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The effect of prenatal radiation exposure on the developing human brain*

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Recently reported dose responses in prenatally exposed Japanese bomb survivors for severe mental retardation (SMR), reduced intelligence, and reduced levels of school performance, are compared. The characteristics of, and differences between, severe and mild mental retardation in man are critically important for such comparisons. The meaning of linearity of dose response is not identical for these different forms of damage. When findings on tissue changes in the brain and in functional tests of irradiated experimental animals are taken into account, the dose response for SMR would be expected to have a threshold as is found using DS86 dosimetry. The dose responses for IQ and for school performance seem doubtfully valid: their underlying assumptions need re-examination.

1. Introduction

The observations reviewed here come mostly from prenatally exposed Japanese bomb survivors. The British National Birthday Trust longitudinal surveys of all births in 1 week in 1958 and 1 week in 1970 record contemporary data on prenatal diagnostic radiography and contemporary records of school performance. But very few prenatal medical X-ray examinations are at 8–15 weeks post-conception, the radiosensitive period of brain development (Schull *et al.* 1986), and the prospects of finding a correlation with level of school performance (if it exists) seem poor.

2. Observations in bomb survivors exposed *in utero*

Populations of bomb survivors irradiated *in utero* have been defined and redefined over the years. There is no formally established birth cohort in the epidemiological sense. When assessing a dose response, those with the lowest dose, the 'controls', have sometimes included individuals who were not in Hiroshima or Nagasaki at the time of the bombing (ATB) but were residing in those cities in 1950 when the initial selections for epidemiological studies were made. Demographic characteristics of these NIC (not-in-city) subjects were later found to differ so much from bomb survivors that they had to be excluded from the controls when studying radiation effects on perinatal and childhood mortality (Kato 1971).

The studies to be reviewed here are on severe mental retardation (SMR), performance in the first years at school, intelligence tests and IQ at ages 10–11 years, and seizures (fits, convulsions, epilepsy) in childhood. The first and fourth of these concern the presence or absence of an effect determined by clinical assessment: quantitative study is in terms of prevalence, the proportion of persons showing the effect at a specific calendar time. The second and third provide a

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numerical score for each person: quantitative study is in terms of difference in score according to level of radiation exposure either for individuals or after grouping according to dose.

Recent reports have analysed the data for each index of effect using intrauterine dose in the mother of the child according to the DS86 system of dosimetry. Some DS86 doses for mothers are not yet known. Some modifications remain to be made because the relation of intrauterine dose to dose in a developing embryo or fetus varies with stage of pregnancy.

When due regard was paid to the stage of pregnancy ATB, a linear dose response without threshold fitted the data on each kind of effect. Most SMR subjects were exposed at 8–15 weeks post-conception (p.c.) (weeks after fertilization of the oocyte), when for radiobiological reasons the developing forebrain would be expected to be most radiosensitive. Reduction in IQ and in school performance were less closely related to this specific stage of development.

3. The relative magnitude of linear risk coefficients for different effects

The coefficients of the linear dose responses for the four indices of effect are given in table 1. Each is positive for SMR and for seizures since prevalence increases with dose. Each is negative for IQ and for school performance because the score is reduced as dose increases.

For exposure at 8–15 weeks p.c. the largest risk per Gy is for SMR. How can this be? SMR is the most severe form of damage: necessarily a larger dose is needed to cause a given degree of effect than for milder forms of damage, not the smaller dose indicated by the risk coefficient.

For exposure at 16–25 weeks p.c. the coefficient for SMR is five times smaller than for 8–15 weeks p.c. For school performance score it is not only no smaller than for 8–15 weeks p.c. but is better established statistically. Taken at face value this implies that basic mechanisms for causing SMR and impairing school performance are different.

The decrease in the linear coefficient for IQ from 8–15 weeks p.c. to 16–25 weeks is smaller than for SMR but larger than for school performance. For seizures neither coefficient is statistically significant and this index of effect will not be con sidered further.

An ICRP Task Group said 'Preoccupation [with severe mental retardation and small head size in bomb survivors exposed *in utero*] has resulted in a dichotomisation of processes which must certainly be continuous and a failure to look at these in their entirety' (para. 63, Schull *et al.* 1986). The basis for considering effects of prenatal irradiation has been that 'It is unwise to perceive the increased risk of mental retardation from prenatal exposure to radiation as a phenomenon distinct from a more broadly expressed impairment of brain function. Mental retardation is a clinical judgment which dichotomizes distribution of qualities of brain function' (Otake *et al.* 1987). These are unsupported assertions that ignore biological aspects of the indices of radiation effect on mental functioning and the differences between them. Attendance at school dichotomizes qualities of brain function outside the field of clinical judgment. Some bomb survivors with SMR may have started school but, if so, soon ceased to attend.

4. Mental retardation in unirradiated human populations

The prevalence of SMR is closely similar in most human populations, a few cases per 1000. Mild (and moderate) mental retardation (MMR) is not like that. It

Table 1. *In utero* exposure to atom bomb radiation and linear dose-responses without threshold using DS86 intrauterine dose for indices of damage to the central nervous system assessed in childhood or adolescence.

Index of damage	Unprovoked seizures[a,b]	Koga IQ[a,c] (a)	Koga IQ[a,c] (b)	School performance score (Hiroshima only)[a,d]	Severe mental retardation[e]
Controls (less than 1 cGy DS86) mean value[f]	0·9–1·6%	109–110		2·86–3·04	0·72–0·24%
Bomb exposure	Linear risk coefficient per cent per Gy DS86 intrauterine dose				
8–15 weeks p.c.					
b	+14·9	−19	−23	−23 to −33[h]	+42·4
(SE)	(10·1)	(4·1)	(5·1)	(13) (15)	(9·8)
	[g] sugg.	**	**	sugg. to *	**
16–25 weeks p.c.					
b	+6·7	−12	−8·9	−27 to −35[h]	+8·5
(SE)	(6·5)	(4·7)	(5·2)	(9) (9)	(4·9)
	[g]	**	sugg.	** **	sugg.
Source of data	Dunn *et al.* (1988), table 3, TR 13–88	Schull *et al.* (1988), table 4a, TR 3–88		Otake *et al.* (1988), table 7b, TR 2–88	Otake *et al.* (1987), table 6, TR 16–87

[a] All subjects with severe mental retardation SMR were excluded from calculation of the tabulated dose responses.

[b] Unprovoked seizures were those without recognizable cause (fever, trauma, etc.).

[c] Subsamples (a) PE86 and (b) Clinical of those irradiated *in utero* were defined differently and overlap.

[d] School performance scores for individuals were available for each of the first 4 years (grades) of schooling. Dose responses were calculated for each year separately. Nagasaki no data.

[e] Cases of SMR associated with a recognizable cause other than bomb radiation were excluded from the controls and from the dose response.

[f] Mean values of 8–15-week controls and 16–25-week controls in that order.

[g] Statistical significance: sugg. $P<0·1$, *$P<0·05$, **$P<0·01$.

[h] The range of linear coefficients for the four school grades. At 8–15 weeks p.c. the value for 1st grade was 23 sugg., 2nd 29 *, 3rd 24 sugg. 4th 33 *. At 16–25 weeks p.c. values in successive grades were 27, 29, 28 and 35 and each was **.

is recognized only in countries with systems of compulsory universal primary education. Its prevalence is at least 10 times higher than SMR and depends markedly on environmental (social) factors (Stein and Susser 1984). Unlike SMR the prevalence of MMR is always substantially higher in children of manual workers than in children of non-manual workers. This difference in prevalence may be maintained even when environmental circumstances change markedly, as when famine during pregnancy was severe enough to increase perinatal mortality (Stein *et al.* 1972). Some cases of MMR are concentrated in particular families, but this is not of itself evidence that the cause is nature (genetic inheritance) rather than nurture (the environment broadly defined).

SMR is commonly recognized in early childhood, a time when its prevalence also decreases. Those affected often have other abnormalities that cause death at

these early ages. Post-mortem study showed anatomical lesions in the brain in 90 per cent. Subjects with SMR are ineducable.

In contrast MMR is usually first noticed after starting education in school. Prevalence does not decrease in childhood but does so markedly after the school-leaving age. Those with MMR may find work that they can do, and may marry and bring up children reasonably successfully; they then disappear from statistics of prevalence. It is claimed that at least 75 per cent do not show brain lesions at autopsy but confirmatory evidence is needed.

These are descriptions, not definitive criteria for diagnosis. Whether IQ tests can serve this purpose has been argued for decades. Usually subjects with SMR and MMR have IQ less than 50 per cent and above 50 per cent, respectively, but separation is not sharp. IQ may be an objective, if imperfect, index of cognitive ability but in practice the concept of mental retardation includes much wider considerations that are not invariant with age as IQ is theoretically supposed to be. 'We would not expect a 7-year-old with an average IQ to cook the family meals, but this task would be well within the ability of a 25-year-old retarded person with a mental age of 7' (Zigler 1987). What an individual can and cannot do is related to chronological age and mental age and to upbringing, as well as to IQ, so that relative standing on IQ tests is defined in terms of fluctuating criteria (Zigler 1987).

SMR cannot be related to level of school performance because those affected are ineducable. MMR is related both to school performance and to level of IQ, and these two indices of effect might be expected to correlate fairly well in so far as each measures cognitive ability.

5. Severe mental retardation in bomb survivors

A bomb survivor with SMR was defined as 'unable to perform simple calculations, to make simple conversation, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalised'. The final diagnosis was made at 17 years old, or earlier if the subject did not survive to that age (Otake *et al.* 1987).

Bomb dosimetry revision does not alter number of cases of SMR or their distribution according to age ATB. Fuller details show that five subjects with SMR had causes other than radiation (table 2). The dose response for the other 25 cases truly reflects effects of bomb radiation. Most irradiated subjects with SMR were exposed at 8–15 weeks p.c. (figure 1, table 2). Neuroblast proliferation in the periventricular zone of the forebrain is programmed to start at 8 weeks p.c. and to cease at about 15–16 weeks p.c. The exact correlation with the period of maximum sensitivity for induction of SMR by prenatal exposure to bomb radiation is good evidence that the cause of the SMR was radiation damage to a specific cell population.

The new finding for the 25 cases is the threshold in dose response for exposure at 8–15 weeks p.c. using DS86 intrauterine dose but not T65DR fetal dose (Otake *et al.* 1987). Threshold values using a linear dose response were significant and were equally significant, with slightly higher values (and 95 per cent bounds), using the orthodox radiobiological model for cell survival with a shoulder (table 3). But coefficients were also significant when threshold dose was taken to be zero (table 3). Thus questions about threshold for SMR cannot be answered by appeal to the observations.

The maternal kerma for 10 of the 15 SMR cases exposed at 8–15 weeks p.c. was from 180 to 550 cGy T65DR (table 2), the exposure range causing death from bone

Table 2. Severe mental retardation in bomb survivors after prenatal irradiation according to level of maternal exposure (T65DR) and causation by other factors (data from Appendix 1, Otake *et al.* 1987).

Clinical findings suggesting a cause other than radiation				Maternal exposure cGy T65DR kerma[a]	Number of subjects	
Present			Absent		Total	Exposed at 8–15 wks p.c.
3	Down's syndrome Sibling also retarded Encephalitis at 4 years old		9	0–5	12[b]	4
1	Down's syndrome		1	28, 17[c]	2	2
1	Down's syndrome		2	96, 81, 87[c]	3	3
0			8	180–310	8	6
0			5	370–550	5	4
–			—		—	—
5		Total	25	Irradiated total	18	15
–			—		—	—

[a]Maternal kerma according to DS86 dosimetry is not yet available.
[b]Five of 12 subjects (including one Down's syndrome) were NIC (not-in-city).
[c]Kerma for the subject with Down's syndrome is the left-hand-most value.

marrow damage. Thus a dose response for SMR caused by fetal exposure to bomb radiation cannot be derived without postulating that simultaneous irradiation of the mother had no influence whatever on the developing fetal brain. Support for this postulate is difficult to find. The only argument used in its defence by the ICRP Task Group was that women with sickle cell anaemia do not have an increased

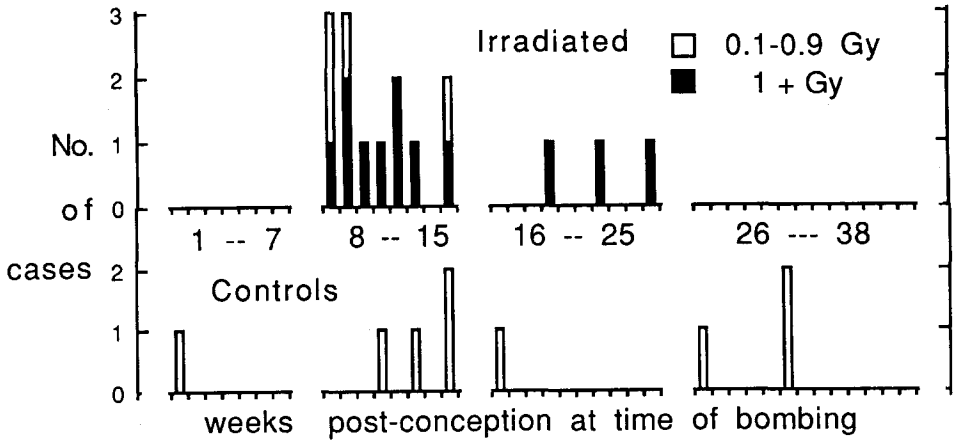

Figure 1. Distribution of 25 subjects with severe mental retardation according to intrauterine age (weeks post-conception) at the time of the atom bombing in Japan. Intrauterine DS86 dose in the controls, 0–6 cGy; in the irradiated as shown. Data in Appendix 1 of Otake *et al.* (1987). The figure excludes five subjects with aetiologies other than irradiation (table 2). The period 8–15 weeks p.c. is biologically distinct from preceding and succeeding weeks p.c. because nearly all the future neurones of the human cerebral cortex are produced by cell division programmed to begin at 8 weeks p.c. and to end at 15–16 weeks p.c. The division of the interval 16–38 weeks p.c. into two approximately equal halves is arbitrary and not determined by any critical biological distinction.

Table 3. Severe mental retardation SMR and DS86 intrauterine dose: dose responses with and without a threshold dose T (data from Tables 8 and 9 of Otake *et al.* 1987).

DS86 sample excluding five cases with aetiologies other than radiation	With threshold (T estimated) b(Gy^{-1})[a]	T(cGy) Mean[b]	T(cGy) 95% bounds	Without threshold (T=zero) b(Gy^{-1})[a]
Linear dose response $P_i=a+b(D_i-T)$				
Grouped[c]	0·74	39	12–60	0·39
Ungrouped	1·10	46	23–62	0·42
Exponential linear dose response $P_i=1-\exp[-\{a+b(D_i-T)\}]$				
Grouped[c]	1·59	51	17–62	0·43
Ungrouped	1·93	55	30–67	0·44

[a] All values significant at the 1 per cent level.
[b] All values significant at the 5 per cent level.
[c] DS86 intrauterine dose Gy: group range with mean in parentheses 0·01–0·09 (0·05), 0·10–0·49 (0·23), 0·50–0·99 (0·64), 1·00–1·99 (1·25), 2·00+(2·91), controls 0·00. The two highest dose groups were combined when calculating dose response parameters.

frequency of mentally retarded children (para. 62, Schull *et al.* 1986). The reference cited (Pritchard *et al.* 1973) noted 127 infants surviving to the end of the neonatal period but not followed further. SMR cannot be diagnosed at a postnatal age of 1 month, and was not mentioned. Moreover the gross perinatal damage in sickle cell mothers and babies was often caused by embolism (infarction), not anaemia.

Thus anaemia of pregnant women after radiation exposure in the lethal range remains a possible mechanism for indirect effects on the fetus. Other phenomena seen in the first few days after high-level exposures are projectile vomiting (possibly injuring the fetus) and rapidly fluctuating biochemical changes following resorption of several kilograms of dead cells in maternal marrow and lymph nodes. Cell damage in the placenta is another possibility (cf. Case 1, Driscoll *et al.* 1963; see legend figure 6).

6. Intelligence tests and IQ

The calibration of intelligence tests in terms of IQ is empirical. A large number of 'normal' subjects is tested and the test scores achieved are fitted to a normal (Gaussian) distribution centred on mean=100 with standard deviation (SD) usually 14–16. The consequence (for SD=15) is:

Percentage of all test scores	2	7	16	25	25	16	7	2
IQ points	—70—	—80—	—90—	—100—	—110—	—120—	—130—	

Half the subjects have test scores lying between IQ 90 and 110. IQ is 70 at 2 SD below the mean and 130 at 2 SD above the mean. The rough boundary between SMR and MMR, IQ=50, is at 3·33 SD below the mean, about 1 in 1200 persons. As a particular IQ test continues in use, the mean in tested populations may drift from its original value 100, as in Hiroshima school-children controls in whom mean IQ was 109–110 for the Koga test (table 1).

No theory justifies fitting intelligence test scores to the normal distribution. Empirically a fit is found for many quantitative phenomena in biology over the middle of their range, and so has proved useful in many contexts, e.g. routine testing of activity of preparations of non-synthetic drugs, and derivation of LD_{50} for a single brief exposure to radiation. A fundamental problem is that the tails of the normal distribution approach zero and 100 per cent asymptotically, but biological observations do not: at the lowest and highest frequencies, observations always fail to fit. The range of adult heights fits the central region of a normal distribution but no adults have heights below 30 cm or above 5 m. Moreover, when everyone in a large population is tested for intelligence, there are usually too many subjects in the lower tail of the curve causing a bulge in the otherwise smooth bell-shaped curve of the normal distribution (Zigler 1987).

The action of radiation must be primarily on test scores of individuals, not on derived IQ. A dose response for mean IQ is based on two assumptions: that the fit of intelligence test scores to a normal distribution is not modified by irradiation and that the mean of the distribution of test scores varies with radiation dose. Figure 2 illustrates a normal distribution of test scores, with mean score at 50 per cent and mean IQ = 100, and a second score distribution derived by reducing each score in the first distribution by the same factor. The factor 0·66 corresponds to brain dose 33 cGy when mean IQ is reduced by 20 points per Gy (approximately as found in bomb survivors irradiated *in utero* at 8–15 weeks p.c., table 1). The modified test score distribution has exactly the same shape as the normal distribution from which it is derived, and so is itself a normal distribution.

If intelligence test scores after irradiation meet the two assumptions underlying the dose response for IQ, the predominant action of prenatal irradiation would be to reduce the highest test scores, those above the mean, as shown in figure 2. A loss of test scores concentrated at the upper end of the range is the theoretical consequence of the frame work of interpretation applied to IQ in bomb survivor children (and also might be expected intuitively) but is not known to have occurred. Until it has been looked for and found, the assumption that the mean of a normal distribution of

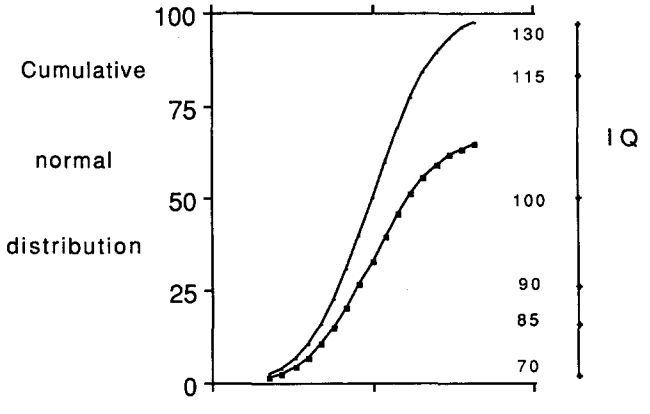

Figure 2. Distribution of intelligence test scores per cent (standard deviation SD = 15) (left-hand curve) and of IQ (vertical scale on the right) in a population of normal subjects. The curve ■—■ was obtained by multiplying each intelligence test score by 0·66. Its mean is at 33 per cent on the unmodified normal distribution of test scores and at 93 on the IQ scale.

intelligence test scores, the IQ, depends linearly on radiation dose does not have a biological justification.

Different intelligence tests do not test the same thing. The correlation between the Koga and Tanaka tests in schoolchildren at Nagasaki was only 0·30 (Schull *et al.* 1988). Two children had discordantly high IQ and low school performance scores: both were deaf (Otake *et al.* 1988). One child with an average school score had an IQ of about 60: repeat tests gave IQ 102 and 112 (Otake *et al.* 1988). Such phenomena may be commonplace in intelligence testing.

Assessing radiation damage to cognitive abilities is never straightforward. Lack of motivation or a minor illness can affect a child's intelligence test score on a particular occasion. Radiotherapy of the brain, often used in childhood leukaemia, is commonly believed to reduce IQ in the majority, younger patients being most affected (cited by ICRP Task Group, Schull *et al.* 1986). A critical analysis of published information (including that cited) concluded, however, that the methodologically stronger studies found few differences between brain-irradiated leukaemic children and comparison subjects, and that the differences in any study were not severe (Williams and Davis 1986). These authors commented that there was a strong tendency to regard IQ, achievement and neuropsychological tests as solely measures of cerebral integrity and not as complex measures of intellectual and adaptive functioning (which is what they really are; cf. Zigler 1987).

7. School performance scores

The performance scores routinely recorded in Japanese schools in the 1950s were determined by comparisons within a class, not by reference to an external standard, and according to a fixed plan. For each of the seven school subjects one child in 20 was given a score -2 or $+2$, four children in 20 a score -1 or $+1$ and the remaining 10 a score of zero (table 4). A child's score for the school year was the average of the seven. These yearly averages were used to see how levels of school performance varied with level of prenatal exposure to bomb radiation (Otake *et al.* 1988).

This fixed plan for distribution of scores within a school class forces the scores into a normal distribution (table 4). Thus, if school performance depends on IQ, the two measures should be well correlated. At Nagasaki the correlation was 0·54 (Otake *et al.* 1988). But school scores for music, handicrafts and gymnastics on the one hand, and arithmetic and language on the other, will not depend on identical aspects of brain function.

The lowest and highest school scores correspond to 2 SD below and above the mean, a maximum range much smaller than for IQ points. But school scores are available for four successive school grades (years) and linear coefficients for the four grades are highly consistent (footnote h, table 1).

Problems of interpretation may be even greater with school performance scores than with IQ. Because the school scores were not related to an external standard, a class of children all with a low mental ability would have the same mean score as a class consisting solely of normal children. Furthermore assessment of a child's ability by a teacher depends on the teacher's *a priori* expectations and, as is well known, a teacher's expectations are self-fulfilling: they do indeed influence a child's performance. Did teachers in Hiroshima schools know which children in a class were bomb survivors? Expectations about the performance of each bomb survivor child could hardly escape being influenced by the impression on teachers in the

Table 4. Assessment of school performance in prenatally exposed bomb survivors (data from Otake *et al.* 1988)..

	School subjects: language, social studies, mathematics, science, music, handicrafts and drawing, gymnastics			
Subject score[a]	Percentage in class[a]	RERF score[b]	Cumulative percentage	Centre of cumulative percentage range (probits)[c]
−2	5%	1	0–5	3
−1	20%	2	5–25	4
0	50%	3	25–75	5
+1	20%	4	75–95	6
+2	5%	5	95–100	7

[a]The fixed scheme by which performance scores were to be allocated among the children in a school class according to a predetermined distribution.

[b]Otake *et al.* (1988) increased each school score by 3.

[c]The scale of the normal distribution under the probit transformation is one probit per SD with 50 per cent = probit value 5·0.

same school of the performance of a single such child with SMR. Unconscious bias when allocating school performance scores to individuals seems a possibility. Nevertheless a dose-related reduction in level of school performance was not found for exposure at 0–7 weeks or 26–38 weeks p.c. Given the basic uncertainties it does not seem profitable to ask why school performance scores showed as large a decrease per Gy for exposure at 16–25 weeks p.c. as at 8–15 weeks p.c. (table 1).

8. Tissue studies in irradiated fetal brain, human and experimental

In the developing human forebrain at 8–15 weeks p.c. the periventricular neuroblasts are dividing rapidly and their post-mitotic progeny, the neurone precursor cells, are moving systematically from their birth place into outer layers of the forebrain cortex. Dead cells in the outer cortex after irradiation are either post-mitotic cells suffering 'interphase death' (as lymphocytes do) *in situ* or cells dying at their birth place and subsequently moving into the cortex (passively; dead cells cannot migrate actively). Whatever their origin, dead cells persist for only a few hours before fragmenting and disappearing by autolysis or phagocytosis.

The cells that die can be distinguished by serial study at different times after irradiation. Human material is not available, but experimental data are decisive. At 4 h after 2 Gy X-rays, recognizably dead cells are distributed widely throughout the future cortex (figure 3). Most must be post-mitotic neurone precursors (Hicks *et al.* 1962). Four hours is too short for cells killed in the proliferative zone to be spread widely throughout the pallium. Thymidine-labelled cells in a normal fetal rat take 24 (even 48) h to arrive in the cortex (Hicks *et al.* 1961, 1962; Hicks and d'Amato 1966). Thus loss of neurone precursor cells can be the consequence both of death of the cells themselves and of their progenitors, the proliferating neuroblasts, the relative proportions depending on the magnitude of the dose and the stage of development when irradiated (Driscoll *et al.* 1963).

A dose of 2 Gy X-rays to fetal rats causes lesions of substantial size to develop in the cerebral cortex (figure 4). Mechanisms of production were studied intensively by Hicks *et al.* (1957, 1959). Cell death is followed by enhanced proliferation of

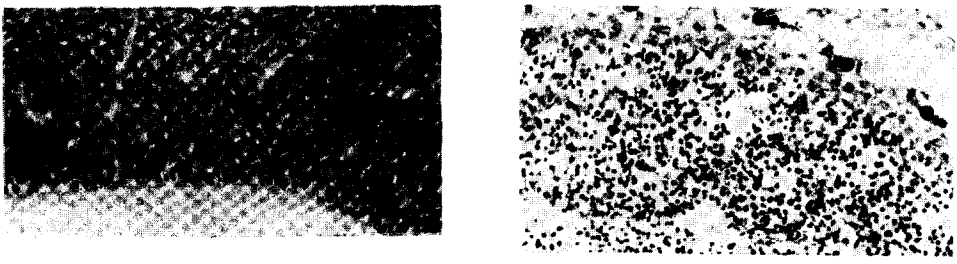

Figure 3. Normal vertex pallium of 17-day fetal rat (left) compared with identical structure 4 h after 2 Gy X-rays (right). (Figure 4 of Hicks and d'Amato (1961), acid fuchsin and fast green, ×125), reproduced by permission of the authors. Most of the irradiated cells are dead (black dots).

neuroblasts. Cell 'rosettes' originate from surviving cells retaining the capacity to divide and dividing in an abnormal environment (Hicks and d'Amato 1966). They are not caused simply by failure of individual neurone precursor cells to migrate. Rosettes in the retina characterize experimental fetal irradiation and also aborted human fetuses heavily irradiated in the 2nd month of pregnancy (Goldstein and Wexler 1932). After 2 Gy to fetal rats the adult cerebral hemispheres are abnormally small (Hicks and d'Amato 1961, 1966, Hicks *et al.* 1962).

Such gross lesions were not seen with a dose below 1 Gy. After 1·5 Gy 50–75 per cent of primitive cells may be killed (then disintegrating) but regeneration of proliferative cells was virtually complete in 48 h (d'Amato 1982). Microrosettes were seen, but resolved. Some animals recovered nearly completely, others had only relatively minor defects (Hicks *et al.* 1984).

After rats received much lower doses, 20–40 cGy X-rays, on the 16th–18th day p.c., serial observations showed retarded differentiation of the cortex (but no dead

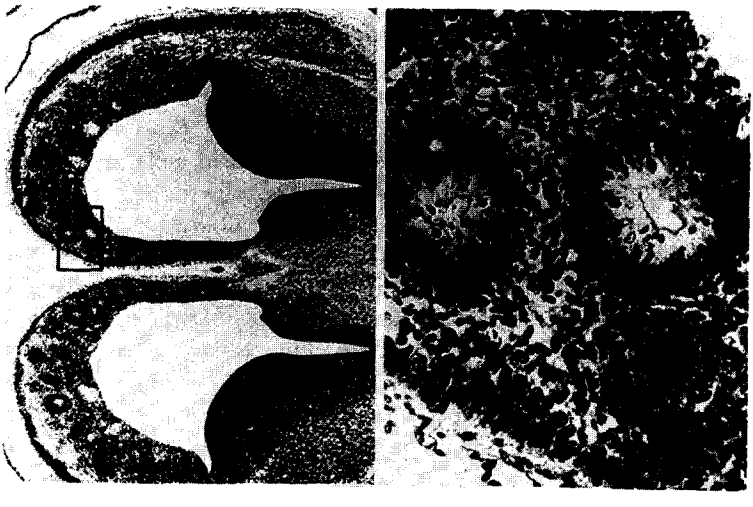

Figure 4. Frontal section of 19-day fetal rat that had received 2 Gy X-rays on the 13th day p.c. (Plate 18 of Hicks and d'Amato 1966, reproduced by permission of the authors). Cortex much thinner than normal and contains many cell formations termed 'rosettes' (left, H&E, low power). A neocortex is forming alongside, and despite the presence of, 'rosettes' (right, high power).

cells). The paucity of neurones in all layers of the adult cortex (figure 5) was caused by injury to the proliferative–migratory cell system at the time of irradiation. Overall volume changed little but the matrix of layer 6 was disordered. After 10–30 cGy in less than a minute the nerve cells affected would not have been generated until 2 days later. The change in the precursor proliferative cells was such that the programmes for migratory cells to reach their proper destination were retained, but how many to send was forgotten (interpretation by Hicks and d'Amato 1980).

Cell-killing is a prime initiator of the responses that the fetus puts forth to restore itself following injury, whether the outcome is recovery or malformation. The regenerative response is the fetus' attempt to restore its losses. However, little is known about how cell-killing initiates those responses (Hicks *et al.* 1984).

In pioneer quantitative studies, using the intrauterine dose range 5–100 cGy, damage apparently without threshold could be measured for misalignment of neuronal processes in cortex layer Va and for reduced diameter of the corpus callosum in the postnatal mouse (Konermann 1986). No information about statistical uncertainties was given for either response.

Large brain lesions, 'massive ectopic grey areas', have been seen in humans with SMR, at autopsy or *in vivo* by magnetic resonance imaging. They were found in two bomb survivors with SMR, one *in vivo* and one at autopsy with an abnormally small brain (intrauterine dose 1·18 Gy DS86, maternal kerma 3·75 Gy T65DR), but not in an autopsy of a control (<0·01 Gy) with SMR and a small brain (Otake *et al.* 1987). Such lesions seem even less likely to be caused by failure of migration of individual neurone precursor cells than are cell rosettes. The brain of only one

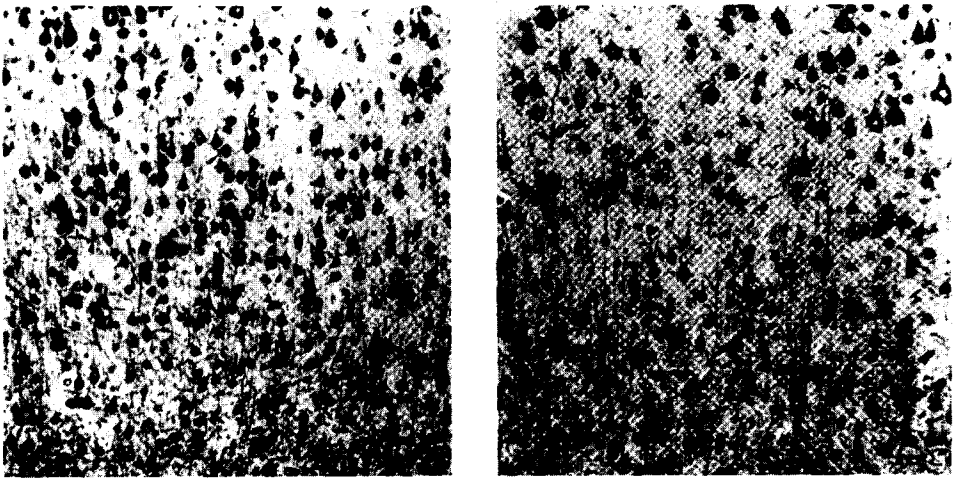

Figure 5. Paucity of neurones in layer 6 of the dorsolateral cortex of an adult 9-week-old rat given 0·3 Gy X-rays as a 16-day fetus (right) compared with a normal 9-week-old rat (left) (figure 2 of d'Amato and Hicks 1965, cresyl violet and Luxol fast blue, ×155, reproduced by permission of the authors). Layer 6, like other cortical layers in the X-rayed rat (figure 1 of d'Amato and Hicks 1965) contained fewer cells than normal but also was disordered. The normal columnar arrangement of the neurones was considerably jumbled. Serial examinations of litter mates at various other times after the same irradiation showed no obvious difference between irradiated and control fetuses in the periventricular proliferating cell populations or elsewhere. The picture in the adult shown here was established by 2 weeks after birth.

human fetus has been examined soon after irradiation just after the sensitive stage (Case 1, Driscoll *et al.* 1963). The day after 5 Gy γ-rays at 16–17 weeks p.c. many cells in the outer forebrain cortex were dead, an 'accumulation of recently arrived migratory primitive cells' (figure 6). The finding was as in rats examined by the same authors at similar times after smaller but briefer exposures to X-rays (Driscoll *et al.* 1963).

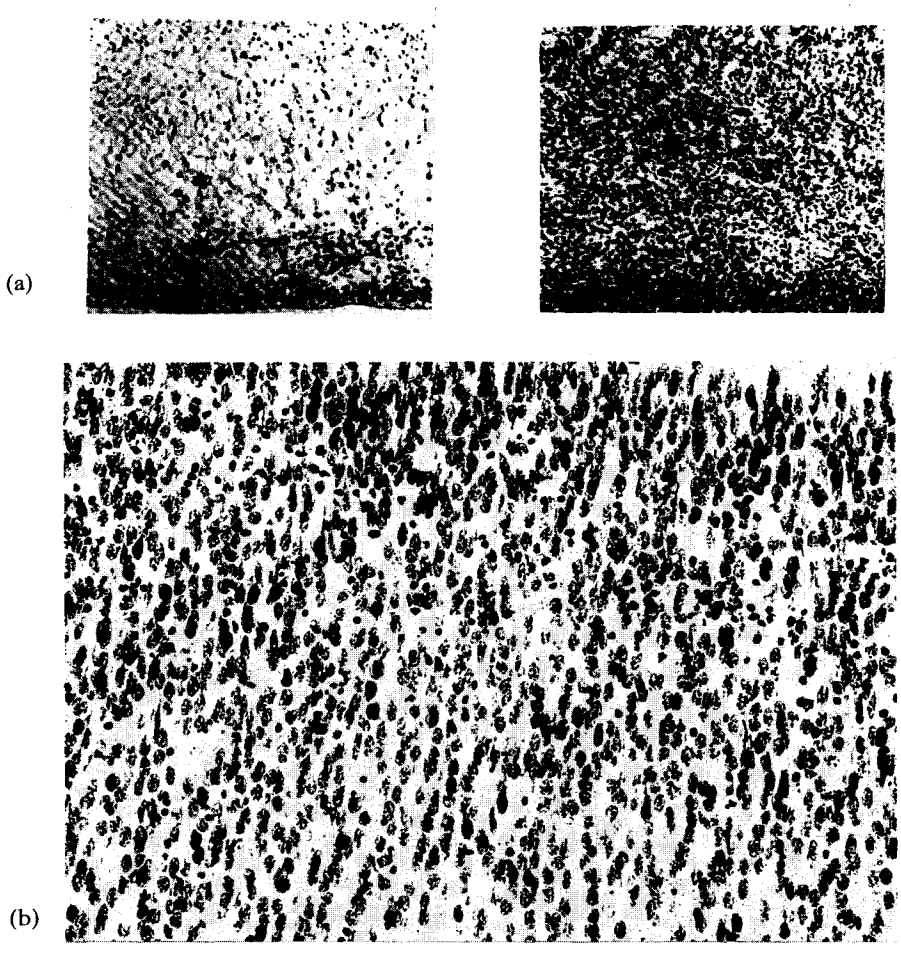

Figure 6. 16–17 weeks p.c. human fetus that accumulated 5 Gy γ-ray dose to the centre of the head in 28 h from a radium implant in its mother's cervix cancer (Case 1, Driscoll *et al.* 1963) and was examined 24 h after the midpoint of therapy (Driscoll *et al.* 1963, S. P. Hicks, personal communication, 1989). (a) (left) The forebrain showing gross loss of neurone precursor cells compared with the normal fetus in (a) (right) (Plate 13 of Hicks and d'Amato 1966, H&E, ×100, reproduced with the permission of the authors). (b) Outer cortex (Case 1, Hicks and d'Amato 1966) showing dead cells as small dense black circles: nuclei of viable cells are much less densely stained (photomicrograph ×300 of section H&E, kindly provided by S. P. Hicks, cf. figure 2 of Driscoll *et al.* 1963). Another fetus, similarly exposed at 22 weeks p.c. and receiving 16 Gy, was too heavily exposed for use here (Case 2, Driscoll *et al.* 1963). The surface granular layer of the cerebellum was depleted of cells but less so than the frontal cortex. (Crown–rump lengths given by Driscoll *et al.* (1963) show that the stated weeks of pregnancy are truly weeks p.c.).

9. Experimental studies of brain function after irradiation

After fetal doses large enough to cause gross malformation of cerebral cortex or cerebellum, young rats performed well in functional tests, e.g. of visual pattern discrimination (Hicks *et al.* 1962). At present the functional significance of morphological abnormalities cannot be precisely measured (Hicks and d'Amato 1980).

The time at which five test reflexes are acquired during the 2nd–4th postnatal weeks was unaffected by 0·1, 0·2 or 0·4 Gy X-rays to fetal rats on Day 9 or 17 p.c. (Jensh and Brent 1987). No observations were recorded on the quality of performance of the reflexes.

Squirrel monkeys exposed to 1 Gy γ-rays at 80–90 days p.c. showed impairment of visual acuity, emotional stability and cognitive development at 30 days old (Brizzee and Ordy 1986). Exploratory and general activities were depressed at 2, 7 and 14 but not 21 and 28 postnatal days. Learning by visual discrimination (rewarded by food) was impaired at 30–90 days and at 1 year, but at 2 years of age was no different from controls. In contrast, when a learnt response was extinguished by interchanging the positive and negative visual clues and a new response was then learnt ('reversal learning') impairment was still there at 2 years of age. These tests of CNS function in primates are clearly more sophisticated than those employed in rodents. They may be affected by whether postnatal rearing is by the mother or in a nursery. The results seem to show that lesser degrees of induced fetal damage may be repairable postnatally.

The effect of 0·5 Gy *in utero* was tested in fewer squirrel monkeys and reported only for the first 30–90 days after birth. Some tests of behaviour were unaffected; some seemed impaired. A dose of 0·1 Gy caused no change in behaviour: no details were provided and more work is to be done.

10. Modification of degree of effect by protraction of exposure

Relatively short critical periods of radiosensitivity for gross non-specific damage (e.g. fetal mortality) and for gross malformations regularly follow a single brief exposure exceeding 1 Gy. The mechanism seems to be the complete or nearly complete inactivation of the clone of cells from which an organ primordium originates (Mole 1987). Since critical periods are not found after single brief doses below 1 Gy, they cannot provide evidence about the influence of protraction of exposure on the prevalence of maldevelopment when total dose is below 1 Gy.

Other radiobiological phenomena may have an ameliorating influence, e.g. the repair of sublethal cellular damage between successive doses or during a continuous exposure. This expectation is well confirmed by the progressive decrease in tissue damage in several different parts of the developing rat forebrain with increase in the time interval between two X-ray doses up to 12 h and when the number of fractions within a 12 h period is increased (Brizzee *et al.* 1967). Total dose was 1·5 Gy but no result with smaller doses seems to be available. Protraction will also assist the maintenance of cell number by cell division during the overall exposure; but few relevant investigations have been reported on the CNS (Konermann 1987).

11. Relationship of function and structural change in the brain

Thoughtful discussions of this major question with experimental examples are given by Hicks and d'Amato (1975 and 1978).

The corpus callosum is the main nerve fibre pathway connecting the two cerebral hemispheres. Damage to the developed structure in the adult human is followed by a defined pattern of altered mental function. Brain imaging of adults

in vivo, however, may show unexpectedly a complete or partial congenital agenesis of the corpus callosum, often with multiple associated developmental anomalies (Ettlinger 1977). Some cases are without any indication of neurological or intellectual abnormality. In others the clinical picture is non-specific and variable, and whether the defects in mental function are then the result of associated anomalies (as some suppose) cannot be determined.

The corpus callosum was the most radiosensitive structure in the developing mouse brain. Its postnatal diameter was reduced (apparently without threshold) by about 25, 12 and 5 per cent, respectively, after 0·5, 0·25 and 0·125 Gy X-rays at 13 days p.c. (figure 7 of Konermann 1986). But the example of congenital agenesis of the corpus callosum in man suggests that it may be rash to base expectations about radiation-induced impairment of CNS function following intrauterine exposure simply on evidence that this has caused structural defects. Tests of CNS function in parallel with measurements of corpus callosum diameter are needed; cf. the unexpectedly good performance in tests of visual discrimination by rats with gross induced malformations of the CNS (Hicks *et al.* 1962).

12. A personal assessment

The assumption that radiation-related damage to the developing brain stems largely, if not solely, from neuronal death has been said to rest on the large proportion of bomb survivors with SMR who have small heads (Otake *et al.* 1987). On the contrary, the significance of loss of neurone precursor cells rests directly on observations after experimental doses well below 1 Gy. Tissue lesions are then minimal and associated with small changes in number of neurones and alignment of their processes.

The distinction between malformation and maldevelopment (Mole 1982, 1986) is crucial. CNS malformations characterize SMR in prenatally exposed bomb survivors (current evidence) and also brain damage in experimental animals given fetal doses above 1 Gy. Malformations are not seen in animals with fetal dose well below 1 Gy. The reason is radiobiological. Prenatal initiation of malformations in any organ, not merely the CNS, requires that enough spatially adjacent cells are sufficiently damaged. When dose is sufficiently small the random distribution of ionizing tracks in tissue means that damaged cells are individually at a distance from each other.

If SMR depends on malformation of the CNS, then linear extrapolation of observations on SMR at fetal doses exceeding 1 Gy to doses much less than 1 Gy will be invalid. A threshold dose for SMR would be expected. DS86 dosimetry provides a dose response with a threshold (table 3), and so an escape from the dilemma posed by a response without threshold that SMR is then more easily caused by irradiation than lesser degrees of CNS damage.

Reduction in IQ by prenatal irradiation may be expected when this alters numbers of cortical neurones and their interconnections (maldevelopment). But current numerical values for risk coefficients can be questioned: assumptions underlying their derivation need to be examined and justified.

Reduction in level of school performance by prenatal irradiation should be the most useful criterion for practical application in radiological protection and the bomb survivor data are highly consistent. But the performance scores were not related to external standards and might be unwittingly biased by *a priori* expectations about bomb survivor children.

The slower rate of change during intrauterine development in man should reduce the damage from a given dose as compared with other mammals (Mole 1982, Konermann 1987).

As already noted, protraction of radiation exposure *in utero* should reduce the amount of damage compared with a single brief exposure of the same magnitude. This implies that risk estimates derived from bomb survivor experience should be reduced for almost all practical applications in radiological protection. When there is no human evidence about damage to mental function by protracted irradiation, the magnitude of a reduction factor to be applied to bomb survivor data will have to be derived from experimental findings, as in the analogous case of radiation-induced carcinogenesis.

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