# SOURCES AND EFFECTS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects of Atomic Radiation

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## NOTE

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# ANNEX I

## Late deterministic effects in children

CONTENTS

# INTRODUCTION

1. Deterministic effects of ionizing radiation in humans are the result of whole-body or local exposures that cause sufficient cell damage or cell killing to impair function in the irradiated tissue or organ. The damage is the result of collective injury to substantial numbers or proportions of cells. For any given deterministic effect, a given number or proportion of cells must be affected, so that there will be a threshold dose below which the number or proportion of cells affected is insufficient for the defined injury or clinical manifestation of the effect to occur [F1, I1]. With increasing radiation dose fewer cells survive intact, and therefore the deterministic effects increase in severity and frequency with the dose [U3]. If the radiation exposure is severe enough, death may result as a consequence of the exposure. Death is generally the result of severe cell depletion in one or more critical organ systems of the body.

2. Ionizing radiation can impair function in all tissues and organs in the body because of cell killing; however, tissues vary in their sensitivity to ionizing radiation [F1, I1]. The ovary, testis, bone marrow, lymphatic tissue and the lens of the eye belong to the most radiosensitive tissues. In general, the dose-response function for these tissues, i.e. the plot on linear axes of the probability of harm against dose, is sigmoid in shape. Above the appropriate threshold, the effect becomes more severe as the radiation dose increases, reflecting the number of cells damaged. The effect will usually also increase with dose rate, because a more protracted dose causes the cell damage to be spread out in time, allowing for more effective repair or repopulation [I2]. This type of effect, which is characterized by a severity that increases with dose above some clinical threshold, was previously called "non-stochastic". The initial changes on the cellular level occur essentially at random, but the large number of cells required to result in a clinically observable, non-stochastic effect gives the effect a deterministic character. For this reason such effects are now called "deterministic" effects. The dose levels that result in the clinical appearance of pathological effects are generally of the order of a few gray to some tens of gray. This clinical threshold or critical dose is based on clinical examination and laboratory tests. The time of appearance of tissue damage ranges from a few hours to many years after the exposure, depending on the type of effect and the characteristics of the particular tissue.

3. Radiation-induced deterministic damage in a tissue or organ will often have a more severe impact on the individual during childhood, when tissues are actively growing, than during adulthood. Examples of deterministic sequelae after radiation exposure in childhood include effects on growth and development, hormonal deficiencies, organ dysfunctions and effects on intellectual and cognitive functions. In this Annex, a review is made of late, deterministic damage to normal tissues in children caused by ionizing radiation. Life shortening is not discussed due to the paucity of data. Other effects of radiation exposure, such as cancer induction, hereditary effects and early radiation effects, are not considered. One objective of this review is to try to determine the critical dose levels for the appearance of clinical deterministic effects. Such dose levels will depend on the end-points considered and on the sensitivity of the techniques for measuring the effects. Permanent rather than transient biochemical changes are emphasized in the attempts to define the threshold doses.

4. The Committee reviewed the deterministic effects of radiation in Annex J of the UNSCEAR 1982 Report [U3]. The basic concepts of cell survival were reviewed, including the factors influencing tissue response to fractionated or continuous exposures to radiation. That review of effects was based mainly on results of animal experiments and clinical observations of adults who had received radiotherapy. Its main objective was to identify the nature of effects in various tissues and the doses and modalities of irradiation that cause the effects. It was the Committee's opinion that better quantitative results in man would be required, although it was recognized that such data were difficult to obtain. For effects in children, the need for data and the difficulties were considered to be even greater.

5. The information in this Annex on the possible deterministic effects specific to the exposure of children comes from the application of new methods to derive data and the continued monitoring of patients who received radiotherapy and other individuals exposed to doses high enough to cause deterministic damage to specific tissues or to the whole body. For practical applications it is important that attempts should be made to quantify this damage in terms of the degree of detriment. Owing to the paucity of data, it is not really possible to quantify effects by age in most situations.

# I. DETERMINISTIC EFFECTS OF RADIATION EXPOSURES

6. Although the pathobiology of radiation-induced late deterministic effects is poorly understood, it is reasonable to believe that late damage can result from a combination of loss of parenchymal cells, injury to the fine vasculature and/or dysfunction of the fibrocytes and other cells [C1]. Radiation-induced late tissue injury of a deterministic nature appears to have its origin in the sterilization of a large proportion of the stem-like cells of the tissue or organ in question, although these cells may be only a small proportion of the total number of cells in that tissue/organ. The consequent injury results from the natural loss of post-mitotic cells that are not replaced or from the loss of cells that are stimulated into mitosis. The timing of tissue injury depends on the natural proliferation characteristics of cells and also on kinetic changes resulting from the radiation exposure that are characteristic of the tissue [U3]. In addition to the loss of functional cells, supporting blood vessels may be damaged, resulting in secondary tissue damage. Damage to the capillary network has been implicated in the degenerative changes that are accompanied by a progressive reduction of functional capacity [F1]. Other mechanisms for late effects include increased vascular permeability, which causes plasma proteins to leak into interstitial spaces, resulting in the deposition of collagen and leading to atrophy of parenchymal cells. There may also be some replacement of functional cells by fibrous tissue, reducing organ function. The clinical effect that ensues depends on the specific function of the tissue in question.

7. Various processes of repair and repopulation will increase the threshold level of dose when radiation is given over a long period or when a second period of irradiation is encountered sometime after an earlier exposure. The exact role of repopulation, recruitment and intracellular repair of radiation injury over long periods is not clear [C1]. Another aspect that is not well understood is the effect of prior radiation therapy on late injuries following a second course of radiotherapy. There is repair of sublethal damage related to fraction size and fraction number, as well as to dose rate. There appears to be a wide range in the amount of repair that can occur between radiation doses or at decreasing dose rates, which seems to be a tissue-specific phenomenon [C1]. Increasing tolerance occurs as a function of time (days to weeks between fractions) in organs expressing late damage and is thought to be based on slow cell renewal.

8. Late radiation effects often occur in tissues with little or very little proliferation. The radiation effects have been attributed to parenchymal depletion secondary to endothelial changes in small blood vessels or to the direct depletion of parenchymal or stromal cells [R1, R2, R3, T1, W1]. The dose-survival relationship for late effects differs from that of acute responses. Injury to slowly responding tissues is more dependent on fraction size. When conventional radiotherapy fractionation schedules have been altered to fewer fractions of larger doses, an increase in late complications has ensued, with little or no difference in the severity of acute effects [T2]. Studies in animals indicate that the dose-survival characteristics of target cells for late injuries are different from those of target cells of acutely responding tissues. The slopes of the isoeffect curves as a function of dose per fraction are greater for late effects, indicating a greater influence on sparing from dose fractionation for late effects [T2, W2]. The data for low-LET radiation in adults show a wide range of sensitivities of different tissues [I1, R1]. Few tissues show clinically significant effects after acute exposures of less than a few gray, with the exception of the gonads, lens and the bone marrow, which show higher sensitivities.

9. There is little direct correlation between acute reactions and late effects of radiation [B1, R2, R3]. It is, therefore, the late radiation effects that are the dose-limiting factors in curative radiotherapy. Interactions with other treatment modalities may also limit the radiation dose. For example, chemotherapy administered during, before or after irradiation may reduce the tolerance of the tissues exposed to ionizing radiation [R3, W1]. In radiotherapy, normal tissues are unavoidably included in the target volume, and it is the effects in these tissues that limit the dose that can be tolerated. There is still poor understanding of the exact tolerance of a given organ or tissue and of changes in tolerance caused by variations in fraction size, target volume, duration of treatment, dose rate and the presence of various chemical compounds. For a variety of tissues or organs, a critical radiation dose for a limited volume of this tissue has been established empirically, mainly in adults. This dose is usually defined as the dose that will produce a small but detectable incidence of serious complications resulting from the radiation effect on the normal tissue, and often 5% of serious complications is considered reasonable in radiotherapy [C1, R1]. This critical dose or dose range is different from the term "tolerance dose", historically used in radiation protection. Most clinical practice involves daily fractionation with approximately 1.5-2 Gy four or five days per week. In the following paragraphs this will be referred to as conventionally fractionated radiotherapy. Rubin et al. [R1] and Molls and Stuschke [M41] have published data on acceptable doses in radiotherapy and have presented estimates of radiation doses for deterministic effects in organs and tissues of adults and children. There are wide variations in the critical dose from one tissue to another (Tables 1-2).

10. There is great variability in the latent intervals between radiation exposure and the clinical manifestation of late deterministic effects, which may develop at times varying from months to 10 or more years after treatment. The latent interval depends on the tissue or organ affected and is, for example, up to 2 years for myelitis, one to several years for nephritis, 1-5 years for eye effects and 6 months to many years for fibrosis in subcutaneous and connective tissues [T2]. The rate at which radiation injury becomes manifest in a tissue reflects the rate of turnover of target cells and their progeny [F1].

11. Only a few large epidemiological studies of deterministic effects in children exposed to ionizing radiation have been published. Most data are obtained from clinical follow-up of small groups of patients successfully treated for paediatric tumours. In the 1950s and early 1960s the prognosis for a child with a malignant tumour disease was grave, and for many types of tumours death would follow in a matter of months. With the introduction of modern surgery, high-voltage radiotherapy and chemotherapy, the prognosis has improved considerably, and today a large proportion of children with paediatric tumours are cured. The proportion of two-year survivors, which implies the cured fraction, in 1980 ranged from approximately 40% for patients with neuroblastoma or brain tumours to 80%-90% for patients with Wilms' tumour or Hodgkin's disease [S1]. Consequently, many children are now surviving into adulthood, making it possible to study the late effects of their treatment. Increasing reports of late effects have led to systematic investigations by groups of paediatric cancer treatment institutions, such as the Childrens Cancer Study Group in the United States and Canada and the International Late Effects Study Group.

12. In this review of deterministic effects in children, the various observed effects have been grouped according to the organ or tissue affected. It is generally difficult to single out the specific effect of radiation in children with paediatric tumours, as most have also been treated with other modalities, e.g. surgery, cytostatic drugs and/or hormones. Most clinical evaluations are, moreover, based on small numbers of patients, and often appropriate control groups are lacking. Furthermore, the long duration of the illness, the need for hospitalization, the lack of school attendance and other social factors may have had an impact on certain effects measured, such as neuropsychologic functioning. The fact that most data are obtained from studies of patients with paediatric tumours makes it even more difficult to draw conclusions that can be generalized to the general paediatric population. One reason for this is that groups of children treated for malignant disease may include individuals with a genetic predisposition to cancer, some of whom can perhaps have a higher sensitivity to other radiation-induced effects as well. In general, there is a great variability in the ages of the patients studied, and many studies have also assessed patients at widely different ages. A sizeable portion of eligible patients are often not assessed: the children may not be available for evaluation, owing to, for example, their refusal or that of their parents, the disease itself or geographical factors. These selection criteria obviously also affect the interpretation of data.

13. Radiation therapy has been claimed to account for about 80% of the long-term sequelae in surviving children with neoplasms [M1]. Severe disabilities were noted in 41% of 200 children treated for cancer who had no sign of disease for at least five years after therapy [M2]. The disabilities included severe cosmetic changes (16%), severe growth retardation (10%), the need for special education (8%), gonadal failure (7%) and other apparent organ dysfunctions (12%). Hypothyroidism (3%), minimal scoliosis and hypoplasia (22%) were some of the mild to moderate disabilities. Li and Stone [L1] studied late effects in 142 patients treated for childhood cancer and observed major defects in treated organs in 52% of the patients. Despite this, a large proportion of the patients had fully active lives, 61% had attended college, 53% were married and 32% had progeny.

# II. RADIATION EFFECTS IN TISSUES AND ORGANS

## A. BRAIN

### 1. Organic effects

14. The developing human brain is especially sensitive to ionizing radiation. Previous UNSCEAR Reports have considered the general developmental effects of prenatal irradiation [U2, U4]. A review of the results of the study of survivors of the atomic bombings in Japan, as well as reviews of other epidemiological investigations relating to prenatal exposure to ionizing radiation and effects on the brain, are presented in Annex H, "Radiation effects on the developing human brain". The mechanisms of observed effects from exposure in fetal life are different from the mechanisms in a nearly fully developed brain. This Section reviews data on late effects following exposure of the brain of infants and children.

15. The response of the normal brain to radiation depends on the total and fractional doses of radiation, the duration of exposure, the exposed tissue volume and the age of the exposed subject. The outcome of iatrogenic radiation damage to the normal brain depends on the magnitude of the damage and the brain's lack of cellular repopulation. Although partial recovery takes place between fractionated exposures, the brain has very little repair function [K1, M3]. After birth, the period of greatest radiosensitivity of the human brain is during the first two years of life, before maturation is completed. Treatment involving the whole brain is more likely to have an adverse effect on younger children by interfering with neural development before maturation of the brain is complete.

16. There is a large body of evidence indicating that radiotherapy to the central nervous system is associated with adverse late effects [B2, B3, D1, D26, F2, K2, K3, O1, P2]. This delayed type of damage is believed to be the effect of injury to the fine vasculature and/or loss of parenchymal cells, resulting in ischaemic necrosis and loss of parenchymal function [A1, C1, C2, S2]. Vascular changes may occur after relatively low radiation doses. Glial cells proliferate during the first years after birth and are therefore sensitive to ionizing radiation. A decrease in the replacement of glial cells and the associated interference with myelination have also been postulated as causes of delayed radiation injury [M4].

17. Treatment-related sequelae of the central nervous system have been documented in children with brain tumours and acute leukaemia, as well as in children having other tumours that require treatment of the central nervous system. The concept of treating the central nervous system of children with acute lymphoblastic leukaemia was developed in the 1960s in order to avoid leukaemic relapse of the central nervous system [A2, A3]. Most patients with leukaemia or solid tumours other than of the brain do not have primary disease of the central nervous system, and the effects of treatment can therefore be better distinguished from the effects of disease. In addition, the radiotherapy in these patients generally involves relatively low radiation doses in the brain. Analysis of radiation effects in brain tumour patients is more difficult because of the much higher radiation doses and the possible effect of the tumour on brain function. In a follow-up study of 102 subjects treated for brain tumour in childhood [L2], 40% of the subjects had mild to moderate disabilities but were living independently, 9% were capable of self-care and 4% required institutionalization. Moderate or severe disabilities were reported in 13 of 30 (43%) irradiated patients and in 11 of 72 (15%) who did not receive radiotherapy. Functional deficits were more common among those treated before two years of age.

18. Five distinctive forms of late effects in the central nervous system have been described: necrotizing leukomyelopathy, leukoencephalopathy, mineralizing microangiopathy, cortical atrophy and necrosis. Necrotizing leukomyelopathy is a spinal cord lesion that does not appear to be related to radiotherapy, since the majority of cases have been observed in non-irradiated patients [P2]. Leukoencephalopathy is a syndrome caused by demyelination; it develops in patients who have received cranial irradiation with intrathecal and/or systemic methotrexate treatment [P1, P2, R4]. Histopathologically, leukoencephalopathy is characterized by demyelination, beginning with axonal swelling and fragmentation and progressing to necrosis and gliosis [B4]. Leukoencephalopathy presents as multifocal coalescing areas of necrosis in the deep white matter, and in the late stage white matter is reduced to a relatively thin gliotic calcified layer. Cortical grey matter and basal ganglia are not affected. Clinical findings range from poor school performance and mild confusion to lethargy, dysarthria, ataxia, spasticity, progressive dementia and even death.

19. Both intrathecal methotrexate and cranial radiotherapy affect endothelial pinocytosis, and damage to the endothelial barrier could be involved in late effects following such treatments [L3]. The interactions between methotrexate and radiation within the central nervous system may be due to the overlapping neurocytotoxicity of the two treatment modalities or to methotrexate acting as a radiosensitizer. Irradiation of the central nervous system may also increase the permeability of the blood-brain barrier or may slow the turnover of cerebrospinal fluid and clearance of methotrexate from the central nervous system. This would alter the distribution of methotrexate in the central nervous system so that some areas accumulate higher amounts of the agent [B4]. Significant levels of methotrexate can also be found in the spinal fluid after it has been administered systemically. The risk and severity of leukoencephalopathy are directly proportional to the total radiation dose, the cumulative dose of systemic methotrexate and the number of therapeutic modalities used (Figure I) [B2, B4]. The highest incidence of leukoencephalopathy is found in patients receiving radiotherapy and methotrexate administered both intravenously and intrathecally. The least neurotoxic combination appears to be intrathecal plus intravenous methotrexate. If radiotherapy to the central nervous system must be combined with methotrexate therapy, the least neurotoxic approach appears to be to administer these modalities in sequence [B2].

20. Leukoencephalopathy has been reported after 20 Gy or more in combination with intrathecal methotrexate [M6, P3, R4]. No evidence of leukoencephalopathy has been found in children for whom intra-

venous or intrathecal methotrexate was discontinued before radiotherapy. Leukoencephalopathy has not been reported after fractionated radiotherapy of the central nervous system with 18-24 Gy alone and rarely with intrathecal methotrexate alone [B4, K4]. Leukoencephalopathy can also occur after a single dose of 10 Gy whole-body irradiation prior to bone marrow transplantation [A4, D2, J1]. Almost all such reported cases have occurred in children, suggesting that the maturing brain is more susceptible. These patients were usually given intensive chemotherapy and cranial radiotherapy with 20-24 Gy over a few weeks prior to the whole-body irradiation. Leukoencephalopathy occurred within a few years of whole-body irradiation in these patients and has usually resulted in severe neurologic deterioration.

21. Mineralizing microangiopathy affects predominantly cerebral grey matter and sometimes cerebellar grey matter and is characterized by focal calcifications in the central nervous system. This degenerative and mineralizing disorder is believed to result from radiation-induced damage to the small vessels [B4, P2, P4]. Histopathologically, calcifications are found in small blood vessels occluding the lumen with mineralized necrotic brain tissue around the vessels. Neurological abnormalities, such as poor muscular control, ataxia, headaches and seizures, have been observed in patients with this complication. Mineralizing microangiopathy is not fatal, and its effect on neuropsychologic functioning may be minimal, although permanent destruction of specific regions of the brain may occur. Mineralizing microangiopathy has not been found in children who did not receive cranial radiotherapy [P4]. It occurs predominantly in children who received 20 Gy or more. Between 25% and 30% of patients who survive more than nine months after intrathecal methotrexate and cranial irradiation with 24 Gy have evidence of mineralizing microangiopathy. The lesion occurs more often in young children [B4, D5]. When mineralizing microangiopathy and leukoencephalopathy coexist, the clinical manifestations of the leukoencephalopathy will predominate.

22. Cortical atrophy is perhaps the most common manifestation after treatment of the central nervous system. It is the result of multiple areas of radiation-induced focal necrosis causing loss of cortical tissue and production of ventricular and subarachnoid space dilatation [C3, D3, D4, D5]. The cortex of atrophic brains is microscopically characterized by an irregular, neuronal loss from all six layers. Astroglial proliferation is sometimes present, usually confined to the marginal layer. Cerebral atrophy occurs after fractionated cranial radiotherapy in nearly half of the patients receiving >30 Gy to the entire brain. The latent period between radiotherapy and the onset of atrophic changes detectable with computed tomography is 1-4 years or even longer [D3].

23. After cranial radiotherapy with 25-65 Gy to the whole brain (delivered at ≤2 Gy per day) to treat brain tumours, cortical atrophy has been found in half of the children [D5], abnormalities of the white matter in 26% and calcifications in 8% of the patients. Cortical atrophy has also been demonstrated in one third of children with acute lymphoblastic leukaemia receiving 24 Gy prophylactic cranial irradiation and intrathecal methotrexate [K2]. Crosley et al. [C3] found evidence of abnormality of the central nervous system at autopsy in 93% of 91 children treated for acute leukaemia. Moderate to severe atrophy was observed in 13% of patients receiving no prophylactic treatment of the central nervous system, in 19% of patients receiving radiotherapy given in 1-2 Gy fractions over 2-15 days (the total brain dose was not stated), in 43% of patients given intrathecal methotrexate and in 47% of patients who received both chemotherapy and radiotherapy. Atrophy did not correlate with leukaemic infiltrations or vascular or infectious processes. Children with the most severe atrophy were the ones who were youngest at onset (mean age: 2.5 years).

24. Cerebral necrosis is a serious sequelae and is usually diagnosed 1-5 years after treatment but may develop more than a decade later. It is characterized by an insidious onset of clinical features [K2]. Post-irradiation myelopathy occurs with rapidly increasing incidence at doses above 45-50 Gy with conventional fractionation. The dose per fraction is critical, and almost all cases of necrosis following total doses of <60 Gy had fractions of >2.5-3.0 Gy [K1, M7, S2]. An interaction between chemotherapy and radiotherapy has been observed for methotrexate in children but has been difficult to show for other agents. A total dose of 50 Gy with 2 Gy per fraction or 55 Gy in 1.8 Gy fractions over six weeks, five daily fractions per week, is considered to be tolerable in adults [A5, K2, S56]. A more recent estimate has been given by Bloom [B35], who assumed that the maximum tolerable radiation dose for children up to 3 years old is 33% lower than in adults, and for children 3-5 years old the dose has to be reduced by 20%.

25. Very few data are available on the effects of hyperfractionated radiotherapy. Freeman et al. [F3] studied 34 patients 3-18 years old (mean: 7 years) who were irradiated for brain stem tumours with 1.1 Gy twice daily with a minimum interval of 4-6 hours, to a total dose of 66 Gy given in 60 fractions over 6 weeks. In the 16 patients who were alive at one year (only 7 were free of progressive disease), there was no clinical suspicion of radiation-related injury. Microscopical examination of the brain in 8 patients failed to show any injury attributable to the radiotherapy.

26. Abnormalities are frequently observed by computed tomographic scanning in long-term survivors of childhood acute leukaemia treated with cranial radiotherapy and intrathecal methotrexate [B5, B6, C14, D24, E1, M5, O2, O3, O13, O14, P5, P7, R5, S55]. Abnormal brain scan findings may not become apparent until many years have elapsed since therapy. The type of brain abnormalities detected include intracerebral calcifications, white matter hypodensity and cortical atrophy (Table 3). Patients who received 24 Gy in 2 Gy fractions with intrathecal chemotherapy appear to have a higher incidence of each of the various abnormalities detected by computed tomography than those who did not receive radiotherapy. On average, there is a 40% incidence of brain abnormalities after 24 Gy in 12 fractions over 2.5 weeks combined with intrathecal methotrexate, although the incidence varies from study to study, depending on the number of patients and length of follow-up. At brain doses of 18-20 Gy combined with intrathecal methotrexate or after intrathecal plus intravenous methotrexate, the average prevalence of brain abnormalities detected is 10%-15%.

27. Magnetic resonance imaging appears to be more sensitive than computed tomography in demonstrating treatment-related neurologic damage in irradiated children. The types of changes observed by magnetic resonance correlate well with the type and severity of the neurologic dysfunctions [A6, C4, K5, P6]. Constine et al. [C4] observed radiation-induced changes in the white matter in 90% of the patients by magnetic resonance imaging, and 68% of these changes were not visible by computed tomography. Enlargement of the sulci was demonstrated in 76% by magnetic resonance imaging and in 52% by computed tomography. Patients treated on a hyperfractionated schedule (1.2 Gy per fraction) had less severe changes, despite the fact that some received over 70 Gy.

28. *Summary.* The available clinical data on deterministic radiation effects on the brain in children are based on small and often heterogenous groups of patients with varying age at exposure and varying lengths of follow-up. Well-designed epidemiological studies of late effects are lacking, and it is therefore not possible to draw any firm conclusions about the radiation effects on the brain and the exact critical dose levels for the appearance of various clinical pathological entities. There is evidence that the incidence of late brain effects will increase as the number of fractions is decreased and the fraction size is increased. The most important effects in the brain following radiotherapy to the central nervous system are leukoencephalopathy, mineralizing microangiopathy, cortical atrophy and cerebral necrosis. Radiotherapy involving the whole brain is more likely to have more severe adverse effects in young children by interfering with neural development before maturation of the brain is complete. Brain changes have been demonstrated with computed tomography and magnetic resonance imaging after 18 Gy of fractionated radiotherapy to the brain. Leukoencephalopathy has been observed after >20 Gy in 1.8-2 Gy daily fractions to the whole brain together with systemic methotrexate and has rarely been reported after 18-24 Gy without methotrexate (Table 4). Leukoencephalopathy has been found in children who were given a single dose of 9-10 Gy whole-body irradiation, but they had generally received cranial radiotherapy prior to the whole-body treatment. Mineralizing microangiopathy has rarely been reported following radiation doses below 20 Gy in 1.8-2 Gy fractions in combination with methotrexate. Cortical atrophy has been observed after 18 Gy in 1.8-2 Gy daily fractions combined with intrathecal methotrexate. A whole-brain dose of 50 Gy in 2 Gy fractions over 6 weeks is generally considered to be a critical dose in adults for radiation-induced necrosis. For children up to 3 years old, the dose should be reduced by 33% and for children 3-5 years old the dose has to be reduced by 20%.

### 2. Neuropsychologic effects

29. Individuals vary in personality characteristics and mental abilities, and tests have been designed to measure such differences. Ability tests are among the most widely used tools in psychology. They can be divided into achievement tests (designed to measure accomplished skills and indicate what the person can do at present) and aptitude tests (designed to predict what the person can accomplish with training), although the distinction between these two types of tests is not clear-cut. The intelligence quotient (IQ) is an index of mental development and expresses intelligence as a ratio of mental age to chronological age. Heredity plays a role in intelligence, and environmental factors such as nutrition, intellectual stimulation and the emotional climate of the home will influence where within the reaction range determined by heredity a person's IQ will fall. Ability tests are, despite their limitations, still the most objective method available for assessing individual capabilities [A7].

30. Intelligence and academic achievement testings of long-term survivors of childhood cancer reveal a high incidence of memory deficits, visual-spatial skill impairment and attentional deficit disorders. Available data identify radiotherapy to the central nervous system and the synergism with intrathecal chemotherapy as primary etiologic factors in the neuropsychologic sequelae of survivors of childhood cancer [G1, M8]. The brain is particularly sensitive to biologic insults during periods of rapid growth and development, which after birth comprise the first four years

when glial cells proliferate and myelination occurs. Therefore the age at which the child receives cranial irradiation is of importance, and the younger the age of the child at the time of exposure the more serious the intellectual deficit will be. The effect of age at which brain damage occurs depends heavily on the type of psychological ability measured and the instruments for that measurement as on well as the location, extent and permanence of the damage. Multiple factors may be involved in the causation of intellectual deterioration, and the interpretation of IQ may be confounded by the type, location, extent and permanence of lesion, hydrocephalus, age of the child at the time of diagnosis, the aggressiveness of the surgery, radiotherapy and chemotherapy, lack of school attendance, and by anxieties and fears experienced by the child at the time [D1, E3, M8]. Parental social class or parental education level have in some studies been found to be strong predictors of IQ in the survivors of acute childhood leukaemia [T7, W3]. This emphasizes the importance of controlling for social class differences.

31. Neuropsychologic dysfunction with behaviourial or intellectual impairment may occur in up to 50% of children with brain tumours [B6, B7, B8, D6, D7, D8, D9, D10, D11, E2, H2, K6, L2, M9, M10, R6, S3, S4]. These children have received high radiation doses to the brain, and the direct effects of tumour and/or increased intracranial pressure may have contributed to the development of the intellectual problems. Radiotherapy is the most important factor for cognitive sequelae in long-term survivors of paediatric brain tumours who received brain doses of 40 Gy or more in 1.8-2 Gy daily fractions [D8, D9, E2, J2, K6, L4, S3]. In some studies a strong correlation has been observed between IQ and radiotherapy, and young children have generally shown the greatest IQ losses.

32. Radiotherapy to the central nervous system in acute childhood leukaemia (usually 24 Gy fractionated over 2.5 weeks) has been associated with subsequent adverse neuropsychologic effects [C4, C5, C7, E3, E4, E5, H3, I3, K5, L22, M2, M5, M6, M11, M12, O3, O17, P5, R7, R8, R9, S5, T4, T14]. The most common finding is decrements in general intelligence. Other documented effects include general memory impairment, difficulties with short-term memory, distractibility, deficits in abstract reasoning, quantitative skills, visual-motor and visual-spatial skills [C6, D9, E3, E4, J3, M4, M6, M11, M13]. Neuropsychological dysfunction has been reported in up to 30% in children with acute leukaemia, although the deficiencies have been mild, and the children have usually functioned well within the wide normal range. Some studies suggest that adverse effects on intellect are not noted until 2-5 years after treatment. Prophylactic radiotherapy with 24 Gy is associated with poorer intellectual function than is intrathecal chemotherapy (Figure II). Mean overall intelligence scores in irradiated children are, in general, 10-15 points lower than mean scores in non-irradiated children. Performance skills are usually more affected than verbal skills, irradiated patients scoring an average of 15-25 points lower than the mean performance IQ of non-irradiated children [B2, B7]. The younger the child is at the time of irradiation, the greater the neuropsychologic deficit [C7, H4, J3]. Children treated with 24 Gy plus cytotoxic agents for acute leukaemia generally display greater neuropsychological disabilities in a variety of neuropsychologic tests [B9, C5, E3, E5, L5, M11, M12, R8, R9], although some studies have failed to detect such deficits [H4, M8, S6, V2]. Overall, data show that radiotherapy in conjunction with methotrexate has a deleterious effect on later cognitive development. Intrathecal methotrexate as the only prophylactic therapy does not appear to be associated with any global or specific neuropsychologic impairment [P5, T5]. There is some evidence that chemotherapy combined with radiotherapy impairs intellectual functions to a greater extent in children with acute leukaemia who are less than 5 years of age than in older ones [E3, E4, E5, J3, M12].

33. Neuropsychologic late effects can also be seen after doses to the brain of 18 Gy from fractionated radiotherapy [M13, O1, O4, O17, R7, T4, T6]. Studies by Tamaroff et al. [T4, T6] suggest that a dose to the brain of 18 Gy or 24 Gy in children with acute leukaemia in combination with intrathecal methotrexate may have similar deleterious sequelae for neuropsychologic functions. Patients receiving radiotherapy had significantly lower mean full-scale IQ scores and performance IQ scores than non-irradiated children. Ochs et al. [O1, O4, O17], on the other hand, did not observe any significant difference in initial or final full-scale IQ scores between long-term survivors of acute leukaemia having received 18 Gy cranial fractionated radiotherapy plus intrathecal methotrexate and those having received methotrexate only. However, statistically significant decreases in overall and verbal IQ and arithmetic achievement were found in both groups. Thus, 18 Gy of cranial radiotherapy and intrathecal methotrexate may be associated with comparable decreases in neuropsychologic function.

34. A clear dose-response relationship for impaired neuropsychologic functions has, however, not yet been established. Ron et al. [R10, R30] studied a cohort of 10,842 Israeli children who were irradiated for tinea capitis at a mean age of 7 years, receiving a mean brain dose of 1.5 Gy (range: 1.0-6.0 Gy), a control group of ethnicity-, sex- and age-matched subjects from the general population and another control group of siblings. For a subgroup taking scholastic aptitude tests between 1966 and 1970, the irradiated children

achieved lower examination scores. For males born between 1949 and 1955, irradiated subjects achieved lower examination scores on IQ and psychologic tests, completed fewer school grades and had a slight excess of mental hospital admissions. Males with multiple irradiations had twice the mental hospital admission rate of males with a single irradiation (34.0 versus 17.4 per 1,000); there was no such difference among females. The standardized risk ratio for mental hospital admissions was 1.0 for non-irradiated males, 1.1 for males having one treatment, 2.4 for two treatments and 4.8 for ≥3 treatments (test for linear trend, $p < 0.01$). There were also changes in the electroencephalogram among the irradiated subjects and significant differences between the irradiated and control subjects in visual-evoke-response averages, providing further evidence of impaired brain function following the radiotherapy. Children irradiated at less than six years had a relative risk of 1.7 (95% CI: 1.1-2.8) for mental hospital admissions, whereas for older children that relative risk did not differ significantly from 1 [R10].

35. An indication of an excess of admissions to mental institutions was also observed in a survey of American children with tinea capitis after similar radiation doses [O5, S7]. Shore et al. [S7] studied 2,215 patients given radiotherapy for tinea capitis in childhood. The brain received 1.5-1.8 Gy at the surface and 0.7 Gy at the base. There was a 30% excess of psychiatric disorders in the irradiated group overall when controlling for race, sex, socio-economic status, age at therapy and interval from treatment to disease. Omran et al. [O5] made a psychometric and psychiatric evaluation of 177 subjects treated 10-29 years earlier for ringworm of the scalp. Radiotherapy was given to 109 subjects, and 68 received topical medications. Average age at treatment was eight years in both groups. The irradiated group manifested more psychiatric problems and were judged more maladjusted in the testings when controlling for educational level and family psychiatric disorders. However, the psychiatrist's overall rating of current psychiatric status showed only a borderline difference between the two groups.

36. The Israeli and American studies of children irradiated for tinea capitis suggest that doses to the brain of 1-2 Gy would be associated with late neuropsychologic effects. The dose given to these patients is the lowest that has been reported to lead to functional neuropsychologic disturbances after radiotherapy in childhood. However, it is difficult to identify mechanisms that could explain these functional changes after such relatively low radiation doses. Furthermore, the observations are not supported by clinical follow-up of patients treated for childhood tumours, and the possibility that confounding factors are responsible for this observed association cannot be ruled out. The trauma of baldness and of having had treatment for tinea capitis may have caused some of the psychological problems. Also, at least in the Israeli cohort, parts of the brain received higher doses than the mean doses of 1-2 Gy.

37. *Summary.* The incidence and extent of neuropsychologic dysfunction among children given radiotherapy to the central nervous system are difficult to define. A variety of factors complicate the study of a possible association between effect and dose, including the underlying disease and associated clinical findings, other treatment modalities, the impact of illness on body image and school attendance, and perhaps also parental social class. Most studies contain a small number of patients of varying ages, who received a variety of treatment modalities and had varying follow-ups. Several studies, however, indicate that radiotherapy increases the risk of adverse neuropsychologic effects. Younger children, particularly those less than five years of age at time of treatment, are more severely affected. Clinical follow-ups of survivors of paediatric cancers have demonstrated a decline in IQ after doses to the brain of 18 Gy with conventional fractionation. In general, performance skills are more affected than verbal skills. It is difficult to distinguish the impact of radiotherapy from that of methotrexate. It is possible that intrathecal methotrexate administered prior to radiotherapy in children with acute leukaemia may be associated with less intellectual impairment than its administration during and after radiotherapy. Two epidemiological studies of children irradiated for tinea capitis of the scalp suggest adverse neuropsychologic effects after 1-2 Gy to the brain, with parts of the brain having received more than the mean doses in at least one of the studies. It is likely that these observations can be at least partially explained by confounding factors. The available data on neuropsychologic effects after radiotherapy in childhood do not allow an analysis of the possible effect of the fraction size on neuropsychologic functions, since most studies deal with conventional fractionation schedules.

### 3. Neuroendocrine effects

38. Growth depends on a delicate interplay of endocrine and metabolic factors, and secretion of growth hormone from the pituitary gland is necessary for normal growth [S31, W4]. Growth hormone deficiency is usually defined as an impaired response of serum growth hormone to various provocative tests. The commonly used tests include stimulation with arginine, ornithine, insulin-induced hypoglycemia, L-dopa, growth-hormone-releasing hormone or exercise. Neuroendocrine abnormalities have been observed in

children with tumours who received cranial radiotherapy. The abnormalities primarily involve the hypothalamus and/or the pituitary gland and range from impaired growth hormone response to complete panhypopituitarism [A8, A10, D8, D11, D12, D13, O6, P8, R11, S8, S9]. Radiation-induced damage to the hypothalamic-pituitary axis is the dominant cause of the observed abnormalities and the major site of radiation-induced damage causing hypothalamic-pituitary dysfunction appears to be the hypothalamus, although the pituitary gland itself may also be damaged. The most sensitive endocrinological target is the cells producing the growth hormone releasing hormone in the hypothalamus, and impaired growth hormone secretion is the most commonly finding [S10, S11]. Growth hormone is always the first and often the only anterior pituitary hormone to be affected by radiation damage, and panhypopituitarism occurs only after doses above 50 Gy. Radiotherapy appears to have an almost immediate suppressive effect on the hypothalamic-pituitary axis [D25]. Younger patients seem to be at greater risk for neuroendocrine damage [B8, D9, O7, S12]. Chemotherapy may contribute to growth impairment, but the effect is usually temporary when it is given alone. In this Section it is mainly the effects on growth hormone production that are discussed; the effects on thyroid-stimulating hormone are discussed in Section II.B, and the effects on gonadotropins, in Sections II.C and II.D.

39. Cranial radiotherapy and growth hormone deficiency are not the only causes of impaired growth in children treated for intracranial tumours. Other possible contributing factors to the impaired growth of these children include impaired spinal growth following spinal irradiation (see Section II.E), chemotherapy, poor nutrition and tumour relapse. The different results in various studies of growth hormone production in children receiving similar radiation doses to the central nervous system may be due to the use of different methods for studying growth hormone and/or to variation in time intervals between exposure and growth hormone determination. After 24 Gy of cranial radiotherapy, there are normal growth hormone responses to arginine but not to insulin stimulation, higher doses are associated with abnormal growth hormone responses to both [D14]. Since insulin-induced hypoglycemia is believed to affect receptors in the hypothalamus and arginine causing them to stimulate the pituitary gland, lower radiation doses affect the hypothalamus and higher doses also destroy pituicytes involved in growth hormone secretion [D1]. There is a correlation between the radiation dose to the hypothalamic-pituitary axis and the growth hormone response to stimulation, but a dose threshold below which no pituitary dysfunction follows has not yet been defined [C10, S10]. Although children treated for acute leukaemia may have biochemical growth hormone deficiency, they usually have a normal longitudinal growth pattern. Children with brain tumours, on the other hand, are more likely to have clinically significant endocrine dysfunction because they receive higher radiation doses. Growth hormone deficiency becomes apparent within a few months after the completion of radiotherapy for brain tumours, and after 30 Gy or more to the hypothalamus or pituitary gland using conventional fractionation, severe growth retardation has been observed in more than 50% of the survivors of childhood brain tumours [A9, C9, D1, D9, H5, O6, O8, P8, R12, R23, S4, S10, S11, S13, S14, S15, S16].

40. Absorbed doses to the brain of 30 Gy or more fractionated over several weeks result in significant long-term reduction in growth hormone secretion and impaired growth. Stunted growth has been most frequently observed among children irradiated for brain tumours at an age of 6-10 years, and it occurs in about 50% of those who have received >30 Gy to the hypothalamic-pituitary region fractionated over several weeks [A9, A11, D6, D9, O4, O6, O8, S11]. After a hypothalamic-pituitary dose of 37 Gy or more delivered in 2 Gy fractions five times per week, the 24-hour growth hormone profile is disturbed, with low overall secretion and few peaks of low amplitude but with a discernable diurnal rhythm [L6]. The normal diurnal rhythm of growth hormone secretion may be blunted but is not completely lost. There is a prompt rise in growth hormone after stimulation with growth-hormone-releasing hormone, and this response decreases with time after radiotherapy (Figure III). Patients with brain tumours who have received radiation doses of 50 Gy or more exhibit the most severe abnormalities, and multiple pituitary hormonal deficiencies may occur [B10, P8, R8, S17, S18].

41. Clayton [C12] assessed growth hormone secretion in 82 children who received cranial or craniospinal radiotherapy with up to 48 Gy (estimated by a schedule of 16 fractions over three weeks) to the hypothalamic-pituitary region. Stepwise multiple regression analysis showed that dose ($p < 0.01$) and time from radiotherapy ($p < 0.05$), but not age at therapy, had a significant influence on growth hormone response. Growth hormone deficiency developed more rapidly in those who received higher radiation doses. Shalet et al. [S14] noted a significant inverse correlation between dose and growth hormone response in 56 children with brain tumours or acute leukaemia and evaluated two years or more after radiotherapy. Thirty-seven patients (66%) had impaired growth hormone response, and all but one received >29 Gy to the hypothalamic-pituitary axis. Only five patients who received such a dose had normal growth hormone response, and four of them were older than 13 years at the time of treatment. In another study,

Shalet et al. [S11] found normal growth hormone response to hypoglycaemia in 14 children with brain tumours prior to treatment, and growth hormone deficiency occurred after a brain dose of 25-29 Gy in 7 patients within two years of radiotherapy. Of 13 children in whom growth could be assessed, 12 had poor growth.

42. Cranial irradiation with 24 Gy in 12-16 fractions over 2-2.5 weeks for acute leukaemia has also been associated with a measurable reduction in growth hormone response, although growth remains relatively unaffected at this dose [M14, M15, M16, M17, O9, P2, S19, S20]. Others have claimed whole-brain irradiation to be an important cause of short stature in survivors of childhood acute leukaemia [D15, K7, O7, P8, W5]. Some data suggest that a significant number of children less than 4 years of age with acute lymphoblastic leukaemia are short before the onset of therapy [B11]. Some data suggest that the effect of radiation on growth hormone secretion can be reduced by decreasing the dose per fraction. Shalet et al. [S19, S21] studied growth hormone levels and growth in 17 leukaemic children who received 25 Gy in 10 fractions over 2.5 weeks and in 9 children who received 24 Gy in 20 fractions over 4 weeks. Of the 17 children who received 25 Gy in 10 fractions, 14 had subnormal growth hormone response to insulin, compared to 1 of 9 patients who received 24 Gy in 20 fractions ($p < 0.002$). Arginine stimulation test was carried out in 16 children given 25 Gy and in 7 children receiving 24 Gy, and impaired response was seen in 6 and 1 patients, respectively. The greater impairment of growth hormone response to insulin hypoglycaemia following irradiation with 25 Gy in 10 fractions to the hypothalamic-pituitary axis suggests that the hypothalamus rather than the pituitary gland was the site of damage. There was no difference in mean standing height standard deviation score between the two irradiated groups, but they both differed significantly in this respect from normal children.

43. Griffin and Wadsworth [G2] compared the growth of 66 children with acute leukaemia to the growth of normal children matched for age and sex by calculation of the standard deviation score. All patients had cranial radiotherapy with 24-25 Gy in 15-20 fractions over 21-28 days, and 24 of them also had spinal radiotherapy with 10-24 Gy in 5-20 fractions over 7-28 days. The standard deviation score for height [calculated as $(\bar{x}-x)/SD$ where $\bar{x}$ = mean of the normal population; $x$ = the measurement; SD = standard deviation] of the patients fell significantly in the first year of treatment (Figure IV). This was specifically related to craniospinal radiotherapy but not to age or chemotherapy. Robison et al. [R13] studied 187 children (mean age: 5 years) with acute leukaemia who received either cranial irradiation with a median of 24 Gy (range: 14-28 Gy) in 1.2-2 Gy fractions five times a week plus intrathecal methotrexate; craniospinal irradiation alone (24 Gy); or craniospinal irradiation plus abdominal irradiation (12 Gy). At diagnosis no significant difference was observed in the height distribution compared to expected population standards. After treatment, an excess was observed in the proportion of patients in the lower percentiles in conjunction with a decrease in the proportion of patients in the highest percentiles. The only factor found to have a significant impact on attained height percentile was radiotherapy.

44. Children with acute leukaemia have a high frequency of biochemically abnormal growth hormone response to stimuli, but growth hormone deficiency is uncommon. Impaired response to stimuli, suggesting abnormality in the hypothalamic-pituitary axis, does not necessarily indicate absolute growth hormone deficiency. The presence of growth hormone abnormalities is not necessarily correlated with clinical findings of short stature [O7, S19]. Most of the adverse central nervous system sequelae in patients with acute leukaemia have been observed among those who received 24 Gy of cranial radiation and intrathecal chemotherapy.

45. The dose required to prevent leukaemic infiltration into the central nervous system can now be safely lowered from 24 Gy to 18 Gy [N1]. Few data exist on the effect on growth of radiation doses below 24 Gy. In some studies, growth impairment has been similar after 24 Gy and after 18 Gy [R13, S22, W5]. Others have observed that growth impairment in children with acute leukaemia has been less frequent and generally milder below 24 Gy [B12, C11, C23, G2, S19, V1, V2]. Cicognani et al. [C23] found that children who had received 18 Gy in 10 fractions had complete growth recovery and normal growth hormone responses to pharmacological tests. Children who had received 24 Gy in 12 fractions showed significantly lower standard deviation scores for height than at diagnosis and had impaired growth hormone response.

46. After a single whole-body dose of 10 Gy, severe growth retardation appear in most children [D2, S23]. Many if not most of these children also received cranial radiotherapy prior to the whole-body irradiation. The majority of paediatric patients treated with whole-body irradiation have decreased growth rates on longitudinal growth velocity curves, and growth hormone levels have been subnormal in about one third of the patients [D14, S24, S25]. Sanders [S24] reported subnormal levels of growth hormone in 87% of children who received both cranial radiotherapy and whole-body irradiation, compared to 42% of those who received whole-body irradiation only. Deeg et al. [D2] observed normal growth velocity curves in

transplant-treated children who did not receive whole-body irradiation, whereas irradiated children had impaired growth and decreased growth velocity. Growth hormone levels were subnormal in about one third of the irradiated patients.

47. Some data suggest that fractionation will reduce the adverse effects of whole-body irradiation. Barrett et al. [B13] reported growth hormone deficiency in 6 of 8 children after a single whole-body dose of 10 Gy and in 3 of 8 children who had a fractionated whole-body dose of 12-14 Gy in 6 fractions given twice daily for 3 days. Sanders et al. [S23] evaluated growth in 144 patients following marrow transplantation for childhood leukaemia at a median age of 10 years. All children had received multiagent chemotherapy, and 55 had received a median of 24 Gy (range: 18-29 Gy) to the central nervous system, 5 of whom had also received a median of 12 Gy to the spine. A whole-body dose of 9.2-10 Gy in a single exposure was given to 79 patients, and 63 patients had a fractionated regimen of 2.0-2.3 Gy per day for 6-7 days for cumulative doses of 12-16 Gy. Growth hormone levels were measured in 43 patients 1-8 years after transplant, and growth hormone deficiency was present in 27 subjects (63%). Of these, 21 patients had received pre-transplant cranial irradiation. By three or more years after transplant, boys who received single whole-body exposure were 8.0 ± 2.3 cm shorter than boys who received fractionated whole-body exposure ($p < 0.03$). Among boys who had not received cranial irradiation, those given single whole-body exposure were 15.2 ± 3.2 cm shorter than those given fractionated whole-body exposure ($p < 0.04$). Girls showed similar trends that were not statistically significant.

48. Hiroshima survivors exposed to >1 Gy at ages 0-19 years were shorter and weighed less than the overall population. Those who were less than 6 years old and who also received >1 Gy [B14] at the time of the bombings were shorter still, on average. The analyses were based on the T65 dosimetry. Exposure to high radiation doses markedly reduced mean height for those who were very young at the time of the bombings, but this effect diminished with increasing age. Average height for those aged 0-5 years at the time of the bombings was significantly smaller for the >1.0 Gy dose group than for the groups 0 Gy (not in city), 0-0.09 Gy and 0.10-0.99 Gy for both males and females: smaller by 4.4 cm or more for males and by 2.5 cm or more for females (Table 5). For those aged 6-11 years at the time of the bombings, smaller heights were again found for the >1 Gy dose group, although to a lesser degree. For subjects aged 12-17 years at the time of the bombings, no apparent differences between the four dose groups were found. When the high dose group was further divided into 1.00-2.49 Gy and ≥2.50 Gy groups, the mean heights were less for both males and females aged 0-5 years at the time of the bombings in the ≥2.50 Gy group. The difference from the 1.00-2.49 Gy group was statistically significant for males. Average heights of females aged 6-11 years at the time of the bombings and for males and females aged 12-17 years at the time of the bombings were approximately the same for the two dose groups (Table 6). In Nagasaki, the effect of dose on height was not statistically significant, although the mean height of Nagasaki females aged 0-5 years at the time of the bombings was least for those who were exposed to >1 Gy (Table 5). Among males, those exposed to 0-0.09 Gy at ages 0-5 years at the time of the bombings showed the smallest mean height. For both the 6-11 year and 12-17 year groups, however, the mean height for boys in the high dose exposure group was the smallest. A reanalysis based on the same T65 dosimetry was undertaken of the relationship between attained adult height and radiation dose of 628 survivors of the atomic bombings in Hiroshima and Nagasaki aged less than 10 years at the time of the bombings [I4]. Average height tended to be lower as exposure increased, except among Nagasaki males (Table 7). Two-way analysis of variance of height in relation to sex and dose by city showed that height was significantly different by sex and total kerma in Hiroshima. In Nagasaki, however, it was significantly different by sex but not kerma total dose. Growth and development of stature depends on nutrition, socio-economic conditions, the quality and quantity of radiation received and, possibly, other factors. Contrary to the report by Belsky and Blot [B14], the results of Ishimaru et al. [I4] suggested that diminished stature was not significantly related to age at the time of the bombings for individuals exposed before the adolescent growth spurt, something which was probably due to the small sample size. The observed difference between the two cities may change with new analyses based on the new DS86 dosimetry.

49. Children on the Marshall Islands exposed to radioactive fallout in 1954 were also found to have a significant reduction in height, which was probably mainly due to radiation-induced hypothyroidism [R14, S26] (see Section II.B).

50. Children with radiation-induced growth hormone deficiency can now be treated with growth hormone, although there are as yet no long-term studies of the effects of such a therapy in a large number of children. Some data suggest a significant growth response to therapy in children who received cranial irradiation alone, whereas the response in patients receiving cranio-spinal irradiation has been less satisfactory [G3, S20].

51. *Summary.* Irradiation of the central nervous system may produce damage to the hypothalamic-pituitary axis, resulting most commonly in impaired

growth hormone secretion. The hypothalamic cells producing the growth-hormone-releasing hormone are the most sensitive endocrinological target. Growth hormone deficiency can be expected in approximately 75% of children treated for brain tumours, and a growth velocity or height below the 10th percentile can be expected in 70%. The growth hormone deficiency is permanent. Patients with acute leukaemia have in general received lower doses to the central nervous system but growth hormone secretion is still affected. After 25-30 Gy, the growth hormone response to insulin-induced hypoglycaemia is impaired within two years of irradiation. After 24 Gy in 12-16 fractions, there is also a measurable reduction in growth hormone response to stimuli. Growth has been less affected after 24 Gy than after higher radiation doses in the brain, suggesting that the normal physiologic requirements of growth hormone secretion have been met. No effect on growth hormone secretion has been observed below 18 Gy. A 10 Gy whole-body dose in a single fraction results in severe growth retardation in the majority of children, who generally have been pretreated with chemotherapy and cranial radiotherapy. Fractionation appears to be of importance for the effect on growth hormone secretion and growth, and increasing fraction size will result in a higher proportion of patients with subnormal growth hormone response. Growth impairment is seen more often after a single-dose whole-body irradiation with 10 Gy than after a fractionated regimen of 12-16 Gy in 2 Gy fractions over a week. It is not possible to define the lowest dose capable of impairing growth hormone secretion, since available data are obtained from small studies with varying ages at exposure and lengths of follow-up, as well as different methods for assessing the growth hormone level. Such a dose appears to be lower than 18 Gy from fractionated exposure. Growth has been affected in the survivors of the atomic bombings in Japan at acute doses of >1 Gy, especially among children less than 6 years of age. This effect may be due to a combination of brain damage, damage to the spine, nutritional factors etc.

## B. THYROID GLAND

52. Hypothyroidism is the most common late deterministic effect of the thyroid gland following exposure to ionizing radiation. Thyroid nodularity is considered to be a stochastic phenomenon and is therefore not discussed in this Section. Clinical damage to the pituitary and thyroid glands is usually manifested several years after exposure and is preceded by a subclinical phase [F4]. Direct damage to the thyroid gland by radiation can cause primary hypothyroidism, whereas damage to the hypothalamic-pituitary axis may produce secondary hypothyroidism. Primary hypothyroidism has been demonstrated in 40%-90% of patients with paediatric tumours given 15-70 Gy to the thyroid gland and followed for up to six years [B10, C5, C13, D16, F4, G4, K8, O8, P9, S9, S23, S27, S28]. The onset of hypothyroidism may be several months to years following the radiotherapy. Administration of oral thyroxine during radiotherapy does not appear to prevent later thyroid hypofunction [B15]. Radiotherapy alone and with chemotherapy have been associated with similar high incidences of hypothyroidism. Patients treated with chemotherapy only have generally not had any significant thyroid hypofunction, although transient thyroid dysfunction has been reported [G4, G5, H7, L7, S27, S28, S29].

53. The incidence of overt [low serum T4 and elevated thyroid-stimulating hormone (TSH)] and compensated (normal serum T4 and elevated TSH) hypothyroidism varies with the radiation dose in the thyroid gland, the length of follow-up and the way in which the thyroid function was determined. Thyroid surgery, iodine-containing contrast material and age of the patient at the time of radiotherapy may contribute to the development of hypothyroidism. The effect of age at the time of radiotherapy on the development of hypothyroidism is a matter of controversy. In one study, 48% of patients with Hodgkin's disease who were younger than 20 years of age at the time of treatment had elevated TSH levels compared to 33% of older patients [G4]. Green et al. [G5], observed that 7 of 15 children with Hodgkin's disease and irradiated at the age of less than 13 years developed hypothyroidism, compared to 3 of 12 among those who had been older than 13 years. In a study by Tarbell et al. [T9] of patients irradiated for Hodgkin's disease, the 15-year actuarial risk for hypothyroidism was 64% among patients aged 16 years or less, as compared to 29% among those older than 16 years. Others have not identified age as a contributory factor [D16, K8, N2, S28, S29]. The possibility that the thyroid is more sensitive in childhood is also supported by the high incidence of increased TSH levels in children irradiated for Hodgkin's disease [D16, S27].

54. Elevated TSH levels have been observed in children who received radiotherapy for brain tumours after 25-30 Gy to the hypothalamic-pituitary axis or 24 Gy to the thyroid gland [C26, D6, H6, O6, S15]. Various studies show that hypothyroidism is dose-dependent. In a study by Glatstein et al. [G4], no patient had an elevated TSH level after 15 Gy to the thyroid, as compared to 44% of the patients receiving 40 Gy or more. Kaplan et al. [K8] found elevated TSH levels in 15% of patients who received <30 Gy and in 68% of those who received higher doses. Logistic regression analysis showed that both higher radiation dose (≥30 Gy) and lymphangiography increased the risk of having an elevated serum TSH level. Constine et al. [C15] measured thyroid function

in 119 children irradiated for Hodgkin's disease. Radiotherapy was delivered over 4-5 weeks: 24 children received a neck dose of 26 Gy or less (mean: 22 Gy) and 95 received >26 Gy (mean: 44 Gy). More than 75% of the children receiving >26 Gy had elevated TSH levels, compared to 17% of those treated with lower doses. A weak correlation with age ($p < 0.05$) was found, and the doubling dose for the mean peak TSH value was 11 Gy (Figure V).

55. Most of the experience in radiation-related late effects in the thyroid has been gained from the treatment of Hodgkin's disease. Compensated hypothyroidism occurs in up to 75% of the treated children, and uncompensated hypothyroidism has been observed in less than 30% of the children [C14, D16, D17, F4, F5, G4, G5, M18, S17, S27, S28, S29, T8]. Patients irradiated for lymphomas or head and neck cancers have generally received 24-60 Gy fractionated over several weeks. In some studies lymphangiography prior to radiotherapy has been shown to increase the risk of hypothyroidism [G4, G5, K8, S27, S28, S29]; in others, it has not [C14, G5, N2, T8]. Lymphangiography may increase thyroid damage from subsequent irradiation for the following reason: the iodine released from the contrast material could inhibit thyroid hormone synthesis and secretion within a few days, thereby causing increased thyrotropin secretion and consequent stimulation of thyroid cells at the time of irradiation [K8]. An expanded extrathyroidal pool of iodine may increase susceptibility to hypothyroidism in irradiated subjects.

56. Lower radiation doses may also increase the risk of hypothyroidism. In children with acute leukaemia receiving cranial irradiation with 18 Gy, the thyroid dose is 3%-8% of the cranial dose [R15]. Hypothyroidism has been observed in up to 20% of long-term survivors of childhood acute leukaemia after 18-25 Gy of cranial or craniospinal radiotherapy with conventional fractionation [N3, R16, R18, S12]; others have failed to observe such an effect after cranial doses of 8.5-24 Gy in 2 Gy fractions [O7, V1]. Mean thyroid doses of 4-10 Gy in infancy or childhood from fractionated radiotherapy for benign disease has not been associated with clinical hypothyroidism, although follow-up lasted as long as 25 years [H8, R19]. In contrast, hypothyroidism has been reported in 7 of 9 Russian children after radiotherapy for skin angioma with thyroid doses of >1.1 Gy [T15].

57. Thyroid hypofunction can occur after whole-body irradiation. Children who received a regimen of chemotherapy in preparation for a transplant have an incidence of thyroid dysfunction that is not greater than normally observed among non-transplant children [S24, S25]. Radiotherapy appears to be the major, if not the sole, cause of subsequent thyroid hypofunction in these patients. In terms of its effects on thyroid hypofunction [T17], single-dose radiotherapy has been claimed to be equivalent to a total radiation dose 4-5 times larger when it is delivered in conventional fractions. Sanders et al. [S23, S24] studied 142 patients 1-17 years old after bone marrow transplantation to treat haematological malignancies. All patients had received multiagent chemotherapy, 55 had been pretreated with 24 Gy fractionated cranial radiotherapy and 12 had received 12 Gy spinal irradiation. Whole-body irradiation was delivered as a single dose of 9.2-10 Gy ($n = 79$) or 2-2.2 Gy daily for 6-7 days to 12.0-15.8 Gy ($n = 63$). Among children who received 10 Gy single whole-body exposure, 56% had compensated hypothyroidism and 13% had overt hypothyroidism, and the figures for children who received fractionated whole-body irradiation were 21% and 3%, respectively. These differences most likely reflect the shorter observation times after fractionated exposure (median nine years versus five years). Longer follow-up is needed to determine whether there is any real difference between the two types of whole-body exposure. Katsanis et al. [K9] evaluated thyroid function in 80 patients after bone marrow transplantation for aplastic anaemia or acute leukaemia. Median age at the time of transplantation was 10 years (range: 2-21 years). Patients with aplastic anaemia received high-dose chemotherapy and total lymphoid irradiation with a single dose of 7.5 Gy, and leukaemia patients received either whole-body irradiation as a single fraction of 7.5-8.5 Gy ($n = 33$) or fractionated whole-body irradiation with 13.2 Gy ($n = 20$) in 1.7 Gy fractions twice daily for four days. Of 27 patients with aplastic anaemia plus total lymphoid irradiation, 11 showed thyroid hypofunction, as compared with 9 of 53 patients with acute leukaemia plus whole-body irradiation. The five-year actuarial risk estimate of hypothyroidism after total lymphoid irradiation was 42% (95% CI: 23%-61%), which was significantly different from 10% after fractionated whole-body irradiation (95% CI: 0%-23%) ($p < 0.05$), but not different from 21% after single-dose whole-body irradiation (95% CI: 7%-35%).

58. The thyroid gland has the capacity to actively concentrate iodine, and radioiodine can therefore deliver considerable radiation doses to the gland, a fact that has been and is still used in diagnostic and therapeutic medical procedures [D18, G6]. The most commonly used radioiodine is $^{131}I$, which has a half-life of eight days. Most data on hypothyroidism after $^{131}I$ exposure emanate from studies on patients with hyperthyroidism, and their experience may not be directly transferable to a normal euthyroid population. In patients with hyperthyroidism, hypothyroidism is common even after surgery or treatment with antithyroid drugs [B17, H10]. The thyroid uptake of $^{131}I$ is higher in hyperthyroid patients, but the turnover of

the nuclide is more rapid. It may therefore be possible to approximate the experience of hyperthyroid patients to that of euthyroid subjects [M19, M20, N4]. In adult hyperthyroid patients treated with a single dose of $^{131}$I, the cumulative probability of hypothyroidism is related to the $^{131}$I activity administered per unit thyroid weight [B16]. Holm et al. [H9] observed an annual hypothyroidism of 3% the first 24 years after $^{131}$I therapy for hyperthyroidism. There are only very limited data on the effects of thyroid absorbed doses from $^{131}$I of <25 Gy and the effects in children. NCRP Report No. 55 [N4] cited unpublished data from Hamilton and Tompkins, who observed that 8 of 443 subjects (2%) less than 16 years old and judged to have normal thyroids became hypothyroid after diagnostic $^{131}$I tests. The incidence of hypothyroidism was 0% per year in 146 subjects who received <0.3 Gy in the thyroid, 0.15% per year in 146 subjects who received 0.3-0.8 Gy and 0.23% per year in 151 subjects after thyroid doses of >0.8 Gy. A linear model with a threshold was postulated for hypothyroidism; owing to the large functional capacity of the thyroid gland, a large number of cells would have to be affected to result in hypothyroidism. Hayek et al. [H11] observed hypothyroidism in 8 of 30 (26%) patients between the ages of 8 and 18 years who received $^{131}$I therapy for hyperthyroidism. The mean amount of $^{131}$I administered was 240 MBq, and the mean follow-up was nine years. Freitas et al. [F6] found a 92% prevalence of hypothyroidism in 51 patients aged 6-18 years after $^{131}$I therapy for hyperthyroidism (mean $^{131}$I activity, 520 MBq).

59. In 1954, following detonation of a megatonne nuclear device at Bikini, 250 inhabitants of the Rongelap, Ailingnae and Utirik atolls of the Marshall Islands were exposed to radioactive fallout [C16, L8, R14]. This consisted of whole-body gamma-irradiation, beta-irradiation of the skin from fallout deposited on the skin, and internal absorption of radionuclides from the ingestion of contaminated food and water. The most serious internal exposure was that to the thyroid gland, from radioiodines in the fallout. The estimated thyroid dose varied from 0.3 to 3.4 Gy among those aged 18 years or more to 0.6-20 Gy among those less than 10 years of age. Many uncertainties were involved in the dose calculations, and particularly in the thyroid dosimetry. The most widespread late effects of fallout exposure among the Marshallese have been related to radiation injury to the thyroid gland. The growth status of children exposed to fallout radiation has been studied in 67 unexposed and 38 exposed children, 4 children exposed *in utero*, 39 children born to exposed parents and 53 children born to unexposed parents [S26]. Retardation in both statural growth and skeletal maturation has been observed among exposed boys, as compared with unexposed children. The retardation was noted among boys who were under 5 years of age when exposed to the fallout, being most prominent among those aged 12-18 months at the time of exposure. No significant differences were noted in the growth patterns between exposed and unexposed girls and between children born to exposed or unexposed parents.

60. The incidence of subclinical hypothyroidism was 31% among children less than 10 years of age at exposure after an estimated thyroid dose of >2 Gy. No case of hypothyroidism occurred in this age group at lower doses (Table 8). Among subjects 10 years or older, one case (1%) of hypothyroidism was observed at an estimated thyroid dose of <1 Gy, one case (8%) at 1-2 Gy and four cases (9%) at doses higher than 2 Gy. Only two of the subjects exposed at less than 10 years of age had clinical hypothyroidism. The incidence of hypothyroidism began to increase approximately one decade after exposure. A thorough re-evaluation of the absorbed dose in the thyroid was done by Lessard et al. [L9]. The recalculated cumulative external doses of gamma rays were close to the initial estimates, but doses from internally deposited radionuclides were much higher. Most of the thyroid dose resulted from short-lived radionuclides. The re-evaluation of the thyroid absorbed dose makes the observed results compatible with those of other studies with similar doses [R20].

61. Rallison et al. [R21, R22] observed two cases of hypothyroidism in 1,378 children exposed to $^{131}$I fallout from nuclear weapons tests, compared to four cases in 3,801 non-irradiated control subjects. The follow-up time was, on average, 16 years, and the mean thyroid dose was estimated to be <0.5 Gy. The difference in the incidence of hypothyroidism between the two groups was not statistically significant. Clinical examinations were performed in 1990, and levels of free T4 and thyroid stimulating hormone were measured in children living in Russia, Belarus and Ukraine at the time of the nuclear plant accident in Chernobyl in 1986 and in children born in 1989 [I8]. There was no evidence that thyroid function had been affected in a way that could be detected either clinically or by laboratory testing at that time.

62. Thyroid disorders were studied 30 years after exposure in 978 individuals under 20 years of age at the time of the bombings in Hiroshima and Nagasaki [M21, M22]. The estimated doses from the atomic bomb fallout radiation were based on T65 dosimetry. There were 200 males and 277 females in the >1.0 Gy exposed group and 219 males and 282 females in the unexposed (0 Gy) group. Of these, 128 were aged 0-9 years and 349 were 10-19 years at the time of the bombings in the >1.0 Gy group; and 139 subjects were aged 0-9 years and 362 were 10-19 years at the time of the bombings in the unexposed group. There were

no significant differences in mean serum TSH levels or mean serum thyroglobulin levels between the 0 Gy (unexposed) group and the >1 Gy (exposed) group. In a recent analysis [N7] of 2,774 subjects of the Nagasaki Adult Health Study cohort, the prevalence of hypothyroidism was 5% in exposed subjects and 2% in controls. Inoue et al. [I7] studied nearly 2,600 individuals from the same cohort and observed hypothyroidism in 3% of the subjects. The fitted relative risk increased from 1 for those less than 5 years at the time of the bombings to 3 for those 30 years at the time of the bombings.

63. *Summary.* Thyroid dysfunction may result from irradiation of the thyroid gland or the hypothalamic-pituitary axis. A substantial proportion of patients receiving radiotherapy for various paediatric tumours have impaired thyroid function. The incidence of hypothyroidism varies with the definition used and is highest when elevated TSH levels are used to define the impairment. Young children seem to be more sensitive to radiation-induced hypothyroidism. Various studies show that hypothyroidism is dose-dependent. The prevalence of hypothyroidism is increased in leukaemic children who have received cranial radiotherapy of 18-24 Gy over 2-2.5 weeks. The thyroid doses in these cases have been calculated to be 3%-8% of the brain dose, i.e. 1-2 Gy. However, the children also received associated chemotherapy, which may affect the risk for hypothyroidism. No epidemiologic study has demonstrated hypothyroidism in children after a thyroid dose from external irradiation <1 Gy. There is limited evidence that dose rate may be of importance and that the risk of hypothyroidism is reduced when fraction size is reduced. There are insufficient data on the effects of $^{131}I$ to determine a possible threshold dose for the induction of hypothyroidism.

## C. OVARY

64. The ovary is a highly radiosensitive organ, and single doses of 0.6-4 Gy have caused temporary sterility in adults, with higher doses required to produce the same effect when fractionated. Permanent sterility results from 2.5-10 Gy in a single dose and from 6 Gy with protracted exposure [F1, I1, U3]. The radiosensitivity of the ovary depends on the degree of maturity, and the threshold for permanent sterility decreases with age, although the age-related differences are hard to estimate [A12, F1]. The fact that the ovary of a young woman is more resistant is explained by the reduction, over time, in the fixed pool of oocytes, since these cells are not replaced. The radiation dose required to destroy all the oocytes is therefore larger in younger than in older women. Ovarian dysfunction has been observed in more than 50% of adolescents and young women after doses of 2.5-4.0 Gy. Recovery has been age-related. After 4 Gy, permanent amenorrhea and infertility have occurred in approximately one third of younger women and in all women older than 40 years of age [A12, H12].

65. The most common cause of ovarian dysfunction in patients treated for paediatric tumours is direct damage to the gonads by radiation and/or cytotoxic agents. The observed ovarian effects have basically been fibrosis and follicle destruction with elevated levels of luteinizing hormone and follicle stimulating hormone. Irradiation of the hypothalamic-pituitary area can also result in gonadotropin deficiency or hyperprolactinaemia, which may impair subsequent reproductive function [A13, R23]. Quiescent ovaries have been found in children after radiotherapy with 20-30 Gy to the abdomen over 21-30 days, either alone or combined with chemotherapy [H13]. Chemotherapy used for a short time has been reported to be without effect on the small follicles, whereas prolonged treatment destroys them [M23].

66. Pelvic or abdominal irradiation has been associated with ovarian failure, resulting in elevated levels of follicle-stimulating hormone, amenorrhea and failure to develop secondary sexual characteristics [G7, O9, S32, S33, W6]. In a study by Wallace et al. [W6], ovarian failure occurred before 16 years of age in 19 patients irradiated in childhood for abdominal tumours with 30 Gy in 16-26 fractions over 21-38 days. An upper limit for the LD50 of the human oocyte was estimated at 4 Gy. Stillman et al. [S33] observed signs of ovarian failure in 12% of 182 long-term survivors of childhood cancer. Of 25 patients (68%) with both ovaries within the treatment fields (mean ovarian dose: 32 Gy), 17 showed ovarian failure, as compared with 5 of 35 patients (14%) whose ovaries were on the border of the treatment field (mean: 2.9 Gy), none of 34 patients with one or both ovaries outside the treatment field (mean: 0.5 Gy) and none of 88 patients receiving no radiation to the ovaries. The likelihood of ovarian failure in patients with both ovaries in the field was 19.7 (95% CI: 5.3-72.8), higher than those for other irradiated patients. Subsequent fertility has been observed in prepubertal girls after pelvic doses of 10-30 Gy, despite follicular depletion and elevated follicle-stimulating hormone levels [H13, L11, S32].

67. Horning et al. [H12] studied 103 women aged 13-38 years (median age: 19 years) with Hodgkin's disease treated by chemotherapy alone (n = 34), total-lymphoid irradiation alone (n = 19) or irradiation plus chemotherapy (n = 50). The pelvic dose was 30-40 Gy, delivered with conventional fractionation. Menses were present in 94% after total-lymphoid irradiation alone, 85% after chemotherapy alone and in 48% after total-lymphoid irradiation plus chemo-

therapy, of which 47%, 56% and 20%, respectively, were regular. Chemotherapy was associated with the highest and combination therapy with the lowest probability of regular menses. The probability of regular menses decreased with age at treatment (Figure VI). When age at treatment, interval after completion of treatment, stage of disease, number of cycles of chemotherapy and pelvic radiation dose were included in a multivariate analysis to determine factors predicting regular menses, only age was significant for any of the three treatment modalities.

68. Irradiation of the central nervous system and chemotherapy can destroy gonadal function by causing damage to the hypothalamus or direct damage to the gonads themselves [B18]. Various hormonal effects have been observed after cranial or craniospinal radiotherapy with 25-50 Gy fractionated over 3-4 weeks, e.g. elevated, normal or reduced levels of gonadotropins, secondary amenorrhea and lack of pubertal progression [A13, B10, C17, L10, R23, S15]. Leiper et al. [L12] observed early puberty in 10% of 233 children given cranial radiotherapy with 18-24 Gy in 10-15 fractions over 2-3 weeks for acute leukaemia at a mean age of 4 years. Three girls had precocious puberty, i.e. signs of sexual maturation occurring before 8 years. Early onset of menarche after cranial radiotherapy has also been observed by others [B19, M15, Q1, R23, S15]. Others have reported normal levels of gonadotropins and oestrogens after 24 Gy cranial radiotherapy in 2 Gy fractions over 2.5 weeks [D5, O7, V1].

69. Hamre et al. [H14] assessed gonadal function in 163 children treated for acute leukaemia at an average age of 6 years and who were randomized to receive 18 or 24 Gy to one of three fields: cranial, craniospinal or craniospinal plus 12 Gy abdominal, including the ovaries or testes. Gonadal evaluation 4 years later showed elevated levels of follicle-stimulating hormone and/or luteinizing hormone in 36% of the patients. There was an association between elevated gonadotropins and the radiotherapy field: 9% of patients who had cranial fields had elevated levels, as compared to 49% for craniospinal fields and 93% for craniospinal plus abdominal fields ($p < 0.001$). Girls receiving 24 Gy had a relative risk of 14 for elevated follicle-stimulating hormone and 8.7 for elevated luteinizing hormone compared with girls receiving 18 Gy. Craniospinal plus abdominal radiotherapy was significantly associated with abnormal gonadotropin levels and lack of pubertal development.

70. Patients who receive only chemotherapy prior to bone marrow transplantation have normal pubertal development and normal levels of gonadotropins and sex hormones. The majority of children receiving 10 Gy single whole-body exposure experience a delayed onset of puberty, and their gonadotropin levels reflect primary gonadal failure. Nearly half of children receiving fractionated whole-body irradiation have normal pubertal development and normal gonadotropin levels [B13, D2, S24, S34]. Ovarian failure appears to develop in almost all females of postpubertal age after whole-body irradiation with 10-12 Gy. Normal gonadotropin levels have been observed in the majority of girls who were prepubertal at the time of transplantation.

71. Sanders et al. [S23] studied ovarian function in 142 children (52 girls) treated with bone marrow transplantation at the median age of 10 years. All patients had received chemotherapy, and one third of the patients also had received radiotherapy to the central nervous system. Patients were given chemotherapy and whole-body irradiation, as a single dose of 9.2-10 Gy (n = 79) or as fractionated doses of 2-2.3 Gy daily for 6-7 days to a cumulative dose of 12-15.8 Gy (n = 63). Of 35 girls who were prepubertal at transplant, 10 had delayed development of secondary sexual characteristics at evaluation 4 years later. Gonadotropin and oestradiol levels were determined for 11 of 16 girls older than 12 years of age, and 7 had elevated levels of follicle-stimulating hormone, low levels of oestradiol and delayed onset of puberty. Gonadal failure occurred in nearly all who were postpubertal at transplant, with amenorrhea and elevated levels of luteinizing hormone and follicle-stimulating hormone. It was not possible to determine how many of these endocrine abnormalities occurred as a result of treatment administered prior to transplantation. No information was provided on the effect of fractionation on gonadal function.

72. Sarkar et al. [S35] studied fertility in 33 subjects after $^{131}I$ therapy for thyroid cancer in childhood or adolescence. They received a mean $^{131}I$ amount of 7,250 MBq, with a range of 2,960-25,560 MBq, and the estimated cumulative gonadal dose ranged from 0.08 to 0.69 Gy. The incidence of infertility and miscarriage did not differ significantly from that in the general population.

73. *Summary.* The effects of radiation on the ovary are age- and dose-dependent. The ovary of young women is less sensitive to radiation-induced deterministic effects because of their higher number of oocytes, although it is difficult to define the magnitude of these differences. A variety of factors complicate the study of a possible association between radiation dose and the effects on the ovary, including the underlying disease for which treatment was given. Unfortunately, most studies have been performed on a limited number of patients of varying ages at exposure, who received a variety of treatment modalities and had varying lengths of follow-up. The available data therefore do not allow an analysis of the dose-effect

patterns to define a critical dose for different gonadal parameters, nor can the impact of the fraction size be determined, since most studies have used fractionation schedules with about 2 Gy per day. An ovarian dose of 20 Gy or more causes microscopically evident damage and results in increased levels of gonadotropins and follicle-stimulating hormone. Amenorrhea has been observed in more than 10% of patients exposed in childhood with ovarian doses of 0.5 Gy on average and in two thirds of girls who received 3 Gy, on average, to both ovaries. Infertility occurs in approximately one third of girls receiving 4 Gy, as compared to almost all women over 40 years of age. The radiation dose required to ablate ovarian function seems to be around 20 Gy for girls, and the greater number of oocytes explains the higher doses needed for castration. Amenorrhea and the failure to develop secondary sexual characteristics have been documented in prepubertal girls following 10 Gy of whole-body irradiation, and ovarian failure has been seen in all pubertal women, of whom 50% had menopausal symptoms. Cranial radiotherapy may disturb sexual maturation by damaging the hypothalamus or the pituitary gland. Evidence of hypogonadism and of precocious puberty has been reported. Since chemotherapy may also cause ovarian dysfunction, the age of the patient, the amount of chemotherapy and the combined use of radiotherapy are all important factors in assessing ovarian injury.

## D. TESTIS

74. The germ cells of the testis are the cells of the male reproductive system that are the most sensitive to exposure to ionizing radiation. Their depletion results in impaired fertility, the degree of which is dose-dependent. In adults, few stem cells survive a dose of 3-5 Gy, and sterility may be permanent. The lowest single acute dose that will impair fertility in adults is of the order of 0.15 Gy [R24]. Fractionated treatment may have more effect than single doses, e.g. 20 doses of 0.25 Gy each cause more rapid depletion and a slower recovery than a single dose of 5 Gy [L13, U3]. Blot et al. [B40] observed no clear evidence of sterility in 14 men exposed to the atomic bombings *in utero* with maternal doses ranging from 1 Gy to more than 6 Gy, nor among 66 men exposed to similar doses before 15 years of age. Data suggest that fractionated irradiation of 20 Gy is required to produce an incidence of more than 50% sterilization for more than five years [L14]. As little as 0.2 Gy can cause germinal epithelial damage with decreased sperm count and an elevated level of follicle-stimulating hormone [R24]. The damaged epithelium may recover with time, which related to the total dose received. A threshold dose required to damage the germinal epithelium in childhood has not been established, and doses as low as 0.1 Gy have been reported to cause temporary sterility, although >2 Gy and possibly about 6 Gy are needed to produce permanent aspermia [I1, U3]. Assessments of the effects of conventionally fractionated irradiation on testicular function indicate that gonadal function is compromised at doses as low as 0.5 Gy and that a cumulative dose of 2 Gy results in testicular dysfunction persisting at least three years [S36, S37]. There are no substantive studies of the effects of low-dose radiation on testicular function in boys, and it is generally not possible to distinguish between gonadal toxicity from chemotherapy and from radiotherapy.

75. The ability of the Leydig cells to produce testosterone appears to be appreciably reduced after testicular irradiation with high doses (24 Gy), resulting in androgen deficiency, testicular atrophy and clinical hypogonadism with elevated levels of follicle-stimulating hormone in the majority of boys [B20, L15, S20, S40]. The prepubertal boy appears more sensitive to radiation-induced Leydig cell damage than the adult male after testicular radiotherapy with 27-30 Gy in 20-28 fractions over 27-38 days [S38]. Normal Leydig cell function has been observed after testicular irradiation for childhood leukaemia with 12-15 Gy in 2 Gy fractions, although high gonadotropin levels suggest subclinical Leydig cell damage [C19]. According to Shalet [S20, S39], a fractionated testicular dose of <10 Gy in 20 fractions over 4 weeks does not appear to impair Leydig cell function in boys, whereas 24 Gy over 2.5-3 weeks causes Leydig cell failure.

76. The testicular germinal epithelium is more susceptible than Leydig cells to chemotherapy-induced damage and appears to be more sensitive to moderate doses of alkylating agents after puberty than before [S36]. In contrast to that given to prepubertal boys, chemotherapy given during puberty may result in injury to both Leydig cells and the seminiferous epithelium and may thus have profound effects on both endocrine function and germ cell production [A13, C18]. The use of alkylating agents has been associated with testicular dysfunction that may be related to age and the total dose of the agent used. Recovery of spermatogenesis is variable. Others have found that chemotherapy for acute leukaemia may be compatible with normal gonadal development [B21, B22].

77. Of 10 men who had radiotherapy for Wilms' tumour in childhood with estimated testicular doses of 2.7-9.8 Gy, eight had oligo- or azoospermia and seven had elevated follicle-stimulating hormone levels [S39]. Only one man had evidence of Leydig cell dysfunction. Shalet et al. [S39] also studied a second group of eight prepubertal males who had received testicular doses of 1-30 Gy. Despite these substantial doses, which are higher than those required to cause tubular

in the postpubertal male, plasma testosterone and gonadotropin levels were normal. Only one boy had an elevated follicle-stimulating hormone level. The radiation-induced damage to the germinal epithelium thus resulted in raised levels of follicle-stimulating hormone after puberty but not before. In respect of pelvic radiotherapy and/or chemotherapy for Hodgkin's disease in childhood, Green et al. [G7] did not observe any difference in gonadal function between nine boys and male adolescents who received a gonadal dose of 1 Gy and seven patients who received only chemotherapy. Six and five men, respectively, had elevated levels of follicle-stimulating hormone up to eight years after completion of treatment.

78. Abnormal puberty and gonadotropin deficiency have been observed in about 10% of children irradiated to the hypothalamic-pituitary region with 25-50 Gy over 3-4 weeks [L10, R23]. After cranial radiotherapy for leukaemia in childhood, varying results have been observed. Quigley et al. [Q1] found evidence of germ-cell damage in 25 boys who received chemotherapy and 24 Gy in 15 fractions over three weeks. Germ-cell damage was confirmed by the absence of germ cells in testicular biopsy specimens and by the small size of the testes in all boys. Boys reached puberty at a mean age of 12 years. Plasma sex steroids were normal, but the level of luteinizing hormone after stimulation with gonadotropin-releasing hormone was elevated in pubertal children, suggesting compensation for decreased gonadal function. Sklar et al. [S41] evaluated testicular function in 60 long-term survivors of childhood acute leukaemia who had been randomized to cranial radiotherapy with 18 or 24 Gy (n = 26), 18 or 24 Gy plus intrathecal methotrexate (n = 23) or 24 Gy craniospinal radiotherapy plus 12 Gy to the abdomen including gonads (n = 11). Treatment was delivered in 1.2-2 Gy daily fractions, and the scattered dose in the testes was 0.4-3.6 Gy after craniospinal radiotherapy. Primary germ-cell dysfunction on average five years after cessation of therapy was significantly associated with type of radiotherapy field: 55% after craniospinal plus abdominal field, 17% after craniospinal and 0% after cranial radiotherapy ($p < 0.01$). Leydig cell function was unaffected in the majority of patients regardless of type of radiotherapy. Leiper et al. [L12] observed early puberty in five boys treated with 18-24 Gy in 10-15 fractions over 2-3 weeks. The mean age for onset of puberty in these children was 9 years, which was greater than two standard deviations from the mean. Precocious puberty, i.e. signs of sexual maturation occurring before 9 years, has also been reported [B19, L12]. Von Muehlendahl et al. [V1] noted normal levels of luteinizing hormone and follicle-stimulating hormone in 17 boys after 8-18 Gy of cranial radiotherapy. Jaffe et al. [J4] evaluated reproductive function in 27 male long-term survivors of childhood cancer treated during prepuberty and puberty with a mean testicular dose of 1.9 Gy (range: 0-25 Gy). Sperm samples were obtained from 23 subjects, and the 4 who refused had fathered healthy children. Four patients were oligospermic and 14 were azoospermic. The four sterile men had received at least 1.4 Gy to the testes without chemotherapy and as low as 0.08 Gy in combination with alkylating agents. Sterility was mainly associated with alkylating agents.

79. After chemotherapy and whole-body irradiation with a single exposure of 10 Gy, delayed pubertal development occurred in one of 12 boys (he also received testicular irradiation); four were still prepubertal at evaluation and seven boys had normal pubertal development [B13]. Four of the boys with normal pubertal development had elevated levels of follicle-stimulating hormone with normal luteinizing hormone and testosterone. Another seven boys received fractionated whole-body irradiation with 12-14 Gy in 6 fractions over three days, and five of them were still prepubertal and two had achieved puberty, one after testosterone administration. Deeg et al. [D2] observed that 5 of 16 boys subjected to whole-body irradiation developed secondary sex characteristics appropriate for their age and 11 had delayed onset of puberty. Forty-one male patients who were past puberty at the time of transplantation developed primary gonadal failure and azoospermia. Two had recovery of spermatogenesis approximately six years after transplantation, and one of them had two normal children. Gonadal failure therefore appeared to be nearly universal after whole-body irradiation with 10-12 Gy in patients of postpubertal age. Sanders et al. [S23] studied gonadal function in 90 boys 1-17 years old who had bone marrow transplantation after prior chemotherapy and radiotherapy to the central nervous system (n = 55). Whole-body irradiation was given as a single dose of 9.2-10 Gy or fractionated doses of 2-2.3 Gy daily for 6-7 days to a cumulative dose of 12-15.8 Gy. At evaluation on average four years later, 21 of the 63 boys who were prepubertal at transplant had delayed development of secondary sexual characteristics. Gonadal failure occurred in nearly all who were postpubertal at transplant.

80. *Summary.* The effects of radiation on the testis are age- and dose-dependent. Radiation appears to have its greatest effect on the germ cells rather than on Leydig cells. It is difficult to draw any certain conclusions regarding the effect of ionizing radiation on the gonadal function in boys and male adolescents. The data have been obtained from studies based on heterogeneous materials, with great variation in age at exposure and treatment modalities. Furthermore, gonadal function has been assessed in many different ways. The threshold radiation dose that will damage the germinal epithelium in childhood cannot therefore

be clearly defined at present. Testicular function may be compromised at doses as low as 0.5 Gy. Leydig cell function appears more resistant to ionizing radiation, and impaired function occurs after 10 Gy or more. Testicular function is also impaired by chemotherapy and may also be abnormal prior to therapy for malignancy that does not involve the testis. Irradiation to the prepubertal gonads may not always result in irreversible damage. Whole-body irradiation has been shown to produce primary gonadal failure of various degrees in the majority of boys receiving 10 Gy, regardless of pubertal status. In most of these patients, Leydig cell function appeared adequate.

## E. MUSCULOSKELETAL SYSTEM

81. Two processes of bone formation occur within the human skeleton: membranous bone formation and enchondral bone formation [P10]. Flat bones and the cortices of long bones are formed by membranous bone formation, in which there is no pre-existing cartilage template, and osteoid tissue is laid down adjacent to existing collagen, cartilage or bone. In enchondral bone formation, which is responsible for longitudinal bone growth, new bone is formed at the epiphyseal growth plate. Chondroblast proliferation is responsible for widening of the epiphyseal growth plate and lengthening of the bone, and osteoid is formed by osteoblasts. External irradiation affects, in particular, dividing chondroblasts and small blood vessels. Membraneous bone formation is disturbed to a lesser extent than enchondral bone growth. Epiphyseal irradiation causes arrest of chondrosis due to direct effects on the chondrocytes and secondary vascular effects. Radiotherapy also disrupts the normal processes of resorption of bone at the epiphysis. Actinomycin D and adriamycin enhance the effects of radiotherapy [E6]. Bone absorbs less radiation in the megavoltage range than in the orthovoltage range, and it has been believed that there is less growth disturbance in bone after megavoltage therapy. However, the major radiation changes occur in the chondroblasts and the fine blood vessels of the physis. Since both are materials of unit density, it is reasonable to expect growth disturbances to be largely independent of radiation voltage quality.

82. The first evidence of growth disturbances following x-ray treatment in patients under 20 years of age was reported in 1929 by Hueck et al. [H15]. In adults, cartilage tolerates 40 Gy over 4 weeks or >70 Gy over 10-12 weeks, and bone tolerates 65 Gy over 6-8 weeks. Higher doses cause necrosis [C24]. These tissues are more sensitive in children, and some growth retardation may occur after 1 Gy, depending on the age at irradiation and the conditions of exposure [I1, T10]. The maximum growth depression has been observed in children treated up to the age of 6 years and in young puberty [G9, P10, R25, R26]. Roentgenographic changes of the bone in children less than 1 year of age occur after conventionally fractionated radiotherapy of >4 Gy, while a dose of >18 Gy with similar fractionation is required to produce significant changes in children 1-2 years of age and >26 Gy is required in older children [N5, T10]. Other skeletal changes occur in children at doses >20 Gy, including scoliosis, kyphosis and slipped capital femoral epiphysis.

83. Growth in children can be adversely affected by direct radiation damage to long bones and spine, malnutrition, steroid therapy, cytotoxic drugs, the presence of residual tumour and endocrine complications [B3, B23, B24, B25, D17, G8, P11, P12, S20, S42, T10, W7]. The effects of radiotherapy on the skeleton are related to the anatomical site, the target volume, the radiation dose, the source and pattern of the radiation used, the age of the patient and chemotherapy. These effects may be seen in any bone but are most often observed in the spine after fractionated radiotherapy with cumulative doses of 20 Gy or more [P13]. The severity increases with increasing radiation dose and with decreasing age at time of treatment. Mature bone and cartilage may also be devitalized by ionizing radiation without showing clinical consequences until stressed by, for example, infection or trauma. Prednisone and doxorubicin depress cartilage responsiveness to somatomedin and also growth-hormone-stimulated somatomedin production [P12]. It is difficult to quantify the effects of ionizing radiation on growing bones for several reasons:

(a) there is a lack of large groups of patients of various ages in whom the same epiphyseal cartilage has been irradiated with a range of doses;
(b) the tumour itself and other treatment modalities can contribute to the growth disturbance;
(c) patients must be followed until growth is completed;
(d) often patients with growth disturbances have deformities corrected surgically, making it impossible to quantify the damage [G8].

84. Children less than 6 years old and at the time of the adolescent growth spurt, i.e. during periods of rapid bone growth, are especially sensitive to irradiation of the vertebral column. Impaired growth has been observed after total doses of 25 Gy, and higher doses to the entire spine result in suppression of spinal growth and decreased sitting height [D17, P10, P11, S25]. Probert et al. [P10] observed changes in both the sitting and standing heights of 44 children treated with megavoltage radiation, particularly among those receiving >35 Gy in 2-2.5 Gy fractions, whereas only slight changes were observed among those receiving <25 Gy with similar fractionation (Figure VII). Shalet

et al. [S43] measured growth after radiotherapy for brain tumour in 37 children who had received craniospinal irradiation with 27-35 Gy to the vertebrae in 17-20 fractions over 3-4 weeks and in 42 children who received cranial radiotherapy. The cranial dose was not stated. All had completed their growth at the time of evaluation, and at that time there were significant differences between the two groups on standard deviation scores for standing height and sitting height, but not for leg length. The younger the child was at the time of treatment the greater the subsequent skeletal disproportion; the estimated eventual loss in height was 9 cm when spinal irradiation was given at 1 year, 7 cm when given at 5 years, and 6 cm when given at 10 years.

85. Growth retardation has also been observed in children injected with $^{224}Ra$ for intended treatment of tuberculosis of bone and soft tissue [M24, S44]. Spiess et al. [S44] obtained the adult heights of 133 patients injected as juveniles. Radium-224-induced growth retardation was greatest in young children, who had the greatest amount of potential growth after exposure. The growth retardation increased with radiation dose, and there was a 2% decrease in potential growth post-irradiation per gray for average skeletal doses up to 20-25 Gy.

86. Functional and cosmetic disabilities involving bone, teeth, muscle and other soft tissues have been reported to occur after radiotherapy in up to 38% of survivors of paediatric cancers, in particular after treatment for solid tumours [D19, L16, M2, M25, S43]. The clinically significant problems often involve bone abnormalities, such as scoliosis, atrophy or hypoplasia, avascular necrosis and osteoporosis. Scoliosis may occur following radiotherapy to segments of the spinal column in patients with solid tumours [H16, J5, S42, S45, W8]. Scoliosis has been most apparent in children treated with orthovoltage radiation to fields extending to the midline, resulting in asymmetric radiation of the vertebrae. The degree of scoliosis has increased with dose and has been mild after 20-32 Gy and significant after higher doses [O10, P10, R27]. Vertebral abnormalities have been less pronounced with high voltage radiotherapy and with radiation fields encompassing the entire vertebrae, and significant scoliosis below 35 Gy is uncommon [H16, P10, T11]. The cases of scoliosis that occur at present are usually not so severe that orthopaedic intervention is required.

87. Slipped epiphyses can develop in patients who have received radiotherapy to the proximal femoral epiphysis, combined with chemotherapy, in childhood [B26, L17, R1, S46, W9, W10]. Silverman et al. [S46] studied 50 patients under 15 years of age who had radiotherapy that included the non-fused capital femoral epiphyseal plate in the treatment field. Mean dose to the epiphyseal plates was 23 Gy (range: 1.5-53 Gy), and 10% of the 83 plates at risk showed epiphyseal slippage or other severe radiographical abnormalities. Children under the age of 4 years at the time of irradiation were at higher risk (47%) than older children (5%). No complications occurred below 25 Gy and no dose-response curve was obtained. A mean difference of up to 12 cm in clinical length between unirradiated and irradiated extremities has been observed after ≥6 Gy to the epiphyseal plates [G8]. Figure VIII shows the relationship between age at irradiation, dose and shortening for 20 patients who had epiphyseal plate irradiation. Damage increased dramatically at doses up to 40 Gy but levelled off beyond that. Shortening was strongly age-dependent, amounting to 9-12 cm in several patients who were less than 1 year old. When growth expected to remain after irradiation was taken into account, age at irradiation did not influence the final effect, and the radiation dose was the most important factor. Radiation-induced aseptic necrosis of the femoral heads have been observed in children after doses of 30-40 Gy [L17]. Chemotherapy may be a contributing factor, since aseptic osteonecrosis has been reported in children after chemotherapy alone [P14]. Slipped proximal humeral epiphysis has also been reported after slightly higher radiation doses than those received by children with slipped capital femoral epiphysis [E6]. That the shoulder is not as stressed as the hip may be the reason why slipped proximal humeral epiphysis is less frequent than slipped femoral epiphysis.

88. Bony hypoplasia of the orbit with facial asymmetry was reported in half of 50 children with orbital rhabdomyosarcoma after 50-60 Gy in 5-6 weeks [H17]. The degree of hypoplasia appeared to be higher the younger the child was at the time of treatment. Other common findings were asymmetry of the face and/or neck and the presence of dental problems, both of which occurred in 58% of the patients. Evidence of muscle atrophy or fibrosis of the subcutaneous tissues was evident in 40% of the patients in the head or face and 33% in the neck. Hypoplasia of bones in treated sites was documented in one third of the patients and judged to be largely due to radiotherapy. Similar late effects have been observed by others [E7, G10].

89. Radiotherapy may also have adverse effects on developing dentition, including root abnormalities, incomplete calcification, delayed or arrested tooth development and caries [B27, D19, H18, J6, M26]. These and other maxillofacial abnormalities, such as trismus, abnormal occlusal relationships and facial deformities are more severe in patients irradiated at an earlier age and at higher doses. Jaffe et al. [J6] observed dental and maxillofacial abnormalities in 82% of 45 long-term survivors of childhood cancer

after maxillofacial radiotherapy. Younger patients and those treated with higher doses, i.e. rhabdomyosarcoma patients (median dose: 55 Gy) as opposed to Hodgkin's disease and leukaemia patients (median dose: 35 Gy, $p < 0.001$) had more severe abnormalities. In a study by Sonis et al. [S47], abnormal dental development occurred five or more years later in 94% of 97 children with acute leukaemia treated before 10 years of age with intrathecal methotrexate alone (n = 19) or in combination with 18-24 Gy cranial radiotherapy (n = 78). All children who received treatment before 5 years of age and those who received radiotherapy had the most severe abnormalities. Tooth breakage due to tooth resorption has been common among patients injected with $^{224}$Ra, especially those injected as teenagers [S48]. The incidence of tooth breakage increased significantly with dose. The tooth fractures resembled those observed in radium dial painters in the United States [R25]. Children given a single whole-body exposure of 10 Gy for marrow transplantation have developed similar disturbances in dental development and facial growth similar to those seen after 18-65 Gy fractionated radiotherapy to the maxillofacial region for leukaemia or solid tumours [D20, S25]. The most severe effects have been seen in children irradiated when they were less than 6 years of age.

90. Anthropometric analyses were performed in 1990 on children living in Russia, Belarus and Ukraine at the time of the nuclear plant accident in Chernobyl in 1986, and in children born in 1989 [I8]. The main conclusion from these studies was that there were no significant differences in height or weight between the control and contaminated regions.

91. *Summary.* Growth in children can be adversely affected by direct radiation damage and by malnutrition, other treatment modalities, the presence of residual tumour, and endocrine late radiation effects. Most clinical data are based on small and heterogeneous groups of patients treated in different ways at varying ages. The skeletal effects have also been assessed in a variety of ways, and it is not possible to give any estimates of late deterministic effects based on large-scale epidemiologic data. Skeletal changes in children generally occur at doses exceeding 20 Gy and include scoliosis, kyphosis, slipped femoral epiphyses, hypoplasia, growth retardation, dental problems etc. Absolute shortening of the long bone depends on the absorbed radiation dose and the age at the time of irradiation. Exposure at ages less than 6 years and during puberty appears to have the greatest effect on growth retardation. However, other studies have observed that when growth expected to occur after irradiation was taken into account, the age at irradiation did not influence the final effect, and the radiation dose was then the most important factor. Scoliosis and kyphosis are common after spinal or flank irradiation following doses of >20 Gy. Slipped femoral capital epiphysis does not occur below 20 Gy, and this late effect is more common in children under 4 years of age at the time of irradiation. A dose exceeding 20 Gy is required to arrest encondral bone formation, and doses of 10-20 Gy cause the partial arrest of bone growth. There is little alteration in bone growth below 10 Gy of fractionated exposure directly to the bone. No radiation-related effect on height has been observed in children living in Russia, Belarus or Ukraine at the time of the Chernobyl accident.

## F. EYE

92. Ionizing radiation, chemotherapy and corticosteroids have all been found to increase the risk of cataract formation [C20, H19, I1, O11, P15, S49, U3]. Different components of the eye have different sensitivity to ionizing radiation, and the lens is especially sensitive when uniformly irradiated. There are different forms of cataract, and radiation-induced cataract is in its early stages a characteristic lesion, which is defined as a posterior subcapsular opacity. The threshold dose for cataract in adults is about 2 Gy of x rays from a single exposure and 4-6 Gy when fractionated over 3-13 weeks [F1, M27]. Minimal stationary opacities have been observed after single doses of 1-2 Gy, and with 5 Gy more serious progressive cataracts occur [U3]. The threshold dose for cataract formation is increased by non-uniform irradiation [B28]. Higher radiation doses yield more progressive cataracts with a greater loss of vision. The average latent period is 2 years but may be up to 35 years. The combination of radiotherapy and chemotherapy enhances the risk for cataract formation [F7]. Other late radiation effects in the eye include retinopathy, optic neuropathy and lacrimal gland atrophy. These types of injuries rarely occur below 45 Gy.

93. Decreased vision due to cataract formation in the treated eye is common in children treated for orbital rhabdomyosarcoma after doses to the tumour of 50-60 Gy in 2 Gy fractions over 5-6 weeks [H17]. The time to first reported evidence of cataract varied from one to four years after radiotherapy. Other reported structural late effects include changes in the cornea or retina, enophthalmos, and stenosis of the lacrimal duct.

94. Qvist and Zachau-Christiansen [Q2] estimated the minimum lenticular dose to produce cataract in children to be 13.8 Gy from radium moulds; the maximum non-cataract dose for infants was 9.9 Gy and for school-aged children, 11.4 Gy. Notter et al. [N8] observed cataracts after considerably lower doses in 234 patients who had been irradiated with $^{226}$Ra-containing applicators for skin haemangioma between

1920 and the mid-1950s. An ophthalmologic examination was conducted in 1961-1965. Of 468 eyes examined, cataract was observed in 51 (11%). No cataract was observed in the 246 eyes receiving <2.5 Gy in the lens. The prevalence of cataract was 8% (100 eyes) after a lenticular dose of 2.5-3.5 Gy and 54% (122 eyes) after higher doses.

95. Stefani et al. [S37, C25] reported on the development of cataract in 899 patients receiving multiple injections of $^{224}Ra$ for the intended treatment of tuberculosis or ankylosing spondylitis. Cataracts were found in 6% of the 218 juvenile patients and in 5% of the 681 adult patients. In those with known injected activities, juveniles receiving >1 MBq $kg^{-1}$ of $^{224}Ra$ had a cataract incidence of 14% (11 of 80) compared to 0.8% (1 of 131) receiving less than that amount. The cataract incidence increased significantly with dosage in both juveniles and adults.

96. The dose received by the lens in cranial radiotherapy for acute leukaemia is of importance for the induction of cataract [K10]. The dose to the lens is approximately 15%-30% of the midline dose, depending on the type of treatment fields. Nesbit et al. [N3] found one case of posterior subcapsular cataracts in 50 survivors of childhood acute leukaemia. In contrast, Inati et al. [I3] observed a 50% incidence of cataract formation in 69 children with acute leukaemia given 24 Gy cranial radiotherapy in 13 fractions over 2.5 weeks, intrathecal methotrexate and high doses of steroids. All cataracts were small and did not impair vision. In another study of 34 long-term survivors of acute leukaemia, all 18 patients in the non-irradiated group had normal results in eye examinations, while 4 of 16 of those receiving 24 Gy to the whole brain in 12 fractions over 2.5 weeks had ocular abnormalities [W11]. None of the ocular findings could, however, be definitely attributed to radiation, and all patients had normal visual acuity.

97. Posterior subcapsular cataracts occur in the great majority of patients after 10 Gy of single whole-body exposure but in only about 20% after 12-15.8 Gy of fractionated exposure [A14, B13, C8, D21, L23, S24, V7]. Among 105 patients given 10 Gy single-dose whole-body irradiation, 80% developed cataracts by six years compared to 19% of 76 patients given fractionated whole-body irradiation (12-15 Gy in 2-5 Gy fractions over 6-7 days) and 18% in patients who did not receive radiotherapy [D2]. This last figure indicates that factors other than irradiation, e.g. steroids or previous treatments may have contributed to the development of cataracts. Nearly all cataracts developed after a single exposure need to be removed, whereas a smaller fraction of those developed after fractionated exposure require removal.

98. In a study conducted among subjects of the Adult Health Study of Hiroshima and Nagasaki, a significant excess risk for posterior subcapsular changes was observed for all ages in the group receiving >3 Sv in comparison with those in the control group among residents in Hiroshima but not in Nagasaki [C21]. The study was based on the T65 dosimetry and the examination was conducted on 2,385 persons. The relative risk of cataract for persons in Hiroshima exposed to >3 Sv was 4.8 in persons under age 15 years at the time of the bombings, 2.3 in persons 15-24 years at the time of the bombings and 1.4 in persons more than 25 years at the time of the bombings. The relative risk for posterior subcapsular changes in Hiroshima for persons under age 15 years at the time of the bombings was 2.8 in the 1-1.9 Sv group, 4.3 in the group receiving 2-2.9 Sv and 5.3 in the group receiving >3 Sv. A comparison of relative risks in the different age groups suggested a stronger effect in Hiroshima for persons under age 15 years at the time of the bombings. These results support the hypothesis that younger individuals are more sensitive to radiation-induced cataract than older individuals. A more recent assessment of the dose-effect relationship for cataract induction has been made using the DS86 dosimetry system [O15, O16]. This new study confirms the previous findings of a higher sensitivity in young persons. The magnitude of log relative risks for cataracts in persons aged 40, 50, 60 and 70 years at the time of examination was 8.2, 6.4, 4.6 and 2.8-fold higher, respectively, than in persons aged 80 years at the time of examination. The best-fitting relationship for posterior postcapsular changes suggested a linear-quadratic dose-response.

99. *Summary.* The available data on radiation-induced cataract formation in adults suggest a sigmoid dose-response relationship with an apparent threshold. This threshold varies from 2 to 5 Gy after x rays and gamma rays given as single exposure and is about 10 Gy for doses fractionated over a period of months. Data on radiation-induced cataracts in children are scarce and are based on small groups of patients receiving different treatment modalities. Cataracts have been reported after 24 Gy cranial radiotherapy for childhood leukaemia resulting in 5-7 Gy in the lens. Cataracts have been observed after 2.5 Gy or more in the lens, and in one study the prevalence of cataract was 8% (100 eyes) after a lenticular dose of 2.5-3.5 Gy. Whole-body exposure of 10 Gy in childhood has also been associated with cataract formation in the majority of cases, whereas fractionated whole-body irradiation with 12-15.8 Gy is associated with cataract in about 20% of the patients. Cataracts were observed in the survivors of the atomic bombings in Japan exposed to >3 Gy, and the risk for cataract was higher in persons less than age 15 years at the time of the bombings than in persons older than that.

## G. CARDIOVASCULAR SYSTEM

100. Ionizing radiation affects small and large vessels within the treatment field, and changes may develop within months and up to two decades after radiotherapy [K2]. The main changes that occur consist of premature atherosclerosis with vascular occlusion. The heart was formerly thought to be relatively resistant to ionizing radiation. The increasing use of radiotherapy to the mediastinum, however, has been associated with well-documented instances of cardiac abnormalities. Late effects following radiotherapy have been reported in both adults and children and usually occur as cardiomyopathy, coronary artery disease, pericardial effusions or constrictive pericarditis [A15, B29, B30, D17, G11, G12, K11, L1, P9, R28, T9]. Interstitial myocardial fibrosis and coronary artery changes have been reported after 30 Gy, and pericarditis has been reported after 15 Gy [B29, G12, K12, M28, M29]. In children as well as in adults, a dose of 40 Gy to the heart appears to be the critical dose for clinical cardiomyopathy.

101. The incidence of post-irradiation pericarditis increases with dose and fraction size [S50]. In patients irradiated for Hodgkin's disease, the frequency of radiation-related pericarditis correlates with the pericardial dose [C22]. Carmel and Kaplan [C22] found a 7% incidence of pericarditis after doses <6 Gy, 12% after 6-15 Gy, 19% after 15-30 Gy and 50% after >30 Gy. Symptomatic pericarditis may first appear as late as 45 years after therapy [B29, G13, H20, K12, S51]. Kadota et al. [K12] evaluated cardiopulmonary function in 11 children who received radiotherapy for Hodgkin's disease with a mean dose of 36 Gy (range: 20-55 Gy) with conventional fractionation. Mean age at radiotherapy was 11 years, and evaluation was performed, on average, nine years later. Ten patients had no clinical evidence of cardiopulmonary dysfunction, and one had constrictive pericarditis. Four had thickened cardiac valves on echocardiography, without significant stenosis or insufficiency. Only three had normal cardiopulmonary function, and the others had one or more abnormal tests.

102. Mäkinen et al. [M30] evaluated cardiac sequelae in 41 individuals who had received chest radiotherapy or doxorubicin for childhood cancer at a median of 17 years earlier. Radiotherapy had been used in 21 patients, and in 13 of them irradiation was directed at the heart with doses of 12-60 Gy in 8-30 fractions over 12-47 days. Of the 41 patients, 20 (49%) showed some abnormality in cardiac tests (e.g. abnormal ECG or echocardiogram, reduced exercise capacity), and each additional year of follow-up was associated with a 1.3-fold increase in pathologic cardiac findings. The risk of an abnormal cardiac test result in the 13 patients who had received radiotherapy to the heart was 12.8 times the risk for other patients (95% CI: 1.8-90.8). No detailed analysis of the effect of radiotherapy was presented.

103. The anthracyclines doxorubicin and daunomycin are cardiotoxic and may cause electrocardiographic changes and congestive heart failure. There is a dose-response relationship between the total dose of anthracyclines and cardiomyopathy, and children appear to be more susceptible to drug-induced cardiomyopathy [P16, P17, S52, V3, V4]. Several studies have shown that mediastinal irradiation enhances the myocardial toxicity of anthracyclines [B31, G14, M31, P16, P18]. Gilladoga et al. [G14] observed severe cardiomyopathy with congestive heart failure in 16% of 50 children receiving adriamycin and in 3% of 60 children receiving daunomycin. Four of 8 children who also had incidental cardiac irradiation prior to or during adriamycin administration had severe cardiomyopathy. In contrast, Von Hoff et al. [V5] observed a lower risk of cardiomyopathy for children than for adults at any given cumulative doxorubicin dosage.

104. *Summary.* Radiation exposures cause occlusion of both small and large blood vessels. Cardiac abnormalities have been observed particularly following irradiation of the mediastinum. Patients may have abnormal cardiac function without clinical evidence of such dysfunction. Myocardial fibrosis has occurred after 30 Gy. The few data available suggest that 40 Gy with conventional fractionation can be considered as a critical dose for clinical cardiomyopathy in both children and adults. The anthracyclines are cardiotoxic and enhance the effects of mediastinal irradiation.

## H. LUNG

105. The lung is the most radiosensitive organ in the thorax. The mechanism for respiratory damage in young children may be different from that in adults or in adolescents. Specific radiation effects in children can include the impaired formation of new alveoli or failures in the development of the thoracic skeleton and thus a reduced size of the lung [B32, R17]. Interstitial fibrosis of the lung, resulting in decreased total lung capacity, vital capacity and diffusion, is a late effect that has been observed in adults after doses of >30 Gy and above [D22, H21, L1, L18, M18, M32, S54]. The effect in children appears to be similar for the same dose and fractionation schedules [D17, S53, T9, W12]. Children younger than 3 years at the time of treatment may be at higher risk for lung dysfunction [M32]. The effects depend on the target volume and on the concurrent use of chemotherapy [W13]. Interstitial pneumonitis and pulmonary fibrosis have also been reported after chemotherapy in children and adults [A16].

106. Restrictive lung volume with total lung capacity between 62% and 80% of normal capacity was recorded after treatment for Hodgkin's disease in 5 of 11 patients (mean age: 11 years) who received mantle field radiotherapy with 20-55 Gy [K12]. Six children had reduced exercise tolerance, manifested by reduced maximum oxygen uptake (<65% of predicted) and exercise duration (<75% of predicted). Miller et al. [M32] observed reduced forced vital capacity and/or total lung capacity in half of 29 children with childhood cancer. The incidence of pulmonary dysfunction was high in both irradiated children and in individuals who did not receive radiotherapy to the thorax.

107. After fractionated pulmonary radiotherapy for Wilms' tumour at age 2-4 years with a lung dose of 20 Gy, children may develop dyspnoea and evidence of interstitial and pleural thickening on chest x-ray examination up to 14 years after treatment [W14]. Mean total lung volumes may be reduced by approximately 40% after such radiotherapy owing to effects on lung growth and on chest wall growth. Restrictive lung changes after fractionated radiotherapy with 11-14 Gy to the whole lung have been reported in other studies of children with paediatric tumours [B32, L19]. Benoist et al. [B32] studied the effects of whole-lung irradiation on lung function in 48 children treated for Wilms' tumour with pulmonary metastases. The mean age was 3 years, and all patients received fractionated radiotherapy with 20 Gy bilateral pulmonary irradiation over three weeks plus actinomycin D. Greatly reduced sagittal and frontal thoracic diameters were observed in nearly all of the cases 3-4 years after radiotherapy. Lung volumes and dynamic lung compliance and functional residual capacity decreased with time. Static pressure volume curves, blood gases and carbon monoxide transfer were normal, making it unlikely that post-radiation pulmonary fibrosis was involved.

108. Littman et al. [L19] evaluated pulmonary function in 33 patients treated for Wilms' tumour and followed for up to 20 years after diagnosis. All but five children received at least one course of actinomycin D. Eighteen children who did not receive lung irradiation had normal pulmonary function. Radiotherapy was given to 10 children for pulmonary metastases and to 5 children as prophylaxis with a lung dose of 12-14 Gy and varying fractionations. Patients treated for metastases had findings suggestive of moderately reduced lung volumes, whereas patients receiving prophylactic treatment had essentially normal lung volumes. Vital capacity and functional residual capacity were significantly lower in the irradiated group of patients than in the non-irradiated patients. Residual volume was lower in the irradiated group as was forced expiratory volume. The fact that patients who were treated for metastatic disease had greater abnormalities in pulmonary function than those irradiated for prophylaxis suggests that the presence of metastatic nodules and additional lung treatment could have aggravated the effects.

109. Two studies did not observe any impairment of lung function in patients 15 years old or less after whole lung irradiation with 20 Gy in 1.5-2 Gy fractions five times per week [B39, Z1]. According to Margolis et al. [M34], the maximum safe dose to the whole lung for patients receiving actinomycin D is 15 Gy in 1.5 Gy fractions. However, doses lower than that may affect pulmonary function. Wohl et al. [W14] reported that total lung capacity averaged 71% of the expected value in six children treated with fractionated and bilateral pulmonary irradiation for Wilms' tumour and evaluated more than seven years later. The exposures at the midplane of the chest ranged from 8-12 Gy delivered over an average of 11 days. The total lung capacity for eight children receiving no radiotherapy was 94% of the expected value. Springmeyer et al. [S53] found restrictive ventilatory changes in 79 patients with haematologic malignancies or aplastic anaemia one year or more after bone marrow transplantation. There was a mean loss in total lung capacity of 0.8 and in vital capacity of 0.5, but these changes were not significantly associated with whole-body irradiation.

110. *Summary.* The lung is a radiosensitive organ, and radiotherapy during a period of lung growth and chest wall growth primarily results in a reduction of the subsequent size of both lungs and chest wall. Respiratory damage in young children is more severe than in adults at the same doses. The effects depend on the target volume and concurrent use of chemotherapy. Interstitial fibrosis may occur 6-12 months after absorbed doses to the lung of 30 Gy or more. A lung dose of 15 Gy in 1.5 Gy fractions is generally considered as the maximum safe dose in children receiving radiotherapy to the whole lung and simultaneous treatment with actinomycin D. However, restrictive lung changes have been reported after doses of 11 Gy or more in children treated for paediatric tumours, and reduced total lung capacity has been found after 8 Gy or more to the whole lung with similar fractionation.

## I. BREAST

111. Breast development is readily inhibited by radiotherapy in infancy, and severe hypoplasia of breast tissue has been reported in women having a history of breast irradiation in childhood [D19, F8, F9, G15, H22, K13, U11]. Breast hypoplasia or aplasia have also been noted as sequelae after radiotherapy for paediatric tumours in childhood [F8]. The knowledge

of dose-effect patterns is scarce [I1, I5]. Moss [M35] stated that an exposure giving a skin dose of 15-20 Gy over eight days would impair breast development. According to Rubin et al. [R2], a dose exceeding 10 Gy to the prepubertal female breast of conventionally fractionated x-ray therapy may result in the absence of breast development in 1%-5% of the patients.

112. Fürst et al. [F9] studied the prevalence and degree of breast hypoplasia in 129 women irradiated in infancy or childhood for haemangioma in the breast region. The patients were treated in 1934-1943 at an age of 4 years or less. Radiotherapy was mainly given with applicators containing $^{226}$Ra, with flat applicators or needles and/or tubes having been used. Mean absorbed dose to the breast anlage for the whole cohort was 2.3 Gy (range: 0.01-18.3 Gy). Breast asymmetry was estimated by responses to a mail questionnaire to all patients and by the clinical examination of 53 patients living in Stockholm county. Breast hypoplasia on the treated side was reported by 57% of the patients and on the contralateral side by 8%. Among women reporting a smaller breast on the untreated side, the mean dose to the treated breast was 0.5 Gy (range: 0.01-1.0 Gy). In 28 of the 53 clinically examined patients, breast hypoplasia exceeding 10% was found on the treated side, and five patients had hypoplasia of more than 10% on the contralateral side (Figure IX). The frequency and the severity of impaired breast development increased with the radiation dose. In this study, the possibility of a threshold dose for radiation-induced breast hypoplasia could neither be established nor ruled out, and the results suggested that the available risk estimates for breast hypoplasia underestimate the effect [I1, R2]. At lower doses, the dose-effect relationship may be confounded by normal variations in breast size. At higher doses and with larger fields than were used in the Swedish study, there may also be a radiation effect on the chest wall with subsequent growth impairment.

113. *Summary.* The sensitivity of breast tissue in the irradiated child is recognized, with low threshold doses for the occurrence of clinical effects. One study has reported that hypoplasia occurs in more than 50% of children treated with radiotherapy at less than 4 years of age with doses to the breast of the order of 2 Gy. Higher doses cause increased incidence and severity of impaired breast development.

## J. DIGESTIVE SYSTEM

114. Late radiation effects of the gastro-intestinal tract develop months or years after exposure and include fibrosis, stricture, intestinal perforation and fistula formation [R1]. The liver appears to have a low threshold for late injury, and in adults veno-occlusive disease has been observed after single doses of 10 Gy or 18-30 Gy with conventional fractionation [F10]. The damage is due to changes that interfere with mitosis in the irradiated hepatocytes and to vascular changes [I1]. Radiation-induced liver disease is characterized structurally by progressive fibrosis and obliteration of central veins, possibly by injuring preferentially the endothelial cells of central veins [F10, L20]. Veno-occlusive disease may also be caused by antineoplastic drugs, and hepatic fibrosis has been observed in children receiving chemotherapy [M36, N6].

115. The risk for radiation-induced liver damage increases when large volumes of the liver are irradiated or when the liver is irradiated after resection. A larger dose can be tolerated if only part of the liver is exposed [F1, I6, K14]. In children, Tefft et al. [T13] noted liver abnormalities after radiotherapy to the liver with doses of 12-30 Gy. This could be related to the greater sensitivity of the younger child, who generally also received the lower doses. Thomas et al. [T11] observed liver fibrosis in 3 of 26 long-term survivors of Wilms' tumour who had received at least 30 Gy to the liver in 1.5-2 Gy fractions. Hepatic disease, ranging from abnormal liver enzymes and thrombocytopenia to death, has also been reported by others [S45, T12].

116. Hepatitis following irradiation and chemotherapy at doses and volumes of irradiation ordinarily considered within the tolerance of hepatic function has been reported [K15]. Fatal liver damage occurred in a 13-year-old boy who had received adriamycin before and during radiotherapy of 24 Gy in 17 fractions over 28 days to the upper abdomen including the entire liver. A 13-year-old girl had moderate clinical liver changes following 25 Gy in 23 fractions over 32 days with adriamycin administered before and during irradiation. In this case much of the right lobe was shielded during radiotherapy. About 20 patients have been reported to have developed liver disease after fractionated radiotherapy with 12-40 Gy to the liver in childhood together with chemotherapy [J7]. Most patients were asymptomatic, and their condition was discovered because of hepatomegaly or abnormalities shown in a routine liver scintigram. When hepatitis is observed following radiation exposure, especially if exposure is received in conjunction with chemotherapy, it is important to note that not only post-irradiation effects but also toxic and infectious complications requiring appropriate therapeutic and prophylactic measures will occur.

117. The small intestine has a high radiosensitivity but is somewhat spared by its mobility. Thus, repeated exposure of a particular segment is avoided. This is not the case for the rectum, which is fixed to adjacent

tissues and consequently experiences the effects of radiation more frequently [H1]. In adults, the risk of small bowel complications depends on radiation dose, volume of bowel irradiated and fractionation schedule. Surgery increases the risk of developing radiation enteropathy. The manifestations of late radiation enteropathy are considered to be due mainly to vascular and connective tissue damage. Mage et al. [M37] reported late gastro-intestinal effects in 17 children receiving abdominal fractionated radiotherapy with 30-55 Gy. Stenosis, submucous infiltrations and mesenteritis were observed 2-13 months after radiotherapy. No details of the radiotherapeutic regimens were given. The combined effects of radiation damage to the mucous membrane and exacerbation of already existing gastro-intestinal infections can cause perforation and ulceration.

118. Donaldson et al. [D23] reviewed late radiation effects in the gastro-intestinal tract of 44 children receiving whole abdominal radiotherapy for lymphoma, Wilms' tumour or teratoma. Of 14 long-term survivors, 5 developed severe radiation injury with small bowel obstruction within two months after completion of radiotherapy. Their mean age at the time of therapy was 6 years, and the abdominal dose was 31 Gy (range: 10-40 Gy) delivered in 7-20 fractions over 11-39 days. Surgery contributed to the presence of abdominal adhesions and fibrosis.

119. *Summary.* The risk of radiation-induced liver damage increases with increasing volume of the liver irradiated and after liver resection with regenerating liver tissue. Some data suggest that children are more sensitive to such late effects than are adults. Liver abnormalities have been observed after 12 Gy with conventional fractionation and often in combination with chemotherapy. Clinical radiation-induced hepatitis has rarely been reported at doses below 30 Gy in 0.9-1.0 Gy fractions five times per week. Case-reports have presented data on liver damage in children after 24-25 Gy in 1.1-1.4 Gy fractions with concomitant use of anthracyclines. Radiation effects in the gastro-intestinal tract include fibrosis, stricture, perforation and formation of fistulae. There are hardly any data available on such effects in children.

## K. KIDNEY

120. The urinary system shows a wide range in radiosensitivity, with the kidney being the most sensitive organ, the bladder having an intermediate sensitivity and the ureter being more resistant, although the full length is seldom irradiated [U1]. Late radiation sequelae of the kidney are directly related to the total dose to the tissue and are characterized by tissue necrosis and fibrosis, which may occur a few months to several years after exposure [F1, K16, L21, M38, M39, U1]. The critical dose for the kidneys in adults is usually set at about 23 Gy over five weeks. Rubin [R3] suggested the critical dose for 5% chronic nephrosclerosis to be 20 Gy with conventional fractionation. Radiation nephritis results from lesions of the tubules and microvasculature of the kidney. Radiation injury to large and medium-sized arteries can also result in stenosis or occlusion [M38]. The severity of radiation injury seems to be a function of the radiation dose and the size of the vessel. Larger doses and smaller vessels are more likely to end in total occlusion, whereas larger vessels or smaller doses result in stenosis or hypoplasia of the vessel. Children are more susceptible to vascular injury, because of their small, growing arteries and relative sensitivity to a given dose of radiation. Radiation injury to the renal artery may produce a renovascular hypertension, which can be distinguished from the more common radiation nephritis.

121. Renal injury is more severe in children, and they have limited tolerance for combined chemotherapy and radiotherapy. A normal creatinine clearance and glomerular filtration rate may be anticipated below a fractionated dose of 15 Gy when actinomycin D is used concurrently, but progressive renal insufficiency occurs after doses of 20 Gy and more [J5]. However, radiation nephritis has been reported 20 years after 14 Gy to the kidney in childhood [O12]. Reduced creatinine clearance has been found in 18% of 108 children who underwent nephrectomy for malignant disease and received <12 Gy to the remaining kidney and in 33% among those receiving 12-24 Gy [M33]. In another study, Levitt et al. [L24] observed that children with Wilms' tumour and less than 2 years old who received chemotherapy with >12 Gy to the remaining kidney had a worse renal prognosis than other children. In children exposed *in utero* in Hiroshima and Nagasaki, urinary examination revealed transient proteinuria, which was not found in adults [F11].

122. Radiotherapy for Wilms' tumour has also been associated with late effects in the kidney [A17, K16, M40, V6]. McGill et al. [M40] reported post-irradiation renovascular hypertension in a boy who received chemotherapy and fractionated radiotherapy with 30 Gy to the abdomen at the age of 9 months and in another boy 14 months of age who received 51 Gy to the abdomen. Severe hypertension developed 6-8 years later. Koskimies [K16] reported three patients aged 1-2 years with Wilms' tumour who developed hypertension more than 10 years after receiving >36 Gy postoperatively to the tumour area. The hypertension was considered to be of renal origin for three reasons: the likelihood of renal damage was supported by gross macroscopic changes in the nearby organs; two patients had proteinuria indicating renal damage; and

other causes known to cause secondary hypertension had been excluded. In another study of 14 patients with Wilms' tumour evaluated at a median of 17 years later, four had elevated diastolic blood pressure and two had mild proteinuria [B33]. That study provided no data on the radiotherapy. Arneil et al. [A17] reported nephritis four months after surgery in two children aged 2 and 5 years who received actinomycin D and vincristine followed by 15-20 Gy to the remaining kidney fractionated over 2-3 weeks.

123. Radiation nephropathy is common after whole-body irradiation for bone marrow transplantation [T3, V8]. After 12-14 Gy in 6-8 fractions over 3-4 days, the child may develop anaemia, haematuria and elevated creatinine. This renal insufficiency is due both to the radiotherapy and to the chemotherapeutic regimens employed.

124. *Summary.* Late effects following irradiation of the kidney include nephritis, tissue necrosis and fibrosis, renal dysfunction and hypertension. Available data do not indicate that children are more susceptible to radiation-induced renal injury than adults. Radiation nephritis has been reported after fractionated doses of 14 Gy, and decreased creatine clearance has occurred after doses around 12 Gy. The seemingly higher sensitivity among children can probably be explained by the combination of radiotherapy and chemotherapy, which can enhance the side-effects in the kidney [R3].

## L. BONE MARROW

125. Few studies have been performed to determine the long-term deterministic effects on bone marrow function after exposure to ionizing radiation in childhood, and most available data refer to exposure in adulthood. Rubin et al. [R29] studied the repopulation and redistribution of bone marrow in 27 adults irradiated for Hodgkin's disease with 40-45 Gy of fractionated radiotherapy to large segments of their bone marrow (mantle and inverted fields). Bone marrow scanning techniques using $^{99m}$Tc-sulphur colloid, which parallels $^{59}$Fe activity and can be used to reflect haematopoietic activity, indicated that prolonged suppression of bone marrow occurs immediately following completion of radiotherapy and persists for 2-3 years. Partial to complete bone marrow regeneration after fractionated radiotherapy with 40 Gy occurs in 85% of the exposed bone marrow sites at two years. Mechanisms of this recovery may include increased haematopoietic production in shielded marrow sites, expansion of bone marrow space and infield regeneration of bone marrow. The study suggested that the dose-response data for bone marrow suppression following localized and segmental exposure need to be revised upwards for fractionated radiotherapy. At the 40 Gy level there was evidence of prolonged suppression of bone marrow activity starting in the immediate post-irradiation period and continuing for one year. Regeneration of bone marrow activity and expansion of bone marrow occurred after one year following the 40 Gy treatment and continued to improve with time from the first to the third post-irradiation year. Baisogolov and Shiskin [B36, B37, B38] observed bone marrow hypoplasia in 8% of examined bone marrow from exposed parts in 200 patients irradiated for Hodgkin's disease, and in 89% the marrow was aplastic.

126. Magnetic resonance imaging can detect radiation-induced marrow changes. There are at least two distinct types of late marrow patterns [S57]: homogeneous fatty replacement and another pattern possibly representing haematopoietic marrow surrounding the central marrow fat. These changes have been observed in the lumbar vertebral bone marrow of adults after 15-50 Gy delivered over 3-6 weeks. No similar studies have been performed in paediatric patients.

127. No evidence exists of a late radiation effect of primary disturbance of haematopoiesis in the absence of malignant disease in the populations of Hiroshima and Nagasaki [F12]. There is no evidence for radiation-induced disturbance of granulocyte function, but the age-related accelerated decline in the immunological functions of T-lymphocytes and age-related alteration in the number of certain subsets of circulating T- and B-lymphocytes appear to be radiation-related.

128. The Chernobyl accident does not appear to have caused statistically significant effects on the major haematological parameters of children living in Russia, Belarus or Ukraine at the time of the accident, or who were born later [A18, I8, K17, K18, L25, L29, V9]. There were no differences between control and contaminated settlements. From the calculated and measured radiation dose levels, no changes should have been expected as a direct result of radiation exposure.

129. In children having an intact thymus, immune function recovers more rapidly and does not necessarily have permanent effects. Blomgren et al. [B34] analysed peripheral lymphocyte populations and serum immunoglobulin levels in 10 long-term survivors of Wilms' tumour (age: 0.5-6 years) and 6 long-term survivors of non-Hodgkin lymphoma (age: 3-13 years). All received chemotherapy, and the tumour dose was 7-32 Gy and 2-21 Gy, respectively. Lymphocyte counts, as well as frequencies of E, EA and EAC rosette-forming cells, did not differ from those of healthy controls. Serum levels of immunoglobin E were somewhat lower in patients treated for lymphoma, but for other immunoglobulins there was no difference between patients and controls. The treatment did not have any long-lasting effects on the lym-

phatic system. In comparison, adults receiving radiotherapy for breast cancer developed T-cell lymphopenia that persisted for a decade. Studies on more than 900 children from contaminated areas in Russia and Ukraine have not demonstrated any radiation-related effect on T-cells [L26, L27, L28].

130. *Summary.* Studies of bone marrow suppression, recovery, late marrow changes and effects on the immune system pertain only to adults. Too few data exist on the effects of ionizing radiation on bone marrow and on immune function to determine or even suggest critical levels for clinical effects to appear.

## CONCLUSIONS

131. Deterministic effects of ionizing radiation in humans depend on the dose and can be expected to have thresholds below which the radiation effects are too small to impair function of the irradiated tissue or organ. In children, tissues are actively growing, and a radiation-induced deterministic damage in a tissue or organ will often be more severe than in adults. Examples of such deterministic sequelae include effects on growth and development, hormonal deficiencies, organ dysfunctions and effects on intellectual and cognitive functions.

132. Well-designed epidemiological studies of late deterministic effects are generally lacking, and it is therefore not possible to draw any firm conclusions about the exact critical dose levels at which various late deterministic effects appear. Most data concerning such effects are obtained from the clinical follow-up of groups of patients treated for paediatric tumours. These groups generally comprise small numbers of patients of different ages and who were followed for different lengths of time. The treatment modalities have usually included surgery, radiotherapy and chemotherapy, and it is not always possible to single out the effect of radiation alone. A variety of factors complicate the study of a possible association between effect and dose, including the underlying disease and associated clinical findings, other treatment modalities, the impact of illness on body image and lack of school attendance.

133. The methods for assessing a given deterministic effect vary greatly, and this makes comparisons between different studies difficult. Based on the available findings, some general conclusions can be drawn. Children appear to be more sensitive to radiation than adults, and, in general, younger children are more sensitive than older children. Radiation doses indicated in this Annex are usually given with fractionation over a period of several weeks. The deterministic effects following radiation exposures in childhood are summarized in Table 9.

134. *Brain.* Leukoencephalopathy, microangiopathy and cortical atrophy have been reported after cumulative brain doses of 18 Gy or more given in 1.8-2 Gy fractions or after 10 Gy given as a single whole-body exposure. Necrosis occurs after considerably higher doses, and a whole-brain dose of 54 Gy in 2 Gy fractions over six weeks is generally considered to be a critical dose for radiation-induced necrosis in children older than 5 years. For children 3-5 years old the dose should be reduced by about 20%, and for children less than 3 years old the dose should be reduced by about 30%. Brain doses of 18 Gy or more of fractionated radiotherapy have been associated with neuropsychologic effects and decline in IQ.

135. *Endocrine system.* The most important endocrine effects of radiation exposure are impaired secretions of growth hormone, thyroid-stimulating hormone, gonadotropins, thyroid hormones and oestrogens/testosterone. Impaired growth has been observed after fractionated radiotherapy to the brain with cumulative doses of more than 24 Gy and after >1 Gy in a single exposure among the survivors of the atomic bombings in Japan, whereas impaired growth hormone secretion has been observed in patients after 18 Gy of fractionated radiotherapy. Hypothyroidism has been reported in leukaemic children receiving thyroid doses of 1-2 Gy over 2-2.5 weeks from cranial radiotherapy and chemotherapy. In subjects under 20 years at the time of the bombings in Hiroshima and Nagasaki, those exposed to greater than 1 Gy had a significantly higher incidence of thyroid disorders than those in the unexposed control group. No study has so far demonstrated hypothyroidism in children after a thyroid dose <1 Gy. There are insufficient data on the effects of $^{131}I$ to determine a possible threshold dose for the induction of hypothyroidism.

136. *Gonads.* The effects of radiation on the testis and ovary are age- and dose-dependent. The radiation dose required to ablate ovarian function seems to be around 20 Gy for girls; because of the greater number of oocytes in young girls, higher doses are tolerated before castration. Infertility occurs in approximately one third of girls receiving 4 Gy and in almost all women over 40 years of age. Ovarian failure has been documented in prepubertal girls following 10 Gy of whole-body irradiation and occurs in all pubertal girls. Amenorrhea has been observed in two thirds of girls

who have received 3 Gy on average to both ovaries and in more than 10% of patients exposed in childhood with ovarian doses of 0.5 Gy on average. Ionizing radiation appears to have its greatest effect on the germ cells in the testes rather than on the Leydig cells. Testicular function may be compromised at doses as low as 0.5 Gy. Leydig cell function appears more resistant to ionizing radiation, and impaired function occurs only after 10 Gy or more. Whole-body irradiation has been shown to produce primary gonadal failure of various degrees in the majority of boys receiving 10 Gy, regardless of pubertal status. In most of these patients, Leydig cell function appeared adequate.

137. *Skeleton.* Skeletal changes generally occur at doses >20 Gy from fractionated radiotherapy and include scoliosis, kyphosis, slipped femoral epiphyses, hypoplasia, growth retardation and dental problems. A dose exceeding 20 Gy is required to arrest encondral bone formation, and doses of 10-20 Gy cause partial arrest of bone growth. There is little alteration in bone growth below 10 Gy of fractionated exposure.

138. *Eye.* Data on cataracts from radiation exposure in childhood are scarce. Cataracts have been observed after a lenticular dose of 2 Gy. Whole-body exposure of 10 Gy in childhood has been associated with cataract formation.

139. *Cardiovascular system.* The few data available on cardiovascular effects suggest that 40 Gy can be considered as a threshold for clinical cardiomyopathy in children. A considerable proportion of patients have abnormal cardiac function without clinical evidence of such dysfunction, and the critical dose for cardiovascular effects is therefore probably lower than 40 Gy. The anthracyclines are cardiotoxic and enhance the effects of mediastinal irradiation.

140. *Lung.* The lung is a radiosensitive organ, and a lung dose of 15 Gy in 1.5 Gy fractions has generally been considered as the maximum safe dose in children receiving radiotherapy to the whole lung and simultaneous treatment with actinomycin D. However, restrictive lung changes have been reported after doses of 11 Gy or more in children treated for paediatric tumours, and reduced total lung capacity has been found after 8 Gy or more to the whole lung with similar fraction size.

141. *Breast.* Breast hypoplasia has been reported in more than 50% of children less than 4 years of age receiving breast irradiation with doses of about 2 Gy. Higher doses cause increased frequency and severity of impaired breast development.

142. *Liver and gastro-intestinal tract.* Clinical radiation-induced hepatitis has rarely been reported at doses below 30 Gy at 0.9-1.0 Gy fractions in five fractions per week. However, case-reports have presented data on sometimes fatal radiation-induced liver damage in children after fractionated radiotherapy with 24-25 Gy in 1.1-1.4 Gy fractions with concomitant use of anthracyclines. Non-fatal liver disease has been reported after of 12 Gy or more in children who also received chemotherapy. Radiation effects in the gastro-intestinal tract include fibrosis, stricture, perforation and formation of fistulae. There are hardly any data available on such effects in children.

143. *Kidney.* Late effects following irradiation of the kidney include nephritis, tissue necrosis and fibrosis, renal dysfunction and hypertension. The threshold dose for effects in children has been estimated to be 16-18 Gy of fractionated radiotherapy to the entire kidney in combination with chemotherapy, but it may be even lower since radiation nephritis has been reported after fractionated doses of 14 Gy and reduced creatine clearance after 12 Gy.

144. *Bone marrow.* There are insufficient data on the effects of ionizing radiation on bone marrow and on immune function in children to determine or even suggest critical dose levels for the appearance of clinical deterministic effects.

**Table 1**
**Estimates of doses for 1%-5% and 25%-50% incidences of clinically detrimental deterministic effects in adults at five years after radiation exposure [a]**
[I1, R2]

| *Organ* | *Treatment field* | *Injury at five years* | *Approximate dose (Gy)* | |
|---|---|---|---|---|
| | | | *Effect in 1%-5% of patients* | *Effect in 25%-50% of patients* |
| Bone marrow | Whole | Hypoplasia | 2 | 5 |
| Ovary | Whole | Permanent sterility | 2-3 | 6-12 |
| Testis | Whole | Permanent sterility | 5-15 | 20 |
| Lens | Whole | Cataract | 5 | 12 |
| Kidney | Whole | Nephrosclerosis | 23 | 28 |
| Liver | Whole | Liver failure | 35 | 45 |
| Lung | lobe | Pneumonitis, fibrosis | 40 | 60 |
| Heart | Whole | Pericarditis, pancarditis | 40 | >100 |
| Thyroid | Whole | Hypothyroidism | 45 | 150 |
| Pituitary | Whole | Hypopituitarism | 45 | 200-300 |
| Brain | Whole | Necrosis | 50 | >60 |
| Spinal cord | 5 $cm^2$ | Necrosis | 50 | >60 |
| Breast | Whole | Atrophy, necrosis | >50 | >100 |
| Skin | 100 $cm^2$ | Ulcer, severe fibrosis | 55 | 70 |
| Eye | Whole | Panophthalmitis | 55 | 100 |
| Oesophagus | 75 $cm^2$ | Ulcer, stricture | 60 | 75 |
| Bladder | Whole | Ulcer, contracture | 60 | 80 |
| Bone | 10 $cm^2$ | Necrosis, fracture | 60 | 150 |
| Ureter | 5-10 cm | Stricture | 75 | 100 |
| Muscle | Whole | Atrophy | >100 | |

[a] Based on responses of patients conventionally treated with fractionated therapeutic x- or gamma-irradiation.

**Table 2**
**Estimates of doses for 1%-5% and 25%-50% incidences of clinically detrimental deterministic effects in children at five years after radiation exposure [a]**
[I1, R2]

| *Organ* | *Treatment field* | *Injury at five years* | *Approximate dose (Gy)* | |
|---|---|---|---|---|
| | | | *Effect in 1%-5% of patients* | *Effect in 25%-50% of patients* |
| Breast | 5 $cm^2$ | No development | 10 | 15 |
| Cartilage | | Arrested growth | 10 | 30 |
| Bone | 10 $cm^2$ | Arrested growth | 20 | 30 |
| Muscle | | Hypoplasia | 20-30 | 40-50 |

[a] Based on responses of patients conventionally treated with fractionated therapeutic x- or gamma-irradiation.

**Table 3**
**Effects on the brain in children treated for acute leukaemia detected by computed tomography scans**

| *Treatment* | | *Number of patients* | *Abnormalities* | | *Type of brain abnormalities detected* | *Ref.* |
|---|---|---|---|---|---|---|
| *Radiotherapy dose to the brain (Gy)* | *Chemotherapy* [a] | | *Number* | *Per cent* | | |
| 24 | IT | 23 | 13 | 56 | Intracerebral califications, cortical atrophy | [B6] |
| 24 | IT | 19 | 11 | 56 | Intracerebral califications, cortical atrophy | [P5] |
| 24 | IT | 24 | 13 | 54 | Intracerebral califications, cortical atrophy | [R5] |
| 24 | IT | 32 | 17 | 53 | Intracerebral califications, cortical atrophy | [P7] |
| 24 | IT | 72 | 35 | 49 | Intracerebral califications, cortical atrophy | [C14] |
| 24 | IT | 14 | 6 | 43 | Intracerebral califications, cortical atrophy | [E1] |
| 24 | IT | 25 | 10 | 40 | Intracerebral califications | [M5] |
| 24 | IT | 30 | 12 | 40 | Cortical atrophy | [B5] |
| 24 | IT | 45 | 11 | 24 | Intracerebral califications, cortical atrophy | [S55] |
| 24 | IT | 19 | 3 | 16 | Cortical atrophy | [O3] |
| 24 | IT | 44 | 5 | 11 | Intracerebral califications | [O13] |
| 20 | IT | 27 | 1 | 4 | Cortical atrophy | [D24] |
| 18 | IT | 55 | 5 | 9 | White matter hypodensity, cortical atrophy | [O2] |
| 0 | IV+IT | 12 | 3 | 25 | Cortical atrophy | [E1] |
| 0 | IV+IT | 43 | 8 | 19 | Cortical atrophy | [O14] |
| 0 | IV+IT | 23 | 1 | 4 | Cortical atrophy | [P5] |

[a] IT = intrathecal methotrexate and IT + IV = intrathecal and intravenous methotrexate.

**Table 4**
**Effects on the brain of radiotherapy to the central nervous system in children**

| *Effect* | *CNS therapy* | *Comments* | *Ref.* |
|---|---|---|---|
| Leukoencephalopathy | >20 Gy in 1.5-2.0 Gy fractions plus systemic methotrexate 10 Gy whole-body irradiation | Young children more sensitive | [M6, P3, R4] |
| Mineralizing microangiopathy | >15 Gy in 1.5-2.0 Gy fractions | Young children more sensitive | [B4, D5] |
| Cortical atrophy | >18 Gy in 1.5-2.0 Gy fractions and intrathecal methotrexate | Severest atrophy in young children | [C3, D3, D5, K2] |
| Cerebral necrosis | >54 Gy in 1.8 Gy fractions | | [B35, K2] |

Table 5
Average adult heights of individuals exposed in the lower dose groups in Hiroshima and Nagasaki and under 18 years old at the time of bombing
[B14]

| *Sex* | *Age at time of bombing (years)* | *Average adult height (cm) in dose group* | | | |
|---|---|---|---|---|---|
| | | *0 Gy* | *0-0.09 Gy* | *0.10-0.99 Gy* | *> 1.00 Gy* |
| **Hiroshima** | | | | | |
| Male | 0-5 | 166.4 [a] | 166.1 [a] | 165.9 [a] | 161.5 |
| | 6-11 | 162.3 | 164.2 | 166.3 | 162.2 |
| | 12-17 | 164.3 | 163.6 | 164.3 | 163.4 |
| Female | 0-5 | 153.3 [b] | 153.6 [a] | 152.9 [b] | 150.4 |
| | 6-11 | 152.5 | 153.6 [b] | 153.6 [b] | 150.5 |
| | 12-17 | 152.1 | 152.3 | 152.2 | 151.9 |
| **Nagasaki** | | | | | |
| Male | 0-5 | 166.2 | 166.2 | | 166.2 |
| | 6-11 | 164.0 | 164.1 | | 162.7 |
| | 12-17 | 163.2 | 163.9 | | 161.8 |
| Female | 0-5 | 152.8 | 152.9 | | 150.8 |
| | 6-11 | 152.4 | 151.3 | | 151.5 |
| | 12-17 | 151.8 | 151.6 | | 151.2 |

[a] Significantly different ($p < 0.01$) compared with the average of group exposed to > 1.00 Gy.
[b] Significantly different ($p < 0.05$) compared with the average of group exposed to > 1.00 Gy.

Table 6
Average adult heights of children exposed in the higher dose group in Hiroshima and under 18 years old at the time of bombing
[B14]

| *Sex* | *Age at time of bombing (years)* | *Average adult height (cm)* [a] | |
|---|---|---|---|
| | | *In dose group 1.0-2.49 Gy* | *In dose group > 2.5 Gy* |
| Male | 0-5 | 164.2 (12) | 159.8 (18) |
| | 6-11 | 162.7 (13) | 161.5 (10) |
| | 12-17 | 163.2 (43) | 163.5 (46) |
| Female | 0-5 | 151.8 (11) | 149.8 (23) |
| | 6-11 | 150.4 (17) | 150.5 (11) |
| | 12-17 | 152.1 (58) | 151.7 (59) |

[a] Number of individuals in parentheses.

Table 7
Average height of individuals followed in the Adult Health Study and under age 10 years at the time of bombing [14]

| *Sex* | *Dose range (Gy)* | *Average adult height (cm) ± standard deviation* [a] | |
|---|---|---|---|
| | | *Hiroshima* | *Nagasaki* |
| Male | < 0.01 | 164.9 ± 6.02 (52) | 163.3 ± 5.72 (53) |
| | 0.01-0.99 | 166.4 ± 6.18 (91) | 164.4 ± 5.43 (31) |
| | 1.00-2.99 | 164.4 ± 5.55 (20) | 165.1 ± 5.04 (31) |
| | 3.00-6.00 | 161.0 ± 5.18 (20) | 164.3 ± 6.64 (18) |
| Total | | 164.9 ± 6.11 (148) | 164.1 ± 5.61 (128) |
| $\chi^2$ statistical test [b] | | 1.04 (p > 0.05) | 1.90 (p > 0.05) |
| Female | < 0.01 | 153.0 ± 5.54 (74) | 152.8 ± 4.81 (53) |
| | 0.01-0.99 | 153.6 ± 5.84 (91) | 152.1 ± 4.25 (38) |
| | 1.00-2.99 | 151.1 ± 5.34 (25) | 151.5 ± 5.26 (32) |
| | 3.00-6.00 | 149.9 ± 6.90 (20) | 149.8 ± 5.33 (19) |
| Total | | 152.7 ± 5.87 (210) | 151.9 ± 4.89 (142) |
| $\chi^2$ statistical test [b] | | 2.00 (p > 0.05) | 2.00 (p > 0.05) |

[a] Number of individuals in parentheses.
[b] Homogeneity test of variance for four dose groups; df = 3.

Table 8
Thyroid hypofunction in individuals exposed to fallout radiation in the Marshall Islands [C16]

| *Age at exposure (years)* | *Incidence of thyroid hypofunction for various estimated doses to the thyroid* | | | |
|---|---|---|---|---|
| | *0 Gy* | *< 1.00 Gy* | *1.00-2.00 Gy* | *≥ 2.00 Gy* |
| <10 | 1/229 (0.4%) | 0/64 (0%) | - | 9/29 (31%) |
| ≥10 | 1/371 (0.3%) | 1/100 (1%) | 1/12 (8%) | 4/45 ( 9%) |

**Table 9**
**Estimates of lowest radiation doses associated with late deterministic effects from exposure in childhood to ionizing radiation, usually in the form of fractionated radiotherapy**

| *Organ* | *Effect* | *Dose (Gy)* |
|---|---|---|
| Testis | Germ cell depletion<br>Leydig cell dysfunction | 0.5<br>10 |
| Ovary | Amenorrhea<br>Infertility<br>Ablation | > 0.5<br>4<br>20 |
| Thyroid gland | Hypothyroidism | > 1 |
| Brain | Cognitive functions<br>Histopathologic changes<br>Neuroendocrine effects | 18<br>18, (10 [a])<br>> 18, (> 1 [a]) |
| Breast | Hypoplasia | 2 |
| Eye | Cataract | 2 |
| Lung | Fibrosis | 8-11 |
| Liver | Fibrosis | 12 |
| Kidney | Reduced creatinine clearance | 12 |
| Skeleton | Skeletal changes | 10 |
| Cardiovascular system | Cardiomyopathy | 40 |
| Bone marrow | Hypofunction | Insufficient data available |

[a] Single whole-body exposure.

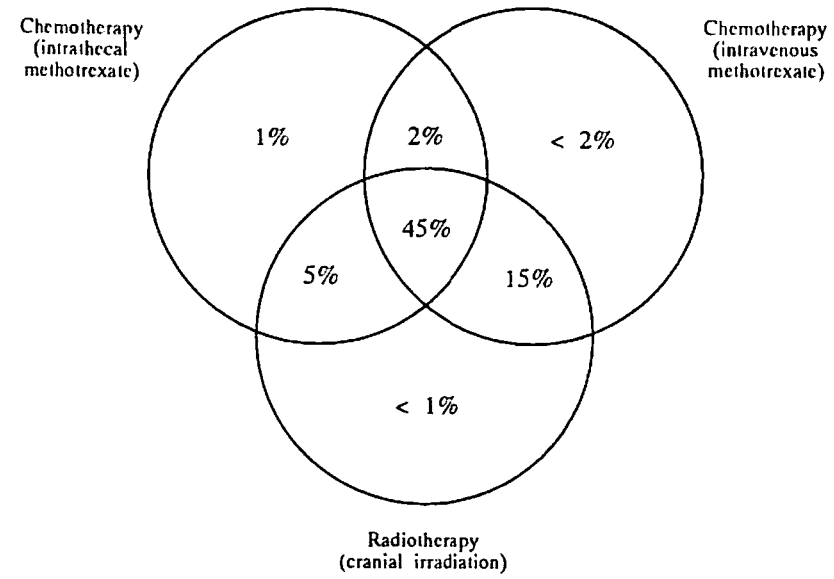


Figure I.
Approximate incidence rates of clinical leukoencephalopathy in patients treated by cranial irradiation, chemotherapy or combination therapies.
[B4]

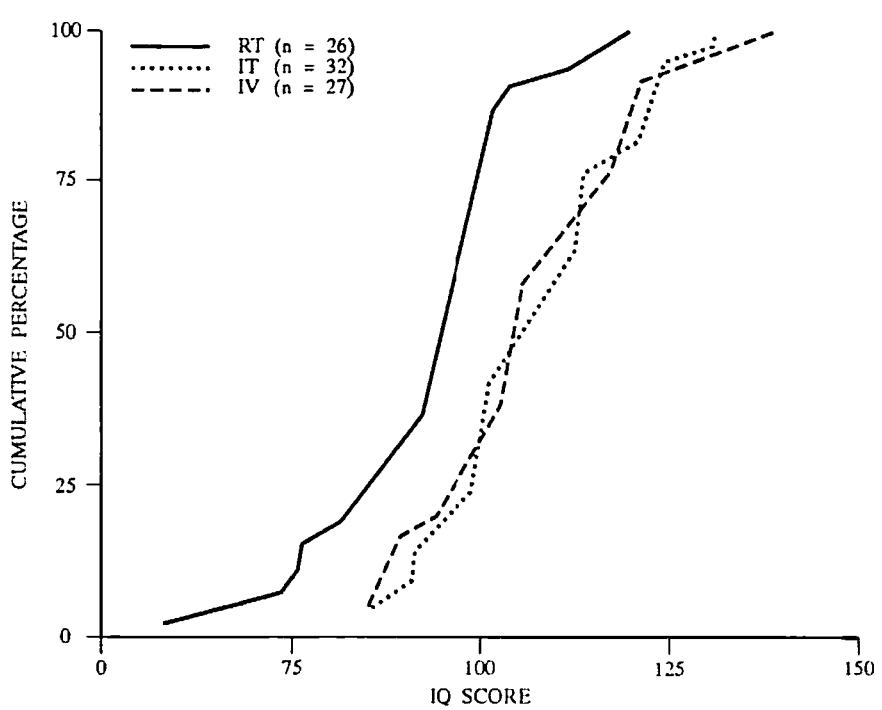


Figure II.
IQ score distribution in children treated for acute lymphocytic leukaemia by cranial radiotherapy (RT), intrathecal methotrexate (IT) or intravenous methotrexate (IV).
[B2]

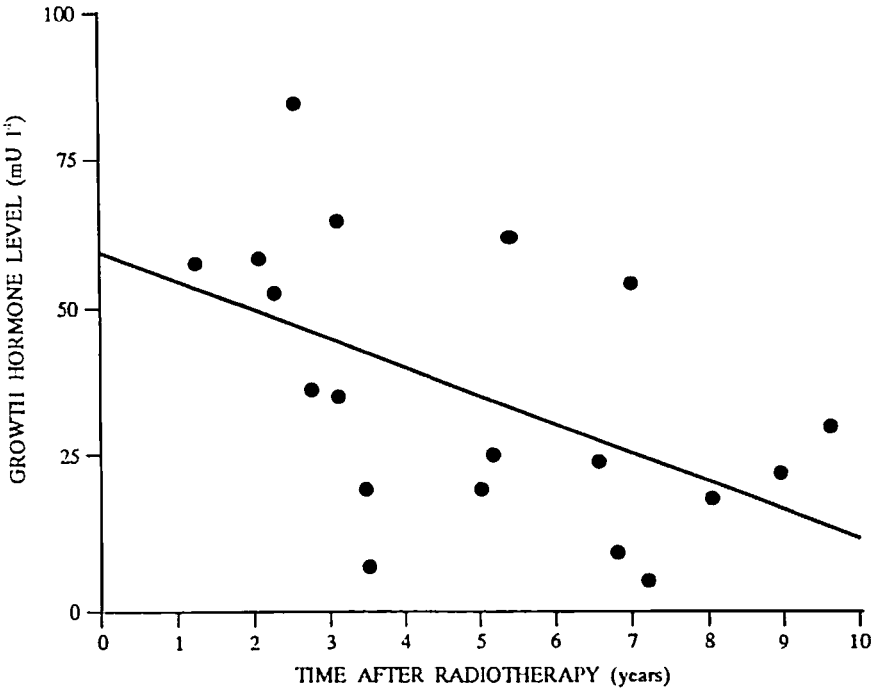


Figure III.
Maximum growth hormone response to growth-hormone-releasing hormone in children treated for brain tumours by radiotherapy.
[L6]

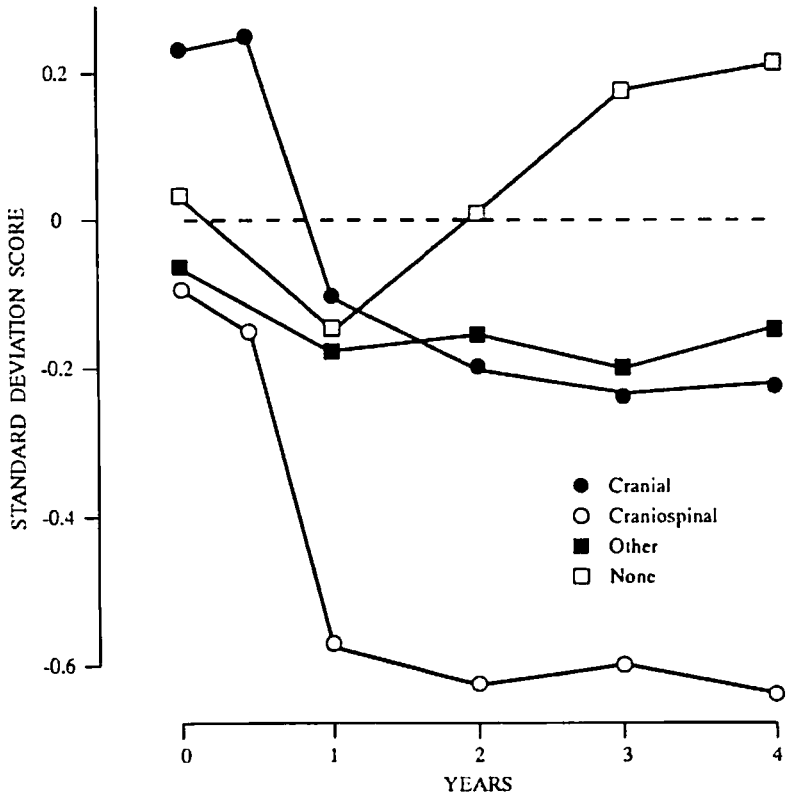


Figure IV.
Mean standard deviation score of height in children treated for malignant disease by radiotherapy to various sites. Results for those receiving cranial and craniospinal treatment were significantly lower ($p < 0.001$) at 1-4 years than at the time of initial treatment.
[G2]

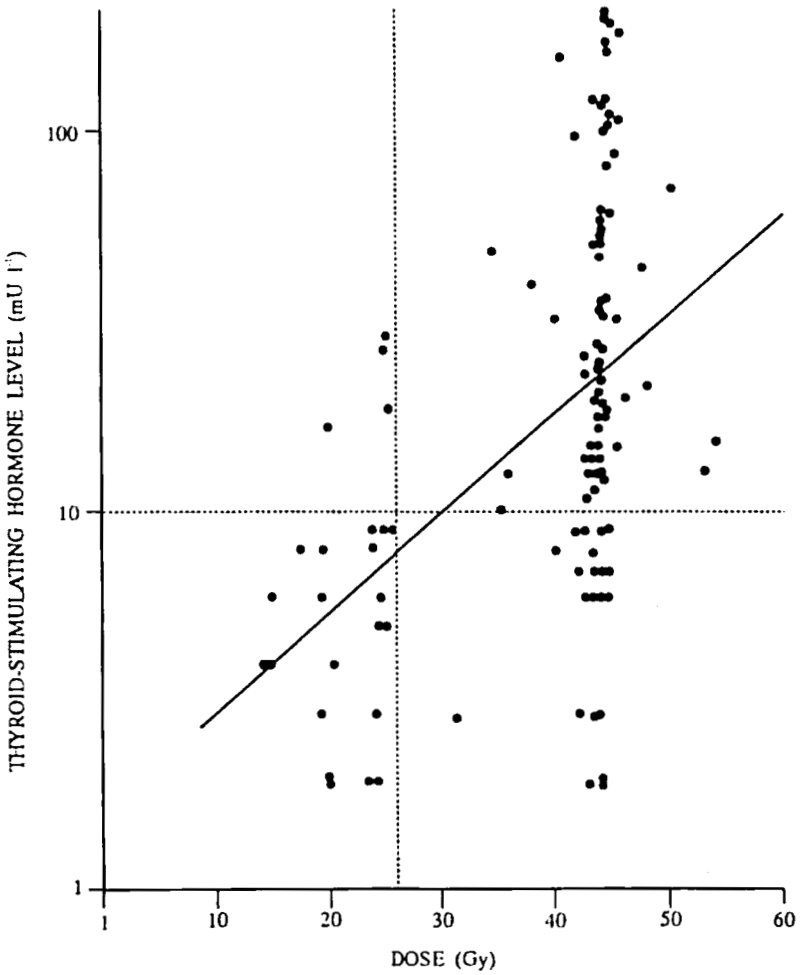


Figure V.
Thyroid-stimulating hormone levels in 116 patients aged 16 years or less treated for Hodgkin's disease by radiotherapy.
[C15]

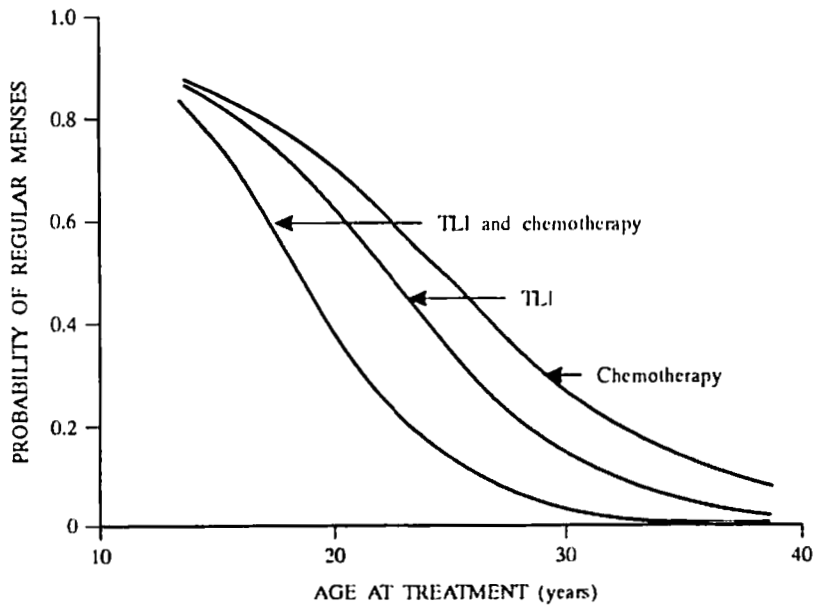


Figure VI.
Probability of regular menses in women treated for Hodgkin's disease by total lymph irradiation (TLI) and/or chemotherapy.
[H12]

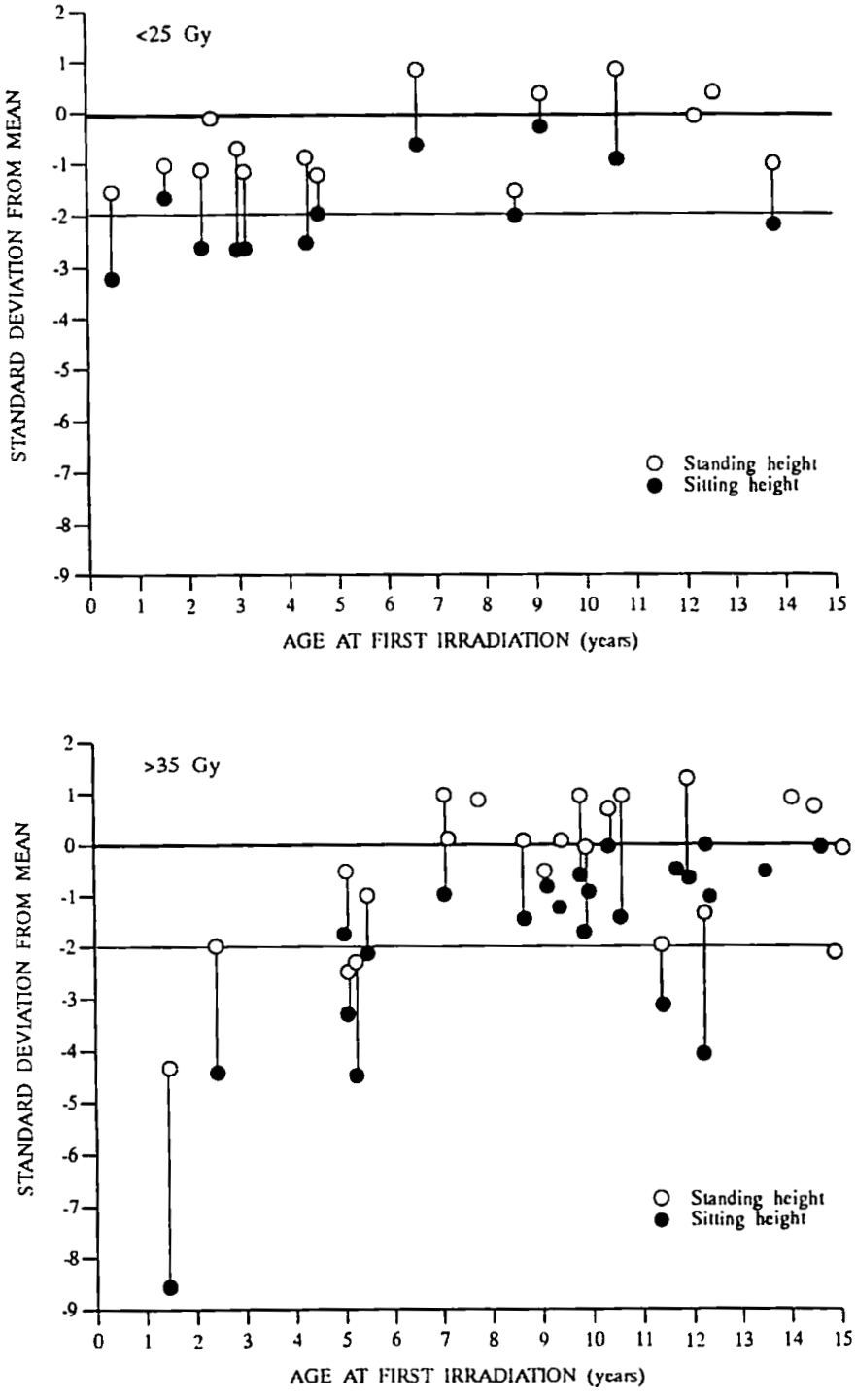


Figure VII.
Deviation from mean standing and sitting heights in children treated by radiotherapy with <25 Gy or >35 Gy.
[P10]

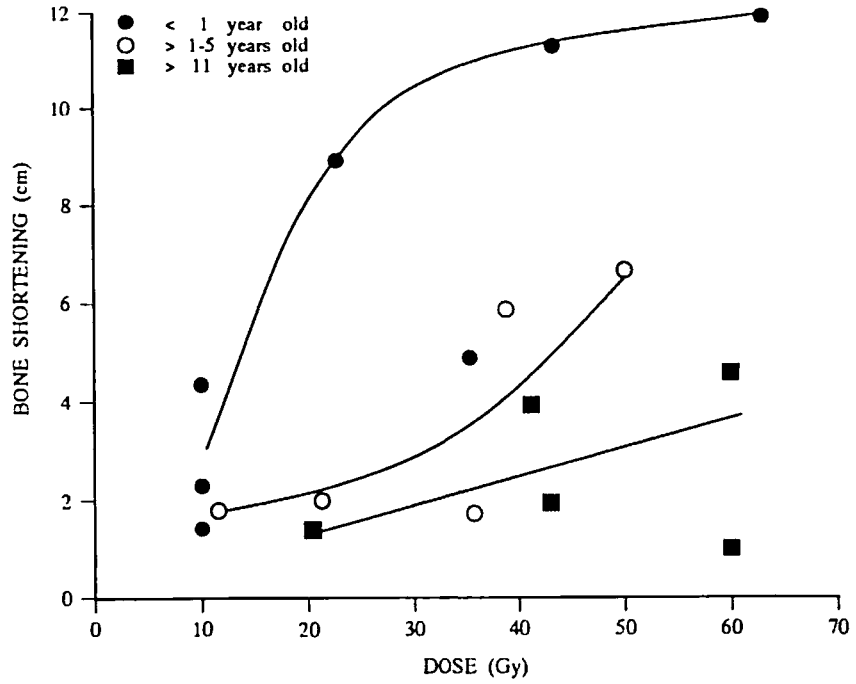


Figure VIII.
Dose-effect relationship for bone shortening in children treated by radiotherapy that included epiphysial plate irradiation.
[G8]

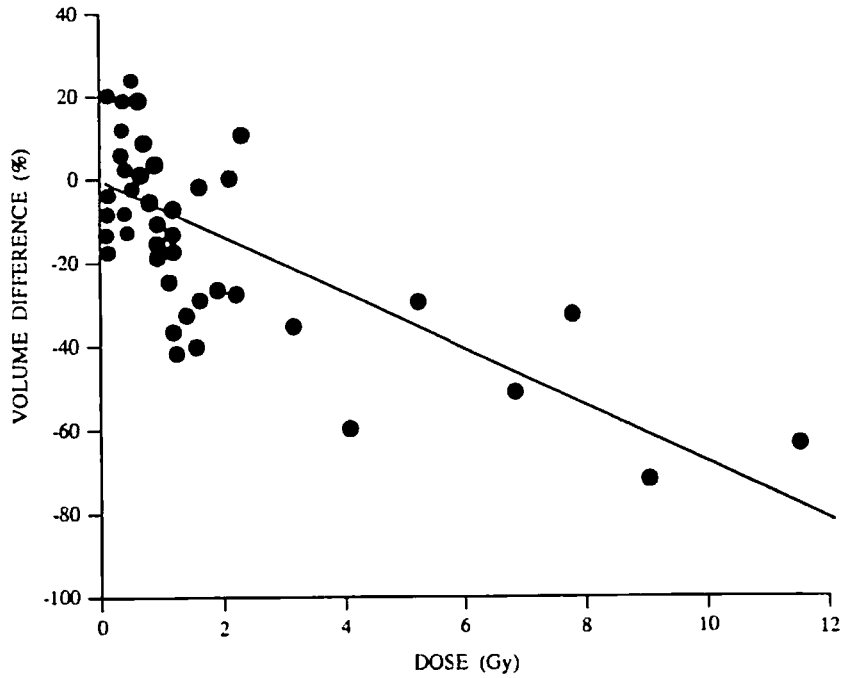


Figure IX.
Difference in breast volume in 53 women treated in childhood for haemangioma by radiotherapy of the breast region.
[F9]

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