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ANNEX G

Early effects in man of high doses of radiation

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

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Introduction

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

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

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

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

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

6. When this Annex was approaching completion, important information on the subject became available in connection with the nuclear accident that occurred at the power plant in Chernobyl, USSR, where about 100 people were exposed to external and internal irradiation amounting to 1 Gy or more. The delegation from the USSR has made available especially to UNSCEAR a report on the data gathered in the wake of the accident. The Committee wishes to

acknowledge with gratitude this important contribution. Since time was too short for a definitive study of the data collected and for their incorporation into the text of this Annex, the Committee decided to present them as an Appendix.

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

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

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

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 [18, 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 I. 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

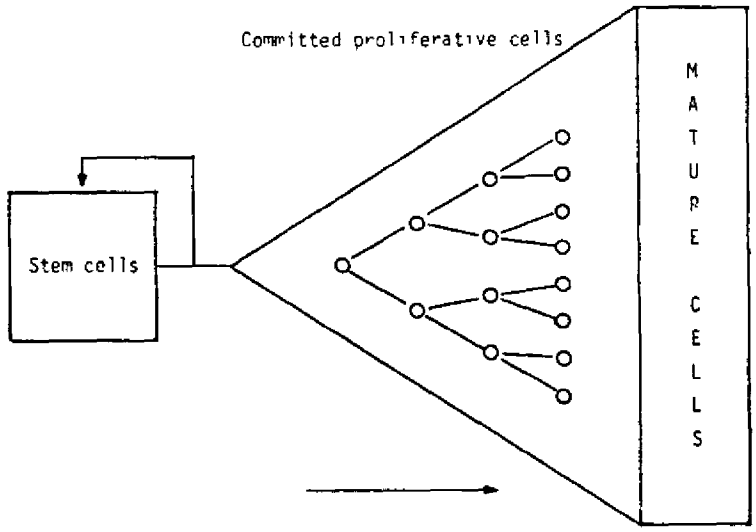

Figure I. Diagrammatic representation of cell population hierarchy where mature cells are produced from proliferative cells. The ancestors of the lineage are the stem cells which renew themselves (left arrow) and which also differentiate into various maturing cell lineages (right arrow).

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

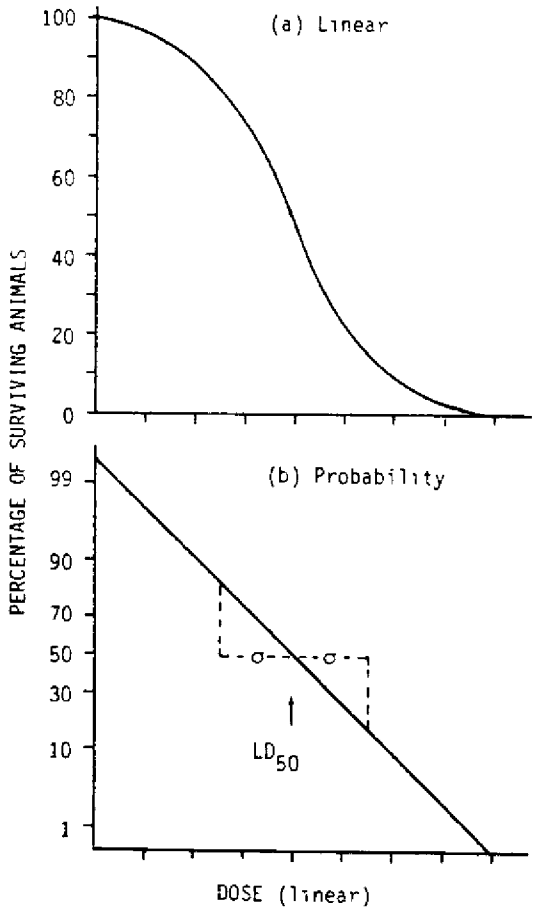

Figure II. Diagrammatic representation of a typical dose-survival curve for irradiated animals, using a linear ordinate or a probability ordinate. The LD_{50} is the dose for 50% incidence, and the slope is characterized by the standard deviation (σ) of the distribution.

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,

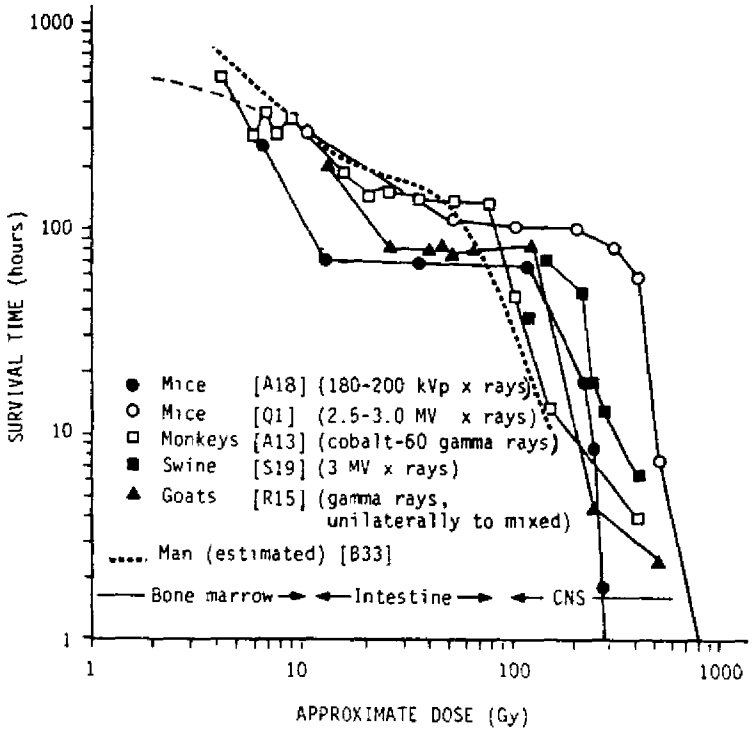

Figure III. Survival time of several mammalian species after various whole-body doses (doses are quoted as approximate maximum tissue doses).
[B16, T24]

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

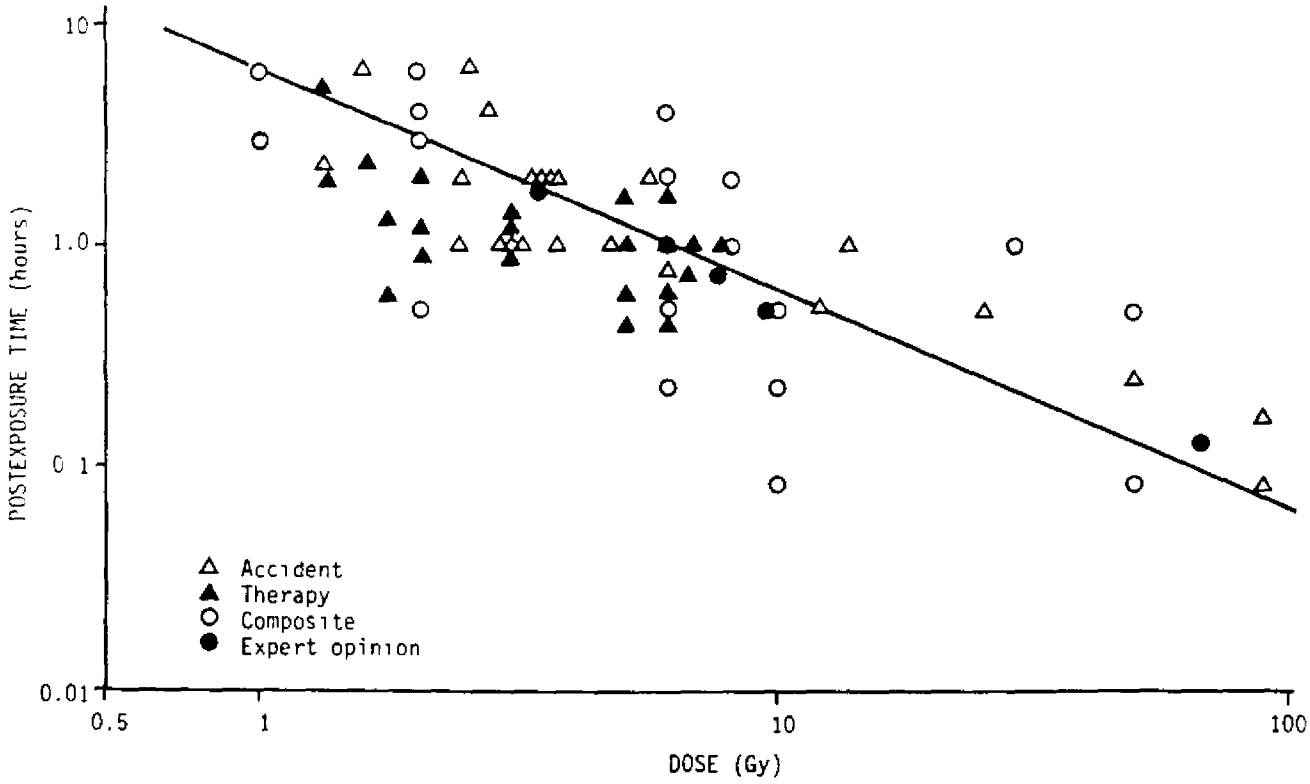

Figure IV. Relationship between time of onset of prodromal symptoms and dose in man. Dose rates ranged from very high (accident cases) down to 0.3 Gy per minute (radiotherapy patients). Approximate midline doses are quoted. (Modified from [B33].)

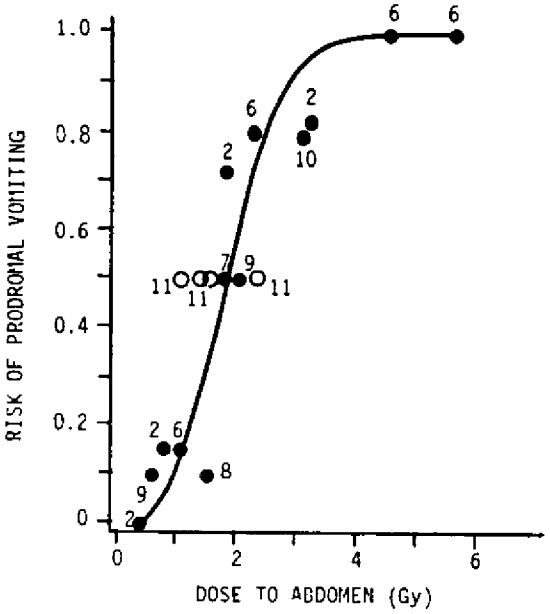

Figure V. Dose-effect relationship for prodromal vomiting within two days in man.
[U5]
2 — accident cases [L4]; 6 — accident cases [T5]; 7 — therapy patients [T17]; 8 — Rongelap natives exposed to fallout radiation [L4]; 9 — midway between the normal arithmetical and log-normal values in the analysis 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.

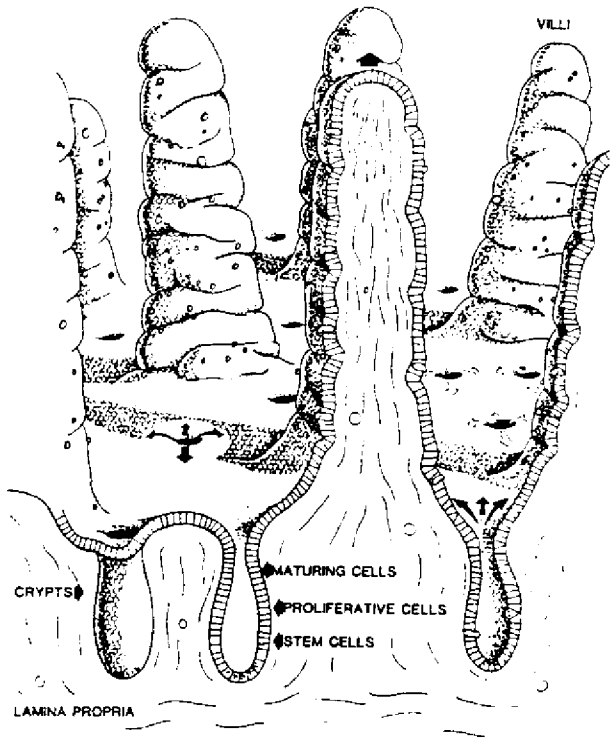

Figure VI. Diagrammatic representation of cell production in intestinal crypts, with new cells migrating on to the functional units, the villi.
(Adapted from [P29].)