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)	Extrapolation number	Ref
Haemopoietic progenitor cells producing			
Mixed-cell colonies	0.91	1.0	[N2]
Colonies of granulocytes and macrophages	1.4	1.0	[S18]
	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
[O4]

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	0.61)	15	14
Yttrium-90	2.20)		

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
O	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 [M23]; Vinca: [M22]

2 Gamma-ray dose for neutron capture in the surface of the body
Y-12 [M23], Vinca. [M22]

3 First-collision charged-particle dose Y-12: [M23], Vinca [M22]

4 Total dose as published (columns 1 + 2 + 3) Y-12. [M23]; Vinca. [M22]

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	Days 1 (24)	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]														(i)			10% mild		
Fever														(f)			10-50% mild to moderate		
Infection														(e)					
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	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)—					
Infection														—(f)—		10–80% moderate			
Ulceration																—30%——			
Fluid loss/electrolyte imbalance							(g)									moderate			
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 $10^3/\mu l$.

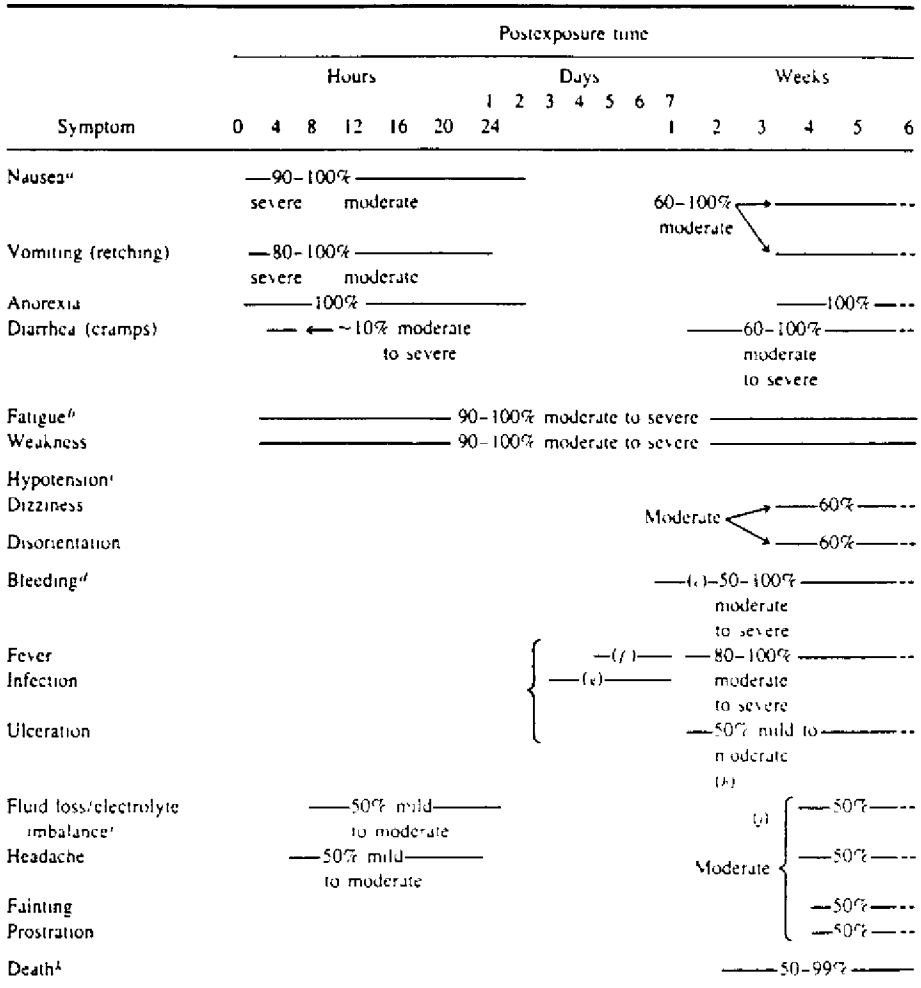
f/ Moderate to severe drop in granulocytes: from 3 $10^3/\mu l$ to 1.0-0.4 $10^3/\mu l$.

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 35/20	6	33	Lung, Hodgkin's disease
32/15 36/20	12	42	Lung, Hodgkin's disease
30/10 38/20 45/30	12	67	Lung, Hodgkin's disease, Hemangiopericytoma, Thymoma
31/10 42/18	10	90	Lung, Breast, Thymoma
41/16 53/25	14	86	Lung, Breast, 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 [L8]

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 111 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 Dose 1 b/	Dose 2 c/	Lymphocytes Cells/ µl	Lymphocytes Time (days)	Neutrophils Cells/ µl	Neutrophils Time (days)	Platelets Cells/ µl	Platelets Time (days)	Outcome
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 45	33 59	36	33	14200	26	As in case 2
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 Cells/ µl	Lymphocytes Time (days) b/	Neutrophils Cells/ µl	Neutrophils Time (days) b/	Platelets Cells/ µl	Platelets 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.