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Biological Effects after Prenatal Irradiation (Embryo and Fetus)

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By

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CONTENTS

EXECUTIVE SUMMARY

(a) The ICRP considered the risks following radiation exposure during prenatal development in its 1990 Recommendations (*Publication 60*). Since that publication, new experimental animal data on biological effects and re-evaluations of human studies after prenatal irradiation have been published. A critical review of these new data has been performed by a task group, and the key findings are listed below.

- The mammalian embryo and fetus are highly radiosensitive during the entire period of prenatal development. The nature and severity of induced biological effects depends on the developmental stage during which the radiation exposure takes place.
- The risk of lethality of the developing organism is highest during the pre-implantation period (up to day 10 postconception). This effect is mainly due to killing of blastomeres, caused by chromosomal damage. In certain mouse strains, radiation exposure induces genomic instability after doses as low as 0.5 Gy of low-linear-energy-transfer (LET) radiation. This form of genomic instability can be transmitted to the next generation.
- In mouse strains with genetic predispositions for specific malformations, it has been observed that these malformations are also induced by ionising radiation during the pre-implantation period. In particular, this is the case after irradiation of zygotes where no threshold is observed in the dose response.
- Malformations are mainly induced after exposure during the period of major organogenesis. In certain stages of major organogenesis (weeks 3–7, post-conception for human development), enhanced sensitivity exists for certain specific malformations. During this developmental period, growth retardation is caused by irradiation. The regenerative capacity decreases as differentiation of tissues and organs progresses.
- After irradiation during the pre-implantation period and the period of major organogenesis, relative biological effectiveness (RBE) values for fast neutrons range from 3 to 10. After chronic and fractionated exposures with low-LET radiation during these prenatal stages, dose-rate effectiveness factors (DREF) in the range of 4–10 have been observed. Adaptive responses could not be observed for embryonic development and chromosomal aberrations during these developmental stages. No human data are available for these parameters and phenomena.
- Comprehensive experimental studies have been performed on the development of the central nervous system in rodents, and on a more limited scale in primates, in order to evaluate the mechanisms of radiation effects on these developmental processes. Early proliferating neuroepithelia are very sensitive but have a strong capacity for cell substitution and tissue re-organisation which reduces with progressing differentiation.
- Neuronal plasticity and natural redundancy of neurons can also compensate for radiation-induced damage during brain development. The most significant

period is the 'window of cortical sensitivity' in the early and mid-fetal period in rodents and weeks 8–15 postconception in humans. Experimental dose–response studies in rodents for structural and functional endpoints including learning and behavioural changes result in dose–response curves with thresholds in the range of 0.1–0.3 Gy low-LET radiation.

- The experimental data are in good agreement with human data from the Japanese atomic bomb study on severe mental retardation (SMR) after exposures during the most sensitive period (weeks 8–15 postconception). The lower confidence bound on the threshold dose is 0.3 Gy for this effect. A radiation dose of 1 Gy would increase the risk of SMR by about 40%.
- For intelligence quotient (IQ) scores, a linear dose–response model provides a satisfactory fit of data from the atomic bomb cohort with irradiation at weeks 8–15 postconception. The decline in IQ values is about 25 IQ points/Gy in this sensitive period. School achievement is also reduced following exposure of 1 Gy. A threshold dose is not apparent for these effects; however, after radiation doses of 100 mGy, these effects are very small.
- From animal experiments, it can be concluded that radiosensitivity for cancer induction is highest in the late fetal period. Female mice have a higher risk than males.
- In industrialised countries, leukaemias, brain tumours, and lymphomas are the predominant paediatric cancers. Few of these cancers are linked with known genetic predispositions.
- The largest case–control study of cancer after in-utero irradiation, the Oxford Study of Childhood Cancers (OSCC), found that radiation increased all types of childhood cancer by approximately the same degree. The second largest study showed a larger relative risk for leukaemia than for solid tumours, while several cohort studies of in-utero radiation found no clear evidence of radiation-induced childhood cancer. The data from the atomic bomb survivors suggest that the lifetime cancer risk from in-utero exposure may be similar to that from exposure in early childhood.
- The OSCC data suggest that cancer induction is at least as likely following exposure in the first trimester as in later trimesters. From the data published to date, it is not possible to determine tissue-weighting factors in order to define cancer risk in different tissues and organs. Adequate human in-utero exposure data are not available to define the dose and dose-rate effectiveness factor (DDREF) for low-LET radiation or the RBE values for neutron or other high-LET radiations.

(b) These conclusions, which tend to strengthen and supplement the recommendations contained in *Publication 60*, have significant implications for protection of the embryo/fetus. The editorial which prefaces this report provides an interim view from the Commission on these implications.

1. INTRODUCTION

(1) The ICRP reviewed the effects of exposure to ionising radiation during prenatal development of mammals in *Publication 60* '1990 Recommendations of the International Commission on Radiological Protection', and has given its recommendations with respect to regulations for radioprotection of the embryo and fetus on this basis. It has long been known that the developing organism is highly radiosensitive; therefore, special regulations are necessary for pregnant women at work and in public places. As such, many efforts have been undertaken in radiation research in order to improve our knowledge about radiation effects and risks through exposures during prenatal development. The most recent data in this research field will be reported in the following chapters, and possible consequences for radioprotection will be considered.

(2) Due to the characteristics of the various developmental processes and the effects that can be induced by toxic agents, such as ionising radiation, at these developmental stages, prenatal development is divided into three main periods:

- pre-implantation;
- major organogenesis;
- fetal period.

(3) Many experimental and clinical data have shown that the response to radiation exposure is highly dependent on the developmental stage during which this exposure takes place. It is very well known that ionising radiation interferes to a high degree with cell proliferation (Hall, 1994). Therefore, biological systems with a high fraction of proliferating cells show high radiation responsiveness. High rates of cell proliferation are found throughout prenatal development. However, although cell proliferation is a key process for the development of radiation effects, the sensitivity of the embryo and fetus is also determined through processes of differentiation and cell migration, and the radiation effects on these biological processes. Therefore, radiation effects in these periods will be considered. Development of the central nervous system starts during the first weeks of embryonic development and continues through the early postnatal period. Thus development of the central nervous system occurs over a very long period, during which it is especially vulnerable. It has been found that the development of this system is very frequently disturbed by ionising radiation, so special emphasis has to be given to these biological processes.

(4) Furthermore, studies have been conducted regarding the extent to which radiation carcinogenesis is possible, which cancers will develop, and whether there are developmental periods with different radiosensitivities with respect to these events. It is well known that the cancer risk is very high after small children are exposed to radiation, and the patterns of cancers are different from those of adults. Questions arise regarding whether this high radiosensitivity also exists for radiation exposures during prenatal development, and whether some embryonal/fetal tissues or organ systems are more radiosensitive than others.

(5) The analysis of risk from prenatal exposures has to be performed on the basis of the developmental stage during which the exposure takes place. For such a risk analysis, precise knowledge about the specific development of the species and the time periods is necessary, and extrapolations have to be conducted from animal experiments to the human situation on the basis of specific developmental stages. Figure 1.1 shows the effects of radiation exposure during prenatal development with regard to lethality and abnormalities.

(6) The highest radiosensitivity with respect to lethality occurs after irradiation during the pre-implantantion period. This effect decreases during major organogenesis, while gross malformations (abnormalities) develop after exposures during this second phase, and no abnormalities and little lethality is observed after radiation exposures during the fetal period. However, the newer data presented in this report indicate that this scheme needs to be seen in a more differentiated way on the basis of new results after exposures during these phases of development.

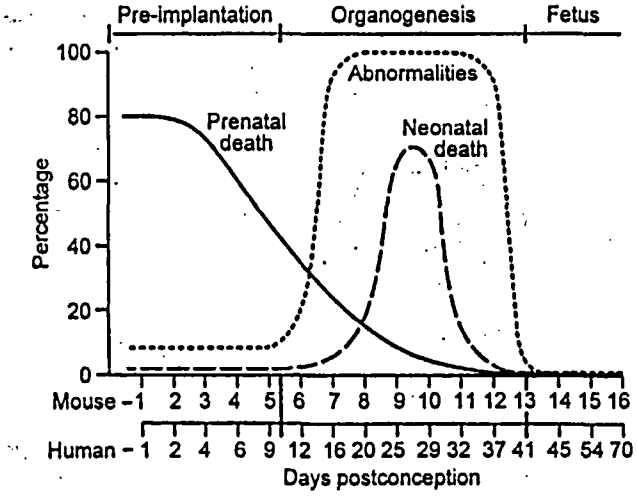

Fig. 1.1. The occurrence of lethality and abnormalities in mice after a prenatal radiation exposure of about 2 Gy, given at various times postconception. The two scales for the abscissa compare developmental stages in days for mice and humans (redrawn from Hall, 1994 with the permission of Hall and the publisher).

1.1. Reference

Hall, E.J. (1994) *Radiobiology for the radiologist, 4th ed.* J.B. Lippincott Co., Philadelphia, PA.

2. RADIATION EFFECTS AFTER EXPOSURE DURING THE PRE-IMPLANTATION PERIOD

2.1. Introduction

(7) For analysis of radiation risk during the pre-implantation period, no observations in humans are available, as conception is not noticed at that time. Therefore, the risk analysis can only be achieved on the basis of animal experiments which have mainly been performed with mice and rats. However, with respect to the pre-implantation period, the advantage is that the duration and general biological processes (cf. cell proliferation and differentiation) during this period are very similar for most mammalian species. Thus the duration of the pre-implantation period is 5 days for mice, 7 days for rats, and 8 days for humans (SSK, 1985; Streffer and Molls, 1987), although the duration of total prenatal development varies to a high degree. At first sight, the pre-implantation period is determined by cell proliferation processes from the zygote (one cell) to the hatched blastocyst (100 cells in mice, 250 cells in humans). The hatched blastocyst is then implanted into the uterus for further development (Carlson, 1994).

(8) After the sperm enters the oocyte, the second meiotic division will be completed and two pronuclei are formed with the male and female genome, respectively. Following the period of DNA synthesis in which the genetic material is doubled in the separated pronuclei, the pronuclei fuse and a diploid genome is formed. After cell division leading to the two-cell embryo, a comparatively long cell cycle time of around 20 h follows before the two-cell embryo divides into four cells. Once the first cell division has occurred, the first gene activation processes occur. Further cell divisions follow comparatively quickly with a cell cycle time of around 12 h (Streffer et al., 1980; Streffer and Molls, 1987). When the pre-implantation embryo reaches around 16 cells, the morula is formed. This occurs around 60–70 h postconception. With the ongoing cell divisions, the single cells become smaller but the total size of the embryo remains almost constant.

(9) The zygote and the later pre-implantation embryo are surrounded by the zona pellucida. This protects the embryo but also makes it necessary that the embryo has its own resources for cellular maturation. There is apparently little interaction between the embryo and the mother during this developmental period. After morulation, the formation of the blastocyst takes place at around 80 h postconception in mice and 100–120 h postconception in humans. During the period when the hatching of the blastocyst from the zona pellucida takes place, differentiation into the embryoblast and trophoblast is progressing and becomes largely completed (Carlson, 1994).

(10) These rapid cell proliferation processes are very similar in all mammals. Modern molecular biological techniques have shown that the first gene expression processes in the newly developing embryo occur during the two-cell and four-cell stages, and the activity of gene expression increases over the following hours and days (Carlson, 1994).

(11) Radiation effects during the developmental period have mainly been observed in mice and rats, but data from rabbits and dogs are also available. Radiation can

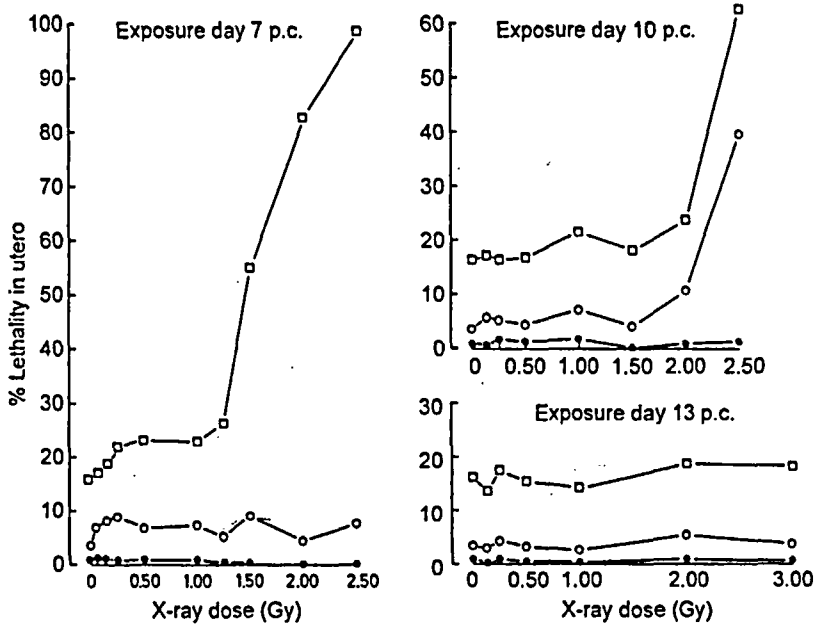

Fig. 3.2. Dose–response curves for intra-uterine lethality of mice after x irradiation on different days of development. Curves represent cumulative percentages for lethality during perinatal (●), fetal (○), or embryonic stages (□). The upper curve thus shows total prenatal lethality at the same stage in each graph. Percentage values are related to the total number of implantations per group visible shortly before birth (Konermann, 1987 with permission from Elsevier). p.c., postconception.

cited above, whereas implications of individual variability within the lower dose range have obviously been disregarded in the past.

Malformations in utero

(53) Biological and experimental side factors taken into account for prenatal lethality are also inherent in the assessment of malformations. In contrast to lethality as a single definite endpoint, further complications arise from both the broad variety of inducible malformations and from the degree of their expression. In the past, numerous experiments with rodents have been performed primarily to determine 'critical periods' for the induction of malformations, mainly based on 'morphological defects visible at birth' or skeletal defects observed in selectively stained fetuses (Russell, 1950, 1954, 1956; Russell and Russell, 1954; Rugh, 1969; Sikov and Mahlum, 1969; Fritz-Niggli, 1972; UNSCEAR, 1977). The phase dependency of malformations can be systematised roughly in so far as systemic defects and more organ-specific defects are concerned. The phase of major organogenesis is preceded by extensive induction processes leading to the formation of the early body axis and the primary central nervous system (see Fig. 3.1). Misinduction may thus cause gross

morphogenetic damage, mainly arising from closure defects of the brain primordia and the neural tube. Among them are brain hernia, spina bifida, and pronounced aplastic (anencephaly) or hyperplastic lesions (exencephaly). During major organogenesis, there is a condensed sequence of differentiation processes during which most organ primordia are formed. The peak incidence of organ-specific malformations is reached in mice after exposure on days 10–11 postconception (Dekaban, 1969; Konermann, 1987).

(54) A major contribution of Russell and Russell (cf. citations above) was to associate the natural sequence of developmental steps with phase-specific irradiation damage. For mice, they defined such 'critical periods of 1 or, more rarely, 2 days' as the 'developmental interval during which radiation must be applied to produce that change if the dose of radiation is the lowest one that gives a detectable incidence of change'. In the sense of a rule, this statement retained more validity than it would appear in view of later criticism (Mole, 1982, 1992). Indeed, Rugh (1966) presented a comprehensive diagram with homologous phases for the induction of malformations in mice and humans containing examples of temporal extended periods. However, in the case of exencephaly, cataracts, and thoraco-abdominal hernias, genetic predisposition of specific animal strains cannot be excluded and it is conceivable that retardation effects such as stunting or microcephaly result primarily from cell loss during extended cell formation periods. Moreover, it is well known that teratogenic induction phases may become longer with increasing dose. Due to these discussions, the term 'stages of enhanced sensitivity' is now preferred to 'critical periods'.

(55) Among the numerous experimental studies on phase-dependent malformations, only a minority have a more or less complete dose–effect series. Due to this and to biological and experimental side factors, discrepancies in the assessment of the lowest teratogenic dose or of thresholds are not surprising, even if data are interpreted in less definite terms as the lowest doses at which various abnormalities have actually been observed. Fritz-Niggli (1972) tabulated literature data on the 'dosis minima' for mice and rats within a dose range of 0.1–0.25 Gy. Low dose responses compiled for different mammals by SSK (1989) refer to doses of 0.25–0.5 Gy in the majority of cases. For mice, 'lowest effective doses' of 0.05–0.25 Gy were assumed by OECD (1988). OECD used the extrapolations to humans made by Kameyama (1982) from mice and rats, although they warned about the danger of such straightforward projections. On the basis of compiled mouse, rat, and human data, Brent and Gorson (1972) estimated the 'minimal malforming doses' for the human embryo to be 0.25–0.5 Gy. Similar to NCRP (1977) and ICRP (2000), they regarded 0.1 Gy at any time during gestation as a practical threshold for the induction of congenital defects.

(56) Evidence derived from dose–response curves shows some inconsistencies. The UNSCEAR report (1977) shows several examples of steep dose–response curves nearing control levels at about 0.5–1.0 Gy and reaching maximum levels at about 2.0 Gy. These refer to externally visible malformations of the head, brain, eye, extremities, digits, or tail. If grouped data of different types of malformation were scored, the curves approximated linearity and had non-zero thresholds. Tribukait and Cekan (1982), performing irradiation experiments with mice on day 9 postconception, were able to establish a well-documented dose–response curve for

grouped external and internal malformations with an inflection point at 0.75 Gy. Below this dose, the proportion of malformed fetuses increased by about 0.1% per 0.01 Gy and increased by 0.57% per 0.01 Gy after the higher doses. In a more recent study, Uma Devi et al. (1994) found, after gamma irradiation of mice on day 11.5 postconception, a significant reduction of head size and brain weight at doses above 0.15 Gy, and detectable levels of microcephaly and microphthalmia at 0.1 Gy. A linear dose response was assumed for these effects within the dose range of 0.05–0.15 Gy.

(57) Studies on skeletal defects have contributed much to the knowledge of low dose responses. This can be attributed to the fact that many single elements of the skeleton show a complex and thus radiosensitive genesis, and also because deviations in the distinctly shaped bone elements are easily detectable. In 1957, Russell extended earlier studies on skeletal defects in mice to doses as low as 0.25 Gy, using a strain with high natural variability in thoracal structures. Various bone elements of the thorax responded to exposures between 0.25 and 1.0 Gy on day 8.5 postconception with significant changes, although not strongly correlated with dose. Peak sensitivity of the vertebral column was reached 1 day earlier. Jacobson (1968) grouped different malformations observed in mice after exposure on day 7.5 postconception according to the skeletal regions (spine, sternum, ribs). He established dose–response relationships with only slight deviations from linearity on the basis of not more than three dose points (0.05, 0.2, and 1.0 Gy). This gave rise to vague speculations that a teratogenic threshold might not exist.

(58) The complexity of skeletal defects has been demonstrated by Knauss (1978) in his comprehensive studies in mice involving a total of 7100 irradiated fetuses and 1100 controls. Exposures to x rays were performed on days 7, 10, and 13 postconception and included small dose intervals from 0.05 to 3.0 Gy. An important point was differentiation of the degree of damage according to physiologically insignificant variations, abnormalities, and gross malformations. If organ-specific abnormalities and gross malformations were scored additively and were related to the total number of surviving fetuses, two basic types of dose–response curve were distinguished. After irradiation on day 7 postconception, the curves for defects to the skull, sternum, and ribs gradually attained a steeper slope, and a similar continuous curvature applies to skull and sternum after irradiation on day 10 postconception. However, a marked inflection point was seen in the curves for vertebral defects on both days of irradiation as well as in the curves for defects to the ribs, legs, shoulder girdle, and pelvis after irradiation on day 10 postconception. The abrupt increase of vertebral defects appeared when doses greater than 0.25 Gy were given on day 7 postconception, whereas all inflection points observed after irradiation on day 10 postconception were shifted to doses of 1.25–1.50 Gy.

(59) Konermann (1982) used these data in order to establish more general dose–effect curves. Seemingly contradictive evidence was found if an anatomically undifferentiated tabulation of the most severe malformation per fetus was made on the one hand, or, on the other hand, the remaining portion of normal fetuses (including smaller variations) was scored (see Figs. IX and X in UNSCEAR, 1986). As visualised on a logarithmic plot of the severely malformed fetuses, the spontaneous

incidence of 0.6% increased by a factor of 3 after exposure to 0.05 Gy on day 7 postconception. Only malformations of the skull and the cervical vertebra contributed to this. Exposure to 0.125 Gy on day 10 postconception was ineffective, while 0.25 Gy doubled the spontaneous malformation rates at this stage. However, from a linear plot of the remaining portion of normal fetuses, pronounced shoulder curves with steeper inclination for exposure on day 7 postconception than for exposure on day 10 postconception were derived. All curves (including the flat curve for exposure on day 13 postconception) showed clear thresholds for transcending the control level in their initial parts, i.e. at about 0.35, 0.9, or 1.1 Gy. A detailed analysis of organ-specific defects revealed that the initial increase of normals above control level was due to radiation-induced stabilisation of the naturally variable rib and sternal segments by which other deviations were numerically overcompensated.

(60) Malformations appear to be a complex criterion for the evaluation of developmental effects, particularly in the low dose range. Most experimental data basically fit sigmoid or shoulder-type curves, indicating thresholds as expected for multicellular, i.e. deterministic, effects (cf. Müller et al., 1994). The position of thresholds for the multitudinous teratogenic phenomena is, however, a matter of controversy. Mole (1992) attributed detailed criticism to most entries on low dose effects cited in UNSCEAR (1977), and also to more recent findings. For teratogenic effects in implanted embryos, he postulated thresholds in the range of 0.40–2.0 Gy after acute x-ray exposure. This is in agreement with older studies in which higher doses were used, and is also consistent with the position of the shoulder region or the inflection points in the dose–response curves mentioned. However, even if it is conceded that genetic predisposition of some animal strains or methodological shortcomings may interfere, evidence of malformations found at considerably lower doses, i.e. within a dose range of 0.05–0.25 Gy, cannot be ignored.

(61) Major sources of disagreement arise obviously from: (i) neglect of individual variability as a basic phenomenon in all organisms including man; and (ii) the way in which teratogenic effects are evaluated. Discontinuity of the initial part of survival curves has been attributed to predisposition to radioresistance (see above), and the occurrence of malformations likewise indicates less morphogenetic stability of subcohorts (cf. Knauss, 1978; Tribukait and Cekan, 1982). It can be anticipated that these phenomena will not become overt unless complete dose–response series with substantial observation numbers are referred to. The second point concerns the mode of evaluation. Skeletal malformations have mainly been related to the total number of surviving fetuses, neglecting spontaneous resorption rates of 10–20% of embryos that are normally included in the evaluation of external malformations. This implies a marked shift in the respective reference levels by which smaller effects may be masked. Moreover, the manifestation of malformations is also affected by embryonic death according to dose and developmental stage (Konermann, 1987). Early embryos with gross inductive effects are thus more likely to be resorbed than locally malformed older embryos (Friedberg et al., 1987). Selection effects interfering with the manifestation of malformations have received only scant attention up to now. Corollaries like these can be taken into account by plots of the remaining portion of normal fetuses related to the respective total implantation number. All

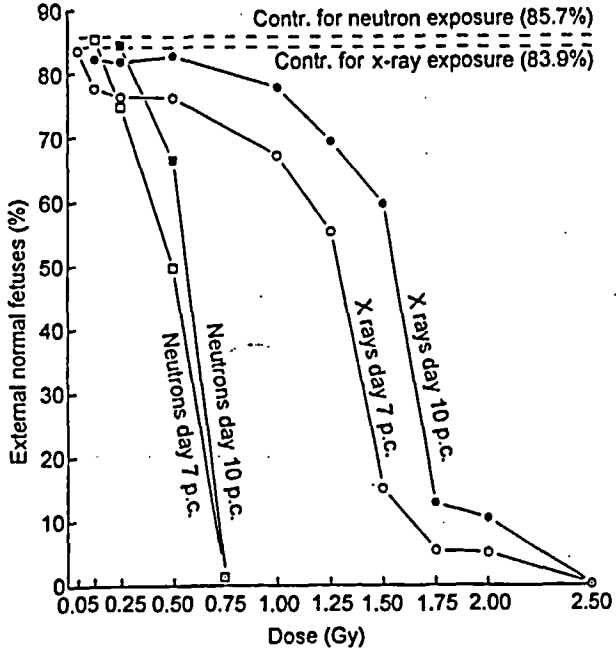

Fig. 3.3. Live fetuses without external defects (%) in mice on day 18 postconception (p.c.) after acute exposure to x rays or neutrons on days 7 or 10 p.c. Percentages are related to the total implantation number of each group (Konermann, 1987 with permission from Elsevier).

types of damage are thus reflected in general terms (Fig. 3.3). After exposure to acute x rays, corresponding dose–effect curves exhibit shoulders preceded by a flat section below the control level. In the case of neutron exposure, steeper curves without shoulders are obtained (see below).

Growth responses

(62) It must not be overlooked that the large amount of data on weight deviations during the perinatal stage only refer to a momentary growth status. Brent and Jensh (1967) took this into account when they defined intra-uterine growth retardation as 'the failure of a fetus to maintain its expected growth potential at any gestational age'. Moreover, radiation-induced deviations in organ and body growth fluctuate and reflect an age-dependent interaction between retardation and compensatory processes, even overlapping the postnatal growth period (Konermann, 1976b). Organismic influences may be involved in retardation effects, but the main mechanism of action is likely to be cell loss (Brent and Gorson, 1972). As a rule, compensation for cell loss is more likely when exposure occurs earlier in development, whereas regenerative capacity diminishes as differentiation proceeds. Concomitant

with incomplete cell substitution, topographically normal but overall retarded organs or fetuses are 'reconstituted' (Rugh, 1962, 1963; Balla et al., 1983).

(63) Among the earliest quantitative studies in growth retardation are those of Russell (1950), who found (in neonatal mice) that the strongest effects after exposure occur during advanced organogenesis, i.e. on days 10.5–11.5 postconception. Doses between 2.0 and 4.0 Gy evoked weight loss of 0.22 g/Gy (normal weight of newborns is about 1.4 g). After lower doses (0.5–2.0 Gy), the highest relative effectiveness to induce fetal weight loss was observed during this phase (Kriegel et al., 1962; Kriegel, 1965). Further studies in mice and rats have shown that doses of 1.0–1.5 Gy may cause growth retardation at any stage after implantation, but the phase of highest sensitivity is not unanimous. Sikov et al. (1969) irradiated rats on day 10 postconception with doses of 0.2 or 1.0 Gy and with 0.5 or 1.85 Gy on day 15 postconception. Birth weight was reduced in all groups with the exception of 0.2 Gy, but postnatal growth was only reduced in rats irradiated on day 15 postconception. Maximum reduction in birth weight together with the highest possible survival rates was achieved in other experiments with rats after exposure to 2.2 Gy on day 18 postconception (Murphree and Pace, 1960; Martin and Murphree, 1969). In contrast, Brent (1977) assumed that rats reach highest sensitivity between implantation and the period of major organogenesis when a dose of 1.5 Gy was applied. Doses of low-LET radiation below 0.3 Gy were not found to affect growth. In view of induction phases, Rugh et al. (1964) performed the most comprehensive study in growth retardation when exposing mice to 1.0 Gy every day between conception and birth. Within an observation period of 4 months after birth, decreased body weight was most pronounced after treatment on day 12 postconception in females and on day 13 postconception in males. The predominant pattern of phase dependency with the highest sensitivity during late organogenesis does not exist after considerably higher doses. Nash and Gowen (1962) observed maximal growth retardation in 40-day-old mice when exposures up to 3.0 Gy were given on days 6.5, 17.5, 14.5, or 10.5 postconception. The sequence of the exposure days corresponded with the degree of retardation observed.

(64) There are only a few studies with a more or less complete dose–response series. Konermann (1982) exposed mice to doses of 0.05–3.0 Gy at various stages between days 2 and 13 postconception and determined growth responses in fetuses near term. Approximately linear relationships between weight loss and doses exceeding 0.5 Gy were established for the different exposure days. Of particular interest was the difference observed in the slopes of these curves, since the gradation was opposite to the discussed susceptibility to lethality and gross induction defects. Exposure on days 5, 7, or 8 postconception thus led to a lower weight loss than exposure on day 13 postconception. The greatest weight loss observed after exposure on days 10 or 11 postconception, consistent with the majority of phase-dependent retardation effects cited above. Remarkably, a slight increase in fetal weight occurred in animals irradiated with doses below 0.5 Gy on days 2–8 postconception, and this weight increase was even more pronounced after exposure to 3.0 Gy on day 2 postconception. In this connection, two different phenomena of growth stimulation have been discussed (Konermann, 1987). Nutrition-dependent overgrowth is a

children from unexposed mothers. Parental socio-economic status was comparable in the three groups. The abdominal/pelvic x-ray examinations were to the stomach and upper gastrointestinal tract (usually including fluoroscopic examinations) for 20 mothers and intravenous pyelography, lumbosacral spine, or genital tract for the remainder. Doses to the organs of interest were estimated to range from 0.5 to 10 cGy, but it was difficult to evaluate fetal doses. The Bayley developmental scales were administered to children aged 1–2.5 years and the McCarthy devlopmental scales to those aged 3–5 years. No group differences were found on neurological examination or on motor or cognitive scores from the Bayley or McCarthy developmental scales. They noted that exposures occurred before week 8 postconception in most cases.

5.7. Discussion

(245) The human data on the neurological effects of prenatal radiation exposure have several constraints that limit the inferences that can be drawn and the precision of the estimates of mental deficits. For one thing, there is almost total reliance on one study. Although the Japanese atomic bomb study is an excellent one, scientific evidence is more persuasive if it is replicable in different populations and circumstances. Second, the atomic bomb data are limited both by the small numbers of study subjects who received high doses and the small numbers in the dose range 1–49 cGy, the critical range for defining the shape of the dose–response curve or the presence/magnitude of a dose threshold. Third, some of the main endpoints have been fairly crude – severe mental retardation as diagnosed by clinical examination, or seizure disorder history obtained by parental report with medical confirmation (but with diagnostic workups that may not have given all the information desired).

(246) In spite of these limitations, two features of the results stand out. There is a clear constellation of effects of prenatal irradiation on the developing central nervous system – mental retardation, decreased intelligence scores and school performance, and seizure disorders. The first three factors showed strong associations with prenatal radiation exposure, while the association for seizure disorders was weaker, perhaps owing to the sparseness and unreliability of the seizure data. The second feature of note is that, for all the endpoints, the period of weeks 8–15 postconception was the most radiosensitive, with the 16–25-week period quite consistently showing sensitivity as well. No indication of mental deficits associated with radiation exposure was seen after week 25 postconception. The atomic bomb data gave no indication of an effect for radiation exposure that occurred during weeks 0–7 postconception, although a compilation of case reports of medical irradiation suggested that there might be such an effect, perhaps limited to very high doses (Dekaban, 1968). However, experimental data do not support an effect on the embryo. A study found no effects on the developing mouse nervous system at doses up to 3 Gy in the first 8 days after fertilisation, which corresponds to approximately the first 8 weeks in humans (Hicks et al., 1952).

(247) The uncertainties in the atomic bomb study estimates of radiation-related mental deficits include a variety of factors (cf. Schull et al., 1990): the sparse data,

especially for mental retardation and convulsions; errors in the ascertainment and diagnosis of mental disorders; errors in estimating doses and postconception age at exposure; the appropriateness of the comparison group; the impact of maternal injury, disease, and nutrition; possible selection factors in whether families emigrated from Hiroshima/Nagasaki; and lack of information about parental intelligence and education. Although these factors may affect estimates of the magnitude of risk in unknown ways, their collective impact is not believed to be sufficient to invalidate the study.

(248) Consideration should be given to the possibility that the mental effects might be due to bias or some indirect mechanism – e.g. nutritional deprivation during gestation or infancy, acute radiation sickness leading to a compromised immune system or depression of fetal haematopoiesis, genetic variation, or physical sensory defects.

(249) Due to the nature of these endpoints (e.g. diagnosis of mental retardation) and of the sources from which they came, plus the fact they were seen only after exposure in a delimited developmental period, it is most unlikely that a diagnostic or reporting bias could account for the results.

(250) Nutritional deprivation is not likely to be the principal cause of the risk seen for several reasons. (i) Although there are data showing that maternal malnutrition may affect brain development, it is primarily limited to marasmic infants who were substantially underweight at birth. There are no reports of underweight or marasmic infants among the atomic bomb survivors (Schull and Otake, 1986). In fact, supplemental rations were provided for pregnant and nursing women in Japan during and after the war, especially among those of >20 weeks gestation. (ii) One might expect nutritional effects to be at least as strong in the third trimester as the second, which was not the pattern of mental deficits seen. (iii) One would expect maternal undernutrition to be relatively independent of radiation dose, in which case it could not account for a dose-dependent effect.

(251) Acute or subclinical radiation sickness has some plausibility as an explanation, particularly the possibility of reduced oxygen transport to the fetal brain caused by depressed haematopoiesis (Mole, 1990). However, there are several reasons why this is not likely to be the main mechanism of damage to the brain. Maternal red blood cell counts may fall to 50–60% of the normal value and haemoglobin levels to 6–8 g, but data on women with sickle cell anaemia who commonly have haemoglobin values in this range do not have an elevated frequency of mentally retarded children (Schull and Otake, 1986). Between week 9 postconception and birth, 80–90% of the haemoglobin found in fetal red cells is fetal haemoglobin which has biochemical characteristics that facilitate maternal oxygen unloading (UNSCEAR, 1993). This maximises oxygen transport to the fetus and provides a protective mechanism against fetal hypoxia.

(252) A fraction of mental retardation is known to be caused by recessive genetic mutations. Consanguineous marriages, which would increase the frequency of expression of these inherited disorders, were common in Hiroshima and Nagasaki at the time of the bombs. Furthermore, the frequency of consanguineous marriages in Nagasaki was inversely related to distance from the bomb hypocentre, which would

create a correlation with dose (Schull, 1958). Schull and Neel (1965) found that children born to first cousins had an IQ that averaged five points less than children from unrelated parents in Hiroshima and Nagasaki. Hence, there is the potential for an indirect genetic effect. Even if one were to make the extreme assumption that an additional 40% of those with higher doses had consanguineous marriages compared with the prevalence in the low-dose group, this would cause an average decrease in IQ of only about two points in the high-dose group, whereas a decrease of the order of 20–30 IQ points was seen in the highest dose group. Thus consanguinity would be, at most, a small contributor.

(253) Another hypothesis might be that possible effects of home environment – acting upon the child's motivation and socialisation – or of key physical impairments, such as visual or auditory defects, are dose related and are causing the effects on intelligence and school performance rather than radiation per se. The hypothesis about home environment seems implausible in that the dose-related intelligence and school deficits were seen only for those irradiated at weeks 8–25 postconception, not across the board. The physical defects might be a possibility, although there is no evidence that this was the case.

(254) Although some of the indirect mechanisms, such as undernutrition, maternal ill health, depressed fetal haematopoiesis, genetic susceptibility, or physical handicaps, could have played some role in producing mental deficits, the severity of the deficits and the critical induction period for them strongly suggests that the radiation insult itself plays the major role in the deficits.

(255) There are a number of gaps in our knowledge concerning the effects of radiation on mental and neurological functioning. The types of potential deficits that have been evaluated are limited. There may be neurological processes that have different critical periods than the 8–15- or 16–25-week periods. If so, endpoints that depend on those processes would likely show a different temporal pattern of induction of radiation effects. For instance, Yoshimaru et al. (1995) noted that spatial memory depends in part on the proper development of the hippocampus formation (dentate gyrus) which arises relatively late in the development of the human brain. The radiation effects for cognitive tests that measure spatial memory may, therefore, show a later critical period than the global assessments of mental functioning have shown.

(256) There are no exposed groups other than the Japanese atomic bomb survivors who have received sufficiently large in-utero brain doses to merit special studies. Among atomic bomb survivors, additional studies could be done. The number of subjects who received brain magnetic resonance imaging (MRI) scans is very small (Schull, 1991); a larger group of people with mental retardation or perhaps low-normal IQ could be studied for structural brain defects. Ideally, MRI could be administered to all of the in-utero-exposed survivors with estimated doses of 0.01 Gy or more who were exposed between weeks 8 and 25 postconception. This would involve about 290 individuals. Examination of this group could provide important insights into the existence of a threshold, as well as the nature of radiation-impaired mechanisms culminating in cortical dysfunction. For example, the number of cases of mental retardation seen in the 16–25-week interval is small; only four with doses of 0.01 Gy or more. Given this limited number, some of these cases, possibly even

all, could have been exposed in the 8–15-week period, with the age at exposure overestimated. This could occur among infants born prematurely. In this regard, it is worth noting that three of the four retarded cases in the 16–25-week period had maternal uterine doses of 1 Gy or more, and the mother undoubtedly experienced some of the symptoms of acute radiation illness. This could have precipitated a premature delivery. If this possibility could be excluded, the logical inference is that the cause of mental retardation among the 8–15 week olds, presumed to be mismanaged neuronal migration, cannot account for the mental retardation seen at the later ages since cortical migration has essentially ceased.

(257) Functional MRI with its capacity to identify activity centres and tracts of neuronal transmission might identify alternative pathways or processes culminating in mental retardation. The everincreasing sensitivity to and localisation of defects with new equipment and techniques could provide valuable new insights. Similarly, a carefully designed series of modern neurocognitive tests administered to a sample from this population might help identify specific cognitive abilities that are compromised by radiation, and this might vary by postconception exposure week.

(258) Nothing is known about individual differences in sensitivity to the effects of radiation exposure on the developing brain. Insofar as the crude statistical indicators of differential sensitivity (namely, changes in variances or skewness) can determine, there do not appear to be strong individual differences in predisposition to mental effects, but these crude indicators probably cannot rule out more subtle differential sensitivity effects.

(259) Little human information is available on the effects of dose protraction or fractionation, or on the effects of radionuclide exposures on the fetal brain. Two studies have evaluated mental retardation among the offspring of mothers who worked at Mayak while pregnant (Patrusheva et al., 1976; Buldakov et al., 1981), and neither found excess mental retardation. Similarly, a study of children exposed in utero to radiation contamination in the Techa River showed no elevation in the prevalence of mental retardation and no association between exposure and scholastic aptitude or achievement (Akleyev and Kisselyov, 2000). Another study of this population (Akleyev et al., 1997) found no association of exposure with neurological signs or either of two neuropsychological tests. Several other studies of mental retardation, IQ (Nyagu et al., 1998; Kolominsky et al., 1999), seizure disorders (Tereschenko et al., 1991, 1992), psychomotor development (Lyaginskaya et al., 1992), and neurological signs (Patrusheva et al., 1973) showed putative associations with prenatal exposure to Chernobyl or Mayak radiation, but the study designs and analyses give too little detail, or methodological weaknesses were noted that limit the confidence in these conclusions. In summary, no clear evidence was found indicating that protracted exposures cause mental sequelae within the limitations of the total radiation doses sustained and the sample sizes studied.

(260) No human information is available on the RBE of prenatal exposure to neutrons or other high-LET radiations in inducing mental deficits.

(261) Two studies have evaluated mental effects of in-utero diagnostic radiation exposure. A Chinese study (Hu and Yao, 1992) found no diminution in IQ following diagnostic radiation exposure to the fetus compared with a matched control group.

Another study of in-utero diagnostic radiation exposure (Ornoy et al., 1996) showed no deficits based on a neurological examination and two psychometric tests of motor and cognitive development. The null results are not surprising, given the small doses involved.

(262) Perhaps the most critical question at this point is whether there is a dose threshold for the neurological and mental effects. The evidence in the atomic bomb study is reasonably persuasive that there is a dose threshold for severe mental retardation, although there is a good deal of uncertainty as to the dose at which the threshold occurs. A formal test for a threshold has not been reported for intelligence scores. Inspection of the IQ data suggests that there might be a threshold in the vicinity of about 0.1 Gy, although this is by no means certain, and it is likely that the confidence interval on any estimated threshold would encompass zero dose. Inspection of the school performance data also suggests the possibility of a threshold at a low dose, but the statistical test for a threshold has not been reported. The atomic bomb data on unprovoked seizure disorders following in-utero irradiation are too sparse to permit a meaningful assessment of dose thresholds.

(263) In *Publication 60*, the summary indicated that the 'downward shift in IQ of 30 points Sv^{-1} ... is consistent with the observation of an incidence (of serious mental retardation) of 0.4 for a dose of 1 Sv' (ICRP, 1991, p. 5). The best estimate of the decrement in IQ at 1 Sv is 21 points for those irradiated at weeks 8–15 postconception and 13 points at weeks 16–25 postconception (Schull, 1988). If one assumes that the population IQ has a mean of 100 and a standard deviation of 15 (which are typical values for IQ tests), then the expected proportion with an IQ of 65 or under is slightly less than 1%. However, if the mean were shifted 21 points to 79, still with a standard deviation of 15, then about 18% would be expected to have IQs of 65 or less. If the mean were instead shifted only 13 points, then about 7% would be expected to have an IQ of 65 or less. Thus fewer than 40% would be predicted to show mental retardation, although the 40% value might be statistically compatible with these expectations given the sparseness of the data.

(264) *Publication 60* also concluded that radiation-induced mental decrement 'is deterministic with a threshold related to the minimum shift in IQ that can be measured' (ICRP, 1991, p. 6). The dose-related shifts in IQ clearly point towards a deterministic effect. The existing analyses provide no clear evidence for a dose threshold with respect to IQ, and it seems likely that a definitive answer is beyond the resolving power of the epidemiologic data that are available.

5.8. References

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infancy by a period of hyperleukocytosis. Acute megakaryoblastic leukaemia is rarely diagnosed in children who do not have trisomy 21 but is the most common form of leukaemia in this condition (Zipursky et al., 1997). Interestingly, there is a paucity of other childhood tumours and adult epithelial neoplasms in Down's syndrome (Hasle et al., 2000).

(308) Recessively inherited disorders leading to a defect in DNA repair, such as ataxia telangiectasia, Bloom's syndrome, and xeroderma pigmentosum, are rare, but almost inevitably lead to tumour in the homozygote during the first three decades of life (ICRP, 1998). Of the recessive genes related to an increased cancer risk, ataxia telangiectasia in the heterozygote may also increase cancer risk (Swift et al., 1987). Radiation has been shown to have a profound effect on the ability of ataxia telangiectasia cells to repair DNA damage, since they fail to halt their progression through the cell cycle when exposed. Although this discussion will focus on the effects of incidental or low-dose radiation as a carcinogen, one should consider the possibility that some other gene or syndrome, in concert with radiation, could predispose individuals to neoplasia.

(309) Recent evidence has revealed another class of genes involved in DNA repair; the genes that predispose to syndromes associated with hereditary non-polyposis colon (McLendon and Tien, 1998). It does not seem likely that these genes operate in childhood. The major mechanism of action of these genes involves an increase in target tissues and an increase in mutation rate; a mechanism that would be important when multiple events are necessary to cause cancer. However, since embryonal tumours probably require only two events, and since these tissues are programmed for a normal increase in target cell number, this mechanism would not affect the probability of developing a clone of transformed cells (Knudson, 1986).

7.5. Second cancers

7.5.1. Radiation effects

(310) Children treated with radiation for a first cancer have an increased risk of developing additional neoplasms in the irradiated sites (Hawkins et al., 1987; Tucker et al., 1987, 1991; Neglia et al., 1991; Breslow et al., 1993). Although therapeutic doses have been shown to affect subsequent cancer risk, with higher doses increasing the risk and young age at exposure being a significant variable for central nervous system and thyroid neoplasms, leukaemia was not among the radiation-associated second cancers seen in many cohort studies. Doses in the therapeutic range are likely to be lethal to haematopoietic stem cells.

(311) Variables determining the increased risk of neoplasia include age at irradiation, normal tissue in the field, and dose. Therapeutic doses range from 12 to 60 Gy depending on the sensitivity of the malignant cells and the underlying normal tissue. Adjacent tissues are often exposed to lower doses because of internal scatter, and second neoplasms often arise in these relatively low-dose sites. Lower doses (less than 30 Gy) are associated with thyroid and central nervous system tumours, while bone and soft tissue sarcomas occur following doses greater than 30 Gy (Tucker

et al., 1987). Dose–response relationships have been observed with excesses ranging from three to 40 times expected. Tissues such as brain, thyroid, bone, and breast appear to be more susceptible if exposed during normal periods of rapid growth (i.e. early childhood or puberty) (Neglia et al., 1991; Tucker et al., 1991; Bhatia et al., 1996). However, embryonal neoplasms are not seen following radiation therapy, even when very young children are treated with doses in the therapeutic range.

(312) Second cancers associated with radiation are considerably more frequent in children who are genetically predisposed. This was first seen in children with the genetic form of retinoblastoma (Meadows et al., 1985; Draper et al., 1986). A report of the largest series of long-term retinoblastoma survivors confirms the high risk of new cancers in those with the genetic form (bilateral and familial cases) – 25% at 50 years – and the elevated risk following radiation – 50% at 50 years (Wong et al., 1997). Multiple primary cancers have also been reported excessively in the Li-Fraumeni syndrome (Hisada et al., 1998). In a cohort study of 200 patients with this syndrome, 30 developed more than one cancer for a cumulative probability of a second cancer of 57% (±10%) at 30 years, and a third cancer of 38% (±12%) at 10 years. Eight neoplasms occurred in the field of radiation. Evidence for an added effect of radiation in the aetiology of multiple tumours occurring at earlier ages than expected and with a shorter latent period comes from the study of patients with Gorlin's syndrome or nevoid basal cell carcinoma syndrome (Meadows et al., 1985). This syndrome is characterised by tumours of the posterior fossa and basal cell carcinomas, the latter often appearing within months following radiation.

7.5.2. Chemotherapy

(313) Chemotherapeutic agents such as alkylating agents and epipodophyllotoxins have been associated with secondary leukaemias (Smith et al., 1994). Alkylating agents and anthracyclines have also been implicated in affecting the risk for bone tumours associated with radiation therapy (Tucker et al., 1987; Newton et al., 1991). Different and characteristic chromosomal alterations accompany the leukaemias that occur in association with alkylators or epipodophyllotoxins, with deletions of chromosomes 5 and 7 in the former, and translocations involving 11q23, the locus of the myeloid leukaemia gene, in the latter (Bhatia et al., 1999). Alkylating-agent-associated secondary leukaemias occur within 7–8 years of exposure and are dependent upon dose and specific agent. For instance, nitrogen mustard, chlorambucil, and the nitrosoureas are more potent leukaemogens than is cyclophosphamide. Dose and schedule are critical in the development of the secondary leukaemias associated with the topoisomerase II inhibitors, such as epipodophyllotoxins, and the usual latent period is between 6 months and 3 years (Pui, 1989). Leukaemias in infants are most often associated with an abnormality involving the myeloid leukaemia gene at 11q23. A case–control study of infants with acute myelogenous leukaemia suggested a dose–response association with maternal consumption of dietary topoisomerase II inhibitors (beans, soy, fruits, vegetables, wine, and black and green tea) (Ross et al., 1996).