. None of the local injuries among Goiania victims were as extensive as in the victims of Chernobyl. The clinical interpretation of this difference was that the Russian victims suffered from combined-injury disease including thermal and beta burns while the Brazilian ones were from radiation only.

6. Lung

171. The lung is spared by the use of low-dose-rate or fractionated irradiation [B32, K1, M38]. The dose for 5% incidence of pneumonitis can be increased from 8.2 Gy to about 9.5 Gy using 0.05 Gy per minute instead of 0.3-0.5 Gy per minute [K1]. The patients receiving low dose rate also received chemotherapy, which may have reduced lung tolerance. Hence the effect of reducing the dose rate may be greater than observed. This possibility is suggested by experiments with mice, where the ratio of LD_{50} values at the two dose rates was 1.8 without the use of chemotherapy [H17] and 1.3 when cyclophosphamide was given [L32].

172. With fractionated irradiation the total dose can be increased even further [M38, P5]. With prophylactic lung irradiation in the treatment of osteosarcoma, no pneumonitis was seen in 40 patients given 20-25 Gy to the lung in daily dose fractions of 1.5 Gy [N8]. This was in contrast to seven patients in whom pneumonitis was observed after 30 Gy delivered at 3 Gy per day. There was no pneumonitis in a further 14 patients given 24-25 Gy in 13 daily doses to the lung [N9].

173. In the Ellis formula [E3], the combined exponents of N and T were estimated to be 0.43, with an NSD of about 9 Gy equivalent (7 Gy with concomitant actinomycin D) [P5]. The combined exponent was deduced from a series of 26 patients treated to at least one whole lung for metastatic lung disease, using cobalt-60 gamma rays or 1-MV x rays, together with a series of fractionation data using lethality in rats after lung irradiation. Although the separate exponents of N and T have not been estimated for man, in mice the exponent of T is about 0.07 [U4]. The exponent of N is about 0.39 between one and eight fractions, and about 0.25 between 8 and 30 fractions [U4]. Alternatively, iso-effective doses for different fractionation schedules using short overall times can be calculated using the α/β formulation, where α/β for mouse lung is 2-4 Gy [T24].

174. A recent analysis has been made of 54 patients with various thoracic malignancies given irradiation to various lung volumes in daily fractionated doses [M38]. No previous treatments had been given. The incidences of pneumonitis in five groups of these patients are given in Table 20. The groupings were made on the basis of biologically equivalent doses in different schedules. No significant differences were observed in the incidence of pneumonitis for patients given irradiation to less than one quarter of the total lung volume and patients with irradiations of between one quarter and one half of the total lung volume.

7. Gonads

175. Contrary to what happens in other tissues, fractionated doses to the testis are more effective than single doses in damaging spermatogenesis in animals [U4], because of the progression of cells into sensitive stages. This is also observed in man [L13]. Compared to single doses of the same total amount (5 Gy), 20 doses of 0.25 Gy produced a more rapid drop in the number of sperm cells, and more time was required for recovery [L13].

176. Most of the quantitative data on the effects of fractionated irradiation on the testis come from the treatment of malignant disease by radiotherapy [I9, U4]. Fractionated doses of 0.5-1.0 Gy produce temporary aspermia beginning at about three months [S1]. Fractionated doses of 2-3 Gy produce long-lasting aspermia at 1-2 months [S1].

177. The few measurements of testicular hormone levels in accident cases receiving protracted irradiation are consistent with the planned study referred to earlier using single doses [R11]. After accidental exposure to iridium-192 gamma rays for various periods of time in a seven-day period, the levels of serum follicle-stimulating hormone were constantly elevated and luteinizing hormone was variably depressed after a dose estimated to have been 1.75 Gy to the testes [W1].

178. The total doses of fractionated radiation needed to cause temporary or permanent female sterility are higher in some studies than in others using single doses [I9, U4], but it is difficult to assess accurately the increase in the total doses. In mice, fractionation clearly has a sparing effect on fertility [R13]. Fractionated doses of 4-7 Gy to the ovaries of older

women induced artificial menopause in the majority of cases. Higher doses, 12-15 Gy, were required in young women [A8].

179. Serum gonadotrophin levels were unaffected by doses of up to 1.5 Gy given in fractions over 28 days to a series of patients treated for Hodgkin's disease by oophoropexy followed by irradiation [T7]. A series of patients received pelvic irradiation for carcinoma of the cervix, to a total dose of 60 Gy using doses of 9-12 Gy per week in 3-5 fractions [B12]. Levels of follicle-stimulating hormone rose immediately following doses of 5.6-24 Gy among different patients; the levels of luteinizing hormone rose after doses of 11.3-26 Gy. The levels of oestradiol in the peripheral blood decreased after doses of 6-12 Gy.

C. INTERNAL EMITTERS

180. Large amounts of internal emitters are required to produce early effects in man. Amounts this large would be received in therapeutic treatments and, possibly, in accidents or from nuclear fallout [D23]; in the case of nuclear fallout, however, external irradiation might provide the majority of the dose and could therefore be responsible for producing the early effects. Large amounts of internal emitters have been used to treat certain cancers. The dosimetry is complicated by tissue distribution, decay rates and clearance rates. More uniform distribution of dose to the body is produced by elements that are not taken up by specific organs (e.g., iodine by the thyroid, phosphorus by the marrow), and the whole-body dose depends on the circulation time before uptake. Dose rate, cumulative doses, spatial distribution of dose and the effects of internal emitters on tissues in animals were discussed in detail in the UNSCEAR 1982 Report [U4].

181. Haematological injury has been reported in man after the therapeutic use of colloidal gold, radioiodine, radiophosphorus and radiosulphur. Radiocolloids have been used to irradiate serosal surfaces following the accumulation of fluid and disseminated tumour cells. An activity of 550 MBq colloidal ^{198}Au in 40 ml saline injected into the peritoneal cavity resulted in total doses to the retroperitoneal lymph nodes, the omentum and the peritoneal serosa of 77.5, 67.5, and 47.5 Gy, respectively. Mild radiation sickness and haematological complications such as persistent leukopenia, were reported [H7]. The dose to the marrow from this treatment is unknown, but it would have been very inhomogeneous. Overdosage using 7,400 MBq of ^{198}Au resulted in estimated doses of 73 Gy to the liver and spleen and 4.4 Gy to the marrow [B40, S23], giving rise to pancytopenia, with a tendency towards recovery by day 60-70. However, on day 69 the patient died of cerebral haemorrhage, with concomitant severe thrombocytopenia.

182. The use of radioiodine to treat metastatic thyroid cancer is limited generally by the dose to bone marrow. Doses of 3,700 MBq of ^{131}I delivered in excess of 0.5 Gy to the plasma and caused sialadenitis in about 50% of patients. Bone marrow depression may be observed after multiple doses or large single doses of ^{131}I; however, this can be avoided by administering doses with individual activities not exceeding 5,500 MBq at intervals of two or more months [H2]. The accumulated dose to the blood can be as high as 5 Gy [S8]. In a large series of patients, about 3 Gy were delivered to the blood from ^{131}I-sodium iodide; after nausea, the most frequent serious complication was depression of the bone marrow [B9].

183. Detailed immunological studies have been performed on 34 patients treated with 1-3 doses of 300-350 MBq ^{131}I for toxic or atoxic nodular goiter [W27]. Blood lymphocyte counts were reduced to 60-80% at both one week and six weeks after treatment, and the frequency of lymphocytes expressing receptors for C3 (EAC-rosette-forming cells) was also reduced. At six weeks there was a small increase in the frequency of T-cells, identified by Leu-1 monoclonal antibodies; this was due to an increased proportion of helper/inducer T-cells, identified by Leu-3 monoclonals. The ^{131}I also decreased the capacity of lymphocytes to secrete IgM when stimulated with pokeweed mitogen. Less effect was seen for IgG and IgA. The mitogenic responses of lymphocytes to PHA and ConA were not changed significantly.

184. Radiophosphorus (^{32}P) has been used widely for the treatment of polycythemia vera. Single or multiple doses are given to reduce the polycythemia, and the activity per treatment, 140-220 MBq, delivers a cumulative dose to the marrow of about 1.4 Gy [S10]. The dose rate decays with a half-life of 6.7 days. Overdosage was reported with a patient who received 14.8 MBq per kg body weight [C33]. This patient showed a mild and reversible pancytopenia. Two patients were given 1,850-2,220 MBq, which delivered a cumulative dose of about 10 Gy to the marrow [G16]. Three weeks later there was agranulocytosis, severe thrombocytopenia and marrow aplasia. Haemopoiesis recovered spontaneously from day 40 after treatment. Blood counts returned to normal in one patient, but mild thrombocytopenia persisted in the other.

185. An immunological study was carried out on 16 patients receiving a single dose of 150-305 MBq ^{32}P for polycythemia [W27]. Blood lymphocytes were reduced 40% by 12 weeks after treatment. The B-cell component was reduced most, but lymphocytes expressing T-cell markers were increased. PHA reactivity was increased, but Ig secretion in response to pokeweed mitogen was reduced.

186. The treatment of chondrosarcoma and chordoma by ^{35}S is limited by the latter's haemotoxicity. In 13 patients, the cumulative activity administered as sequential amounts of 185-222 MBq per kg body weight, was 370-1,780 MBq per kg of body weight, giving a total dose to the marrow of about 9.9 Gy [M7]. The first dose had minimal effects in most patients, but with each successive dose, marrow depression increased and recovery decreased. Thrombocytopenia, leukopenia and, later, anaemia developed progressively and were dose-related.

187. Severe acute injury to the intestinal mucosa has not been reported from internal emitters in man. The highest radiation dose would be received by the large intestine, because the contents of the gut have a long residence time at in this site. The critical cells are the stem cells in the crypts, the dose at this position is the most important. Experiments in dogs indicated an $LD_{50/8}$ corresponding to 130 MBq per kilogram body weight of ^{106}Ru-^{106}Rh, which delivered approximately 40 Gy to the mucosa over about 18 hours [C18]. Comparisons were made of doses from ^{147}Pm or ^{106}Ru-^{106}Rh resulting in death from gastrointestinal injury. These isotopes have widely differing beta energies, and it was calculated that a dose of 35 Gy of either isotope to the crypt cells resulted in the death of 50% of the dogs [S14]. This dose is comparable to a dose of about 13 Gy of external irradiation delivered acutely [B16]. Values of 35-40 Gy in these experiments with dogs are compatible with similar doses of multifractionated external irradiations in man, which are considered to be tolerance doses in radiotherapy [R9].

188. In the few cases where doses to the human lung from internal emitters have resulted in symptoms of pneumonitis, the inhalation has been very protracted and the doses uncertain. For example, a chemist who had been involved in the separation of radium and mesothorium compounds and who had inhaled radioactive compounds over a long period showed signs of radiation damage to the lungs [D5]. Pneumonitis was reported in a man who had been employed for a long time in the luminous paint industry [R1]. Relationships have been described between the initial dose rate in the lung following inhalation of radioactive particles and their effective half-life in the lung, in relation to the survival of different animal species from pulmonary injury, extrapolated to man [W25]. It was deduced that death from lung injury could be expected in all individuals receiving as little as 7 MBq of an inhaled alpha emitter with an energy of about 5 MeV and an effective half-life greater than 100 days.

189. Effects of internal emitters in animals have been discussed in detail by ICRP [17] and UNSCEAR [U4]. For example, in experiments in which dogs were exposed to beta-emitting aerosols of fused aluminium-silicated particles labelled with ^{90}Y, ^{91}Y, ^{144}Ce, or ^{90}Sr, it was found that the dose to the lungs resulting in death from pneumonitis in 50% of the dogs could be increased by a factor of 5 (^{90}Sr) or 10 (^{91}Y) relative to the acute dose of external radiation [M8]. The dosage increase depends on the half-life of the isotope which governs the exposure time. With long-lived alpha-emitters, the clearance rate from the lung is most important.

190. Two individuals died after working with large amounts of tritium; they had received doses which were estimated to have been in total about 3 Gy over six years and about 10 Gy over three years [M39, S31]. A slow but continuously progressive anaemia was observed, rather than changes in the white cell count. Another individual, who received a lower accumulated dose of about 1.5 Gy over four years, showed only a slight hypoplastic anaemia.

191. Many cases of accidental ingestion of radionuclides have been reported [F10]. Bone marrow effects are particularly marked when the compound is taken up in the marrow (phosphorus) or the bones (strontium, radium) and when the half-life is long. Haemopoietic injury has been reported after the ingestion of, and chelation therapy for, 37 MBq americium-241 delivering 5.5 Gy to the bones over five years [T22] and after the ingestion of radium giving 2 Gy over six weeks and more than 50 Gy over three years [G14].

192. Extensive internal contamination with $^{137}CsCl$ occurred in 22 persons in the Goiania accident (1987). Internal contamination in these 22 individuals exceeded 85 mCi (3,100 kBq). One child in the Goiania accident had internal ^{137}Cs levels exceeding 30 mCi (1,100 MBq). Extensive ^{137}Cs internal contamination prompted the use of Prussian Blue for the first time in radiation accident history. Prussian Blue was effective in enhancing the foecal elimination of ^{137}Cs although high levels of internal contamination remain in many of these people.

193. The treatment of individuals following ingestion of large amounts of internal emitters has been discussed in various publications [D23, I2, I3, I4, N15]. The treatments are based on reduced absorption and retention, enhanced excretion or diminished translocation. Internal emitters reaching the gut can be removed to some extent by the use of emetics, lavage and precipitating agents. Colloidal ion-exchange carriers, e.g., zirconium citrate, are effective when administered within hours of exposure but are themselves toxic. Decalcification therapy, designed to increase bone resorption, enhances only slightly the elimination of radium and strontium, and it does not affect the non-alkaline earth elements, e.g., plutonium. Chelating agents such as DTPA and, more recently, LICAM C [M35] are efficient at complexing rare-earth elements and actinides.

D. BIOLOGICAL AND OTHER VARIABLES

194. Many biological variables are known to affect the response of tissues and whole animals to irradiation [U4]. In this section, only those variables will be considered that may contribute to important differences in the response of tissues in man after whole-body irradiation, namely, oxygen concentration, previous treatment by radiation or other cytotoxic agents, and genetic disorders in the general population.

195. The radiosensitivity of well-oxygenated tissues can be reduced by a factor of 2-3 by excluding oxygen at the time of irradiation. This was seen for skin reactions where a tourniquet applied to limbs enabled the dose given in radiotherapy to be at least doubled [V16]. There is evidence of a slight natural hypoxia in a few tissues in man, particularly avascular laryngeal cartilage, which was sensitized by about 10% by the use of hyperbaric oxygen [H15], and skin, which was sensitized by up to 40%, also using hyperbaric oxygen [V2]. The use of the chemical sensitizers metronidazole

and misonidazole in radiotherapy has not produced any sensitization of normal skin [D4], but there is one reported case of increased oral mucositis [A6].

196. Radioprotectors have been considered as one means of decreasing the effects of irradiation. These radioprotectors include thiol compounds, which must be administered before irradiation, and immunomodulators, which can be given afterwards [e.g., G32]. Many studies, for example those using the Walter Reed (WR) thiol compounds, have been carried out in animals. Protection factors of up to 3 have been reported for the bone marrow in mice, and values of between 1 and 2.5 for a variety of other tissues [D27]. This variation depends on the radiation dose, lower values being observed at higher doses, in part to differences in intrinsic oxygenation status among tissues, and perhaps also to their natural endogenous thiol content [D27].

197. Previous irradiation may influence the response to a second treatment if there has not been full recovery of the tissue. This is a well-known phenomenon in animal tissues, particularly in the skin [B26, H13]. At times greater than six weeks after a large first dose, the tolerance dose is reduced by about 10%, and it can be reduced further by repeated priming doses [H10]. In man, there is little quantitative evidence pertaining to skin, but some radical radiotherapy treatments to the larynx, performed up to 30 years after moderately high doses given for thyrotoxicosis, were tolerated remarkably well [H21]. Intestinal tolerance to second irradiations in man is uncertain. In mice, there is a higher resistance [H3], which is due to induced hypoxia [R4]. With bone marrow in man, there is a greater response to a second irradiation given a few months after the first irradiation [M18, T11, T12]. In animals, the $LD_{50/30}$ for a second irradiation can be greater than or less than the $LD_{50/30}$ for animals not having received any pre-treatment; this depends on the size of the priming dose and the time between irradiations [H10].

198. Many cytotoxic drugs decrease the radiation dose required for a given effect. The effect is achieved by the direct cytotoxic action of the drug and/or by synergistic interaction with radiation. This information was reviewed in part in Annex L of the UNSCEAR 1982 Report [U4]. Interaction effects are a major confounding factor in analysing the radiation response of ill cancer patients treated with other cytotoxic agents.

199. A very small sector of the population may be particularly radiosensitive because of inherited genetic disorders. The relevant data were discussed in Annex I of the UNSCEAR 1982 Report and in Annex A of the UNSCEAR 1986 Report [U4, U10]. The best documented of these disorders is ataxia telangiectasia (AT), which is an autosomal recessive disease. In this disease homozygotes may be present at a frequency of 1 in 40,000 and heterozygotes at a frequency of between 0.5 and 5% [S42]. The signs of AT are progressive cerebellar ataxia, conjunctival and cutaneous telangiectasia, frequent sino-pulmonary infections with sometimes abnormal immunity, a generally hypoplastic lymphoid system and a predisposition to cancer. Death often occurs before the age of 20, from either sino-pulmonary infections or malignancies.

200. Three AT patients, children aged seven, nine and 10, were reported to show unusually severe responses to cancer radiotherapy, particularly in respect to skin responses. Gotoff et al. [G5] described the case of a 10-year-old boy with palatal lymphosarcoma who received 30 Gy to the nasopharynx out of a total planned dose of 40 Gy. He developed marked erythema, severe dermatitis and subsequent deep tissue necrosis. It was concluded that an unusually high radiosensitivity was responsible for his death. A nine-year-old boy with Hodgkin's disease received 27.5 Gy out of a planned dose of 40 Gy to the mediastinum [M20]. He developed severe oesophagitis, the skin became pigmented and desquamated and he later died of respiratory problems. Cunliffe et al. [C20] reported a seven-year-old boy with a malignant lymphoma in the upper lobe of the right lung. After 20 Gy, dysphagia and erythema were noted, and after 30 Gy the treatment was stopped because of the severity of the responses. He died three weeks later. In addition, successful treatment of medulloblastoma in an AT patient was reported using conventional techniques but reducing the dose to one third of standard, in accordance with their findings that the sensitivity of the patient's bone marrow cells was three times normal [H49]. In a survey in 1982 of all known radiotherapy treatments of AT patients, five out of seven individuals were considered to be excessively sensitive to radiation [S30].

201. Cultured skin fibroblasts from AT patients were found to be more radiosensitive to gamma rays than those from normal individuals, by a factor of 2-3 [U4, T2]. With 14-MeV neutrons, this factor was 1.2-2 [P26, P27]. Heterozygotes have a sensitivity intermediate between that of homozygotes and of controls [C4, K2, T2], as detected for example between cell strains using low dose rates [P26, P27].

202. Peripheral blood lymphocytes from patients whose illnesses were associated with autoimmunity, such as rheumatoid arthritis, systemic lupus erythematosus and polymyositis, were found to be more radiosensitive by a factor of up to about 4 than lymphocytes from healthy volunteers or from patients whose illnesses were not associated with autoimmunity [H43]. The increased sensitivity was associated with deficiencies in DNA repair.

203. Other genetic disorders predispose to increased chromosomal injury and tumour induction after radiation. These include retinoblastoma [H4], basal cell naevus syndrome [T4, H4], Fanconi's anaemia [R3, B13], Down's syndrome [T2], xeroderma pigmentosum, Bloom's syndrome [U4] and Huntingdon's chorea [M22, K2, A7, T2]. Although the lymphocytes from some patients with Fanconi's anaemia were more sensitive to radiation-induced chromosome aberrations, fibroblasts from the same patients showed no increased sensitivity, using colony formation as an endpoint [D11]. No accurate estimates of increases in tissue radiosensitivity are available.

204. Other genetic factors in the general population that may affect radiosensitivity have been discussed in [P7]. These include familial deficiencies in glutathione metabolism and variations in genetic constitution mimicking the variations in radiosensitivity between mouse strains and mutants, particularly those with haematological disorders. Also, the radiosensitivity of natural killer cells in the immune system has been reported to be controlled by X-linked genes [B35].

205. Skin fibroblasts were taken from unirradiated sites in six patients who had an unusually severe skin reaction after radiotherapy. The fibroblasts were irradiated in vitro, and survival curves were plotted for colony-forming ability. The cells from five of the six patients showed greater sensitivity than cells taken from individuals whose skin response to radiotherapy was normal [S20].

206. In conclusion, it is believed that the proportion of individuals in the general population who, because of genetic disorders, are likely to show a significantly higher radiosensitivity for acute tissue effects is about 1%. While some of these individuals could of course occur in groups of irradiated individuals being used to calculate the $LD_{50/60}$, their rarity in the general population makes it unlikely that they would have any significant influence on the calculated values.

III. PROGNOSTIC INDICATORS AND BIOLOGICAL DOSIMETRY

A. PROGNOSTIC INDICATORS

207. In cases where persons are exposed to high doses, whether as a result of accidents or of irradiations for therapeutic reasons, it is essential to determine the prognosis as precisely as possible in order to be able to decide on the best treatment. The prognosis after near-lethal exposure is based on three types of data: dosimetric, clinical and biological.

1. Dosimetric data

208. Where doses to the body in general and to the bone marrow in particular can be determined with sufficient precision, it is possible to make a relatively accurate prognosis. This is the case with individuals irradiated for medical reasons or for those irradiated as a result of accidents where the distribution of the dose in the body and the dose rate are reasonably well known. Because all the dose-effect relationships suggested for mortality in man have very steep slopes, a very small shift towards lower or higher doses can cause a large variation in the probability of death. It is reasonable to assume that variability within a single species will be less than, or at most equal to, the variability between different species of similar body size. For different species of similar size, the LD_{50} varies by a factor of less than 2 ([U4] and Figures VII and XXII).

209. Taking estimates of $LD_{50/60}$ for all classes of individuals (healthy and sick), situated at the extremes of a probable range of $LD_{50/60}$ between 2.5 and 5.0 Gy (Figure XXI), and comparing them with an overall average $LD_{50/60}$ of about 3.75 Gy, for example, corresponds to probabilities of mortality of about 20% or 90%, assuming the same form of dose-effect relationship. Figure XXI illustrates these variations, showing, for example, that the 10% probability of death lies between approximately 0.5 and 3.5 Gy and the 90% probability, between 4 and 7 Gy. The large uncertainties preclude a formal prognosis only on an estimate of the dose to the bone marrow.

210. The intensive treatments to which exposed individuals are always subjected may completely change the prognosis. The treatments that are offered following accidental exposures are designed to combat intercurrent infections and aplasia, and they may increase the probability of survival. Those that are offered to patients suffering from neoplastic disorders often involve cytotoxic agents, and they may decrease the probability of survival. In the first case, the individuals are mostly healthy; in the second, the disease affecting the patients is an aggravating factor. In accidents, the higher the dose, the more intensive is usually the treatment; consequently, the slope of the dose-effect relationship may be less steep than the slope of the theoretical curve expressing $LD_{50/60}$ in the absence of treatment. It is possible that, after treatment, the $LD_{50/60}$ may be increased by a factor of (at least) 2 or (at most) 3 [L9, R6, T5].

211. The values of $LD_{50/60}$ are influenced by a variety of factors. The main ones are (a) sex: women appear to be slightly more resistant than men [F15]; (b) age: extrapolation from animals to man suggests that the LD_{50} at birth is lower than the LD_{50} for adults by a factor of 2; the value for adults appears to be attained at around puberty, with a subsequent decrease to minimum values in old age; (c) state of health: the LD_{50} is lower in individuals affected by other diseases, particularly if they relate to the bone marrow or if they reduce the natural immune responses; and, finally, the most important factor, (d) the protraction and/or fractionation of the dose with time.

212. In cases of accidental exposure, protraction and fractionation of the dose can have a very important effect; when irradiation is performed for medical reasons, whether it is whole-body irradiation or successive half-body irradiations, the dose is usually given over a few days to a few weeks. This may also be true with accidental internal exposure to long-lived radionuclides. If the dose is spread over a month or more, the LD_{50} may be increased to 10-20 Gy (see Table 19). The use of a model based on cellular responses and comparing single and multiple exposures used in radiotherapy would give a factor of 2, or an LD_{50} of about 7 Gy for protraction over two weeks [L9].

213. All these uncertainties make it very difficult to establish an accurate prognosis based solely on physical dosimetry. This is particularly true in the case of accidents, where, except for criticality accidents, the exposure time is very difficult to determine, giving rise to an additional error whose magnitude may reach

factors of 2-3 or more. Dosimetry is most valuable in the case of very low or very high doses because, whatever the possible error, one can at least establish whether the patient has been exposed in the non-lethal or the lethal part of the curve (broadly, doses up to 0.5-1 Gy or above 6 Gy).

214. The prognosis is related to the nature of the radiation involved. In accidents, one is generally dealing with penetrating radiation, since out of a catalogue of 98 accidents, 61 were caused by irradiators and 14 occurred as the result of criticality excursions in reactors [H20]. In whole-body medical irradiations, penetrating radiation is also usually involved, depending on which of the effects are desired. The prognosis is particularly difficult to establish in cases of criticality accidents with mixed gamma-neutron fields. There are two types of difficulty in reconstructing the dose: (a) the uncertainties in assessing the values of the neutron and gamma-ray components and (b) the choice of an RBE for the neutrons. The latter choice is particularly difficult, because the RBE varies according to the syndrome under consideration; in addition, the neutrons attenuate more rapidly with increasing depth than do the gamma-rays (see Figure XIX). Also, the simple addition of gamma doses and neutron doses multiplied by an RBE factor, may be an oversimplification and a source of additional error, as already discussed.

215. Another important element in the prognosis is the spatial distribution of the dose. In accidents, irradiation is never homogeneous. Therefore, the concept of average dose in the bone marrow, while useful for establishing an order of magnitude, is insufficient for making a precise prognosis. Relatively small volumes of bone marrow that have escaped exposure or have been only slightly irradiated because of the inhomogeneity of the exposure are sufficient to repopulate sterilized haemopoietic areas through cell migration, as long as the marrow stroma has not been damaged.

2. Clinical data

216. An accident victim will be rapidly admitted to hospital following a reactor accident (after an accident with an isolated irradiation source it may be later before the symptoms and signs of radiation injury are recognized, depending on the dose and the part of the body irradiated). At an early stage, the critical period may not yet have been reached, and prodromal symptoms may be of major importance. The prodromal phase, described in section I.C.1, lasts from the first to the seventh day; it precedes a latency period from about day 7 to day 20 after doses resulting in the bone-marrow syndrome (Table 21). The principal gastrointestinal prodromal signs are anorexia, nausea, vomiting and diarrhoea. The average 50% incidence dose is lowest for anorexia (slightly below 1 Gy) and highest for diarrhoea (between 2 and 3 Gy). Table 22, which summarizes the results of Table 2, may allow a quick prognosis for a patient presenting one or more of these symptoms. Vomiting is an easily detectable prognostic indicator, provided that no psychosomatic factor is involved. Figure V, which expresses incidence of vomiting as a function of dose, allows a preliminary assessment of the dose level and therefore of the prognosis. In addition to defining the dose-effect relationship, the intensity of these phenomena may have prognostic value: vomiting and diarrhoea may be isolated or profuse, and they may or may not increase in frequency. Their intensity and frequency are an indication of the severity. The other prodromal signs are indicators of neuromuscular reaction: fatigue, apathy, fever and hypotension (whether or not followed by hypotensive shock).

217. For doses around the $LD_{50/60}$, the most frequent prodromal indicators are anorexia, nausea, vomiting and fatigue. At supralethal dose levels, other indicators appear, such as diarrhoea, fever and hypotension [L4]. However, the prodromal indicators may occur without necessarily being followed by the death of the individual or by an acute irradiation syndrome. The latency period before their appearance is also a good prognostic feature. The earlier and more sustained is the prodromal indicator, the longer and more difficult is the return to normal, and the higher is usually the dose. Figure IV illustrates the times elapsing before appearance of the prodromal indicators; these range from a few hours for doses of around 1 Gy down to about 20 minutes or so for doses of about 10 Gy [B33]. The same data are set forth in Table 23 [I12], which also lists times of delay for the critical period (latency) and prognoses.

218. Fractionation and protraction of the dose influence the appearance and intensity of prodromal symptoms and signs. Fractionation over one to seven days increases the ED_{50} by a factor of 1.5-2.7, depending on the effect under consideration (see Figure XXIV) [L9]. Table 24 compares the ED_{50} values for the principal prodromal indicators after exposures over one day and over about a week [L9]. These doses are based on a retrospective study of 2,000 radiotherapy patients (whole-body irradiation) receiving doses above 0.3 Gy per day. The ED_{10} is estimated to be about one quarter of the ED_{50}. The mean factor for exposures over a week is approximately 2; by extrapolation, it could go up to 3 for longer periods.

219. The appearance of erythema during the prodromal phase is a bad prognostic sign, particularly if erythema covers extensive areas, as this indicates a high dose. The prognosis is poorer if the erythema appears at an early stage, in spite of the fact that the patient may still appear to be in good health. For whole-body irradiations with energies of 0.1-0.5 MeV, erythema becomes manifest after doses of 2-3 Gy; with much higher energies, it will indicate higher doses at depth because of the build-up of dose in the surface layers.

220. The absence of any prodromal symptom soon after irradiation indicates an excellent prognosis: the average dose in the whole organism is probably less than 0.5 Gy and certainly less than 1 Gy. A few isolated, temporary symptoms of moderate intensity

suggest a dose below 2 Gy. From the first days after the accident onwards, the presence of clinical indicators and the observation of their severity allows a more accurate prognosis, and therapeutic decisions can be taken without waiting for the acute symptoms of the later critical phase.

221. Once the critical phase begins, the prognostic elements are much easier to interpret than they were in the prodromal phase. An excellent indicator is the time elapsing before the appearance of the critical phase; the shorter the latency time, the less favourable the prognosis. All cases of accidents involving whole-body irradiation have shown this [H20]. During the critical phase, the appearance of new clinical indicators, an increase in their severity and persistence are bad prognostic signs. Table 25 lists the principal signs that may appear, classified in order of increasing severity, but not necessarily in chronological order of appearance [N4].

3. Biological data

222. The haematological syndrome presents the most serious problem for clinicians. The gastrointestinal and neurological syndromes appear at considerably higher doses: 10-15 Gy in the digestive tract and 50 Gy or more in the central nervous system are required to trigger these syndromes in one week and in a day or two, respectively. In the case of uniform whole-body exposure, the haematological syndrome occurs without fail below 10 Gy and down to a few Gy.

223. The earliest haematological indicator is a reduction in the concentration of blood lymphocytes. The speed at which this phenomenon begins is directly related to the mean bone marrow dose. In general, once the fall has started, its rate, estimated over the first three days, is a good prognostic indicator [H20]. Figure XXVI shows the lymphocyte reduction in six subjects irradiated in the course of three accidents [I13].

224. Other signs are also useful, although later, biological indicators. The fall in granulocytes concentration in the circulating blood to very low levels is an important feature to be monitored, because granulocytopenia is responsible for intercurrent infections, which may cause death. Also important are the thrombocytes, which help prevent haemorrhages. Daily blood counts are the basis for the immediate prognosis and for decisions about transfusions of blood cells.

225. An important element in prognosis is the minimum level of the various blood cells and the date on which this minimum is reached (Figures X, A.II.b and A.V). In three accidents, with doses ranging from 3 to 12 Gy, the time taken to reach the nadir varied from about 4-7 days in the case of lymphocytes and from 10 days to about a month in the case of granulocytes and platelets [N5]. Quantitative data are set out in Table 26, together with the clinical outcome or the prognosis.

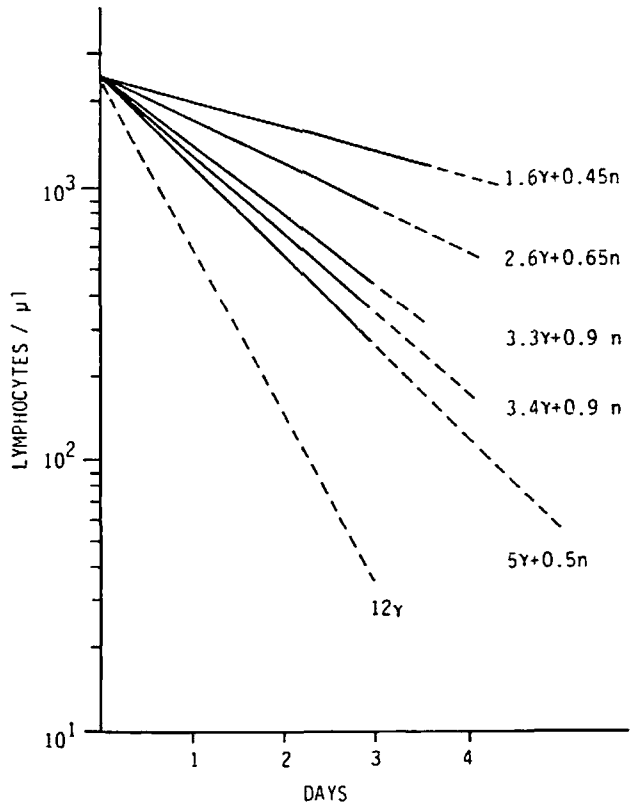


Figure XXVI. Approximate reductions in lymphocytes following accidental exposures to inhomogeneous doses. Data from six individuals exposed in three accidents: Brescia, Italy (1955): 12 γ; Mol, Belgium (1965): 5 γ + 0.5 n; Vinca, Yugoslavia (1958): 3.4 γ + 0.9 n (4.38); 3.3 γ + 0.9 n (4.18); 2.6 γ + 0.65 n (3.38); 1.6 γ + 0.45 n. Original estimates of doses (Gy) related to gamma rays and neutrons are presented separately. Values of dose in parentheses are revised equivalent low-LET marrow doses (see Table 12).
[I13]

226. After prolonged exposures it is difficult to assess the time taken for the haematological syndrome to appear, because it is difficult to fix a starting point for the irradiation period. The minimum values have the same significance for the prognosis as in the case of acute exposure; the length of time at the minimum level is more difficult to interpret for purposes of prognosis, since it seems to be related to the exposure period [H20]. Table 26 indicates minimum values of the same order of magnitude as those in Table 27 [N5].

227. During the critical phase, the duration of marrow aplasia is an important feature. A low blood count lasting for a long time is a bad sign, probably indicating not only a high but also a relatively uniform bone marrow dose and, possibly, a prolonged exposure. In the case of prolonged exposure, the depression is long-lasting and the repopulation rate is particularly slow, a mirror image of the initial slow reduction [H20]. During the phase of recovery, the reappearance of cells (whether mature or not) in the circulating blood, and their gradual increase, are good signs. Lymphocytes and platelets are generally slower in returning to normal than are granulocytes. Very often, all blood-cell types fluctuate considerably around

their normal concentrations when they return to levels within the normal range, but this phenomenon has no prognostic importance.

228. The appearance and persistence of immature cells in the circulating blood is a good sign, because it indicates a good bone marrow response. The cells most frequently found belong to the granulocyte lineage: pro-myelocytes, myelocytes and meta-myelocytes. As a rule, they are present only in small numbers. It is their continuing presence over a period of days, rather than their absolute number, that is the basis for a favourable prognosis. Likewise, the number and variation over time of reticulocytes are important.

229. Other conditions such as a rare blood group, repeated transfusion problems (shock, etc.), sudden anaemia indicating haemorrhage, or leukocytosis indicating an infection, are unfavourable prognostic signs [H20].

230. A detailed examination of the bone marrow is essential for several reasons. A number of marrow punctures in widely scattered areas selected according to the conditions of the accidental irradiation (that is, the subject's position in relation to the source and the part of the body that has probably been most exposed) will give information about the uniformity of the irradiation. The severity of marrow aplasia is directly related to the distribution of the dose [I14]. Marrow punctures give a much more reliable picture of the bone marrow state than does the circulating blood. However, the prognosis is not necessarily poor if the samples all show a severely depleted marrow; it requires only a few stem cells to repopulate the marrow, and direct examination with differential counting of the bone marrow cell types is an insufficient basis for a reliable medium-term prognosis. It is not unusual for an apparently depopulated marrow to become repopulated to a normal level.

231. It is then necessary to perform further tests on the bone marrow cells; the cells (e.g., CFU-MIX) closely related to the stem cells should be cultured, because their existence indicates the likelihood of subsequent bone marrow restoration. There is, however, a practical problem in that such cultures take quite a long time to grow (around one week), and they require fairly elaborate techniques that cannot normally be carried out on a large scale [I14]. Furthermore, it is debatable whether they are useful in patients with extensive aplasia, in view of the relatively large marrow samples needed for the examination. Since it is exactly those individuals exposed to the highest doses who require a precise prognosis, this culture technique has its limitations.

232. Because it is easier to take blood samples than marrow samples, cultures are generally made of the circulating progenitor cells (GM-CFC). This technique has been used in cancer patients receiving partial-body or whole-body irradiation to assess injury and recovery in haemopoietic progenitor cells [T18]. There are difficulties here too, however. These circulating cells have a low concentration, the culture techniques are elaborate, and the number of GM-CFC in the blood may not adequately reflect the concentration of stem cells in the marrow. For the time being, therefore, this method remains qualitative and its true value uncertain.

233. Quantitative marrow scintigraphy can be used to evaluate the regions of the bone marrow that are still functional; this technique produces quantitative findings quite rapidly [I14, P16]. The pattern can be followed for about a week. It is possible to study, in each region of the bone marrow, the degree of iron turnover (incorporation by the erythrocytes and release by the reticulocytes) and its uptake. It is also possible to distinguish extra-medullary haemopoietic regions and to measure their relative effectiveness. However, studies such as these relate to the erythroid lineage, not to the most important granuloid lineage, and transient erythroid recovery may occur in the absence of stem-cell recovery.

234. Cytogenetic dosimetry, which may be performed in a few days, allows an estimate to be made of the mean dose in the body. Counting the number of abnormalities in circulating blood lymphocytes (mainly dicentrics, rings and fragments) and comparing this number with reference values gives an accurate estimate of the mean dose. This approach has its limitations in cases of highly inhomogeneous acute exposures during which only some of the lymphocytes are irradiated and for which the dilution factor is not known, as well as in cases of prolonged exposure. Study of the electroencephalogram is equally useful but has the same limitations with regard to prolonged exposure. All the above techniques are discussed in section III.B.

235. Urine analysis is useful from several standpoints (see section III.B.2). It evaluates the state of the irradiated individual's renal function, which is essential to outlasting the critical, life-threatening period. It may confirm hidden haemorrhaging, by indicating haematuria, or renal malfunction associated with glycosuria or proteinuria. It is not, however, essential for determining the actual radiological damage and its consequences.

236. Biochemical analysis may throw some light on metabolic disturbances. These include disturbances that affect the regulation of the water balance, which, if extensive, can jeopardize survival. The prognosis will depend on the quality of the treatment utilized, and daily checks are indispensable. A routine check must cover (a) renal functions (urea, creatinine, calcaemia, phosphoraemia and blood ionogram); (b) liver functions (lactic dehydrogenase, transaminase, alkaline phosphatase and bilirubin); and (c) nutritional indicators (electrophoresis of peptides and proteins, and serum iron).

237. A thorough bacteriological check would make it possible, in the event that infection is discovered, to take measures that would allow a favourable prognosis, at least in the short term. The aim here would be to detect any latent infections (especially dental, otorhinolaryngeal or urinary) or opportunist infections, which are frequent in subjects with immune deficiencies. Again, the prognosis will depend on the effectiveness of the treatment. Septicaemia, fungal

infections and infections involving bacteria that are particularly pathogenic and/or resistant to antibiotics present special problems.

238. Sperm analysis is also a useful prognostic indicator. Changes attributable to irradiation are discussed in section I.D.5, and Figure XVIII shows sperm counts as a function of dose and time. The prognostic value of a sperm count is great, because the changes are very sensitive indicators at relatively low doses [I9]. A first sample must be obtained less than 40 days after the accident and a second sample, after the second month. Table 10 shows the effects of irradiation on spermatogenesis and the prognosis for fertility [L4]. It should be noted that the threshold dose for permanent sterility does not rise significantly when the dose is fractionated over some days or a few weeks. This is attributed to differentiation of the spermatogonia, which pass from relatively resistant early stages to type B, more sensitive, with a D_0 value in the region of 0.2 Gy [U4].

239. As is clear from the foregoing discussion, a prognosis founded on only one parameter or one class of parameters (dosimetric, clinical or biological) is bound to be very uncertain. To be valid, a prognosis must be founded on an entire range of data, and the wider the spectrum of these data and the better their coherence, the more refined will be the predictions. Table 23 summarizes the kinds of data that are useful in prognosis [I12], and Table 28 recapitulates the threshold levels of the signs and symptoms that can be detected by specialist teams and that appear after low doses [N5].

B. CLINICAL AND BIOLOGICAL DOSIMETRY

240. The many ways of estimating dose can be divided into two main kinds of investigation: (a) clinical dosimetry, which compresses the observation discussed in sections I.C and I.D (the relative value of these observations is discussed in section III.A) and (b) biological dosimetry, which comprises all the laboratory examinations that might allow an evaluation of the dose received by the individual, its distribution in the body, the time span of dose delivery and the quality of radiation involved. Biological dosimetry relies on haematological, biochemical, cytogenetic and neurophysiological examinations [E10, I13, J11, J12, K19, N14], which have different degrees of dosimetric value. Some are only qualitative (biochemical examinations, for example), others have considerable prognostic value (cytogenetic and neurophysiological examinations, for example); the majority are difficult to interpret in cases of protracted or fractionated exposures.

1. Dosimetry based on haematological data

241. Quantitative morphological haematology (cell count, differential count, platelet count etc.) is discussed in sections I.C.4. and III.A. Irradiation causes changes in the circulating blood components (cells and plasma) and in the haemopoietic tissues, and the examinations have to be more rigorous than routine examinations.

242. The morphology of the cells can be changed by irradiation. Frequently, the number of binucleate lymphocytes is higher than normal [H20, J13, J14, R17]; however, their appearance is generally delayed, so this measure is of little interest for immediate diagnostic purposes. Other abnormal features have been observed in the peripheral blood lymphocytes of persons irradiated with high doses, including (a) nuclear changes; (b) nuclear pycnosis; and (c) micronuclei, which are the result of chromosomal abnormalities but can be detected more easily and more quickly than karyotype abnormalities. These changes can be observed at relatively low doses, typically 0.25 Gy in vivo and 0.02 Gy in vitro [I15].

243. The number of peripheral lymphocytes displaying a defective nuclear structure has been shown to be related to dose for doses above a few Gy, administered in vitro and in vivo [W14]. This phenomenon has been studied in rats and in humans, but it cannot be readily used for dosimetric purposes because the damaged cells are trapped by the reticulo-endothelial system and rapidly disappear from the bloodstream; blood samples must therefore be taken soon after irradiation and incubated in a culture medium for several hours.

244. The incidence of nuclear pycnosis in lymphocytes irradiated in vitro is also related to dose. In animals (rats, rabbits) there is a linear relationship up to about 1 Gy, with a low threshold at about 0.05 Gy [I15]. However, this method is unreliable because pycnotic lymphocytes vary so widely among non-irradiated subjects. Moreover, it has been shown that in animals, pycnosis varies with the size of the cell and the nucleus/cytoplasm ratio [R18].

245. At doses between 1 and 8 Gy [I15], irradiation reduces the uptake of tritiated thymidine in vitro by the lymphocytes following treatment with phytohaemaglutinin. This explains the reduction in mitoses and cellular transformations during irradiation. Although it should be regarded as only semi-quantitative, this method is sometimes used in cases of accidental irradiation [W15].

246. Irradiation also affects the electrophoretic mobility of lymphocytes and the distribution of cellular volumes [S25]. This was noted in rabbits after doses of 2 and 4 Gy, where there was an increase in the number of large cells in the second week after irradiation. At the same time, in the categories of cells characterized by their degree of mobility, the category showing the first changes manifested the phenomenon only briefly, starting about five minutes after exposure and lasting for about 30 minutes. The explanations offered for this vary: an increase in cellular metabolism that produces functional changes in the lymphocyte or, alternatively, differences in the cell populations at the outset, with the most mobile groups able to undergo certain alterations outside the circulation and then to reappear with a different volume [I15].

247. Various immunological changes have been measured after regional irradiation [W17], in surface markers, mitogen and antigen responses and cytotoxic functions (see section I.C.4). Some of these changes persist for up to 10 years, but there have been no detailed studies of their potential use as biological indicators of radiation dose.

248. Leucocytes other than lymphocytes also show malformations after irradiation. There are few quantitative data, and such data as there are, are of little use in establishing a diagnosis or prognosis. These changes only confirm exposure; it is not so far possible to correlate them with dose or to know their relative importance. The most common changes are (a) giant polynuclear cells (hypersegmented polyploid granulocytes); (b) cells with small alterations in their nuclear structure, such as small chromatin adnexa; (c) the presence of immature granulocytes; and (d) mitotic abnormalities in erythroblasts and granulocytes [B16, F5, I15, I16]. These abnormalities occur only infrequently. The reduction in the number of monocytes may be related to the inhomogeneity of the dose, in the sense that when severe monocytopenia appears rapidly, it is a sign that a very large proportion of the bone marrow has been irradiated [I15]. Conversely, if a significant part of the haemopoietic marrow has escaped irradiation, there may be only a temporary reduction in the number of monocytes, or even monocytosis with an increase in the number of immature cells [I16].

249. Erythroblasts can be found in the blood stream after irradiation, always in very low proportions [B16, I15]. Reticulocytes are useful indicators in prognosis [H20]; a dramatic fall in reticulocyte count is often a sign of early fatality.

250. Serum glycoproteins increase in the presence of infection, inflammation or neoplastic and idiopathic disorders. The effect of irradiation on the concentration and distribution of protein-bound carbohydrates in the serum of mice and dogs has been studied [I15]. A considerable increase has been reported in animals exposed to lethal doses, while no notable change has been reported in animals receiving lower doses. It is not possible to treat all glycoproteins as one entity to be used as a dosimetric indicator. However, following the separation of various elements, changes in concentration have been noted for transferrin, haptoglobulin, the β_2 glycoproteins and the α_2 macroglobulins [E8]. A common feature of all these proteins is their richness in bonded carbohydrates.

251. Because the bone marrow function is extremely important for prognosis, all tests of its proliferative ability may a priori be regarded as useful dosimetric indicators. The analysis of bone marrow cannot in any case be a substitute for studies of the peripheral blood, which are currently the most reliable biological dosimeter.

252. The mitotic index in bone-marrow cells is one of the most accurate biological indicators, and also has a certain prognostic value. Changes in the mitotic index are related to the dose, but doses of 1 Gy or lower produce little change [K12]. After a few Gy in man, there is an initial drop in the mitotic index, recovery at about day 8 and a further fall before it returns to near normal by day 24 [F9]. In the Y-12 accident, the marrow of individuals who had received estimated doses of 2.4-3.7 Gy had practically no mitotic cells. For higher doses, the cell count dropped slightly from day 3 after exposure. The most commonly observed morphological change was the presence of giant neutrophil precursors from day 2 to day 16.

253. Some authors have proposed a test based on the marrow's capacity to respond to stimulation: injection of ethiocholanolon causes granulocytes stored in the bone marrow to migrate into the bloodstream [G18, I15, V15]. The ethiocholanolon is a testosterone metabolite, δ-4-androstane-3, 17-dionin. It is an androsterone isomer, with the configuration 5β-H (A:B cis); androsterone has the configuration 5α-H (A:B trans). The ethiocholanolon test was first used in patients suffering from malignant blood disorders; given the relationship between the responses to this test and the quality of the peripheral granulocytic cell pool, it was considered to be a good guide to the therapy of these blood diseases [V15]. Furthermore, ethiocholanolon affects neither the mononuclear nor the thrombocytic cell lines. The granulocyte outflow starts quickly and lasts for about 16 hours after the injection. Because of its low toxicity and the good reproducibility of the response, the method using ethiocholanolon is superior to methods using other leucocyte-mobilizing agents. A positive response indicates active medullary production of granulocytes.

254. Many of these methods have now been superseded by cell culture techniques for bone marrow. These techniques are at present fairly reproducible; mixed-cell colonies originating from cells closely related to the stem cells and granulocyte/macrophage colonies arising from granulocytic precursor cells may appear in cultures even using marrow punctures that have indicated, morphologically, a lack of haemopoiesis. Quantitative medullary scintigraphy, in conjunction with the iron-59 test, gives a picture that can be used to assess the impairment of the marrow.

255. Because the mature cells are resistant and have a long lifetime (approximately four months), it is difficult to use erythrocytes directly as early biological indicators of radiation damage, although the erythroid precursor cells are radiosensitive. Iron is incorporated only into the precursor cells, and the iron-59 test, in conjunction with the other tests of medullary function, allows the erythroid cell populations to be evaluated.

256. A greater denaturation of haemoglobin in erythrocytes by phenylhydrazine was reported in occupationally exposed persons, compared with the normal population [G22]. In patients with bronchial carcinoma given fractionated doses (1.2-1.5 Gy per day), an increased denaturation was observed when the cumulative dose reached 7-9 Gy [G22]. However, no increase was noted when erythrocytes from normal individuals were given doses between 1 and 8 Gy in vitro [G23].

2. Dosimetry based on biochemical data

257. Any changes in the blood biochemical parameters may be regarded as interesting signs. Glycaemia cannot be taken as a biological indicator because of its high degree of stability in the body. It is not unusual to observe hyperglycaemia from day 1, followed by pronounced hypoglycaemia (0.5 g/l) on about day 3 and a return to normal that takes about a week, after some fluctuation around the normal level [J13, J14, J15]. In the same way, fluctuations in plasma electrolytes and plasma proteins increase as the dose rises. However, the data are not accurate enough for these indicators to be used quantitatively [J15]. The features often noted are disturbances such as hypochloraemia, hyponatraemia or hypokalaemia during the first week [J13]. Electrophoretic analysis of the protein fractions shows the largest reduction (greatest at about two weeks) in the albumins. A dose-dependent appearance of a humoral factor in blood serum, which inhibits incorporation of ^{125}IUdR into cells in culture, was reported in mice [F7]. The technique has not yet been developed for man, partly because the thymidine concentration is only one-tenth that in mouse serum and partly because of other technical difficulties [F8, S29].

258. Hyperamylasemia can be produced by irradiation [B51, C38, K20, T30]. The pancreas is not very sensitive (doses up to 2 Gy have no effect), but amylase increases are detected if the salivary glands have received more than 0.6 Gy [W18]. The increases are maximal on day 1 after radiation, returning to normal by day 3, but a clear dose-dependence has not yet been established.

259. The variations in the chemical composition of the urine are of more significance than those of the blood. The urinary electrolytes may reveal changes in potassium excretion (extra-physiological fluctuations) and in the excretion of sodium and chlorine, which declines during the first few days after exposure [J13]. The 17-ketosteroids increase substantially during the first few days, before returning to normal by the end of the first week [J13].

260. After radiation exposure, there is a considerable enzymatic breakdown of nucleic acids and proteins, especially in lymphatic tissues [A29, H42, S38]. As a consequence, the urinary excretion of nucleosides and amino acids, as well as their metabolites, increases. A dose-dependent increase of deoxycytidine from normal low levels [I15] was observed in the urine of rats during the first day after a whole-body irradiation with 0.5-2.5 Gy [G30]. An enhanced excretion was also found in man after radiotherapy [B55, S39]. Similar effects were reported for the excretion of thymine in rats [Z5]; however, this was not seen in man [B55]. Thymine is metabolized to β-aminoisobutyric acid (BAIBA). The excretion of this substance is considerably increased in mice, rats and man after irradiation [S39]. After accidental human irradiation, an increase from 100-200 μmoles per litre of urine to 250-650 μmoles per litre was observed [G19, J14].

261. There is a general increase in the levels of amino acid in the urine of animals and humans during the first day after irradiation [S39]. The relative enhancement depends on the absolute excreted amount and on the metabolism of the specific amino acids. Because these factors are very complex and different for each amino acid (a decrease in urinary excretion can occur with some) no general rule is observed [S39, J14]. Accordingly, the excretion of amino acids is not usually an appropriate indicator.

262. There are, however, some amino acids or their metabolites that show a dose-dependent change in urinary excretion after irradiation. One of these is taurine, which is the metabolic end-product of cysteine. Its excretion increases 1-2 days after irradiation in the urine of rats and mice [K22, S26, S38]. Excretion increases with radiation dose in the range 0.75-2.5 Gy. In man, an enhanced urinary level of taurine was also observed after accidental irradiation [A29, J14]. It has been suggested that the increased excretion of taurine after irradiation may be related to intracellular taurine elimination due to changes in cell permeability [S26] and to the breakdown of lymphatic tissues [D12]. However, metabolic studies in mice show that the biosynthesis of taurine is also altered [H42, S40].

263. Some days after irradiation the urinary excretion of taurine decreases below normal values [L30]. This effect is due to metabolic changes of vitamin B_6-dependent decarboxylases and other enzymes which are decreased, as in the condition of vitamin B_6 deficiency [S38]. As a consequence of such metabolic alterations, the urinary excretion of kynurenic acid and xanthurenic acid (metabolites of the amino acid tryptophan) increases after irradiation of mice and rats [A29, H42, L30, S38, S39]. This effect was also observed in man [L29]. These changes occur in a dose range of 4-8 Gy, which, in mice and rats, causes severe radiation sickness prior to death [S39]. From these studies it can be concluded that biochemical indicators may be useful for certain dose ranges. Thus, the breakdown products of nucleic acids and taurine may be useful indicators in a lower dose range (0.5-3 Gy) and metabolites like kynurenic and xanthurenic acid, in a higher dose range (4-8 Gy).

264. Creatinine could serve as a measure of radiological damage to the irradiated muscles that are no longer able to metabolize it in the normal way [G20]. The level of creatinuria has never been correlated with dose, but it may confirm the uniformity of irradiation. In accidents where a relatively large portion of the body has not been irradiated, such as the Lockport accident in 1960, the level of creatinuria (creatine/creatinine ratio) scarcely increased. In accidents involving whole-body irradiation, such as occurred at Oak Ridge (Y-12) in 1958 and at Mol in 1965, the level was significant, with three conspicuous peaks in one instance (day 2, end of first week and end of second week) [J14].

265. In recent years a number of new biochemical indicators of severe radiation damage have been proposed. For example, a method has been suggested for the quantitative evaluation of damage to the

membranes of erythrocytes in the peripheral blood [M50, M51, M52]. Inhibition of the incorporation of labelled precursors of the DNA in bone-marrow cells has been used in a method worked out by Porschen et al. [P31]; the authors used their method to monitor irradiation even in small doses (some tenths of Gy). There are also data on determining the total content of desoxyribonucleotides in the blood and urine of patients irradiated for therapeutic purposes [S46, T31]. However, due to the paucity of such studies, it is difficult to evaluate the value of these indicators.

3. Dosimetry based on cytogenetic data

266. The analysis of chromosome aberrations in the circulating lymphocytes is widely used to assess the dose. Even in cases of partial-body exposure, the chromosome changes are excellent indicators of the absorbed dose. The evidence to justify the technique is well founded and covers various irradiated populations (in nuclear medicine, radiotherapy and accidents) and very wide ranges of dose [B42, K13, L15, L16]. The technique provides a reliable indication of the acute dose, since lymphocytes are widely dispersed in the various tissues and organs, have a reproducible radiosensitivity and a long life, and circulate rapidly in the body [D13].

267. Many types of radiation-induced chromosomal aberrations may appear in irradiated lymphocytes, but the dicentric aberration is currently taken as providing the most valuable information on dose. This is because the dicentric aberration is almost unique to ionizing radiation and occurs rarely in persons exposed only to normal background radiation. Centric rings occur only 5-10% as frequently as dicentrics in control or irradiated lymphocytes and are thus too infrequent to be used as a sole measure of dose. Some researchers combine the centric and dicentric yields. Acentric fragments, by contrast, have a higher background frequency, which probably reflects their induction by a large number of chemical mutagens. The confounding effect of many environmental non-radiological insults reduces the acentric's value as a measure of dose, although elevated acentric yields may qualitatively support dose estimates derived from the dicentric incidence..

268. Human T-lymphocytes have a long lifetime; a small proportion of them survives for decades. The rate of replacement is quite slow, so that in the few weeks after exposure the dicentric yield remains fairly constant. After a partial or inhomogeneous acute exposure, the lymphocytes that were in the irradiated volume of the body in both the vascular and extravascular pools are rapidly mixed with unirradiated cells. An equilibrium is reached by about 20 hours [T25], and thereafter the dicentric yield in cells from a sample of peripheral blood will provide an estimate of the average whole-body dose.

269. The dose-response for dicentric aberrations in the irradiated lymphocytes of normal individuals is little affected by factors such as the donor's age or sex. The dose-response obtained for irradiation in vivo does not differ significantly from that for irradiation in vitro [C46], so that the aberration yield observed in cells taken from an irradiated subject may be interpreted by reference to the appropriate calibration curve in vitro. In vitro curves have been established for a large range of radiation qualities, including all those likely to be encountered in accidents [L25]. Within any one laboratory, the calibration curves for dicentrics have proved to be very reproducible, provided that the cells are examined at their first post-irradiation mitosis. This is now reliably achieved by including bromodeoxyuridine in the culture medium and staining the chromosomes by fluorescence plus Giemsa [S37].

270. For low-LET radiations, the yield of aberrations, Y, conforms well to the quadratic relationship $Y = c + \alpha D + \beta D^2$ where c is the background incidence (about one dicentric in 10^3 cells), D is the dose, and α and β are fitted coefficients. A dicentric aberration requires the interaction of two breaks, each induced in separate G_0 or G_1 chromosomes. An explanation of the quadratic relationship may be that when both breaks are produced by the passage of a single ionizing track, the yield is represented by the linear term αD. The βD^2 term thus represents those dicentrics that are produced when the two breaks are caused by separate ionizing tracks. The latter term becomes more important when the dose increases.

271. In general, high-LET radiation, such as fission spectrum neutrons and alpha particles, give a linear dose response relationship, $Y = c + \alpha D$ (Figure XXVII). For these types of radiations the ionizing events are so densely distributed along the track that there is a high probability that one track will deposit energy in both chromosomes. RBE values at low doses, calculated as the ratios of the alpha coefficients of two radiations of different quality, may represent the relative hazards of the two radiations at low routine occupational levels [I21]. At higher doses, such as are likely to cause overt symptoms of sickness, the values of RBE decrease markedly [L36]. With neutrons, as their energy increases the average LET decreases and the linear model requires a second (quadratic) term, e.g., with 7.6 MeV and 14.7 MeV neutrons. RBE values for specific energies of neutrons have been proposed [B44, P18].

272. Another feature of the dose-response curves for high- and low-LET radiation is the relative importance of the dose rate. For high-LET radiation with a linear dose response, this is unimportant. For low-LET radiation, the equation $Y = c + \alpha D + \beta G(x)D^2$ can be used, where the number of initial chromosome breaks falls exponentially with time according to the factor $G(x)$. In practice, the dose-squared term reduces until the response can be considered to be linear for x- or gamma-radiation doses of a few Gy, if delivered at a more or less uniform rate over 24 or more hours.

273. An important problem in assessing the dose to an appropriate degree of precision is the number of metaphase cells that have to be examined. As a rule, evaluation of 100-500 metaphases is sufficient to estimate a dose at irradiation levels of medical

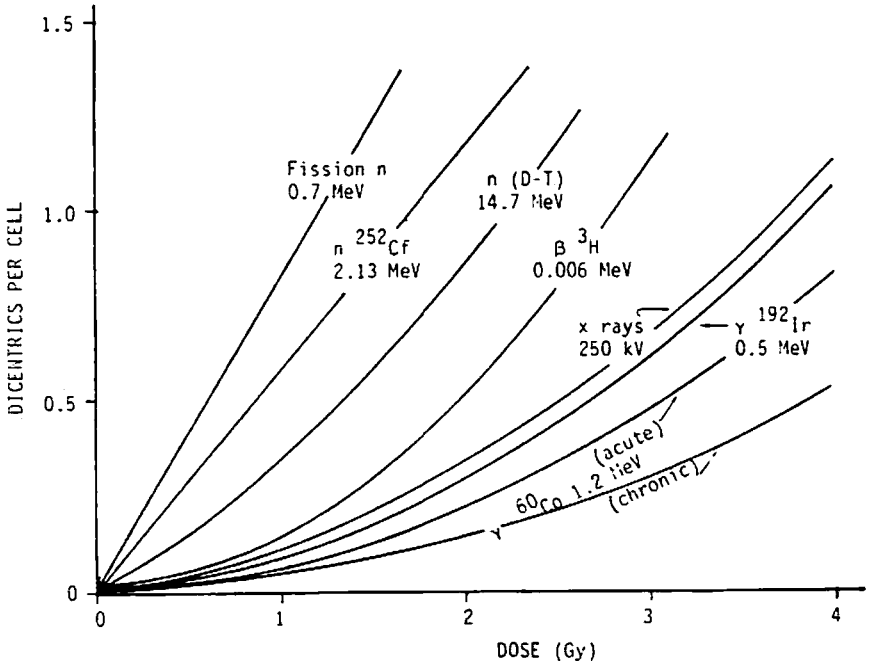


Figure XXVII. A series of generalized dose-response curves for dicentric chromosome induction for human lymphocytes irradiated in vitro.
[D13]

significance [D14, J15, L15]. With a few hundred cells scored from an irradiated subject, the statistical uncertainty on the dicentric yield is the main component of the 95% confidence limits on the dose estimate. It is much greater than the uncertainty attached to the in vitro calibration curve [L17], so that for practical purposes the latter may be ignored when calculating confidence limits. An example of an in vitro curve and the confidence limits for an exposure to gamma-radiation is given in Figure XXVIII. Examples of the use of such curves in cases of accidents have been described [D15, L18].

274. For a uniform exposure to low-LET radiation, dicentrics in the scored cells follow the Poisson distribution [D13]. However, in accidental irradiation, the exposure is almost always non-uniform, often involving just part of the body. This results in an overdispersed distribution of aberrations. The degree of departure from the Poisson distribution may be used to estimate the volume of blood exposed and its average dose [D14]. This has recently been tested in an international collaborative experiment in which partial-body exposures were simulated in vitro. The resultant estimates of dose and volume irradiated were acceptably close to the true values [L28]. The calculations require a number of simplifying assumptions [I22], but they produce values that are probably more meaningful than the average whole-body dose for accidents in which clearly only part of the body has been irradiated. However, estimates of blood volume exposed may not reflect closely the proportion of body mass exposed [L39].

275. Many chromosome aberrations, including breaks and various exchanges of the chromosome or chromatid

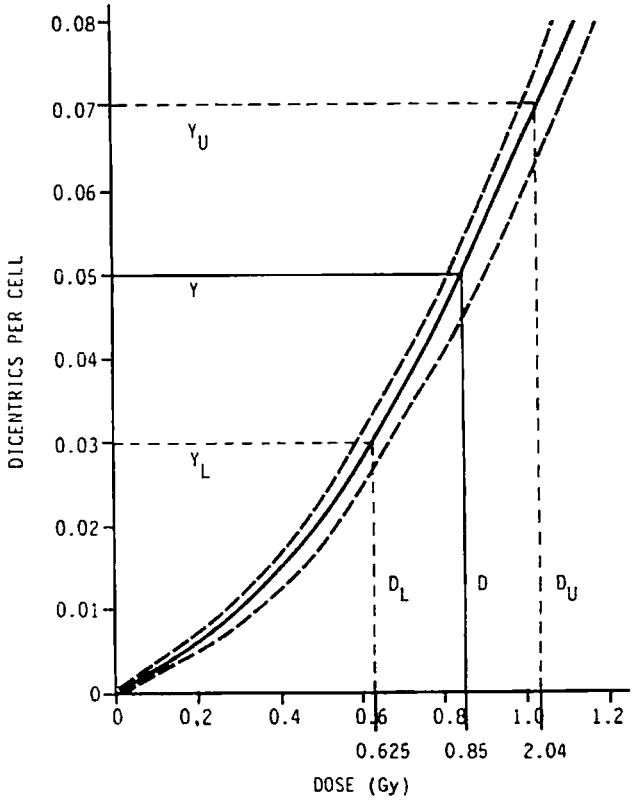


Figure XXVIII. Estimation of a dose of 0.85 Gy from a yield of 0.05 dicentrics per cell (25 in 500) by reference to an in vitro calibration curve for gamma-radiation using human lymphocytes. Statistical uncertainties on the curve are shown by the dashed curves. The upper (Y_U) and lower (Y_L) Poisson standard errors on the yield give 95% confidence limits of 1.03 and 0.625 Gy (D_U and D_L) on the dose estimate.
[I22]

type, involve acentric fragments. The absence of a centromere in these fragments prevents the correct distribution of genetic material during cell division, and they are lost or incorporated in only one of two daughter cells. In the daughter cell the fragment may either join with the main nucleus or remain in the cytoplasm and form a micronucleus [K14, R19]. Recent data indicate that 20-30% of acentric fragments may become micronuclei at mitosis [B54, W23]. Micronuclei may also occur as a consequence of completely aberrant configurations with more than one centromere because such structures frequently cause difficulties in chromosome separation during anaphase. They may also result from normal chromosomes which are left over because of a defect in the mitotic spindle.

276. Counting of micronuclei has been suggested as a dosimetric method for situations which include the evaluation of damage of chemical origin and the identification of particularly sensitive individuals with higher than average potential risks of developing cancer or genetic disorders. In principle, counting of micronuclei appears easier, faster and less expensive than the scoring of chromosome aberrations [I16, H33].

277. There is a higher background incidence of micronuclei than of dicentric aberrations and this may in part reflect the higher background incidence of acentric fragments due to environmental chemical mutagens. This means that the lower limit of dose detection by micronuclei is perhaps 0.25 Gy, thus making the technique less sensitive than that of scoring the dicentric yield. The frequency of micronuclei after x-irradiation of human lymphocytes in vitro reaches a peak after 96 hours of culture [F6, C29]. However, by this time lymphocyte cultures have become asynchronous and individual variability in cell cycling kinetics is likely to impose considerable uncertainty in the quantification of the dose response.

278. The method can be better standardized by scoring cells which have undergone a known number of mitoses. This can be achieved by differential staining of nuclei in cells which have incorporated bromodeoxyuridine [P17], and scoring cells which have previously incorporated tritiated thymidine in S-phase or by scoring cells which have been blocked at the end of mitosis using cytochalasin B [F6].

279. Currently, the cytochalasin-B blocking method is gaining considerable popularity. This technique ensures that micronuclei are scored only in those cells that have just completed their first post-irradiation mitosis. The dose-effect relationship appears to be similar to that observed with aberrations, in that the response for low-LET radiation is quadratic and at low doses it is linear [F6, F16]. Data for exposure to high-LET radiation are not yet available. The micronucleus technique is far easier and faster than scoring for dicentrics and is more amenable to automated methods of analysis using pattern recognition systems, e.g., in polychromatic erythrocytes (PCE). Individual variability, particularly at lower doses, poses some limitations. Factors such as dose protraction, fractionation and partial-body exposure have yet to be investigated. The test can be envisaged as being particularly useful after a serious accident when many people may need to be tested quickly.

4. Dosimetry based on neurophysiological data

280. Whole-body gamma-irradiation is accompanied by immediate functional changes in the central nervous system, particularly with respect to spontaneous and evoked cerebral electrical activity. These changes have been shown in animals [B45, C30, M33] and in man [C31, C32]. They appear immediately after exposure and are an important indicator of the direct effect of radiation on the optic nerve [C31]. Radiation may also affect (a) the function of peripheral receptors; (b) nerve conduction; and (c) synaptic transmission. High doses are required to modify the function of the retina, since more than 6 Gy must be administered to cause changes in the electroretinogram. The administration of large doses (~ 10 Gy) of x or gamma rays triggers a process that lowers the excitability threshold and increases the action potential and, more irregularly, the rate of conduction of the nerve impulse. Examination of synaptic transmission produces results that are harder to interpret.

281. Irradiation, even in small doses, may cause changes in the acetylcholine-cholinesterase balance or in other chemical mediators, such as aspartic acid, adrenergic amines, and gamma-aminobutyric acid (GABA). The examination of vascular lesions makes it possible to study the role of disturbances in membrane permeability. Cell metabolism is probably disturbed, as shown by reversible changes in the nuclear chromatin. Furthermore, whole-body irradiation is accompanied by changes in the acid-base balance, essentially hypocapnia and acidosis, which can be restored from the seventh hour onwards for doses of about 1.5 Gy. It seems likely that, even if the development of functional disorders of the autonomic nervous system is not superimposable on the trend of cerebral electrical activity, changes in the acid-base balance of the blood play an important role in the genesis of the disturbances observed.

282. It has been shown by one group of investigators that whole- or partial-body gamma-irradiation of the organism can act as a stimulant or as an agent of injury, depending on the level of dose, the dose rate, the irradiated volume and, above all, the percentage of the body irradiated [C31]. There is direct stimulation of the brain and particularly of the structures in the bulbar protuberance and the hypothalamus, as well as of all the synapses in the organism. This direct stimulation is followed by an indirect stimulation of the brain by the convergence of impulses originating in the spinal cord and the bulbus in the direction of the brain. Depending on the strength of these direct or indirect stimuli and the number of impulses arising in the subcortical structures, there is an immediate defence response; the intensity and nature of this response from the central nervous system, the modifications to the autonomic nervous system and the changes in cerebral activity and behaviour will differ

with respect to both their general expression and their development. These various effects combine to create an acute functional metabolic encephalopathy.

283. Disturbances in the neurophysiological equilibrium are indicated by (a) changes in excitability, consisting of successive phases of inhibition and excitation; (b) an increase in irritability in the form of paroxysmal abnormalities, ranging from a burst of slow activity through an isolated spike to a deformed spike-wave to grouped bursts of spike-waves, with rare convulsive spasms (in the case of high doses); and (c) the impossibility, at LD_{50} doses, of structures such as the hippocampus maintaining basic rhythms. On the electroencephalogram, changes in the excitation waves are noted; there is a slow-down in cerebral activity (appearance of slow, regular and broad waves), recurring spasms, slow activity or groups of slow waves, and isolated and then grouped spikes. All these phenomena are characteristic of radiation-induced effects.

284. After analysing cerebral electrical activity in the monopolar, conventional and harmonic modes, it is possible to quantify the energy changes in the power density spectrum and thus to describe objectively the slow-down in cerebral electrical activity. This is achieved by calculating the extent of drift and the percentage of the recording time during which the modifications in the EEG are observed [C32]. The dose-effect relationships obtained in animals show a response above 0.25 Gy. This response appears at 15 minutes after exposure. A comparison of whole-body and head exposures makes it possible to separate the effects of direct and indirect stimulation, the latter being under the influence of the convergence of ascending impulses from the whole body. The persistence of the effect observed above 0.25 Gy during the hours following irradiation tends to indicate changes in protein synthesis and the coding of information of the neurons. This dosimetric method is a valuable tool, especially if the assessment is done long after irradiation and in cases where it has not been possible to undertake chromosome analysis immediately after transfusions of blood components. The changes are persistent, particularly in cases of high doses. In survivors of doses of near the $LD_{50/60}$, the normal electroencephalographic patterns seem to take several years to reappear [C30].

5. Other dosimetric findings

285. In cases of exposure to mixed gamma-neutron fields, the dose, its neutron component and its spatial distribution can be estimated by determining the presence of ^{24}Na and ^{32}P [I9]. This radiation-induced activity can be measured in the body, blood, urine and biological or other specimens, such as hair, teeth, fingernails, clothes, metallic objects, jewellery, etc. These measurements are well standardized and form part of the physical dosimetry, in the same way as does the reconstruction of the accident. Techniques based on electron spin resonance [N7], applied to bone, hair, teeth and skin after low-LET irradiation, have shown that the signals obtained are quantifiable at lethal or sublethal doses down to about 0.3 Gy [B46, I17]. The electron spin resonance signal is stable at more than two hours after irradiation [T16, S28]. The intensity of the signal is linearly related to dose [B46, O7, I17, T16, S28]; it is greater for incident radiations of low photon energies [T16, O7], but was not detected after doses of 14 MeV neutrons [I17]. The method has been used to assess doses in accidents [S28] and in survivors from the atomic bombs and cumulative doses in occupationally exposed persons [T16].

286. Another assay described recently measures the frequency of variant erythrocytes produced by erythroid precursor cells with mutations that result in a loss of gene expression at the polymorphic glycophorin A (GPA) locus. A linear relationship was observed between variant frequency and dose received 40 years previously [L37].

287. Other techniques have also been suggested for use in biological dosimetry but have not yet been developed for man. One example is cell death in hair follicles (dose-dependent from about 0.1 to 1.0 Gy) and consequent changes in hair width (dose-dependent from 1 to 10 Gy) [P10, P20]. Another is spermatogenesis, which is very sensitive to irradiation and could be used as a biological indicator of dose [H37]. DNA-synthesizing cells (spermatogonia and preleptotene spermatocytes) can be measured rapidly using flow cytometry, and their concentration in mice shows marked dose- and time-dependent changes [H37].

IV. CONCLUSIONS

288. The Committee has reviewed a large body of data on the effects occurring in man within two to three months of whole-body doses above approximately 1 Gy of low-LET radiation. These data were gathered from three main sources: radiotherapy treatments, radiation accidents and the Japanese exposed to the atomic bombs in the Second World War. Homogeneous doses to the body are usually received only in the case of deliberate exposures in the course of radiotherapy, while non-homogeneous doses are usually received in accidental or warfare situations, and the effect of irradiating organs to different doses must be considered. A patient's response to whole-body radiation may also be confounded by the use of other cytotoxic agents, by disease and by medical treatment after irradiation. Data collected on patients exposed to external or internal irradiation during the nuclear accident at the Chernobyl power plant in April 1986, supplied by the delegation of the USSR, were also examined. These findings are presented in the Appendix. Finally, information on experimental work with animals was used to help interpret the responses.

289. Many of the acute effects of radiation in early-responding tissues are mediated through the death of cells when they attempt to divide. The incidence of cell death is dose-dependent, and cells that have retained their capacity to divide after irradiation can be studied, using precise techniques, in vitro and in vivo.

These surviving cells contribute to the post-irradiation recovery of the tissues. Cell death can also occur independently of cell division, as, for example, the interphase death of lymphocytes.

290. Tissues that are most sensitive to irradiation are usually hierarchical in organization, in the sense that they are structured into different compartments, each of which feeds new cells into the next compartment. One can describe, therefore, the compartment of undifferentiated stem cells, that of the differentiating and dividing precursor cells and that of the maturing and mature cells. The stem cells and the proliferative cells undergoing many divisions are the most radiosensitive. After high doses, the loss of mature cells from the last compartment is not compensated by the decreased production of cells from sterilized precursor cells in the first compartment, and this causes tissue function to fail. After high doses, the proportion of individuals showing failure of a given tissue increases as a function of dose. The relationship between dose and the proportion of individuals affected is called the dose-response curve. It can be characterized by the dose at which 50% of the individuals are affected and by the slope of the curve, which reflects the inhomogeneity in response among different individuals. The inhomogeneity results from the random nature of the radiation action, from the variability in response of the individuals in the population or from inhomogeneity in the dose.

291. Loss of tissue function produces clinical symptoms in the irradiated subject, and these symptoms will differ according to which tissue fails. Also, owing to differences in the sensitivity of cells and in the structure and function of each tissue, organs will fail at characteristic times and doses, so that certain symptoms will appear together at certain times after exposure to typical dose ranges, giving rise to the so-called radiation syndromes. Ideally, for uniform whole-body exposure above some threshold of dose, one should be able to observe a prodromal phase (common to all syndromes but of differing probability, severity and duration, according to the dose received) and three syndromes: the neurological, the gastrointestinal and the haematopoietic. In practice, depending on the level of dose, its distribution in space and time and other variables, the syndromes may often merge into each other, and it becomes difficult to recognize them as such.

292. The prodromal phase of responses after whole-body irradiation comprises the symptoms appearing during the first 48 hours. The reactions are mediated through the autonomic nervous system and are expressed as gastrointestinal (anorexia, nausea, vomiting, diarrhoea, intestinal cramps, salivation, dehydration) and neuromuscular (fatigue, apathy, sweating, headache, hypotension) symptoms and signs. The incidence and latency periods for the effects are dose-dependent. The dose inducing vomiting in 50% of individuals is about 2 Gy, and the latency period is about three hours.

293. Doses higher than 100 Gy result in death from cerebrovascular injury in the neurological syndrome within two days. This syndrome is characterized by severe symptoms and signs of the prodromal phase, followed by transient periods of depressed or enhanced motor activity, leading to cerebral coma and death. Doses between about 10 and 50 Gy result in the gastrointestinal syndrome, with most deaths occurring between days 6 and 9 after irradiation. The symptoms in man follow those of the prodromal phase and include anorexia, increased lethargy, diarrhoea, infection and dehydration. There is also weight loss, decreased food and water intake and decreased intestinal absorption. Other superimposed symptoms due to bone marrow failure include a profound drop in the leukocyte count, haemorrhage and bacteremia, which aggravate the injury and contribute to death. The time to death is influenced by the mucosal turnover time in the gut and by other, secondary factors such as infection, haemorrhage and loss of fluid, protein and electrolytes.

294. Lower doses, of a few gray, result in the bone marrow syndrome. The haemopoietic and lymphoid tissues, megakaryocytes, lymphocytes and precursor cells are radiosensitive, and leucopenia is the most important injury. The lymphocyte count is the earliest sensitive index of injury in blood and doses of 1-2 Gy reduce the concentration to about 50% of normal by 48 hours after irradiation. Neutrophils show an initial abortive increase over the first few days. A second abortive rise is seen at about day 10 after 2-5 Gy. This may be followed by a further decline if the stem-cell population fails to recover. The neutrophil count is correlated with the onset of fever. Thrombocytopenia and associated haemorrhages are increasingly important after higher doses. The time course of thrombocytopenia is broadly similar to that of granulocytopenia, but there is no second abortive rise. Thrombocytopenia below 30,000-50,000 per μl is associated with bleeding.

295. Persons exposed accidentally or therapeutically in the low- or mid-lethal dose range show an increased susceptibility to infection. Reported changes in the immune system of persons irradiated regionally include a persistent reduction in T cells of the helper/inducer and suppressor/cytotoxic phenotypes.

296. In addition to the systemic effects described, irradiation can also cause damage to many other tissues and organs. The resulting effects and clinical symptoms vary in their appearance time and severity. They may or may not be part of the syndromes described, depending upon the dose level, the tissue irradiated, the modalities of irradiation, and on other physical and biological variables.

297. Effects in irradiated skin are correlated with the dose and the area irradiated. The effects include erythema, abnormal hair growth, epilation, desquamation (dry or moist) and vascular and dermal injury. The doses that produce an incidence of 50% of abnormal hairs, erythema within four weeks and moist desquamation are, respectively, about 1.5 Gy (3 cm diameter field), 5.7 Gy (10 cm × 10 cm field) and 20 Gy (35-80 cm^2). The dose in the basal layer of the epidermis determines the amount of stem-cell killing and, hence, the degree of desquamation.

Desquamation is maximal at about three weeks after irradiation. With larger areas, smaller doses elicit the same level of damage. The 50% erythema dose is about 3 Gy when the whole skin is irradiated, which is about half the dose for areas of 100 cm^2. High doses to the dermis induce dermal erythema, necrosis, ulceration and sloughing. Vascular lesions are associated with pain in irradiated extremities.

298. Injuries in the mucosa of the mouth and throat include inflammation and swelling, with ulceration and necrosis after high doses. Mucosal injury is greatest in the cheeks, soft palate and hypoglossal area. Mucosal recovery begins by 2-3 weeks after 5-10 Gy, and it is assisted by the administration of antibiotics. Injury of the salivary glands occurs at about eight hours after 6-10 Gy, persisting to about 48 hours.

299. Acute effects on the eye include acute erythema of the sensitive conjunctiva (after 2 Gy), hyperemia of eyelid skin and hyperpigmentation (4-6 Gy), keratitis (4-10 Gy), epilation of the eyebrows and eyelashes, telangiectasia and necrosis (above 10 Gy). After 15-20 Gy local irradiation, there is lacrymation and pain in the eyes, with irritation of the cornea and iris. Even in the absence of infection, these symptoms may last for a few months.

300. Pneumonitis is the earliest sign of radiation injury in the lung, appearing at 1-3 months after doses greater than 8 Gy. The doses to lung tissue giving pneumonitis in 5% and 50% of patients irradiated over the whole body prior to marrow transplantation are, respectively, 8.2 Gy and 9.5 Gy. The time of onset is not significantly dose-dependent between 6.5 and 12.5 Gy.

301. Acute doses of up to 4 Gy cause temporary sterility in some irradiated male individuals, and the dose inducing permanent sterility in all men is more than 6 Gy. The sperm count begins to drop after 46 days. Some of the early differentiating forms of spermatogonia are very radiosensitive, and the progression of cells into these forms explains the higher sensitivity of the testis to fractionated irradiation, as opposed to acute irradiation, dose for dose. Changes in testicular hormone levels and in Leydig cell numbers are also induced. In women, temporary sterility is induced by doses up to 4 Gy, and permanent sterility by 3-10 Gy. Older women are more susceptible, probably because the number of follicles decreases with advancing age.

302. In many cases, particularly when planning radiation protection for accidental or other types of acute exposure, it is useful to think in terms of the dose at which the probability of survival 60 days after homogeneous whole-body irradiation is 50% ($LD_{50/60}$). The data available for deriving the value of the $LD_{50/60}$ in man come from different sources, each of which poses difficulties: radiotherapy patients, accident cases and the Japanese exposed to the bombs in the Second World War.

303. In Hiroshima and Nagasaki, 50% of the deaths after day 20 in a small documented sample occurred between days 20 and 29; in a group 1,000 metres from the hypocentre at Hiroshima, 58.5% died between days 20 and 38. This peak in the death rate reflects marrow failure. The most recent estimates of the $LD_{50/60}$ from the Japanese data after revision of the dosimetry have yielded values of around 3.0 Gy. This is thought to be applicable to the very special conditions prevailing before and after the bombings and to human beings receiving no medical treatment or only minimal treatment.

304. Until Chernobyl, the two accidents involving the largest number of individuals irradiated solely with acute doses were those at Vinca and at Oak Ridge. Only one out of seven individuals in both accidents receiving doses estimated to be between 2.7 and 4.5 Gy died, not primarily from marrow failure.

305. In the Chernobyl accident (see Appendix), 115 individuals were measured to have received acute marrow doses above approximately 1 Gy of gamma rays, as assessed by dicentric aberrations in their lymphocytes. There was also beta-irradiation of extensive areas of skin in many cases, in particular in individuals also receiving high marrow doses, to accumulated skin doses of the order of 10-20 times the marrow dose. The victims received immediate and comprehensive medical treatment in specialist centres. This included barrier nursing, antibiotic treatments, and blood-cell infusions. Of 43 persons receiving marrow doses between 2 and 4 Gy, none died before 60 days (only one died, at 96 days). Of 21 individuals receiving between 4 and 6 Gy marrow doses, seven died between 16 and 48 days. Of 20 individuals receiving between about 6 and 16 Gy, two rejected a transplant but survived more than 60 days after about 8 or 9 Gy. Nineteen from the last two groups, i.e. 4 to 16 Gy, were given either allogeneic bone marrow transplants (in 13 cases) or embryonic liver cell transplants (in six cases) between one and two weeks after exposure. Fifteen of the 19 died before 60 days (and two others at 86 and 91 days), including seven from skin and intestinal injury, the others from infections and other causes. Extensive information was obtained concerning the effects on different organs of acute high-dose irradiation from a nuclear reactor accident, including bone marrow, intestine, oral mucosa, and the eye.

306. Three groups of radiotherapy patients are useful for assessment. None of 20 children and adolescents given 3 Gy to the whole body died within one year of marrow failure. However, the $LD_{50/60}$ for various groups of adults with disseminated cancers was 2.9 Gy in one series and 3.4 Gy in another. These data indicate that for ill cancer patients, the $LD_{50/60}$ is probably about 3 Gy, while for healthy individuals receiving conventional supportive treatment after irradiation it may be substantially higher, approaching or equal to about 5 Gy. The response of Japanese irradiated during wartime and receiving minimal post-irradiation medical care was more like that of the ill cancer patients than that of the healthy groups of individuals irradiated in accidents and receiving medical care.

307. Data on $LD_{50/60}$ for various species of large animals have been used to estimate the probable slope

of the dose-mortality curve for man. The average coefficient of variation among species is about 0.24, and the ratio of LD_{90}/LD_{10} is about 2. This suggests that the dose that would kill few healthy humans is about 3.0 Gy and the dose that would kill most is about 6.0 Gy.

308. Based on experiments with animals, the $LD_{50/60}$ would be expected to be greater for unilateral than for bilateral irradiation, by about 20%. This depends on the penetration of the radiation used. Doses decrease faster with depth for low energy photon or electron beams and for fission neutrons than for higher energy beams. In and near bone, there is a higher dose from low energy photon irradiation and a lower dose from neutrons.

309. In large animals, the $LD_{50/60}$ may be increased by up to about 1 Gy through conventional supportive medications and transfusions of blood elements. However, such a small dose increment can increase markedly the survival rate because of the steepness of the dose-response curve. Bone marrow grafts also increase survival. After a lethal dose in man, $2\ 10^7$ bone marrow cells per kilogram is needed to rescue 50% of individuals, based on experiments with different animal species, and $4\ 10^7$ cells per kilogram for 100% rescue. More allogeneic than isogeneic marrow cells are required for rescue. The shielding of perhaps as little as 10% of active marrow in man may reduce the mortality to zero after doses near the $LD_{50/60}$.

310. It is concluded from the various groups of individuals discussed in this Annex that the $LD_{50/60}$ for humans receiving no or little medical treatment after exposure is likely to be around 2.5 Gy marrow dose and possibly higher. A similar value may pertain to some groups of ill cancer patients receiving good medical care. For healthy humans receiving good supportive medical treatment after irradiation, the $LD_{50/60}$ is likely to be approaching or equal to about 5 Gy. The $LD_{50/60}$ can be further increased by successful marrow transplantation, probably up to around 9 Gy. After these higher doses, there may be some cases of pneumonitis occurring in the second month, unless the lungs were shielded. After even higher doses (> 10 Gy) acute gastrointestinal injury will become more prevalent.

311. Neutrons are more efficient in causing acute injury than low-LET radiations, by a factor of 2-3, using single doses. However, because of the low penetration of neutrons, values of LD_{50} for large animals can be apparently smaller for neutrons than for low-LET radiation. There is little experience in man of mortality after neutrons, except in a few isolated accidents. The neutron component of the doses to the Japanese survivors from the bombs is now considered to be much smaller than had previously been thought, probably less than 3% of the total dose at distances where acute early effects were seen.

312. In radiobiology, a protracted dose or a fractionated dose is known to have less effect than the same total dose given singly. The early effects of high doses in man also follow this general rule. Thus, prodromal responses are somewhat alleviated by dose protraction or fractionation; for example, small doses of 0.2 Gy can be delivered daily for several weeks without inducing nausea. Low-dose-rate or fractionated irradiation markedly reduces injury to the intestine in all species, including man, but dose-mortality relationships for man due to protracted intestinal irradiation are unknown.

313. The relationship between the lowest concentration of leukocytes and the total dose and exposure time has been measured. There is less effect with protraction of the dose. It has also been found that marrow recovery during irradiation is less in leukaemic patients than in other patients with non-haematological malignancies. The greater radiosensitivity of lymphocytes, as compared to granulocytes, applies to fractionated treatments as well as to single doses. Various types of quantitative formulae have been proposed to estimate changes in the $LD_{50/60}$ as a function of protracted irradiation. As the data base is sparse, these are to be taken as very rough guidelines for assessing the effects of changes in dose-time relationships.

314. The tissue responses are also markedly dependent on the mode of delivery of the dose with respect to time. The responses of the bone marrow and the skin to protracted and fractionated doses are fairly well known from radiotherapeutic experience. The lung, too, is spared by protraction. In contrast with all other tissues, protracted doses are more injurious to the testis, owing to the progression of cells into sensitive phases. In women, a larger dose is generally required to cause infertility when fractionated doses are used, but an accurate assessment is not available.

315. Large amounts of internal emitters are required to produce early effects in man. Bone-marrow depression is observed after large, single doses of iodine-131; 5 Gy is the maximum total dose that can safely be delivered to the blood. Radiocolloids have produced mild radiation sickness and haematological complications, as have radiophosphorus and sulphur-35. Severe acute intestinal injury in man from internal emitters has not been reported, and lung injury has been rare. Treatments for intake of radionuclides by ingestion are based on reduced retention, enhanced excretion or diminished translocation. Emetics, lavage and precipitating agents may help prevent gut toxicity. Decalcification therapy and chelating agents continue to be studied.

316. The radiation response of tissues can be modified by physical or chemical conditions or treatments, such as the removal of oxygen, the use of protective or sensitizing chemicals, drug adjuvants or previous treatments with cytotoxic drugs that produce residual tissue injury.

317. A small section of the population may be particularly radiosensitive because of inherited genetic disorders, such as ataxia telangiectasia (AT). Children with AT are more radiosensitive, and cultured skin fibroblasts taken from them are similarly sensitive.

Estimates of the frequency of hereditary conditions that are likely to render individuals particularly radiosensitive are of the order of one per cent in the general population.

318. It is difficult to establish a prognosis for individuals irradiated above the threshold doses for acute effects solely from an estimate of the dose, because of the steepness and uncertainty in the dose-response curves, including uncertainty of the value of the $LD_{50/60}$ for man. Also, there are many confounding factors, such as the presence of intercurrent disease, the effect of shielding and protraction and the quality of the radiation. The type, severity and duration of the prodromal symptoms, including the presence and extent of erythema, may assist in the prognosis. Haematological signs, particularly the lymphocyte count, are good prognostic indicators. The lowest concentrations of the various blood cell types and the time at which such concentrations are reached following irradiation are important inputs for the prognosis, as is the duration of marrow aplasia after high doses. The appearance and persistence of immature cells in the blood is a sign of marrow regeneration and is a favourable sign. Marrow scanning can give an indication of erythropoiesis in different regions, but for estimating the likelihood of long-term recovery, it is necessary to culture very immature cells in the marrow. Urine and bacteriological analysis may assist in prognosis; sperm analysis is important for assessing the dose and subsequent likelihood of fertility. However, to be valid, a prognosis must be founded on many different data and constantly updated.

319. Biological dosimetry relies on many prognostic indicators, as well as on laboratory tests, for which correlations between effect and dose have been reasonably well established. Changes in lymphocytes that are clearly related to dose include the appearance of nuclear abnormalities, pycnosis, tritiated thymidine uptake and electrophoretic mobility. These measurements should be regarded, for dosimetric purposes, as only semi-quantitative. Leucocyte malformations, the level of serum glycoproteins, the presence in the blood of immature granulocytes and erythroblasts and the appearance of reticulocytes are also indicative of irradiation but are not suitable for accurate dose assessments.

320. Tests of the proliferative ability of the marrow may also be regarded as useful dosimetric indicators. A drop in the mitotic index, for example, is a sign of doses higher than 1 Gy. The migration of granulocytes into the bloodstream after the injection of ethiocholanolon suggests the active production of granulocytes by the bone marrow. Cultures of mixed-cell colonies and granulocyte/macrophage colonies give some indication of the concentration of precursor cells in the marrow, as a function of the dose. By contrast, erythrocytes are relatively radioresistant and long-lived, and hence their concentration in the blood is a poor indicator of dose; however, marrow scans for erythropoiesis may be used to estimate marrow doses. Biochemical analyses of the urine are more indicative of dose than similar analyses of the blood, but no test provides a better estimate of the dose than haematological and cytogenetic measurements.

321. Cytogenetic measurements of chromosome dicentrics, rings, fragments and micronuclei provide the most accurate assessment of the average dose, of importance for acute effects, over the body. The linear or linear-quadratic relationships are well established for irradiation of lymphocytes in vitro, for many radiation qualities and dose rates. With neutrons, linear relationships apply, and the relative efficiencies of different energies of neutrons have been measured. Protracted doses are, however, more difficult to estimate.

322. Changes in a number of neurophysiological parameters have been observed after irradiation, and these have good potential for development as dosimeters. The radiation-induced activation of biological and other materials, as well as electron spin resonance measurements, are quantifiable signals at lethal or sublethal doses, down to about 0.3 Gy, that could also be used as dosimetric techniques.

Table 1

Survival parameters for human clonogenic cells assayed in primary culture after single doses of low-LET radiation

Cell type	D_0 (Gy)	Extra-polation number	Ref.
Haemopoietic progenitor cells producing			
Mixed-cell colonies	0.91	1.0	[N2]
Colonies of granulocytes	1.4	1.0	[S18]
and macrophages	1.6	1.0	[B28]
	1.3	1.1	[R21]
	1.2	1.0	[B47]
	1.4	1.0	[G21]
	1.0-1.1	1.4-1.6	[F13]
Colonies of granulocytes and macrophages in diffusion chambers	0.85	0.96	[G12]
Erythroid colonies	0.93-1.3	1.0	[G21]
Colonies of stromal cells	1.0	1.0	[F13]
T-lymphocyte precursor cells	1.2	0.9	[K6]
Skin keratinocytes	0.7-0.9	10-16	[D10]
	0.97	3.1	[P21]
Skin fibroblasts	1.32	0.95	[W11]
	1.40-1.52	2	[W12]
	0.97-1.80	1.0	[A17]
Skin and lung fibroblasts	0.75-1.30	1.0	[C25]
	1.22	1.0	[C26]
Mammary fibroblasts	1.1	2.0	[C24]
Mammary epithelium	1.3	1.0	[Y4]
	1.2	2.4	[C24]
Thyroid epithelium	0.93	2.0	[H31]
	0.7-1.1	1.0-3.5	[M41]

Table 2

ED_{50} estimates for prodromal symptoms of gastrointestinal injury for irradiated patients a/ [L8]

Response	Previous estimates b/ N = 163 c/	Oak Ridge Associated Universities N = 104	Other hospitals N = 400	All hospitals N = 504	All, six nursing notes required d/
Anorexia	0.97 (+0.31) (-0.26)	0.63 (+0.13) (-0.12)	1.29 (+0.56) (-0.31)	0.92 (+0.33) (-0.20)	0.59 (+0.14) (-0.10)
Nausea	1.39 (+0.72) (-0.33)	1.28	1.72 (+0.83) (-0.43)	1.54 (+0.47) (-0.29)	1.18 (+1.54) (-0.50)
Vomiting	1.83 (+1.78) (-0.53)	1.65	2.76 (+2.17) (-0.87)	2.30 (+1.04) (-0.53)	1.76 (+0.76) (-0.41)
Diarrhoea	2.38 (+1.22) (-0.55)	3.70 (+ ?) (-1.72)	2.94 (+ ?) (-1.66)	3.02 (+1.62) (-0.76)	2.86 (+2.30) (-0.86)

a/ In this Table, doses are given in Gy ± 1 SE; they are the average doses to a 26 cm diameter sphere in the epigastric region. Irradiation was to the whole body, and in 84 of the 163 patients (column 2) the dose rate was about 0.01 Gy per minute. The calculations assume a log-normal distribution of incidence versus dose, with an allowance made for the incidence in non-irradiated patients. The responses refer to anorexia, nausea and vomiting within two days and diarrhoea within six weeks.

b/ Space Radiation Study Panel Report [L4].

c/ N = number of patients.

d/ Clinical histories not having this minimum number of consecutive post-irradiation notes were discarded.

Table 3

Cellularity and kinetics in human intestinal mucosa
[P9, W24]

Small intestine	
Cells per villus	~ 4000-8000
Cells per crypt	~ 300- 500
Crypt cells in cycle	< 300
Cell cycle time	36-60 h
Total number of crypts	~ $6\ 10^8$
Total cells produced per day	~ 10^{11}
Transit time (crypt to villus tip)	3- 4 d
Cell cycle times (hours)	
Stomach	12-30
Ileum	30-70
Colon	16-96
Rectum	13-96
Mucosal turnover times (days)	
Ileum	3-4
Colon	3-6
Rectum	6-8

Table 4

Distribution of deaths among a small sample of documented individuals who died after the bombings in Hiroshima and Nagasaki
[04]

Days after bombing to death	Number of individuals	
	Hiroshima	Nagasaki
0- 1	0	29
2- 3	1	8
4- 5	4	28
6- 7	17	40
8- 9	25	44
10-11	4	21
12-13	7	14
14-15	8	18
16-17	7	19
18-19	17	15
20-29	137	87
30-39	80	43
40-49	13	13
50-59	6	11
60-69	11	6
70-79	2	6
> 80	5	8
Unknown	1	2
Total	345	412

Table 5

Cell kinetic data for human epidermis
[P11, P30]

Number of cell layers		
Nucleated (including basal)		~ 5.5
Corneocytes		> 10
Transit time		
Basal to granular	(d)	14 ± 6 (SD)
Granular to surface	(d)	18 ± 6 (SD)
Lifetime surface cells	(d)	~ 2
Basal cells per mm^2		(20-30) 10^3
Labelling index (18-h average)	(%)	~ 4.7
Mitotic index (18-h average)	(%)	~ 0.63
Length of S phase	(h)	9 ± 2 (SD)
Cell cycle duration	(h)	213 ± 84 (SD)
Cells produced per hour per 100 basal cells a/		~ 0.47

a/ Assuming growth fraction = 1.0.

Table 6

Skin "tolerance" doses (Gy) and field sizes
[H19]

Treatment	Field size (cm x cm)			
	6 x 4 (Small)	8 x 10	15 x 20 (Large)	L/S (%)
[P2]				
Single dose	20.0	14.5	11.00	55
3 weeks	50.0	37.5	29.0	58
5 weeks	58.0	43.5	33.5	58

Treatment	Field size (cm x cm)			
	7 x 5 (Small)	8 x 10	15 x 20 (Large)	L/S (%)
[V8]				
Single dose	25.0	17.0	-	-
3 weeks	52.5	45.0	30.0	57
5 weeks	60.0	50.0	35.0	58

Table 7

Doses to a 1 cm circle of pig skin causing dry desquamation
(modified from [M21])

Isotope	Average energy (MeV)	Threshold surface dose for dry desquamation (Gy)	Dose at 90 µm (Gy)
Sulphur-35	0.17	200	12
Cobalt-60	0.31	40	16
Caesium-137	0.55	20	17
Yttrium-91	1.53	15	12
Strontium-90 / Yttrium-90	0.61 / 2.20	15	14

Table 8

Early effects of radiation on the human eye
[M15]

Tissue	Effect	Latent period	Dose (Gy)	
			Single	Fractionated
Lid skin	Erythema, second wave	2-4 weeks	6	-
	Pigmentation	2-3 weeks	4-6	-
	Moist desquamation	2-8 weeks	-	50-60/5-6 weeks
Lid margin	Epilation (incomplete)	1-2 weeks	10	-
	Epilation (complete)	2-5 weeks		20-30/2-3 weeks
Conjunctiva	Hyperemia	Immediate	>5	-
	Conjunctivitis	1-3 weeks	-	=50/4-5 weeks
Cornea	Punctate keratitis	Several weeks	10	30-50/4-5 weeks
	Edema	1-3 weeks	-	40-50/2-3 weeks
	Mild ulceration	Several (3-6) weeks	-	30-40/2-3 weeks
Iris	Iritis	Several days	20	>60/5-6 weeks
Retina	Edema	Several weeks	-	20-35/3-4 weeks

Table 9

Kinetics of spermatogenesis in man
[B11]

Spermatogonial types	Stages from acrosome development	Duration of		Spermatids	
		Cell-cycle (h)	Spermatogenesis (d)	Number of stages	Number of types
A-dark	I-VI	<384			
A-pale	VI-V	384	64	6	6
B	VI-I	209			

Table 10

Effects of single-dose irradiation (low-LET) on spermatogenesis and fertility
[I9, L4, U4]

Dose (Gy)	Effect on	
	Spermatogenesis	Fertility
0.15	Moderate oligospermia	Temporary sterility (?)
0.20	Moderate oligospermia	Temporary sterility a/
0.50	Pronounced oligospermia	Temporary sterility
1.0	Severe oligospermia	Prolonged sterility
2.0	Azoospermia	Prolonged sterility
> 6	Azoospermia	Prolonged sterility

a/ Type B spermatogonia are exceptionally sensitive, with $D_0 \sim 0.2$ Gy.

Table 11

Previous estimates of $LD_{50/60}$ in man (acute doses of low-LET irradiation)

Data source	Midline or marrow dose (Gy)	Year	Reference
All groups	3.0	1950	[W13]
	3.0	1950,1957	[L14, G15]
	2.6-4.0	1960	[N3]
	2.5-2.9	1967	[L4]
	3.15	1974	[N6]
	3.0	1979	[K9]
	3-6	1984	[M13]
Japanese bomb casualties	5.0	1956	[O5]
	2.6	1969	[L8]
	1.54	1986	[R20]
	2.1-2.5	1987	[F15]
	2.4 a/	1987	[F15]
	2.7-3.1	1987	[F15]
Radiotherapy patients	4.0	1964	[M31]
	2.4	1966	[L11]
Accidents, with supportive treatment	3.6	1960,1962	[C13,U1]
	3.4	1975	[R22]
	5.1	1975	[R22]
	3.5	1979	[K9]
	5.25	1979	[K9]
	5.0	1979	[D21,T28]
	4.5-5.0	1983,1984,1985	[M2,M27,M28]
	4.5	1985	[U5]
Accidents, with successful marrow transplantation	11.0	1985	[U5]

a/ Revision of above value of 1.54 Gy.

FACTORS WHICH MIGHT CAUSE THE $LD_{50/60}$ TO BE:

		Section
LOWER		
	Pre-1986 dosimetry for A-bomb data	II.A.1
	Contribution of extensive burns	II.A.1
	Pre-existing illness	II.A.1
	Chronic nutritional deprivation	II.A.1
	Concurrent infections	II.A.1
	Contribution of high-LET radiation	II.A.5
HIGHER		
	Young, female	II.A.1
	Radiation poorly penetrating	II.A.1
	Unilateral irradiation	II.A.3
	Partial marrow shielding	II.A.4
	Good medical support	II.A.6
	Protracted irradiation	II.B.4

Table 12

Marrow doses (Gy) for selected accident cases
[M28, B7]

Subject	1	2	3	4	5	6	7	8
Y-12								
A	2.69	a/	0.96	3.65	0.14	2.60-4.40	3.06	3.30
C	2.50		0.89	3.39	0.13	2.50-4.10	2.84	3.01
D	2.41		0.86	3.27	0.13	2.40-3.90	2.75	3.11
B	1.99		0.71	2.70	0.11	2.00-3.30	2.27	2.72
Vinca								
V (died)	2.14	1.33	0.89	4.36	0.68	(2.30-3.10) 2.73	3.28	4.53
M	2.09	1.30	0.87	4.26	0.66	(2.30-3.10) 2.67	3.20	4.32
D	1.92	1.36	0.91	4.19	0.69	(1.80-2.50) 2.17	3.14	4.05
G	1.89	1.35	0.90	4.14	0.68	(1.80-2.50) 2.16	3.09	3.99
H	1.58	0.99	0.66	3.24	0.50	(1.70-2.30) 2.01	2.42	3.27

a/ Not stated.

Columns:
1 Gamma-ray emission by source = leakage dose = first-collision dose.
Y-12: [H23]; Vinca: [H22].
2 Gamma-ray dose for neutron capture in the surface of the body.
Y-12: [H23]; Vinca: [H22].
3 First-collision charged-particle dose. Y-12: [H23]; Vinca: [H22].
4 Total dose as published (columns 1 + 2 + 3). Y-12: [H23]; Vinca: [H22].
5 Gamma-ray dose from neutron capture in 6-cm annulus of 30-cm cylinder.
6 Marrow dose [B7].
Y-12, first figure: marrow dose if exposed from the front;
Y-12, second figure: if exposed from the side;
Vinca: uncertainty range is ± 15% of the mean.
7 Marrow dose [M28].
Values are for Y-12: 0.8 (column 1) + 0.8 (column 3) + column 5;
for Vinca: 0.8 (column 1) + column 3 + column 5.
8 A further revision of the dosimetry on the basis of lower body sodium levels, results in increased estimates of dose using sodium activation by factors of 1.06-1.20 at Y-12, and 1.29-1.41 at Vinca [M26, M27].

Table 13

Total-body irradiation in man: schematic classification of dose ranges: symptoms, therapy and outcome

	Prodromal symptoms		Clinical characteristics			Therapy, clinical course and outcome				
									If injury is fatal	
Acute dose (Gy)	Incidence (%)	Latency	Syndrome or organ involved	Characteristic symptoms	Critical period after exposure	Therapy	Prognosis	Lethality (%)	Death within	Usual cause of death
> 50	100	Minutes	Neurological syndrome	Cramps, tremor, ataxia, lethargy, impaired vision, coma	1-48 h	Symptomatic	Hopeless	100	1-48 h	Cerebral oedema
10-15	100	0.5 h	Intestinal syndrome	Diarrhoea, fever, electrolytic imbalance	3-14 d	Palliative	Very poor	90-100	2 weeks	Enterocolitis shock
5-10	100	0.5-1 h	Bone marrow syndrome	Thrombopenia, leucopenia, haemorrhage, infections, epilation	2-6 weeks	Bone marrow transplantation, transfusions of leukocytes and platelets, optimal care (isolation, antibiotics, fluids)	Uncertain depending on success of therapy	0-90	Weeks	Infections and/or haemorrhage
2-5	50-90	1-2 h	Bone marrow syndrome	Thrombopenia, leucopenia, haemorrhage, infections, epilation	2-6 weeks	Transfusions of leukocytes and platelets, optimal care (isolation, antibiotics, fluids), bone marrow transplantation	Uncertain depending on success of therapy	0-90	Weeks	Infections and/or haemorrhage
1-2	0-50	> 3 h	Bone marrow	Mild leucopenia and thrombopenia	2-6 weeks	Symptomatic	Excellent	0-10	Months	Infections and/or haemorrhage

Table 14

Symptoms for midline dose range 1.0-2.0 (Gy)
[Y7]

Symptom	Postexposure time: Hours 0	4	8	12	16	20	24	Days 1	2	3	4	5	6	7	Weeks 1	2	3	4	5	6
Nausea[a]	—30-70% mild to moderate—																			
Vomiting (retching)	—20-50% mild to moderate—																			
Anorexia	—50-90%—																			
Diarrhea (cramps)[b]																				
Fatigue[c]	—30-60% mild to moderate—														Mild					
Weakness	—30-60% mild to moderate—														Mild					
Hypotension																				
Dizziness																				
Disorientation																				
Bleeding[d]														—(e)—				—10% mild—		
Fever														—(f)—						
Infection								—(g)—										10-50% mild to moderate		
Ulceration																				
Fluid loss/electrolyte imbalance																				
Headache																				
Fainting																				
Prostration																				
Death[h]																				≤5%—

a/ References for this group of symptoms: A25, A26, A27, B17, B29, C10, C14, C15, C39, C42, C43, C44, E11, G26, G28, G29, H39, H40, J2, L20, L24, M18, M42, M44, N10, N11, N13, O5, O6, P24, R23, S33, S34, S35, S36, T5, V18, W19, W21, Z4.

b/ 10% of the Marshallese victims exposed to 1.75 Gy experienced diarrhea during the first day after irradiation, according to [A25].

c/ References for this group of symptoms: A27, H39, K21, N13, O6, P24, S33, U8, U9.

d/ References for this group of symptoms: A26, A27, B16, B29, C10, C14, C15, C43, C44, C45, C47, D19, K21, L20, L22, M10, M18, M42, N10, O5, O6, P24, R12, U9, V18, W19, W21, Z3.

e/ Slight to moderate drop in platelets: from 3 10^5/µl to 1.8-0.8 10^5/µl.

f/ Slight to moderate drop in granulocytes: from 6 10^3/µl to 4.5-2.0 10^3/µl.

g/ Slight to moderate drop in lymphocytes: from 3 10^3/µl to 2.0-1.0 10^3/µl.

h/ References for this event: A25, B16, L4, O6.

Table 15

Symptoms for midline dose range 2.0-3.5 (Gy)
[Y7]

Symptom	Postexposure time: Hours 0	4	8	12	16	20	Days 1 (24)	2	3	4	5	6	7	Weeks 1	2	3	4	5	6
Nausea[a]	——70-90% moderate——																		
Vomiting (retching)	——50-80% moderate——																		
Anorexia	——90-100%——																—60%—-		
Diarrhea (cramps)	— ← ~10% moderate													Moderate →			—40—-		
																	60%		
Fatigue[b]	——60-90% moderate——																		
Weakness	——60-90% moderate——																		
Hypotension																			
Dizziness																			
Disorientation																			
Bleeding[c]														—(d)—			—10-50%—-		
																	moderate		
Fever														—(e)—					
																	10-80%		
Infection														—(f)—			moderate		
Ulceration																	—30%—-		
							(g)										moderate		
Fluid loss/electrolyte imbalance																			
Headache																			
Fainting																			
Prostration																			
Death[h]																≤5-50% →			

a/ References for this group of symptoms: A25, A26, A27, B17, B29, B52, C14, C39, C40, C47, D19, E11, G2, G25, G26, G27, G28, H39, H40, I20, J2, K21, L20, M10, M42, N11, N13, O5, O6, P24, R6, R23, S33, S34, S35, T5, T23, W19, W20, W21, W22, Y6, Z3, Z4.

b/ References for this group of symptoms: A24, A27, B16, G2, L10, M42, O6, U9, V18, Y6, Z3.

c/ References for this group of symptoms: A26, A27, A28, B16, B17, C14, D19, F14, I11, J2, K21, L10, L20, L22, M10, M42, N10, O5, O6, P24, R6, S34, T23, U9, W19, W20, Z3.

d/ Moderate drop in platelets: from 3 $10^5/\mu l$ to 0.8-0.1 $10^5/\mu l$.

e/ Moderate drop in granulocytes: from 6 $10^3/\mu l$ to 2.0-0.5 $10^3/\mu l$.

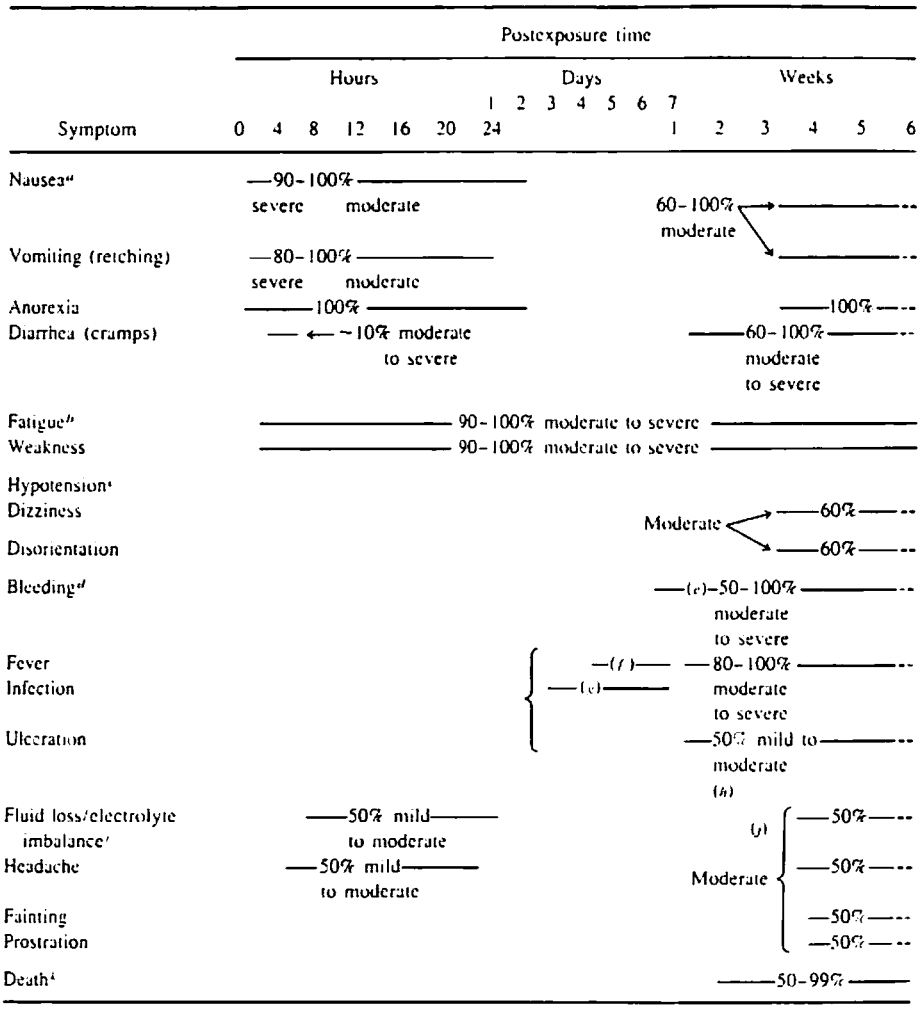
f/ Moderate to severe drop in granulocytes: from 3 $10^3/\mu l$ to 1.0-0.4 $10^3/\mu l$.

g/ Epilation.

h/ References for this event: A25, A27, B16, L4, O6.

Table 16

Symptoms for midline dose range 3.5-5.5 (Gy)
[Y7]



a/ References for this group of symptoms: A24, A25, A26, A27, B16, B17, B29, C14, C39, C40, E11, G25, G26, H39, H40, I20, J2, J19, L20, M42, M43, N10, N11, O5, O6, P24, R12, R23, S33, S34, T5, T23, W19, W20, U9, Z3, Z4.

b/ References for this group of symptoms: A24, A26, A27, B16, G27, H40, I20, M18, O6, P24, S33, U9.

c/ References for this group of symptoms: M43, R12.

d/ References for this group of symptoms: A24, A26, A27, B16, B17, C14, C41, C47, D19, I11, J19, L8, L10, L20, L22, M10, M42, M43, O6, P24, R23, S33, S34, U9, W19, W20, W21, Z3, Z4.

e/ Severe drop in platelets: from 3 10^5/µl to 0.1 10^5-0/µl.

f/ Severe drop in granulocytes: from 6 10^3/µl to 0.5 10^3-0/µl.

g/ Severe drop in lymphocytes: from 3 10^3/µl to 0.4-0.1 10^3/µl.

h/ Epilation.

i/ References for this group of symptoms: A27, B16, L10, O6, R12, U9.

j/ Mild intestinal damage.

k/ References for this event: A25, B16, L4, O6.

Table 17

Modification of $LD_{50/30}$ for single doses, according to direction of the beam
[M28]

	Dog	Sheep	Pig	Goat
Body mass, kg	7-13	32-57	av. 62	60-95
Radiation	1 MV x rays, point source	1 MV x rays, point source	2 MV x rays, point source	2.5 Mev Gamma rays, planar source
Source to midplane of animal (m)	2.1	2.0	2.14	0.25
Diameter of trunk (cm)	14	20-25	28	30
Irradiation conditions	Conscious	Conscious	Conscious	Sedated
Mortality period (days)	0-30	0-60	0-30	0-60
LD_{50} mean ± SE (Gy) a/				
Unilateral exposure	3.37 ± 0.09	2.65 ± 0.11	3.79 ± 0.11	3.94 ± 0.21
Bilateral exposure	2.80 ± 0.08	2.20 ± 0.15	3.16 ± 0.17	3.35 ± 0.26
Difference	0.57	0.45	0.63	0.59
Ratio	1.20	1.20	1.20	1.17
Coefficient of variation				
Unilateral exposure	0.15	0.17	0.11	0.20
Bilateral exposure	0.25	0.28	0.16	0.32

a/ Air kerma at midplane of exposure volume in absence of animal.

Table 18

Examples of adult erythropoietic bone-marrow distributions in several mammalian species
(per cent)

Site	Mice [C22]	Rats [V17]	Dogs [G8]	Monkeys [T15]	Humans: Men [W8]	Humans: Women [W8]	Humans [M30]
Skull)	19.1	4.1	1.0	8.7	8.3	9.4	7.3
Mandible)		2.6	0.1	2.2	1.0	0.7	0.5
Two clavicles	-	0.21	-	0.7	1.0	0.9	0.7
Two scapulae	-	1.5	5.1	3.9	3.8	2.8	2.2
Upper limbs	(5.7)	(8.6)	(11.1)	(12.2)	-	-	(3.7)
Two humeri	4.1 a/	7.0	10.8	9.2	-	-	3.7
Two radii	-	0.4	0.1	1.5	-	-	0
Two ulnae	-	1.0	0.1	1.3	-	-	0
Two wrists (hands)	1.6	0.2	0.1	0.2	-	-	-
Ribs	16.1	6.2	20.5	4.8	18.4	17.3	18.7
Sternum		4.1	2.8	1.5	3.9	3.6	2.6
Vertebrae	(38.1)	(29.7)	(42.6)	(33.1)	(35.9)	(36.6)	(24.4)
Cervical	-	2.4	6.7	2.2	4.1	5.1	4.0
Thoracic	-	9.9	17.6	12.3	17.9	18.0	9.9
Lumbar	-	7.6	15.0	17.0	13.9	13.5	10.5
Sacrococcygeal	8.2 b/	15.5 c/	3.3	1.6	7.7	7.4	7.9
Two hip bones			8.9	12.9	19.7	21.3	20.7
Lower limbs	(12.8)	(39.4)	(7.9)	(20.0)	-	-	(10.6)
Two femurs	6.0	16.9	7.2	13.3	-	-	10.6
Two patellae	-	-	0.0	0.1	-	-	-
Two tibiae		13.5	0.6	5.9	-	-	0
Two fibulae	4.2	8.6	0.0	0.5	-	-	0
Two ankles (feet)	2.6	0.4	0.1	0.2	-	-	-

a/ Includes clavicles and scapulae.
b/ Pelvis.
c/ Includes caudal vertebrae.

Table 19

Accidental human total-body protracted exposures giving marrow doses higher than 1 Gy

Accident	Person(s)	Exposure duration (days)	Approximate marrow dose (Gy)	Outcome	Ref.
Rongelap	64	2	1.75	All survived	[C10]
China a/	Male	5-9	80	Died	[Y1]
	Male	5-9	40	Died	
	Female	5-9	8	Survived	
	Male	5-9	6	Survived	
	Female	5-9	4	Survived	
"Lucky Dragon"	23 fishermen	14 b/	2-7	All survived	[K4]
Algeria a/	Female	38	12-14	Survived	[J3]
	Female	38	12.5-14	Survived	
	Female	38	11-13	Survived	
	Female	38	10-12	Survived	
	Grandmother	38	> 40	Died	
Mexico	Son	24	29-52	Died	[M3]
	Wife	115	20-39	Died	
	Daughter	99	14-19	Died	
	Grandmother	90	18-29	Died	
	Husband	106	9.8-17	Survived	
Morocco c/	Grandmother	82	6-7	Survived	[N5]
	Grandfather	17	0.5-1.5	Survived	
	Cousin	17	2-3	Survived	
Brazil d/					

a/ Very inhomogeneous doses.
b/ Two thirds of dose on first day.
c/ Eight other members of the family and their relatives received exposures over 15 and 45 days, and all of them died. However, assessments of their doses are not available [N5].
d/ Ten individuals received high doses and four of them died (see paragraph 158).

Table 20

Incidence of pneumonitis in man after fractionated irradiation [M38]

Lung dose (Gy)/ number of fractions	Number of patients	Incidence of pneumonitis (%)	Primary diagnosis of tumour
30/15	6	33	Lung,
35/20			Hodgkin's disease
32/15	12	42	Lung,
36/20			Hodgkin's disease
30/10	12	67	Lung,
38/20			Hodgkin's disease,
45/30			Hemangiopericytoma, Thymoma
31/10	10	90	Lung, Breast,
42/18			Thymoma
41/16	14	86	Lung, Breast,
53/25			Sarcoma

Table 21

Clinical course after doses resulting in the bone-marrow syndrome

Phase	Approximate duration
Prodromal	1- 7 days
Latent	7-20 days
Critical	Second or third week to 7 weeks
Recovery	8-15 weeks

Table 22

Gastrointestinal prodromal symptoms at 48 hours in 111 cancer patients [LB]

Symptoms	Doses (Gy)	
	D 10%	D 50%
Anorexia	0.3	0.6
Nausea	0.4	1.2
Vomiting	0.5	1.8
Diarrhoea	0.6 a/	3.0

a/ By six weeks.

Table 23

Summary of symptoms, time course and prognosis in the bone marrow syndrome in man (adapted from [112])

Dose range (Gy)	Prognosis	Appropriate time of delay for nausea and vomiting	Time of delay for critical period	Main symptoms	Time of recovery	Time of death
0-1	Excellent	-	-	-	-	-
1-2	Excellent	3 hours	-	Moderate leucopenia	Several weeks	-
2-6	Uncertain	2 hours	4-6 weeks	Leucopenia, haemorrhage infection	6-8 weeks 1-12 months	< 2 months
6-10	Uncertain	1 hour	4-6 weeks	Leucopenia	Prolonged	< 2 months
10-15	Poor	0.5-1 h	5-14 days	Diarrhoea, fever, electrolyte imbalance	-	< 2 weeks
> 60	Hopeless	0.5 hour	1-48 hours	Ataxia, lethargy	-	< 2 days

Table 24

ED 50 (Gy) for prodromal symptoms in ill cancer patients after whole-body acute or protracted exposure [L9]

Symptom	Exposure period	
	1 day (504 patients)	7 days (103 patients)
Anorexia	0.97	2.0
Nausea	1.4	2.6
Vomiting	1.8	4.9
Fatigue	1.5	2.6 (?)
Diarrhoea	2.3	5.3

Table 25

Main signs and symptoms in the critical phase of the bone marrow syndrome in man (adapted from [N5])

1:	Anorexia Nausea Vomiting Weakness, fatigue Prostration
2:	Sweating, fever Purpura Hemorrhage, epistaxis, gingival bleeding, haematemesis, melaena, haemoptysis Infection
3:	Erythema, epilation, scalp pain
4:	Abdominal pain Abdominal distention Diarrhoea
5:	Oliguria Hyperaesthesia, paraesthesia Ataxia Disorientation Shock Coma Death

Table 26

Minimum values of blood cell counts
after three accidents involving eight individuals
[N5]

(Acute doses from mixed fields in cases 1-7.)

Case a/	Dose (Gy) γ+n		Lymphocytes		Neutrophils		Platelets		Outcome
	Dose 1 b/	Dose 2 c/	Cells/ µl	Time (days)	Cells/ µl	Time (days)	Cells/ µl	Time (days)	
1	3.5+0.9	4.5	37	30	15	26	1900	19	Death (day 32)
2	3.4+0.9	4.3	322	15	48	26	28200	26	Favourable transplantation of bone marrow (day 29)
3	3.2+0.9	4.0	396	29	42	29	14000	26	As in case 2
4	3.3+0.9	4.1	80	29	0	33	25400	29	As in case 2
5	2.6+0.65	3.3	550	33	36	33	14200	26	As in case 2
			45	59					
6	1.6+0.45	-	390	9	916	33	53400	26	Favourable
7	5 +0.5	-	130	4	21	22	10000	22	Favourable
8	12	-	55	8	98	10	26000	10	Death (day 12)

a/ Cases 1-6: Vinca, Yugoslavia (1958).
Case 7: Mol, Belgium (1965).
Case 8: Brescia, Italy (1975).
b/ Dose 1: original estimated doses.
c/ Dose 2: Revised equivalent low-LET marrow dose (see Table 12).

Table 27

Minimum values of blood cell counts
after two accidents involving several individuals
where the inhomogeneous irradiation was prolonged over a few weeks
[N5]

Case a/	Dose (Gy) γ	Lymphocytes		Neutrophils		Platelets	
		Cells/ µl	Time (days) b/	Cells/ µl	Time (days) b/	Cells/ µl	Time (days) b/
9	12-14	41	17	0	9	21000	3
10	12-14	250	22	0-3	7-16	20000	9
11	11-13	124	24	10	21	20000	21
12	10-12	109	30	30	27	20000	26
15	6-7	416	18	63	8	35000	2
16	2-3	560	50	858	44	Normal	-
17	Acute 1.9, chronic 4.0	486	c/	1200	c/	100000	c/

a/ Cases 9-12: Algeria, 1978.
Cases 15-17: Morocco, 1984.
b/ After the end of exposure.
c/ During the first week of hospitalization.

Table 28

Representative effects and related acute doses after whole-body irradiation in man
(adapted from [N5])

Threshold for detection of the effect	Dose (Gy) a/
Chromosome aberrations and sperm-count depression	0.05-0.25
Electroencephalography modifications	0.25-0.5
Vomiting in 10% of exposed individuals	0.5 -1.5
Transient disability and easily detectable haematological changes	1.5 -2

a/ Whole-body dose, which may vary by as much as ± 50%; expressed as midline doses.

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APPENDIX

Acute radiation effects in victims of the Chernobyl nuclear power plant accident

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Introduction

1. This Appendix sets out the essential findings of the clinical observation of a group of patients suffering from acute radiation sickness following the accident at the Chernobyl nuclear power plant on 26 April 1986. The observations were conducted at the specialized treatment centre in Moscow over a period of two years.

2. An initial report on the accident was submitted by the Soviet representatives to the Post-Accident Review Meeting held at the International Atomic Energy Agency in August 1986 and was summarized in IAEA Safety Series Technical Report No. 75 [I18] and in [G33]. The proposal to present this information in its present form was endorsed at the thirty-sixth session of UNSCEAR in March 1987.

3. The basic information on the radionuclide releases and the types of exposures of the irradiated persons coincided with the expected pattern for an accident at a nuclear power plant of similar type: as much as 100% of gaseous fraction of the noble gases and nuclides may have escaped from the plant; caesium, iodine and tellurium isotopes accounted for up to 10-20% of the nuclide inventory, and other radionuclides for up to 30% [I18].

4. The plant personnel and auxiliary staff present at the industrial site in the immediate vicinity of the accident zone were subjected to the combined effect of radiation from several sources: (a) short-term external gamma/beta radiation from the gas emission cloud (in the case of persons in the immediate area of the accident zone at the time of the explosion); (b) external gamma/beta radiation of decreasing intensity, from fragments of the damaged reactor core scattered over the industrial site; (c) inhalation of gases and aerosol dust particles containing a mixture of radionuclides; and (d) deposition of these particles on the skin and mucous membranes at the time of the intensive generation of steam or dust and the wetting of clothing (as a result of them being blown or washed off contaminated objects).

5. However, the most significant factor was the general, external and relatively uniform whole-body gamma-irradiation and the beta-irradiation of extensive body surfaces, coupled (except in two cases) with a very small intake of nuclides through inhalation, predominantly of radioiodine and caesium isotopes. Thus, the basic clinical picture was that of a distinctive acute radiation sickness caused by gamma-irradiation of the whole body and by beta-irradiation of extensive areas of the skin surface.

6. Direct and indirect dosimetry methods were used to determine the nuclide content in the body. A great many tests were carried out, both while the victims were alive and (in 28 cases) after they had died, so that it was possible to estimate the nuclide content in the body and the resultant dose levels. An example of these types of analyses is shown in Figure A.I., giving the distribution of various radionuclides in the lungs.

7. The iodine isotope content in the thyroid gland was determined repeatedly (as many as four to six

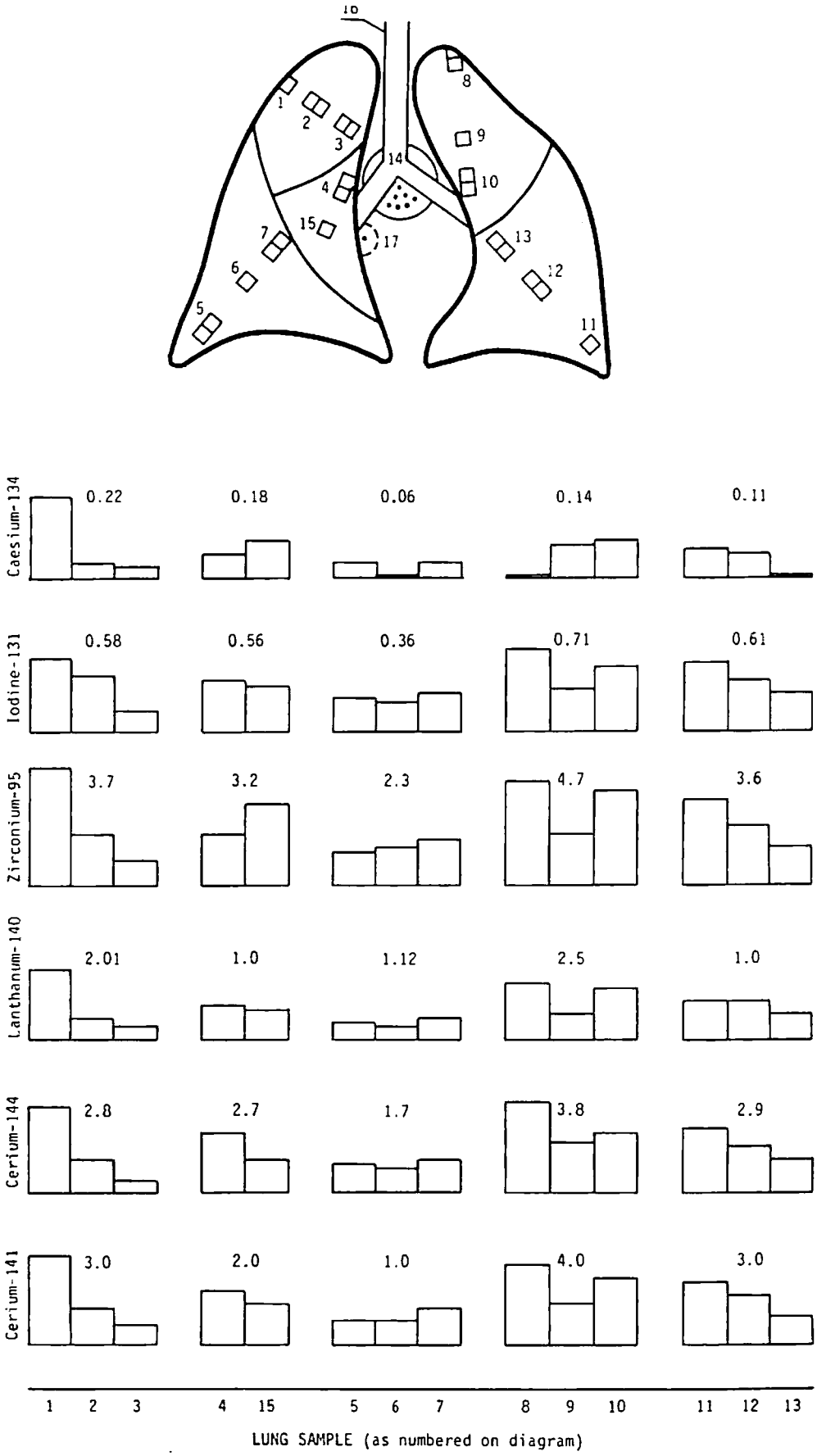

Figure A.I. Location of lung samples taken at the time of autopsy and distribution of the main radionuclides in lung samples. The number above each sample group indicates the approximate relative average value.

times) from the second day after the accident. These measurements showed that ^{131}I accounted for 80 ± 20% of the total activity of all iodine isotopes, ^{133}I for 15 ± 10%, and the remaining isotopes (^{123}I, ^{124}I, ^{126}I, and ^{130}I) for not more than 2%.

8. The calculations for estimating intake quantities from the thyroid measurements were performed according to the recommendations of the International Commission on Radiological Protection [I19]. On the basis of the distribution of thyroid doses in exposed individuals (Table A.1), it may be stated that in the overwhelming majority of cases the thyroid doses were below the levels likely to cause direct injury to that organ (< 3.7 Sv) or of significantly influencing the clinical picture during the onset of acute radiation sickness. Low radioiodine dose levels were also suggested by the post-mortem nuclide measurements of the 28 persons who subsequently died.

9. Internal dose values according to post-mortem measurements for 6 patients are shown in Table A.2. The maximum amount of ^{137}Cs and ^{134}Cs incorporated activity was 7.4 MBq, except for two patients with extensive steam burns, which allowed intake of nuclides through the wound. The post-mortem dosimetry gave 40 and 80 MBq of ^{137}Cs plus ^{134}Cs, and 450 and 1,100 MBq of ^{131}I, for these two patients, respectively. The whole-body internal doses in these two individuals from these nuclides were estimated as approximately 1 Sv and 2 Sv during the two to three weeks before they died, which are commensurable with their external gamma doses. This fact was taken into account during the interpretation of clinical data. Internal doses for other patients did not exceed 1-3% of the external irradiation doses.

10. The transuranic elements (e.g., ^{239}Pu) were studied in urine specimens from 266 persons (635 analyses), including, in some of the cases, analyses conducted before and after the administration of pentacine. The urine activity values and a negative finding after chelation treatment confirmed the absence of a significant plutonium contamination of all the patients observed. Post-mortem tests by alpha spectrometry for transuranic elements showed their presence (74-300 Bq per organ) only in the lungs; curium accounted for as much as 90% of the specimen activity, and plutonium and americium for 10%.

11. Gamma-spectrometric analysis of the first specimens within 36-39 hours of the accident failed to reveal any sign of $^{22,24}Na$ activation, which confirmed that neutron irradiation of the victims was not significant.

12. For most of the victims, the energy peaks of more than 20 radionuclides were detectable in the spectrum of their whole-body gamma measurements; however, apart from the iodine and caesium isotopes previously mentioned, the contribution to the overall dose from the others (^{95}Nb, ^{144}Ce, ^{140}La etc.) was negligible. These measurements, performed while the victims were still alive, were also confirmed through the analysis of autopsy specimens (approximately 35 specimens from each deceased person) (Figure A.I).

13. The dose levels from external irradiation were reconstructed from the indication of several measurements on the basis of previous experience. Subsequently, in three cases with a lethal outcome, these findings were refined using methods earlier proposed by Kraytor for clothing fabrics [B31] and according to the electron spin resonance technique for dental enamel [T16]. These measurements agreed within ± 20% with the dose estimates based on clinical and biological criteria.

14. The total number of affected individuals among the persons present at the reactor site in the early hours of 26 April 1986 was 203, as given in the report presented by Soviet representatives at the Post-Accident Review Meeting in August 1986 [118]. Of these, 115 were treated, beginning on day 2, at the specialized treatment centre in Moscow; it was this group that provided most of the scientific analytical data discussed in this report. At other hospitals in Kiev there were only 12 patients with a clearly defined clinical pattern of second-degree acute radiation sickness and one person with fourth-degree acute radiation sickness, a fact that cannot in any substantial way alter the overall assessment of the data for the entire group of victims.

15. The increase in the total number of affected individuals from 203 to 237, announced in November 1986, was due solely to persons suffering from first-degree acute radiation sickness. There were 31 persons suffering from first-degree acute radiation sickness at the special treatment centre in Moscow and 109 persons in Kiev. The task of establishing a diagnosis distinguishing between first-degree acute radiation sickness and ordinary somatic diseases according to generally accepted criteria is a complex one, and one that continued throughout 1986. On the whole, a critical analysis of the data shows a decrease in the number of persons suffering from first-degree acute radiation sickness in comparison with the number given originally. At the time of writing this report, up to three quarters of these persons are for all practical purposes healthy. Their clinical signs of reaction to the accident during the first three months were neither individually significant nor typical of a reaction to irradiation. Table A.3 shows the distribution of patients with acute radiation sickness according to its degree of severity [B31] in the group selected for scientific analysis.

A. INITIAL DIAGNOSIS OF ACUTE RADIATION SICKNESS

16. The medical unit serving the plant was informed of the accident within 10-15 minutes of its occurrence. First aid to the affected individuals was provided by middle-level medical personnel and emergency teams over a time period from 30-40 minutes to 3-6 hours after the accident. First aid consisted in the evacuation of the victims from the industrial site, the simplest forms of medical attention, the administration of antiemetic and symptomatic (sedative, cardiotonic) drugs, the distribution of potassium iodide and the transportation of persons suffering from a pronounced primary reaction to the medical unit. During the first

12-24 hours after the accident, other persons who were in satisfactory condition were urged to go to the medical unit for examination; a total of 132 persons were hospitalized there during the first 12 hours. One person with severe thermal burns died during the first hour. Another, a reactor operator, could not be found; his working station was located in the collapsed high-activity zone.

17. Within 12 hours, a specialized emergency team arrived at the site and began work. Within 36 hours, this team, together with the on-site medical unit, examined more than 350 persons and carried out approximately 1,000 blood tests, each person undergoing two to three such tests. The treatment with potassium iodide was continued.

18. Within the first three days, 299 persons suspected of suffering from acute radiation sickness were sent to the specialized treatment centre in Moscow and to hospitals in Kiev, and over the subsequent days some 200 additional persons were admitted for examination.

19. The primary diagnostic criteria for assessing the priority for hospitalization were the presence, time of onset and intensity of nausea and vomiting and of primary erythema of the skin and mucosae, and a decrease of the lymphocyte count in the peripheral blood to below $10^9/l$ during the first days following irradiation.

20. The diagnosis of acute radiation sickness was subsequently confirmed in 99 of the 128 persons (firemen, Unit 4 operators, turbine-room duty officer and auxiliary personnel) admitted to the specialized treatment centre in Moscow during the first two days and in six of the 74 victims hospitalized during the following three days. This is an indication of the high specificity of the screening methods used. An additional 10 cases of minor acute radiation sickness were diagnosed among persons present at the site at the time of the accident, who were later admitted to the hospital facility for a variety of reasons. In the reception area the patients were monitored again for contamination and, if necessary, subjected to decontamination measures (washing under a shower with ordinary soap and change of underwear). Blood and urine samples were taken for a quick test of the presence of radionuclides; the patients also underwent measurements (repeated a further 4-6 times during the first 6-10 days) of the radioactive iodine content in the thyroid. Measuring devices consisting of a scintillation detector or a semiconductor detection unit were used for the whole-body counting of radionuclide activity.

B. THE BONE MARROW SYNDROME AND ITS TREATMENT

21. Dosimetric data, together with an analysis of the circumstances of the accident and the presence in a considerable number of the victims of obvious primary reaction symptoms (nausea, vomiting, diarrhoea, hyperaemia of the mucosae and skin, lymphopenia), confirmed that the principal modes of irradiation had been: (a) by external, relatively uniform gamma-radiation; and (b) by deposition of beta/gamma-emitting nuclides on the skin. Radionuclide ingestion was below the level likely to cause acute radiation injury. As already noted, two patients suffered from all three of these irradiation modalities, in combination with extensive steam burns.

22. The important diagnostic task during the first few days after the accident was the assessment of the degree of severity of the bone marrow syndrome resulting from the external gamma-irradiation dose. This was possible through the use of previously devised methods, which are based on the number of lymphocytes and on chromosome aberrations in peripheral-blood lymphocytes or on the incidence of chromosome aberrations in bone marrow cells [B31, B50, G24]. These data were later transformed into a prognosis of the overall dynamics of the blood picture. A subsequent re-assessment of dose levels involving a larger sample of cells scored revealed not more than 5-10% changes in the estimated doses.

23. Dose-effect relationships for these indicators had been derived earlier through the analysis of relatively uniform accidental or therapeutic irradiations of human subjects having normal initial haematological characteristics and exposed to well established doses [P22]. Figure A.II shows the curves (and analytical expressions) for the relationships between the dose and the blood lymphocyte count for each of the first nine days and the average lymphocyte count on days 4-7 and days 1-8 after irradiation. The radiation dose received by each person was estimated according to the number of chromosome aberrations (dicentrics) in a blood-lymphocyte culture, using a dose-effect curve for 100 first-mitosis cells that had been obtained after whole-body gamma-irradiation to treat acute leukaemia patients during a period of full clinical and haematological remission [P23].

24. The formula for calculating of the dose is as follows:

$$D = (-a + \sqrt{a^2 + 4by})/2b$$

This assumes that the yield of dicentrics shows a linear-quadratic dependence on dose:

$$y = (a \pm 2.24)D + (b \pm 0.56)D^2$$

where D is the average gamma-irradiation dose in the body (Gy), y is the dicentric count per 100 cells; $a = 8.36$; $b = 5.70$.

25. Up to day 7 after the accident, the estimates of the average dose of total gamma-irradiation were refined, mostly on the basis of the peripheral-blood lymphocyte counts but also, in the more severe cases and to a lesser degree, on the chromosome aberration count. This made it possible to divide the patients into various prognostic groups [B31], according to the severity of the bone marrow syndrome as follows (see Table A.3):

(I)	slight	(1-2 Gy)
(II)	intermediate	(2-4 Gy)
(III)	severe	(4-6 Gy)
(IV)	extremely severe	(6 Gy and above)

It was also possible to separate those persons who received doses of less than 1 Gy.

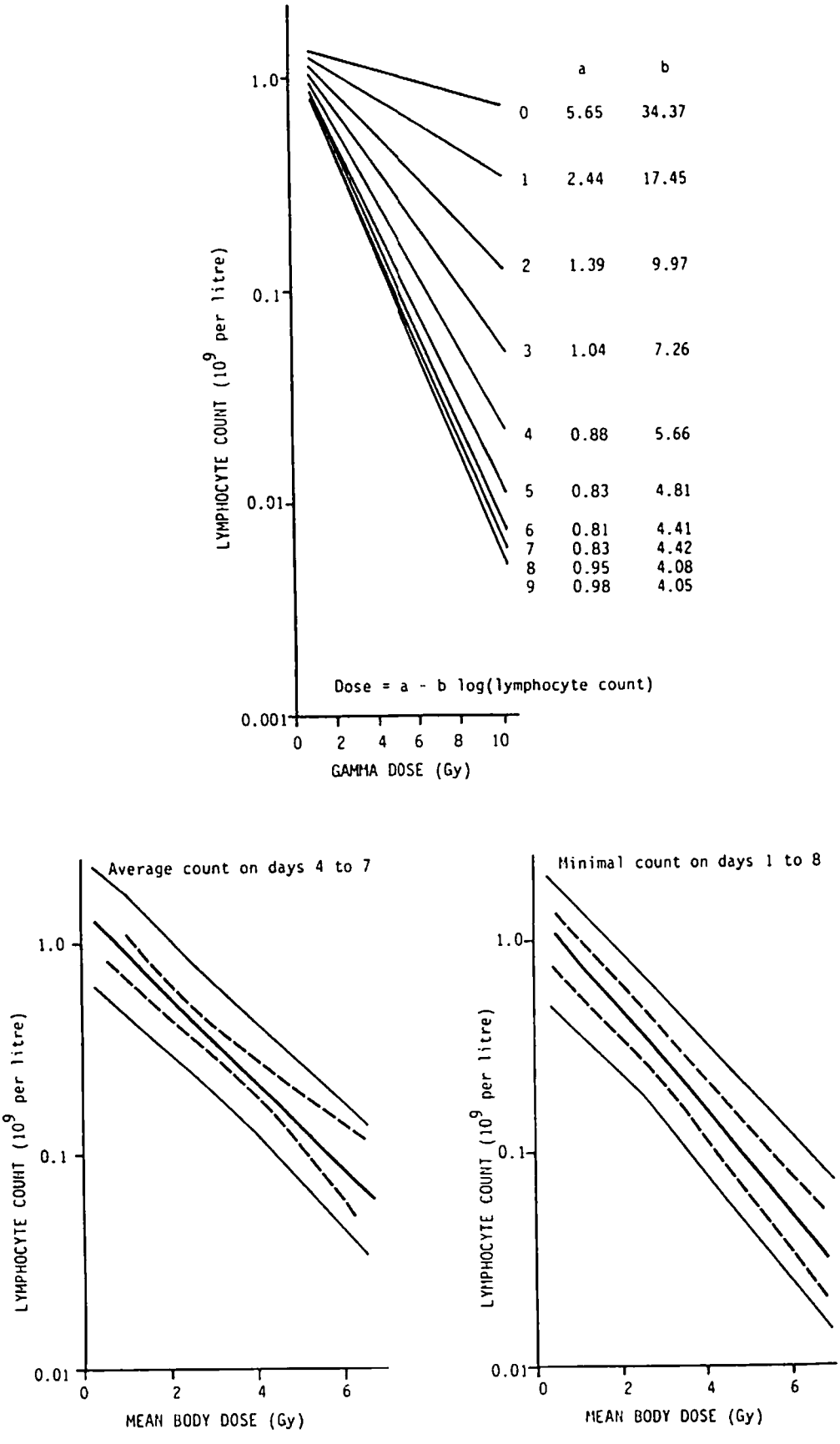

Figure A.II. Estimation of the total gamma dose according to the blood lymphocyte counts. Upper panel: Dose-effect relationships for lymphocyte counts at the days post irradiation shown on the curves; analytical expression and coefficients of these relationships. Lower panels: Curves showing the dependence of average lymphocyte counts on days 4-7 and the minimum lymphocyte count on days 1-8 as a function of the irradiation dose.

26. Particular attention during the first days was directed at identifying persons with an extremely severe and irreversible degree of myelodepression, for whom an urgent decision was required regarding a bone marrow transplant. Additional signs providing further evidence that a patient belonged to this group were (a) vomiting during the first half-hour and of diarrhoea during the first 1-2 hours from the start of irradiation; (b) a swelling of the parotid glands during the first 24-36 hours: and (c) the ascertainment of an irreversible degree of myelodepression using a diagnostic table previously devised (Table A.4).

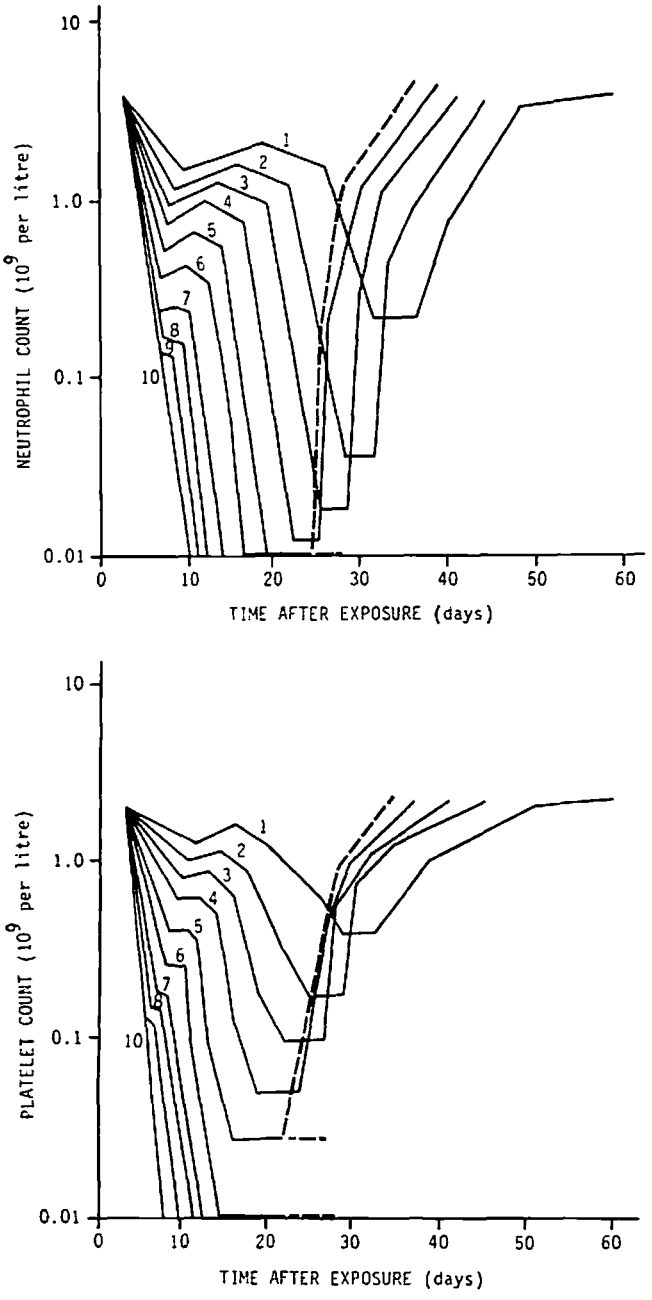

Figure A.III. Standard curves showing the changes of the neutrophil and platelet counts after various doses (numbers on the curves indicate the dose in Gy) in the case of relatively uniform whole-body gamma irradiation of human subjects. [B31]. (The broken segments of the curves at doses of 5-6 Gy indicate that recovery may not occur at these times in all patients.) Upper panel: Neutrophils. Lower panel: Platelets.

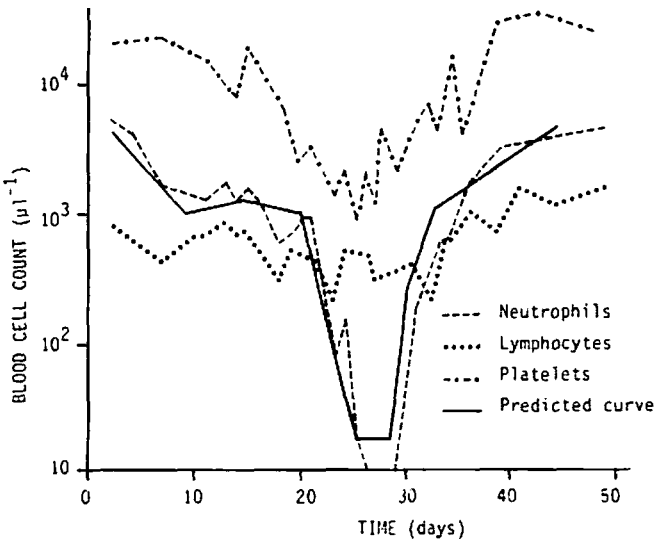

Figure A.IV. Example of the changes in neutrophils, lymphocytes and platelets observed in a patient (case 39) suffering from acute radiation sickness (estimated dose 2.4-3.3 Gy) and the predicted neutrophil curve for a total gamma dose of 3.0 Gy.

27. The results of numerous biochemical, immunological and biophysical indicators are undergoing processing and analysis at the time of writing this report. None of these indicators is as informative as the signs described above. However, it may be noted, for example, that hyperamylasemia was used as a supplementary prognostic test.

28. On the basis of the estimated dose, a prediction was made using standard curves [P22], of the overall trend with time in the neutrophil and platelet counts (Figure A.III). By way of example, Figure A.IV shows the real and predicted neutrophil curves for one patient (case 39). The total gamma-irradiation doses estimated according to the average lymphocyte count from day 4 to day 7 and according to the dicentric yield totalled 2.4 and 3.3 Gy, respectively. The patient's measured neutrophil curve almost coincided with the predicted neutrophil curve for 3.0 Gy of total gamma-irradiation.

29. The calibration curves of neutrophil counts as a function of dose were also used for a final assessment of the magnitude of the total gamma-irradiation dose. The dose calibration curve was chosen that coincided with the measured second depletion phase. Also, use was made of the dose dependency of the second depletion phase, such as the time required for the neutrophil count to decrease to 0.5 10^9/l or the time to reach the minimum of the second depletion phase (Figure A.V).

30. For relatively low doses (1.0-1.5 Gy), the diagnosis was finally established over time periods of up to three months only in those cases that showed typical post-irradiation neutrophil and/or platelet time courses with distinct second depletion and restoration phases. The latter generally developed beginning in the fourth to the fifth week after irradiation. In order to determine these changes, it was necessary to carry out blood analyses not less than two or three times a week

over a period of two to three months. Examples of these curves are shown in Figure A.VI: (a) case 48: doses, estimated according to the lymphocyte count on days 4-7 and the dicentric yield were 1.1 Gy and 1.4 Gy, respectively; and (b) case 97: doses, estimated according to the lymphocyte count on day 9 (the first blood analysis was made at this time because of late arrival) and the dicentric yield were 0.3 Gy and 0.9 Gy, respectively. It should be noted that in the case of low doses, the minimum level for neutrophils occurred later (day 30-50) than for platelets (day 20-40), and the reduction in the number of platelets and their recovery were more clearly pronounced than for neutrophils.

31. On the basis of all these data, a diagnosis of acute radiation sickness with the bone marrow syndrome of the first, second, third and fourth degree of severity was definitively established for 31, 43, 21 and 20 patients, respectively (see Table A.3). The analysis of the observations carried out on these patients is the subject of the exposition that follows.

32. Clinical manifestations of the bone marrow syndrome corresponded to the level and duration of post-irradiation pancytopenia (neutrophils 0.1-0.5 $10^9/l$, platelets 10-20 $10^9/l$). The main signs were fever, infectious complications and petechial haemorrhages in the skin and oral mucosa.

33. Treatment was based on the principles of supportive therapy, including isolation, antimicrobial decontamination of the intestine, administration of systemic antibiotics and replacement transfusions of blood cells. In cases in which there was a prognosis of irreversible myelodepression, transplantations of allogeneic bone marrow and embryonic human liver cells were performed.

34. All patients suffering from a bone marrow syndrome of the second, third or fourth degree were individually accommodated in ordinary hospital rooms. These were adapted to ensure (a) barrier nursing; (b) air sterilization by means of ultraviolet lamps; (c) strict observance by the attending personnel of hand disinfection on entering and leaving the room; (d) mandatory use of individual or disposable gowns, masks, and caps; (e) antiseptic decontamination of footwear; (f) changes of underclothing for patients at least once a day; (g) use of antiseptic agents for washing the walls and floor of the room and the items of use; and (h) individual assignment of antiseptically treated nursing items in the room. This regimen made it possible to maintain the micro-organism population at less than 500 m^{-3} in the room air. Ordinary food was served, with the exclusion of raw vegetables, fruits and canned products.

35. Prophylaxis against endogenous infections was by means of the internal administration of biseptol-480 and nistatin in amounts of six tablets and five million units per day, respectively, for one and 2-3 weeks prior to the development of agranulocytosis (leucocytes 1.0 $10^9/l$, neutrophils 0.1-0.5 $10^9/l$).

36. With the onset of fever, intravenous administration of two or three broad-spectrum antibiotics was prescribed, one of them being from the aminoglycoside

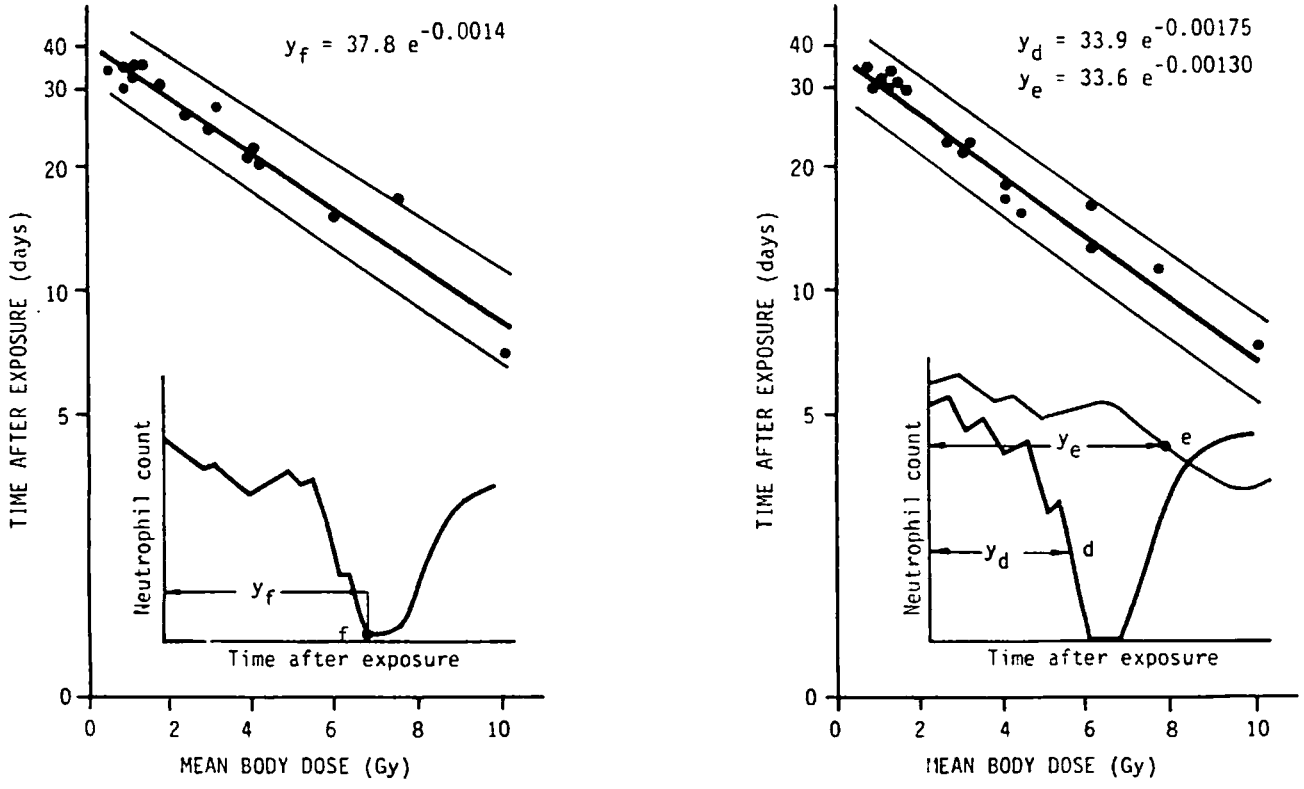

Figure A.V. Estimation of the total gamma dose according to two neutrophil counts: Left panel: time to the minimum of the second phase of depletion; Right panel: time to the "500 neutrophil day" or to the middle of the second depletion.

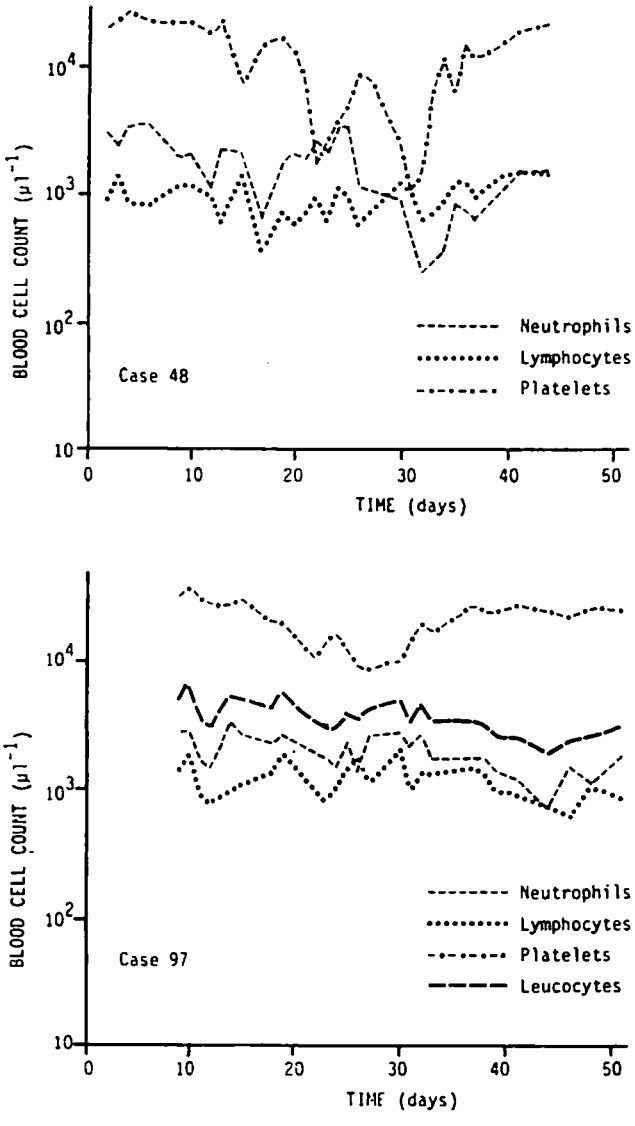

Figure A.VI. Changes in neutrophil, lymphocyte, platelet and leucocyte counts after whole-body gamma irradiation. Case 48, estimated dose 1.1-1.4 Gy. Case 97, estimated dose 0.3-0.9 Gy.

group (gentamicin or amicacin), the cephalosporins (cephzol, cephamecin, cephobide) and the semi-synthetic penicillins with activity against pseudomonas aeruginosa (carbenicillin, pipracil), all in maximum doses. This treatment reduced the fever in more than half of the patients. If within 24-48 hours there was no effect, extensive use was made of gamma globulin (Sandoglobulin), made available by the Sandoz Company (Switzerland). Six grams were administered intravenously every 12 hours, three or four times. The policy adopted was one of early empirical prescription of 1 mg/kg per day amphoterricin-B given intravenously, if the fever had not disappeared within a week of the above mentioned antibiotics, in combination with the intravenous administration of gamma globulin.

37. In this situation, acyclovir was used for the first time, and with good effect, in the treatment of patients with acute radiation sickness suffering from a herpes simplex infection. Not less than one third of the patients with third- and fourth-degree acute radiation sickness were affected by this virus. Acyclovir was not used prophylactically; experience has shown that this should be the case with high-dose whole-body irradiation. An ointment containing acyclovir proved effective in the treatment of skin lesions involving herpes virus.

38. The regimen described above for the empirical treatment to combat infection proved to be highly effective: there was no evidence that deaths were caused by bacterial infection alone in patients suffering from the bone marrow syndrome. This was so even among those with a severe or extremely severe form of acute radiation sickness, provided it was not complicated by burns, radiation-induced enteritis or acute secondary syndromes as a result of a bone marrow transplantation.

39. Blood screenings carried out while the patients were still alive or, in the case of those who died, posthumously, most often revealed epidermal staphylococcus. It will only be possible to evaluate the role of this form of bacteria as an agent of terminal septicaemia when these results have been compared with the histological data from analysis of various organs that have not yet been completed.

40. One of the undoubted successes in the treatment of the bone marrow syndrome in patients with acute radiation sickness was the rational use of fresh donor platelets for the prophylaxis and treatment of bleeding. To make these measures possible, the collection of the thrombocytes was organized on an urgent basis, using the method of fourfold thrombocytopheresis from individual donors at seven blood transfusion centres. For one transfusion, platelets obtained from a single donor (on the average 300 10^9 platelets in 200-250 ml of plasma) were used. Transfusions were carried out when the platelet level in the blood fell to 20 10^9/l or lower, with appearance of the first signs of bleeding. The infusions were repeated every 1-3 days. As a prophylaxis against acute secondary syndrome, the thrombocytes as well as the other blood components were irradiated with 15 Gy before infusion in order to inactivate the immunocompetent cells originating from the donor.

41. Platelet transfusion prevented life-threatening bleeding, even in patients with protracted (more than 2-4 weeks) and severe thrombocytopenia. The majority showed no signs of bleeding at all, although autopsies disclosed microcirculatory failures and porosity of the capillaries in a number of organs. In this situation, successful use was made of cryo-preserved allogeneic and, what is particularly important, autologous thrombocytes. The latter were obtained from patients with second- or third-degree bone marrow syndrome during the first days following irradiation (1-2 sessions) —this had no effect on the post-irradiation behaviour of their platelet counts—and were used with great effectiveness when the patients developed critical thrombocytopenia. No cases of refractoriness to thrombocytes transfusion were observed. On the average, from three to eight transfusions of standard amounts of thrombocytes (300 10^9 cells) were required for the treatment of a single patient with second- and third-degree acute radiation syndrome. Leucocytes

were not used for the prophylaxis or treatment of agranulocytic infections. Requirements for erythrocytes turned out to be considerably greater than expected, even for patients with second- and third-degree acute radiation sickness uncomplicated by severe radiation burns.

42. Figure A.VII illustrates the clinical record of one patient (case 21), showing the typical extent and duration of substitutive and supportive therapy for the bone marrow syndrome. In the case of this patient there were no life-threatening acute radiation injuries to the other tissues.

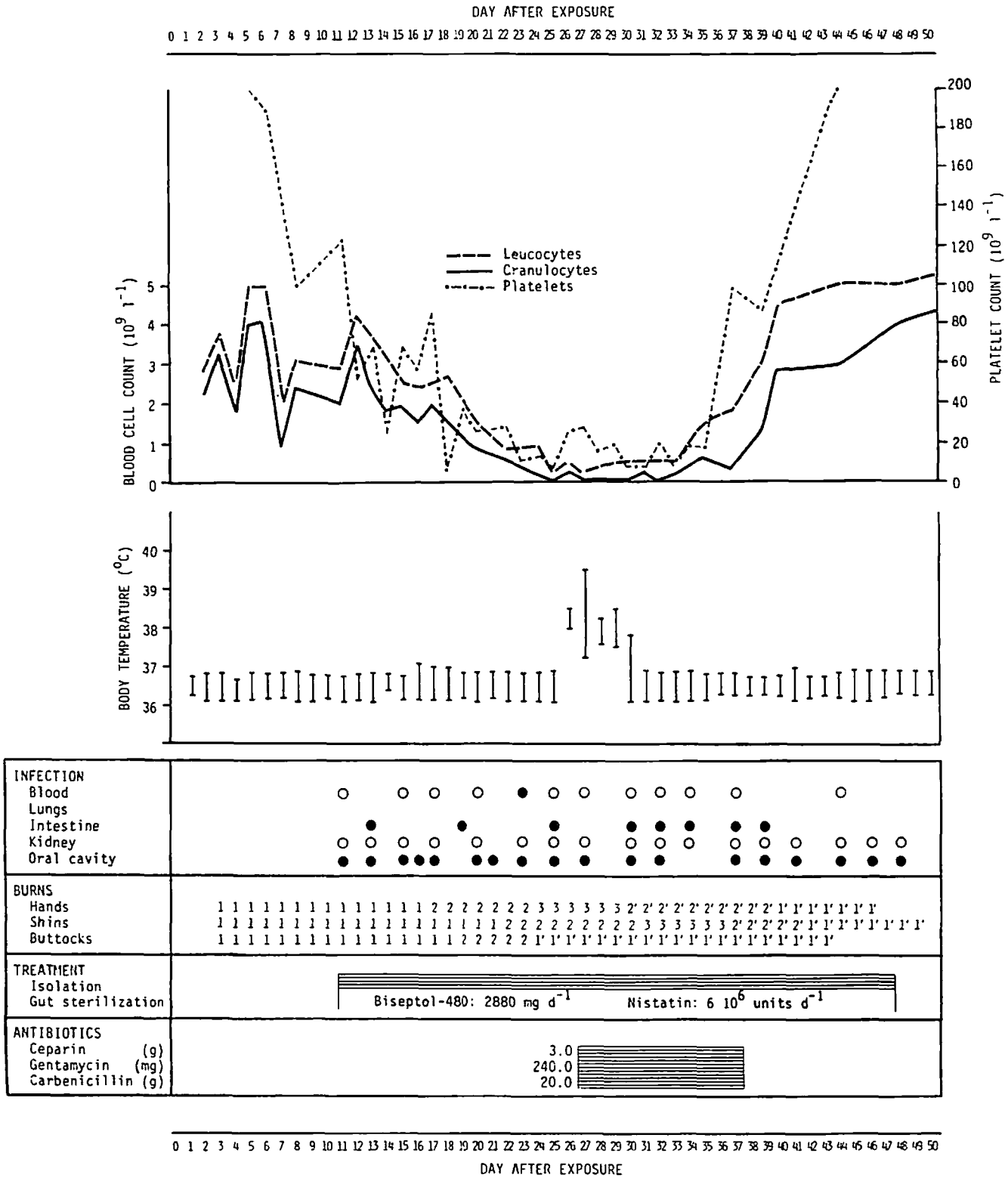

Figure A.VII. Clinical record of a patient (case 21) suffering from acute radiation sickness with bone marrow syndrome of an average degree of severity; whole-body gamma dose of 3.9 Gy, estimated according to the chromosome aberrations in blood lymphocytes. The circles in the infection section indicate the results of bacteriological tests of biological samples (blood, mucus, faeces, etc.); empty circles indicate absence of growth; solid circles indicate the presence of bacteria or fungi. The numbers in the burn segment designate the three degrees of radiation-induced burns.

43. The indication for an allogeneic bone marrow transplantation or an embryonic liver cell transplantation was the whole-body gamma-irradiation dose, estimated according to the peripheral-blood lymphocyte count and the chromosome aberrations at about 6.0 Gy and above. At these dose levels the prognosis expected was for irreversible or extremely protracted severe myelodepression.

44. A total of 13 allogeneic bone marrow transplantations and six embryonic liver cell transplantations were performed. The latter contains haemopoietic stem cells and a minimum of immunocompetent cells, which sharply lowers the risk of an acute secondary syndrome.

45. Seven patients who received allogeneic bone marrow transplant died between two and 19 days (15-25 days after irradiation) from acute radiation injuries to the skin, intestines and lungs.

46. Of six patients who did not suffer fatal skin burns and intestinal injuries and whose total doses had been estimated at between 4.4 and 10.2 Gy, two survived allogeneic bone marrow transplants (gamma-ray doses of 5.6 and 8.7 Gy). Both had haplo-identical female donors (sisters), rejected the partially functioning transplant (at days 32 and 35) and experienced a restoration of their own myelopoiesis, beginning at day 28.

47. Four patients who received allogeneic bone marrow transplantation died between 27 and 79 days (34-91 days after irradiation) from mixed viral-bacterial infections. Two of them had effectively functioning HLA-identical transplants (cases 6 and 28: total gamma-ray doses 5.2 Gy and 6.4 Gy, respectively), and two had early rejection (day 16 and 42) of "haplo + 1" and haplo-identical transplants, but during times when their own myelopoiesis was restored (cases 5 and 16: gamma-ray doses 4.4 and 10.2 Gy).

48. Similarly, all the patients who received embryonic liver cell transplants died from skin and intestinal injuries within a brief period (14-18 days after irradiation), with the exception of one woman of 63 years (case 8, embryonic-liver cell transplant from an 18-week male donor), who lived 30 days, having received a dose of 8-10 Gy. At death (17 days after transplant), numerous mitoses were discovered, against a background of severe marrow pancytopenia, and all the cells had a female karyotype, i.e., regeneration of the host bone marrow had begun.

49. This experience confirms that in an emergency situation like the one described, the group of persons for whom bone marrow transplants would be indicated with a reasonable prospect of success is extremely limited. Seven of 13 patients died as a result of skin and intestinal injuries before bone marrow engraftment could be expected. In Table A.5 a comparison is given of survival or cause of death of patients reiceiving bone marrow transplantations and of patients in a control group.

C. OTHER INJURIES AND THEIR TREATMENT

50. The extensive skin lesions caused by beta-radiation represented a distinctive feature of the injuries suffered in this emergency situation. Radiation-induced skin burns in firemen and personnel from the plant were observed only in combination with radiation injury to haemopoiesis and were therefore an integral part of the general acute radiation sickness.

51. This situation may be regarded as one in which there is an extremely non-uniform distribution of dose as a function of the depth of penetration within the body; the skin doses are estimated to be 10-20 times greater than the bone marrow doses. There was a definite correlation in the severity of the injuries in both tissues.

52. Table A.6 and Figure A.VIII show the distribution of cases involving radiation-induced skin burns of various degrees in patients with acute bone marrow syndrome of different severity. Skin injuries were observed in more than one half of the patients and in virtually every patient suffering from third- or fourth-degree bone marrow syndrome.

53. The aggravating contribution of radiation-induced skin injuries to the overall clinical picture arose not only from their severity, but also from the duration of the injuries, characterized as they are by recurrences of the pathological process. As a rule, the burns occurred at different times on various parts of the body. The most frequent locations during the early period were the wrists, the face, the neck and the feet; later, lesions appeared also on the chest and back, and still later on the knees, hips and buttocks. Exceptions to this sequence were encountered in individual cases.

54. The development of the injury was similar to that described by Cronkite et al. [C16], but in a more severe form. The diffuse hyperaemia in the first few days (primary erythema) was followed after 3-4 days by a period of latency. Secondary erythema in the more severe cases developed after 5-6 days and in the majority of patients from day 8 to day 21. Depending on the degree of the injury, it reached a level of dry (first-degree radiation burn) or moist desquamation with the development of blisters (second-degree burn), or the formation of vesicular-ulcerated and ulcerated-necrotic dermatitis (third- to fourth-degree burn). The re-epithelialization of the desquamated surfaces continued for two or three weeks from the occurrence of the visible injury to the skin. In six patients, the healing of the burns over skin areas involving deep necrosis did not begin until the end of the second month. A characteristic feature in the time course of the burns, and one which could be monitored throughout in this group of victims, was the appearance of recurrent waves of erythema, beginning by the end of the fourth week and continuing up to days 45-60. These changes were characterized by hyperaemia on the previously unaffected skin areas or by the increase in clinical signs of injury at the foci of the primary lesions then in the process of healing. For example, late secondary erythema appeared in the area of the

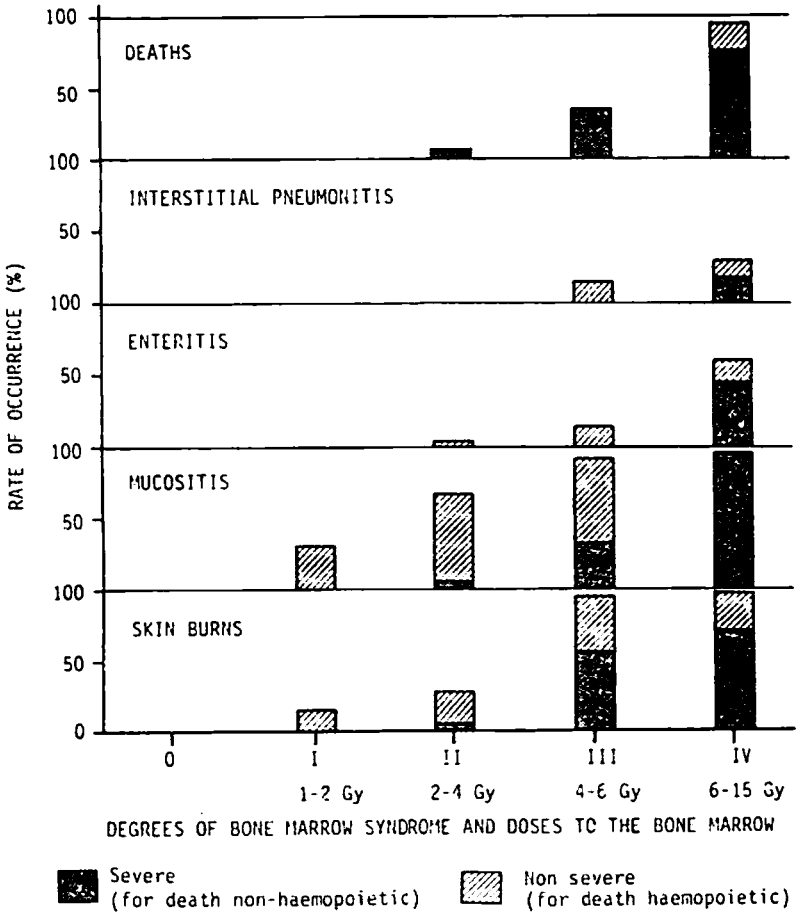

Figure A.VIII. Frequency of deaths and non-bone marrow syndromes for various degrees of bone marrow syndrome in accident victims suffering from acute radiation sickness.

ankles and feet, or on the hips and buttocks, of those patients who during the first three weeks displayed "flowering" burns on their knees. By the time of appearance of this late erythema, the lesions that had occurred earlier in many instances had already been repaired. As a rule, late erythema was accompanied by oedema of the subcutaneous tissues, which was particularly noticeable when located on the knees: pain was experienced in walking; palpation of the skin and underlying tissues (muscles, tendons) caused discomfort. The most severe cases involved fever and a general worsening of the patient's condition. Late secondary erythema was successfully resolved within two weeks by purely topical treatment, although in the more severe cases it was necessary to resort to additional therapeutic means, such as the prescription of glucocorticoids, a form of treatment that fairly rapidly eliminated all manifestations of epidermatitis and subcutaneous oedema, both general and local.

55. As may be seen in Table A.6, the burns suffered by the patients with acute radiation sickness covered from 1% to 100% of the body surface. It may be noted, in this connection, that if there were relatively early (from day 5-6) second- or third-degree burns over an area of even 30-40% of the body, followed by the spread of hyperaemia, these burns were life-threatening. In 19 of the 56 patients suffering from burns, the burns proved fatal (Figure A.VIII). It was found that patients with early secondary erythema over a body area of more than 40% first developed a febrile-toxemic syndrome, followed by renal-hepatic insufficiency and encephalopathic coma with cerebral oedema, resulting in death at 14-48 days after irradiation. A causal link connecting the fatal renal-hepatic insufficiency and the encephalopathic coma to the skin injuries is confirmed by the fact that a similar development of such fatal syndromes was observed in several patients who had neither severe bone marrow syndromes nor intestinal syndromes. However, in the majority of cases, burns were combined with an extremely severe bone marrow syndrome and severe acute enteritis, and in some cases the burns may have been the primary cause of death.

1. Intestinal syndrome

56. The intestinal syndrome was one of the more threatening manifestations of acute radiation sickness. In 10 patients, diarrhoea was observed from day 4 to day 8. This suggested that these persons had received total gamma doses of about 10 Gy or above; all these patients died during the first three weeks following irradiation. The occurrence of diarrhoea after eight days in seven other persons was an indication that they had received lower doses. The presence of radiation-induced enteritis lasting from day 10 to days 18-25 in spite of intensive water-electrolyte-protein supportive treatment suggests that the intestinal syndrome was not the main cause of death.

2. Oropharyngeal reactions

57. Acute radiation-induced inflammation of the oral and pharyngeal mucosa was observed in 82 patients. Its more benign manifestations (first and second degree of severity) were characterized by desquamation and oedema of the mucosa in the area of the cheeks and tongue and by tenderness of the gums. These were observed in 42 persons (dose range 1.7-4.0 Gy) from days 8-9 to days 20-25. The basic signs of a more acute oropharyngeal reaction were observed in 40 patients with third and fourth degree acute radiation sickness (dose range 4.5-16.0 Gy), and these were erosions and ulcers of the oral mucosa, sharp pain, and a large production of rubber-like mucus occasionally blocking the throat and causing breathing problems. The first signs appeared as early as days 3-4, attained their maximum intensity by day 10 and then subsided after days 18-20, when there was also granulocytopenia. The process involved no selective localization, as is characteristic of the ulcerated lesions in the area of the tonsils and gums when there are infectious complications. However, in a significant number of cases, the radiation-induced inflammation of the mucous membranes was complicated by secondary microbial and viral infection, which prolonged its course.

58. Another typical finding was the early (days 3-4) appearance of herpes-like rashes forming massive crusts on the lips and facial skin; this was observed in nearly 30% of the patients with severe bone marrow syndrome. Within this group of patients, primarily those suffering from fourth-degree acute radiation sickness, a pronounced radiation-induced parotitis was observed, coupled with an inability to salivate and a high level of amylase in the blood from days 1-4. The swelling of the parotid glands disappeared without special treatment, whereas recovery of salivary gland secretion was slower.

3. Lung reactions

59. Lung reactions were observed in seven patients suffering from third- and fourth-degree acute radiation sickness. Its characteristic signs were a rapidly intensifying dyspnoea together with respiratory insufficiency progressing over a period of two to three days culminating in death. Autopsies revealed large, blue lungs with pronounced interstitial oedema, without destruction of the mucous membranes of the trachea and bronchi. As a rule, interstitial pneumonitis developed several days before death, generally in combination with extremely severe lesions of the skin and the intestine. The times to death were 14-30 days after irradiation.

4. Causes of death

60. The frequency of non-haemopoietic injury increased as a function of total dose (Figure A.VIII). Clinical observations indicated the essential role of skin injuries in pathological processes prior to death. Among the patients that died, in two thirds of them there was extensive and severe radiation and thermal skin burns, which were considered life-threatening. In five cases skin injuries were the sole cause of death, because there was neither radiation enteritis or irreversible myelodepression. Deaths were observed between 10 and 96 days after exposure. The clinical picture in all fatal cases was characterized as following a difficult course, because in every case two or three radiation syndromes had occurred with complex toxicity, infection and circulation disorders. A summary listing of patient identification and causes of death is given in Table A.7.

61. A detailed clinico-morphological analysis made it possible to identify the predominance, within specified time periods, of particular lethal syndromes. Up to day 24, a total of 19 patients (65%) died. In one half of these patients the competing causes of death were skin and intestinal reactions (cases 3, 4, 10, 14, 15, 17, 20, 23, 26, 2097; in all the cases the gamma-radiation dose in the bone marrow was estimated to be greater than 10 Gy). Four patients showed acute radiation injury in the lung (cases 2, 9, 12 and 27; the doses were, respectively, 9.2, 9.7, 9.3 and 8.3 Gy), and, of these, two (cases 2 and 9) suffered also severe injuries to the skin. Two patients died of combined thermo-radiation burns (cases 24 and 25; the gamma-radiation doses in the bone marrow were estimated to be 3.7 and 5.7 Gy, respectively, in combination with internal irradiation doses. Within this time-frame, one patient (case 62, dose about 6 Gy) died almost exclusively from severe radiation burns at a time when haemopoiesis had begun to be restored. Three cases (cases 17, 26, 62) had involvement of mycobacterial sepsis. One patient (case 30, dose about 5.5 Gy) died of bleeding caused by mechanical injury to the subclavicular vein during catheterization, and another (case 7, dose about 4.7 Gy), suffering from severe radiation injury to the skin, died of post-transfusion shock. Characteristics of the deaths on days 11-24 were marked circulatory problems during the terminal period. This was shown by the relatively high frequency of signs indicating cerebral oedema and focal haemorrhaging into the brain and spinal cord.

62. Six patients died during the period from days 25-48. All six cases were characterized by extremely severe complications of a toxic or infectious nature. Two patients (cases 31 and 34) involved subtotal skin injuries (bone marrow doses about 6.7 and 5.8 Gy, respectively, with death occurring on days 32 and 48, respectively), coupled with practically restored haemopoiesis. The immediate cause of death in these cases was severe respiratory insufficiency and cerebral oedema. In one patient (case 28, dose about 6.4 Gy; death on day 48) the cause of death was severe, graft-versus-host disease and fungal and viral infections. One additional patient (case 5, dose about 4.4 Gy) died on day 34 of severe pulmonary and renal insufficiency, caused, most likely, by the transplantation of HLA-non-identical bone marrow and by post-transplant immunosuppression using cyclosporin and methotrexate. Two patients (cases 1 and 8, doses about 6.6 and 8.3 Gy) died on days 25 and 30, respectively, with symptoms of severe toxicity and pulmonary insufficiency. In nearly all six cases there were marked circulatory disorders in the lungs, intestines, brain and myocardium.

63. At a relatively late stage, days 86-96, three patients died. One patient (case 6, dose about 7.5 Gy) died on day 86 of graft-versus-host disease complicated by cytomegalovirus (CMV) infection. Cytomegalovirus infection was also the cause of death for another patient (case 16, dose about 10.1 Gy) on day 91. A female patient (case 33, dose about 4.1 Gy) died on day 96 displaying marked disruptions of cerebral blood circulation against a background of renal-hepatic insufficiency and foci of mycococcal infection (pneumonia). This patient suffered also skin injuries from beta-radiation which extended over one third of her skin surface and underwent a severe recurrent wave of erythema with oedema of the subcutaneous tissue.

5. Eye damage

64. Eye injuries were characterized by the early and subsequent involvement of all eye tissues in the pathological process (Table A.8). In this group of patients, damage to the skin and eyelid conjunctiva was caused, to a considerable degree, by beta-radiation.

65. At doses not exceeding 1 Gy there were no visible alterations in the structure of the eyes. In the case of patients suffering from first-degree acute radiation sickness, changes were noted only in the front segment of the eye: there was in individual cases a slight erythema in eyelid skin during the first two to four days and an intensification of the vascular pattern in the lid and conjunctiva of the eyeball. In 40% and 100% of the patients suffering from second- and third-degree acute radiation sickness, respectively, the eyelid skin showed a first wave of of erythema within 6-12 hours of irradiation, and within 2-3 weeks there was a second wave. These cutaneous alterations disappeared without trace, leaving hyperpigmentation and scaling. In all patients suffering from fourth-degree acute radiation sickness, the times to the appearance of the first and second wave of erythema were 1-2 hours and 8-10 days, respectively.

66. Microscopy of the bulbar conjunctiva revealed a number of alterations in the microcirculation: there was a dilation of the venules and capillaries (more rarely the arterioles), and an increase in the number of functioning vessels coupled with a reduced blood flow.

67. Two patients suffering from combined radiation and thermal second-degree lesions on the lid skin and conjunctiva experienced ulcerations on the skin around the eye that did not re-epithelialize for a long time. Epilation of the eyebrows was noted at days 15-17 in 16% of the persons with second-degree acute radiation sickness, and in 67% and 100% of those with third- and fourth-degree acute radiation sickness, respectively. The epilation was partial and transient. Hair growth on the head was fully restored. All patients retained their eyelashes.

68. Corneal damage was manifested in an early reduction in corneal sensitivity coinciding with the first wave of erythema, although first-degree patients did not show such an effect. At later times (days 35-55), superficial radiation-induced keratitis was observed in patients suffering from second-, third- and fourth-degree radiation sickness in 5%, 52% and 100% of the cases, respectively. Also noted were focal defects on the superficial epithelium of the cornea; these defects, which often merged, stained with fluorescein. The radiation keratitis regressed over a period of 1-1.5 months, leaving no opacification of the cornea.

69. Signs of disturbances in the haemodynamics of the retina were related to the dose and the degree of severity of radiation sickness. From a few days after irradiation, a reduction was observed in the level of diastolic pressure in the central retinal artery, followed later by signs of hypotonic angiopathy of the retina. Coinciding in time with the peak of the sickness, other injuries appeared, e.g., retinal oedema along the vessels and increased permeability of the retinal vessels (plasma discharge and haemorrhaging). The low diastolic pressure in the central retinal artery persisted over the entire acute phase.

70. In one severely ill patient (case 29, dose about 8.7 Gy) with fourth-degree acute radiation sickness, who survived the acute phase, the symptoms of angioretinopathy with haemorrhaging and plasma discharge recurred within 4.5 months, accompanied by a persistently low diastolic pressure in the central retinal artery (up to 5-10 mm Hg).

71. In the acute period, the treatment consisted in the topical application of ointments to the scaling surface of the eyelid skin and the instillation of 20% albucid, sophradex and vitamin solutions as eyedrops into the conjunctival cavity.

72. Within observation periods of up to one year, no obvious radiation-induced alterations of the lens were noted.

6. Treatment of radiation burns and other injuries

73. The treatment of radiation burns and other non-bone-marrow syndromes and their complications posed complex and multifaceted problems [J18]. From day 2 through day 8, 15 haemosorption sessions (purification using activated charcoal) were conducted for 13 patients suffering from the most severe skin lesions. Three patients who had been exposed to a total dose range of 2.0-4.6 Gy survived; they underwent haemosorption on a single occasion at days 5-8, i.e., considerably later than the time at which this might have affected the treatment of the bone marrow syndrome. This method of treatment did not change the outcome of the illness by modifying the haemocytopenia.

74. During the haemosorption process, and particularly towards the end of the session, many patients experienced a short-term improvement (lasting from a few hours to a single day), a reduction or disappearance of the pain in the extremities, and also a decrease of the oedema in their tissues. In this connection, contributory effects from the medication accompanying the procedure cannot be totally excluded.

75. A more widely used technique to combat the development of renal-hepatic insufficiency and fatal encephalopathic coma was plasmapheresis. Lesions induced by beta-irradiation over 30-40% and more of the body surface served as an indication for the application of this procedure. Plasmapheresis sessions were conducted for 17 patients from days 18-37. For a number of patients, daily sessions were conducted, up to six times.

76. The positive effect of repeated plasmapheresis was shown by a reduction of bilirubinemia and transaminasemia and a lowering of the nitrate level in patients suffering from renal-hepatic insufficiency caused by skin burns. On occasion, the plasmapheresis sessions were accompanied by reactions of minor severity such as chills and fever; there were no fatal complications. Another method used to treat toxicosis due to skin injuries was the injection of 1,000 ml of freshly-frozen plasma, accompanied by round-the-clock administration of heparin (1,000 active units/hour) with a liquid load (2-6 litres/day) and forced diuresis adequate to the intake volume. A pre-condition for this treatment was the presumption of disseminated intravascular clotting (DIC) syndrome (no typical anomalies in respect of coagulation were present) as a possible cause of encephalopathy and renal-hepatic syndrome. In its most strictly applied form, the heparin treatment method was used with two patients over a period of 7-15 days. The impression was that these patients survived longer than did patients whose condition was similar in terms of severity and extent of their burns. Their renal-hepatic insufficiency was less pronounced; however, a death due to encephalopathic coma was not averted.

77. The topical treatment of the burns required the involvement of a group of surgeons and nurses. A broad range of preparations and agents having an anti-inflammatory, bacteriostatic and regeneration-stimulating effect was used. Good results were achieved with lioxanol aerosol, an anti-burn ointment based on hydrocortisone with locally acting antibiotics, as well as BALIZ-2 solution and collagenous coatings. In each individual case the treatment varied in accordance with the stage of the lesions. Experience gained in the use of bactericidal fabric, both as a dressing material and for supplementary bedding, for patients with extensive burns deserves a particularly favourable comment in this connection [Z2].

78. Treatment of pain, as is typical of radiation injuries, was rather ineffective. At present, there are clearly no suitably effective local anaesthetics.

79. In patients suffering from severe radiation-induced inflammation of the oral mucosa, and enteritis, total parenteral nutrition had a positive effect; this was based on alvesin hydrolysate or an aminoacid mixture, aminone and a 40% glucose solution as the energy material. The treatment was carried out according to the principles and rules described by Dudrick et al. [D18]. This method was tested over a number of years with good results in patients receiving whole-body therapeutic gamma-irradiation at a dose level of 10 Gy for allogeneic bone marrow transplantation. The danger, which has possibly not been fully evaluated, is the probability that certain severely injured, comatose patients may enter a state of hyperosmolarity. Data on plasma osmolarity that would appear to be necessary in a programme of total parenteral nutrition were not provided for all patients.

80. For the majority of patients suffering from first- and second-degree bone marrow syndrome, the period of clinical convalescence was completed by the third or fourth month. A longer period of treatment was required by persons suffering from severe radiation burns and the sequelae of third- and fourth-degree bone marrow syndrome. At the present time, the bulk of the patients have resumed work with the exclusion of any contact with radiation sources.

81. Over the period from the fourth month to one year after the accident, the specialized treatment centre was periodically visited by patients with skin lesions (dystrophic and ulcerated areas and also oedema of the subcutaneous tissues, mainly on the knees and feet). These patients are being treated with agents designed to improve local blood circulation and tissue trophism. Five patients with deep and extensive ulcers on their arms and other areas of the body underwent repeated plastic surgery, and a number of them will require more extended treatment.

82. Immunological examination data, acquired 0.5-1.5 years after the accident, have shown that in the peripheral blood of the patient groups with a history of acute radiation sickness of the second, third and fourth degrees a decline was observed in the number of T-lymphocytes with helper activity along with an increase in the number of T-lymphocytes with suppressor activity. This led to a considerable reduction in the normal ratio between these immunoregulatory lymphocyte sub-populations. At the same time, there was no reduction in the general lymphocyte level or in their T- and B-sub-populations. As an average for the groups, the level of class A, M and G immunoglobulins in the patients' blood serum corresponded to the physiological norm. Similar changes were not observed in the case of patients with a history of acute radiation sickness of the first degree. During this time they experienced no severe or life-threatening infections. In a number of cases an effort was made at immuno-corrective therapy using T- and B-activin.

83. Within these same patient groups, an estimate of the number of respiratory illnesses over the same period of time was conducted retrospectively. It was found that the incidence of illness in the group of 19 patients with a history of first-degree acute radiation sickness did not differ from the incidence of illness for the group of persons for whom no acute radiation sickness diagnosis had been established, and that it averaged 0.3 cases per person per year. During the same period, this indicator approached 1 for 22 patients who had experienced second-degree acute radiation sickness, and 3 for 8 persons with a history of third- to fourth-degree acute radiation sickness.

84. This comparison underlines the importance of the immune system in maintaining anti-infection

resistance in radiation convalescents and raises the question as to the usefulness of conducting supportive immunomodulating therapy courses, long after the incident, for persons who have undergone severe forms of radiation sickness.

85. The experience of the specialized treatment centres in Moscow and Kiev in the organization of medical care of persons exposed in this nuclear reactor accident has been described [N16]. For the survivors, a plan of scheduled follow-up observation is in effect, and decisions as how best to arrange their living and working conditions are being taken.

D. CONCLUSIONS

86. The analytical data presented in this Appendix and derived from clinical observations of the victims of the accident at the Chernobyl nuclear power plant are in agreement with the data in Annex G.

87. However, the fact that such a large group of 115 patients, who had all received uniform whole-body irradiation, was treated simultaneously for acute radiation sickness of varying degrees of severity, represents a unique event that makes it possible to clarify numerous aspects of early effects in man. A complicating factor was the presence of severe and extensive beta-radiation skin injuries in 58 patients which aggravated the course of the sickness in 19 of the 28 who died. Two more patients died during the first days as a result of severe combined injuries (trauma plus thermal burns plus irradiation).

88. The analysis provides a basis for describing the principal clinical syndrome, the bone marrow syndrome, with various degrees of severity in all 115 patients. In the case of some of them the bone marrow syndrome was combined with intestinal and oropharyngeal injuries and radiation damage to the skin, the foreward segment of the eye (keratitis), and the lungs.

89. The treatment provided was in accordance with international practice and proved highly effective for the patient group exposed to doses of 2-4 Gy and for two thirds of the patients who received doses of 4-6 Gy. In the group of patients receiving 6-16 Gy, two patients who received doses of 8-9 Gy survived past 60 days.

90. The average bone marrow dose and the prognosis regarding the further course of the illness were determined on the basis of biological criteria. During the early period, most information was obtained from the karyological analyses, the lymphocyte counts and the primary reaction periods; later, from the granulocyte counts. The remaining indications were of an auxiliary nature. In three cases, the dose value coincided with the electron spin resonance study of dental enamel after death.

91. There is a need for further analysis of the time course of the early effects for a more accurate understanding of the nature of lung and neurological injuries, and for more detailed data on the relevance of biological dose indicators and the reasons for disparities between them. It is hoped that these data will be of use in the preparedness to respond in the event of an accident of a similar type in the provision of medical treatment.

Table A.1

Thyroid doses received by exposed persons

Range of thyroid doses (Sv)	Number of persons
0 - 1.2	173
1.2- 3.7	18
3.7- 6.1	4
6.1- 8.6	4
8.6-11.0	2
11.0-13.4	2
13.4-15.9	0
15.9-18.3	2
18.3-20.8	0
20.8-23.2	1

Table A.2

Doses of victims receiving higher internal exposures

Case number	Thyroid dose a/ (Gy)	Lung dose a/ (Gy)	Whole-body dose (Sv)	
			Internal	External
24	30	2.5	2.0	1.7
25	6	2.0	1.0	4.7
17	1	0.4	0.2	10.0
3	0.3	0.3	0.2	12.0
4	1.2	0.4	0.1	11.0
26	0.5	0.3	0.1	12.0

a/ Doses accumulated until time of death.

Table A.3

Distribution of patients with acute radiation sickness treated at the specialized treatment centre

Degree of severity	Number of patients	Bone marrow dose range (Gy)	Number of deaths	Time to death (days)
I	31	0.8-2.1	-	-
II	43	2.2-4.1	1	96
III	21	4.2-6.4	7	16,18,21,23,34,48,48
IV	20	6.1- 16	20	10,14,14,15,15,17,17, 18,18,18,20,21,23,24, 24,25,30,32,86,91
	115		28 a/	

a/ In addition to the patients who died of acute radiation sickness, one person died at the plant site and another within the first 12 hours following the accident, as a result of thermal burns, at the in-patient clinic in Pripyat where he had been given first aid.

Table A.4

Assessment of irreversible myelodepression according to diagnostic scores in cases of acute radiation sickness

Sign			Diagnostic score a/
Time to the onset of vomiting	(hours)	0.00- 0.4	+ 8
		0.41- 0.8	+ 4
		0.81- 1.2	+ 2
		1.21- 1.6	- 2
		1.61- 2.0	- 6
		> 2.01	-10
Lymphocyte count on the second day	(10^9/l)	0.00- 0.2	+ 6
		0.21- 0.4	+ 2
		0.41- 0.6	- 2
		0.61- 0.8	- 8
		> 0.81	-15
Lymphocyte count on the third day	(10^9/l)	0.00- 0.1	+ 8
		0.11- 0.2	+ 2
		0.21- 0.3	- 2
		0.31- 0.4	- 9
		> 0.41	-10
Lymphocyte count on the fourth day	(10^9/l)	0.00- 0.1	+ 4
		0.11- 0.2	+ 2
		0.21- 0.3	0
		0.31- 0.7	- 2
		0.71- 0.8	- 3
		0.81- 0.9	- 8
Lymphocyte count from day 4 to day 7	(10^9/l)	0.00- 0.1	+ 5
		0.11- 0.2	+ 2
		0.21- 0.3	- 1
		0.31- 0.4	- 5
		0.41- 0.5	-13
		> 0.51	-15
Average reticulocyte count from day 3 to day 5	(10^9/l)	0.0 - 8.0	+ 2
		0.1 -10.0	0
		10.1 -14.0	- 4
		14.1 -18.0	- 6
		18.1 -20.0	-10
Minimum neutrophil count for day 6 to day 7	(10^9/l)	0.00- 0.3	+12
		0.31- 0.6	+ 5
		0.61- 0.9	0
		0.91- 1.2	- 3
		1.21- 2.4	- 6
		2.41- 3.0	- 8

a/ The diagnostic signs are used to determine the diagnostic scores, which are then added together. A sum of +10 is the basis for a prognosis of irreversible myelodepression; a sum of -10 for a prognosis of no irreversible myelodepression. If after the diagnostic coefficients of all the available signs have been added no positive value has been reached, the answer is indeterminate (the available information is insufficient for a differential diagnosis, with an error probability of not more than ± 10%).

Table A.5

Survival or cause of death of patients receiving bone marrow transplantations and of patients in control group

Dose range (Gy)	Bone marrow transplant patients				Control patients		
	Number of patients	Deaths a/	Deaths b/	Number of survivors	Number of patients	Deaths a/	Number of survivors
< 6.5	4	0	3	1	5	0	5
6.5-9	3	2 c/	0	1	4	3	1
> 9	6	5	1	0	5	5	0
Total	13	7	4	2	14	8	6

a/ Skin and intestinal injuries.
b/ Bone marrow rejection (graft-versus-host disease) plus infection.
c/ Positive graft-versus-host disease post-mortem histology.

Table A.6

Distribution of cases of radiation burns of different degree in the presence of acute bone marrow syndrome

Degree of severity of bone marrow syndrome	Total number of patients	Number of patients with radiation burns to various percentages of the body surface		
		0-10%	10-50%	50-100%
I	31	2	1	0
II	43	2	9	1
III	21	3	15	3
IV	20	1	10	9
Total	115		56	

Table A.7

Patient identification, estimated dose, cause and day of death

Degree of severity of ARS	Case number	Bone marrow dose (Gy)	Treatment a/	Day of death b/	Cause of death
II	33	4.1		96	Infection, renal-hepatic insufficiency and skin injuries
III	5	4.4	BMT	34	Infection, post-transplantation immunosuppression
	7	4.7		18	Skin injuries, post-transfusion shock
	24	3.7		23	Thermal and radiation burns
	25	5.7		16	Thermal and radiation burns
	28	6.4	BMT	48	Infection, graft-versus-host disease
	30	5.5	BMT	21	Bleeding from mechanical injury during catheterization
	34	5.8		48	Respiratory insufficiency, cerebral oedema
IV	1	6.6	BMT	25	Toxicity, respiratory insufficiency
	2	9.2	BMT	15	Skin and lung injuries
	3	12	BMT	17	Skin and intestinal injuries
	4	11.8	BMT	18	Skin and intestinal injuries
	6	7.5	BMT	86	Infection, graft-versus-host disease
	8	8.3	LCT	30	Toxicity, respiratory insufficiency
	9	9.7		23	Skin and lung injuries
	10	11.1	LCT	14	Skin and intestinal injuries
	12	9.3		24	Lung injuries
	14	10.9	LCT	18	Skin and intestinal injuries
	15	>10	LCT	14	Skin and intestinal injuries
	16	10.1	BMT	91	Infection, graft-versus-host disease
	17	10	BMT	18	Skin and intestinal injuries
	20	12.4	LCT	17	Skin and intestinal injuries
	23	13.7	LCT	15	Skin and intestinal injuries
	26	12.5		20	Skin and intestinal injuries
	27	8.3	BMT	24	Lung injuries
	31	6.7		32	Respiratory insufficiency, cerebral oedema
	62	6.1		21	Radiation burns (skin injuries)
	2097 (Kiev)	10.2		10	Skin and intestinal injuries

a/ BMT = bone marrow transplantation; LCT = liver cell transplantation.

Table A.8

Type of eye changes and per cent incidence in the victims of the accident

Nature of the changes	Degree of acute radiation sickness			
	I	II	III	IV
First wave of erythema	6.1	39.5	100	100
Second wave of erythema		20.9	80.9	100
Reduction in cornea sensitivity		18.6	100	100
Epilation of the eyebrows		16.3	66.7	100
Keratitis		4.6	52.4	100
Fundus				
Dilation of blood vessels		32.6	74.4	100
Decreased diastolic pressure of the central retinal artery		48.8	95.2	100
Retinal oedema		4.6	-	80
Haemorrhaging		13.9	23.8	80
Plasmorrhaging		4.6	23.8	80

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