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

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

where m is the exposure-time coefficient Alternatively, $D = \text{constant} \times R^{m/(m-1)}$, where R is the dose rate. The formula is applicable over a limited range of exposure times, which, like the value of the coefficient, varies between tissues [T24]. For human skin tolerance, m is about 0 29.

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

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

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

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

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

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

$$D_2/D_1 = n_2 d_2/n_1 d_1 = (\alpha/\beta + d_1)/(\alpha/\beta + d_2)$$

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

1. Prodromal responses

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

145. In monkeys, the latent period to retching or vomiting after 4.5 Gy was increased by a factor of 3 (from 30 to 90 minutes) when the dose rate was reduced from 1.2 to 0.07 Gy per minute [H35, H36]. Most of the increase occurred between 0.5 and 0 15 Gy per minute. In dogs, routine emesis during irradiation with 18 Gy could be avoided by reducing the dose rate from 0.18 to 0.05 Gy per minute [H38].

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

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

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

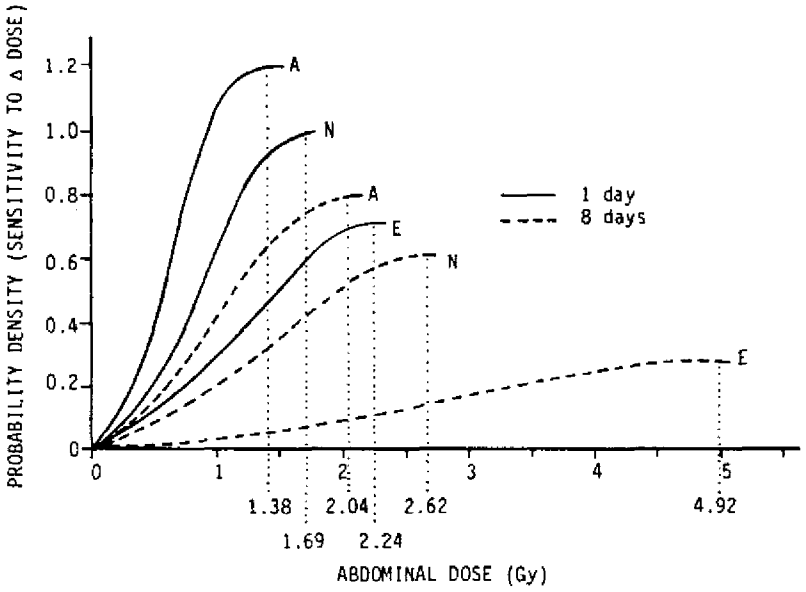

Figure XXIV. Changes in incidence of prodromal symptoms for fractionated doses in man. Fractionation of total body dose over eight days increases the doses required to produce the same incidence of various prodromal symptoms in the exposed population of patients by 1.5 for anorexia (A), 1.6 for nausea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

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

2. Intestinal responses

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

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

3. Haematological responses

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

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

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

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

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

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

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

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

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

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

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

158. An accident occurred in Goiania, Brazil in 1987 [I23] which resulted in initial acute whole-body external exposures followed by low dose rate chronic whole-body exposure from internally deposited ^{137}Cs chloride (from a damaged teletherapy source). In addition, many persons received acute localized radiation injuries (beta/gamma) to the skin and deeper tissues. Twenty-one persons required intensive medical care. Ten persons were critical with dose estimates (cytogenetic dosimetry) ranging from 3-7 Gy. Four persons died as a result of their exposures. In addition to good nursing care, antibiotics and platelet transfusions, the experimental drug granulocyte-macrophage colony-stimulating factor (GM-CSF) was administered to eight patients suffering from the acute radiation syndrome. Four of the patients who received GM-CSF subsequently died as a result of their radiation insult. The efficacy of using GM-CSF was not demonstrated.

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

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

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

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

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

160 A power function was proposed [L9]:

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

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

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

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

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

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

5. Skin

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

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

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

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

167. For early skin reactions, the α/β ratio is generally considered to be in the range 10-20 Gy. For erythema on the chest wall, ratios of 8 4 Gy, 21.9 Gy and 21 5 Gy were determined at incidences of erythema of, respectively, 16, 50 and 84% [T21].

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

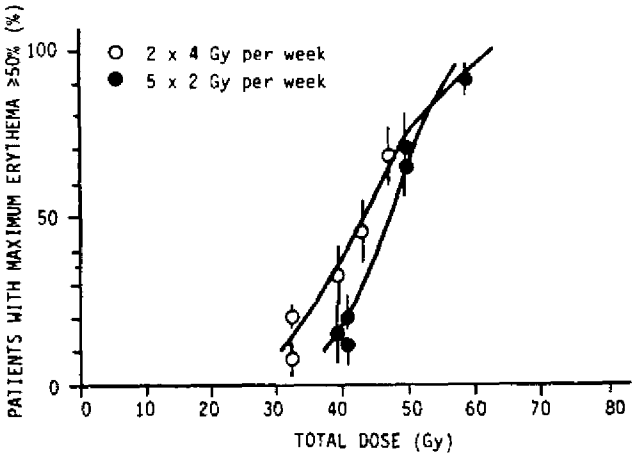

Figure XXV. Dose-incidence curves for human skin erythema. [T21]

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

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

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

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

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

6. Lung

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

172 With fractionated irradiation the total dose can be increased even further [M38, P5]. With prophylactic lung irradiation in the treatment of osteosarcoma, no pneumonitis was seen in 40 patients given 20-25 Gy to the lung in daily dose fractions of 1 5 Gy [N8]. This was in contrast to seven patients in whom pneumonitis was observed after 30 Gy delivered at 3 Gy per day. There was no pneumonitis in a further 14 patients given 24-25 Gy in 13 daily doses to the lung [N9]

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

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

7. Gonads

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

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

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

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

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

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

C. INTERNAL EMITTERS

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

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

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

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

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

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

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

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

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

189. Effects of internal emitters in animals have been discussed in detail by ICRP [I7] and UNSCEAR [U4] For example, in experiments in which dogs were exposed to beta-emitting aerosols of fused aluminium-silicated particles labelled with ^{90}Y, ^{91}Y, ^{144}Ce, or ^{90}Sr, it was found that the dose to the lungs resulting in death from pneumonitis in 50% of the dogs could be increased by a factor of 5 (^{90}Sr) or 10 (^{91}Y) relative to the acute dose of external radiation [M8]. The dosage increase depends on the half-life of the isotope which governs the exposure time. With long-lived alpha-emitters, the clearance rate from the lung is most important

190. Two individuals died after working with large amounts of tritium; they had received doses which were estimated to have been in total about 3 Gy over six years and about 10 Gy over three years [M39, S31]. A slow but continuously progressive anaemia was observed, rather than changes in the white cell count Another individual, who received a lower accumulated dose of about 1 5 Gy over four years, showed only a slight hypoplastic anaemia.

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

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

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

D BIOLOGICAL AND OTHER VARIABLES

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

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

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

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

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

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

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

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

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

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

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