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 apply in the context of human irradiation For example, the final effects will always be modified to a greater or lesser extent, depending on the cause and the conditions of exposure by the nursing or therapeutic procedures applied after irradiation These procedures will presumably increase the value of the LD_{50} relative to its value in the absence of such procedures. Also, the state of health of the irradiated human beings may not be representative of the average state of health in the population, at least not under all conditions of irradiation. For example, the exposure of patients will produce effects that may interact with the effects of the diseases requiring irradiation or with the effects of other forms of therapy, decreasing the value of the LD_{50} relative to its value for normal individuals. The exposure of nutritionally-deprived individuals, e.g., the Japanese in the Second World War, might also produce lower values of LD_{50}. Previous estimates of the $LD_{50/60}$ 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 [15] (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

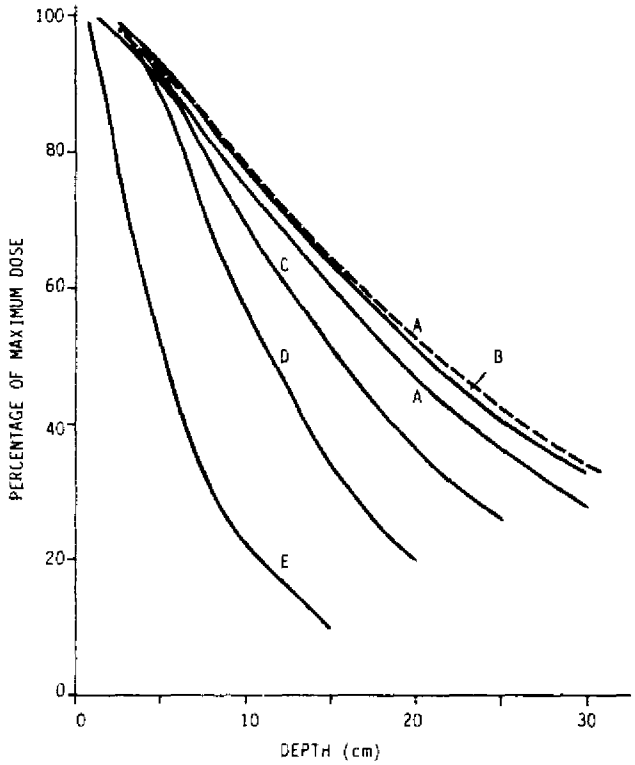

Figure XIX. Depth-dose curves for different radiation qualities. [B20, S4.] Data are tissue-air ratios (corrected for the inverse-square law) expressed as a per cent of the maximum dose:

	Radiation type	*SSD (cm)*	*Field size (cm × cm)*
Curve A	^{60}Co, rays	80	20 × 20 and 35 × 35
Curve B	4 MV x rays	Infinite	20 × 20 or 35 × 35
Curve C	^{137}Cs · 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

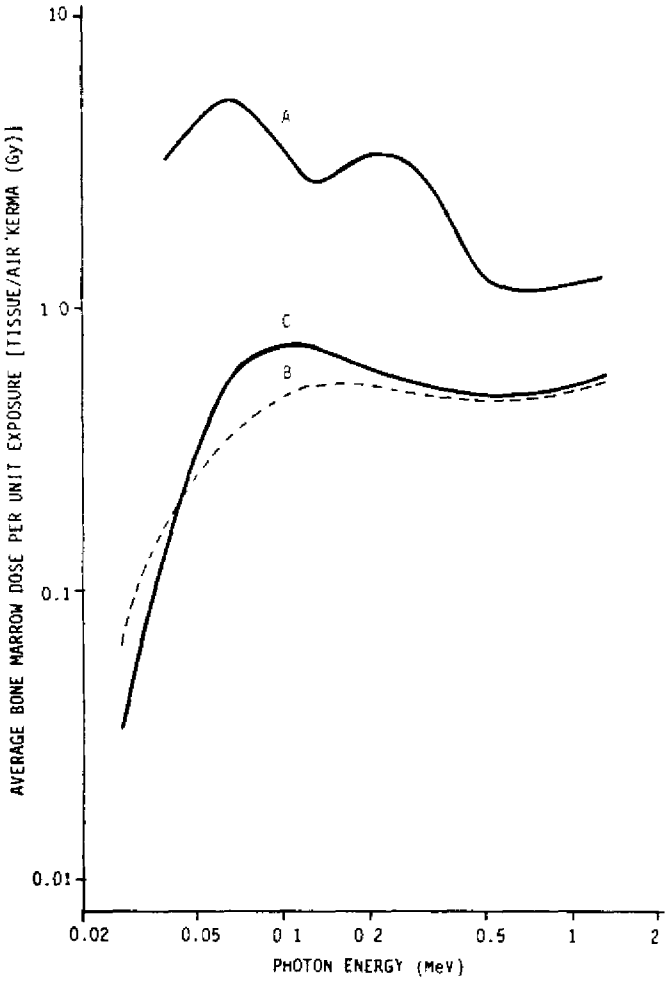

Figure XX. Average dose in bone marrow per unit exposure measured by a personal dosimeter on the front of the trunk (curves A and B) and per unit exposure measured in free air at the position of the centre of the body (curve C). Curve A: irradiation from the back only. Curve B: irradiation from the front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

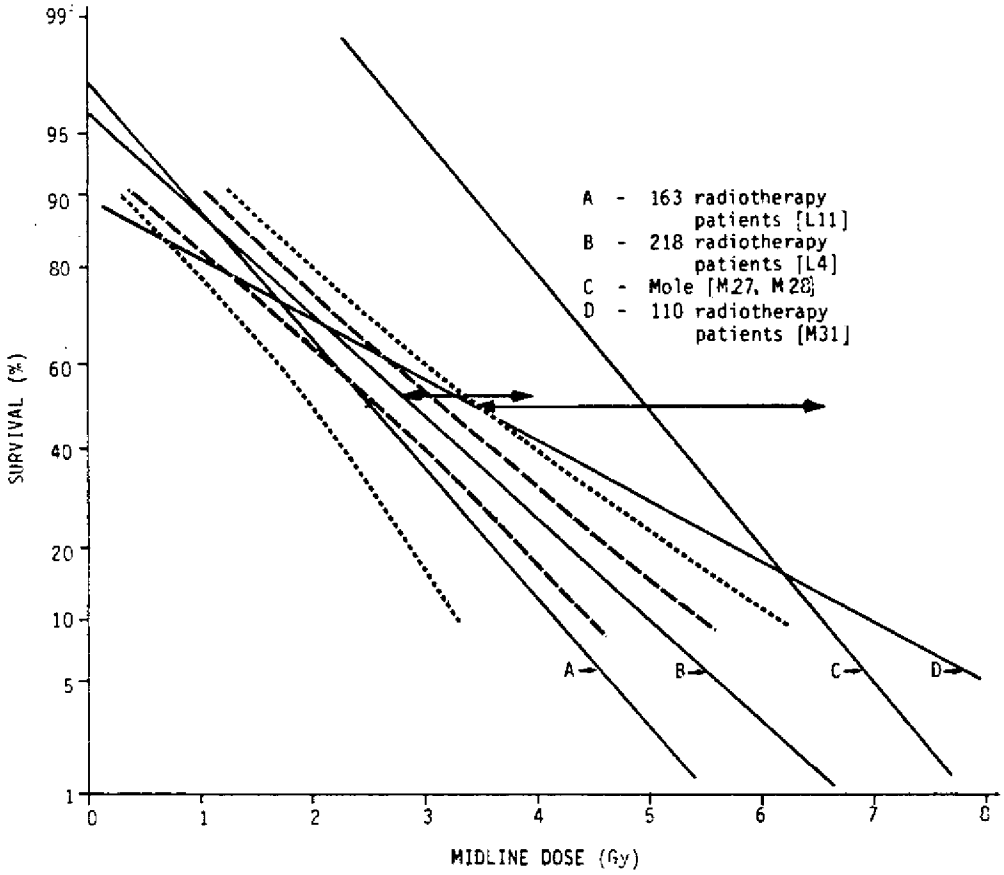

Figure XXI. Estimates of dose-survival curves for man, at 60 days. Curves A and B: Standard error limits (dotted curves at both sides of curve A, dashed curves at both sides of curve B) calculated using probit analysis; Curve C: The line is drawn assuming a coefficient of variation of 0.24, derived using 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 $LD_{95/60}$ 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 $(n + \gamma)$ 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].

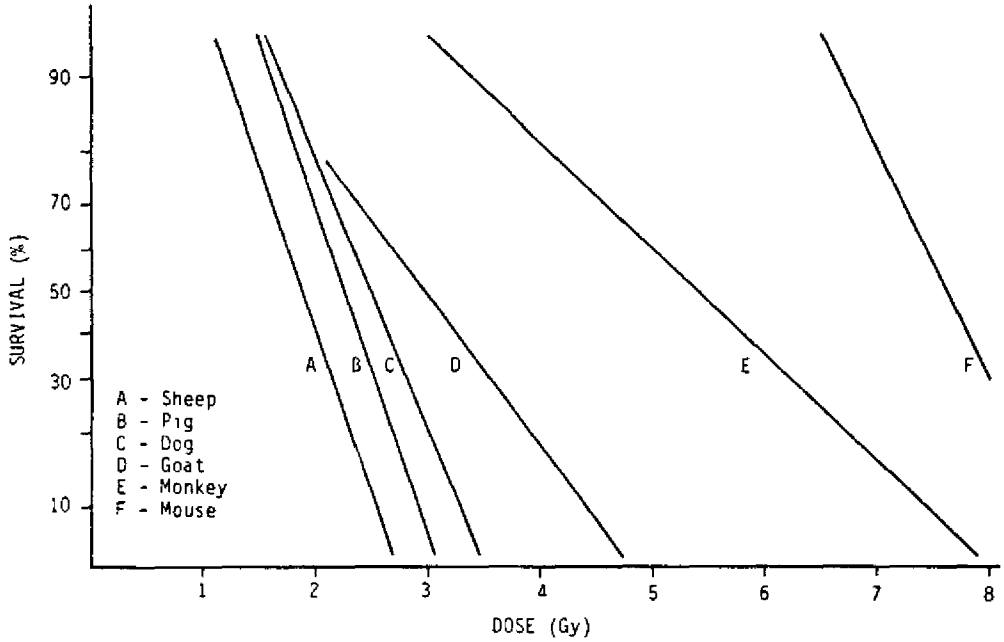

Figure XXII. Midline dose-survival curves calculated from various published experiments using different species of animal irradiated bilaterally.
[T24]

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 [I5]. 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 [I6] 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 [I6]. 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.

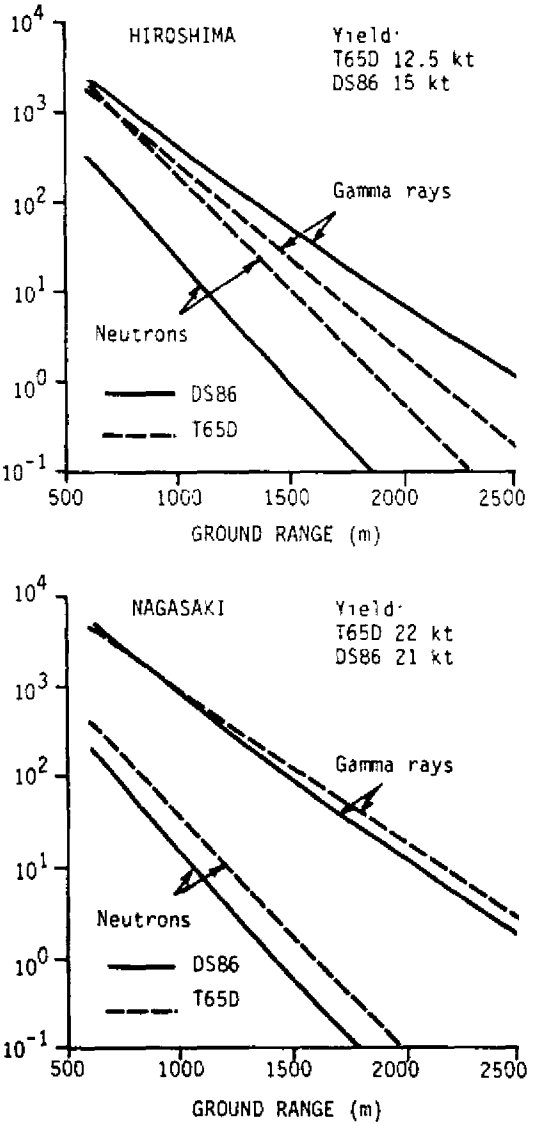

Figure XXIII. Comparison of 1965 estimates (T65D) and revised 1986 dosimetry (DS86) for initial nuclear radiation in Hiroshima and Nagasaki.
[K16]

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 10^8 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 10^8 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