Anhang/Appendix W

Radiobiology of the Developing Organism:

Radiation Exposure in utero

by

William J. Schull
School of Public Health
University of Texas Health Science Center
Houston, Texas

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INTRODUCTION

Studies of the biological effects of exposure to ionizing radiation began in the earliest years of this century, prompted by Roentgen's discovery of X-rays and the isolation of radium by the Curies. As early as 1902 Frieben had described the first case of cancer specifically attributed to exposure to ionizing radiation, and only a year later, in 1903, Bohn reported maldevelopment in the sea urchin following exposure of its eggs to radium. Numerous studies with similar results were soon described, and rapidly established the carcinogenic and teratogenic effects of exposure to ionizing radiation. It is not our purpose to review all of the subsequent experimental research since excellent reviews already exist (see, e.g., 68, 69, 141). Rather our intent is to summarize the findings with regard to prenatal exposure of human beings and those mammals, such as other primates, whose experiences seem more immediately pertinent to the human situation. We focus on two major health-related effects -- the carcinogenic and teratogenic consequences of prenatal exposure.

THE CARCINOGENIC EFFECT OF PRENATAL EXPOSURE TO IONIZING RADIATION

Several excellent reviews of the carcinogenic consequences of in utero exposure to diagnostic x-rays have appeared in the last several years to which the reader seeking more details than space here affords is recommended (12, 28, 91, 142, 144). Briefly, the issue of the risk of cancer subsequent to in utero exposure to ionizing radiation has been a contentious one. This reflects in large measure the seeming difference in findings between the Oxford Survey of Childhood Cancer (135, 136), the largest of the case-control studies, and the cohort of in utero exposed survivors of the atomic bombing of Hiroshima and Nagasaki. The Oxford Survey, which began in the early 1950s, selected cancer and leukemia cases from the official mortality statistics from England, Scotland, and Wales. While the difference has lessened with the downward revision of the doses of the survivors and the upward revision of the doses received in medical irradiation (see, e.g., 8), the disparity between the studies has sparked a lively debate. Proponents of a greater relative risk among individuals prenatally exposed to medical irradiation than has been seen in the Japanese survivors frequently contend that the ascertainment of cases of leukemia was incomplete in the early years of the studies in Hiroshima and Nagasaki and that this accounts

for the difference between the effect of medical irradiation and exposure to the bombings. While this might have been true, given the state of record keeping at that time, there is no compelling evidence to support this conjecture. Moreover, a readily recognized increase in leukemia did not begin to appear among other survivors until two to three years after exposure, and by this time the Japanese system of vital records had been largely rebuilt. It has also been suggested that immune competence among the prenatally exposed was depressed or lost as a result of exposure, and that immunologically compromised survivors might have died of infectious diseases and thus failed to survive to develop leukemia. This conjecture too cannot be supported since no increase in such deaths was observed among the prenatally exposed (see 125 for a fuller discussion).

Other investigators argue, however, that considerable caution must be exercised in interpreting the medical irradiation studies, especially in light of the many possible confounding or biasing factors. In a similar way, the fact that early postnatal irradiation in Japan showed carcinogenic effects only many years later (agreeing with other postnatal radiation effects), whereas the medical series showed their effects soon after birth, raises important radio-biological problems if both findings are the result of irradiation. The doubts are increased by the absence of serious effects in experimental animals, and the constancy of relative risk values for many cancer sites in the medical series is at variance with other data, which suggest site-specific effects. Finally, differentiation of the blood-forming stem cells does not occur during the first trimester of fetal development, so that the excess in leukemia reported in the medical series following first trimester irradiation is difficult to understand (128). However, recently, Doll and Wakeford (28; see also 144) have critically reviewed the Oxford Survey of Childhood Cancer, and conclude that subsequent research has dispelled many of these earlier concerns, albeit not all. They further conclude that in their entirety the Oxford Survey of Childhood Cancer data suggest an increased risk of childhood cancer at a dose of the order of 10 mGy, or a risk coefficient of about 6% per sievert. This value accords well with the 5% per sievert suggested by UNSCEAR (142) and the 4-5% estimated by Mole (81). However, these values are greater than the relative risks estimated by the cohort studies (25, 39, 41, 71, 85, 154) which range between 1-4.7 per sievert but are not significantly different from zero (see Table 1). This discrepancy has not been adequately explained. And the finding of the same relative risk (1.5) for

virtually all forms of childhood cancer after very low doses immediately prior to birth remains puzzling as Boice and Miller have noted (13). Still another enigma involves the occurrence of childhood leukemia among twins. Although the latter receive substantial exposure to prenatal x-rays, cohort studies have consistently found twins to be at a low risk of childhood leukemia when compared with single births (44, 53, 81, 121, 122).

The Atomic Bomb Survivors

The first study of cancer among the in utero exposed atomic bomb survivors was published in 1970 (57); it was based on just those prenatally exposed survivors who could be identified through birth records in the two cities, some 1,250 individuals, and focused on cancers occurring in the first 10 years following birth. No increase in mortality from these malignancies was observed. Subsequently, in 1976, the period of observation was extended to cover all malignancies manifesting themselves within the entire preadult period. Again, no increase was observed, but the sample was small, and death certificates were not available on many of the children who died in the first year following the bombings. Accordingly, efforts were made to expand the study group through the roster of survivors maintained by the Commission and through the national censuses of 1950 and 1960. Even this expanded sample, however, failed to show an increase in childhood malignancies -- only two cases were identified, one of liver cancer and the other of Wilms' tumor. Importantly, but unexpectedly, no cases of leukemia were observed in the pediatric ages.

While the previous remarks concern childhood cancers, the evidence is mounting that the cancers of later years, the so-called adult ones, are increased in frequency among the prenatally exposed survivors in Japan (154). It has been suggested that not only do these cancers occur at earlier ages among individuals exposed to 0.30 Gy or more, but the incidence continues to increase, and the crude cumulative incidence rate, 40 years after the atomic-bombings, is 3.5-fold greater in the $\geq$0.30 Gy group. In the years from 1950-1984, based on the absorbed dose (DS86; see 123 for an explanation of this system of dosimetry) to the mother's uterus, and the augmented sample, the excess relative risk of cancer at 1 Gy is 2.77 with a 95% confidence interval of 1.14-13.48. For the dose group receiving more than 0.01 Gy the average excess absolute risk per 10^4 PYGy (person-year-gray) is 6.57 (0.47-14.49) and the estimated attributable risk is 40.9% (2.9-90.2%). Risks derived from only those cases identified through birth

records are somewhat lower, but not significantly. The excess relative risk at 1 Gy in this group is 2.19 rather than 2.77, for example. It should be noted that these risks include those individuals who were known to have cancer but had not as yet died from their malignancy or some other cause at the time of this review. However, the bulk of the individuals in this study are only now entering the years of naturally increased risk of cancer, and a subsequent follow-up, including deaths through December 1989, is less compelling (155). In the years 1985-1989, no excess of adult-onset cancer was seen and no new cases occurred in the $\geq$ 0.5 Gy group. The overall excess relative risk when this time period is included is about 1, which is not significantly different from zero. It warrants noting, however, that more cancer cases were observed among females than males, but when the analysis is restricted to females no clear change in cancer risk with dose is demonstrable. Interestingly, in the light of the controversy relative to the Oxford Survey alluded to earlier, two cases of leukemia have now been seen among young adults in the Japanese in utero exposed group (one male with acute lymphatic leukemia, diagnosed at age 29, estimated uterine dose 0.04 Gy; one female with acute myelogenous leukemia, diagnosed at age 18, estimated uterine dose 0.02 Gy).

Recently Delongchamp and his colleagues (24) have reexamined these data, extending the follow-up period through May 1992 but *focusing on mortality alone*. They find an excess relative risk of 2.1 at 1 Sv which is statistically significant with a 90% confidence interval of 0.2-6.0. They note nine of the ten deaths occurred among females. There was no recognizable increase in thyroid malignancies. It should be noted, however, that this analysis is based on mortality findings and thyroid malignancies are rarely fatal. Comparison of the risk estimates among the in utero exposed with those females exposed as children did not reveal a significant difference.

Acute versus chronic exposures

Heretofore our knowledge of the risk of cancer associated with chronic, generally low dose exposure to ionizing radiation has rested largely on experimental animals, cells grown in culture, and the occupationally exposed. The accident at the Chernobyl nuclear reactor in 1986 held and continues to hold promise of providing estimates of this risk based on exposure of the general population, including those exposed prenatally. However, as yet, the evidence to emerge is limited; much of what is available will be found in the Proceedings

of the First International Conference held in Minsk in 1996 (see 63, but also see 150).

Interest among the in utero exposed has thus far focused primarily on two malignancies, namely, thyroid cancer and childhood leukemia, although some data are available on the occurrence of neuroblastoma following the accident. We shall consider the findings that have emerged on these different malignancies or groups of malignancies separately.

Thyroid cancer --It is clear that there has been a striking increase in the occurrence of thyroid cancer among exposed children, particularly those exposed in Belarus where the contamination was the highest (see, e.g., 2). Moreover, the increase appears strongly related to the estimated dose (Gy) of ^{131}I based upon ground deposition of ^{137}Cs. Interestingly, this increase was seen sooner after the Chernobyl accident than after the atomic bombing of Hiroshima and Nagasaki, and appears quantitatively more dramatic. As a result, there has been considerable reluctance to attribute the findings to exposure to ionizing radiation, and explanations for the increase have been sought elsewhere. Among the caveats that were raised were the following: Were the additional cases a function of more intensive screening and surveillance? Was the more rapid and greater increase attributable to the difference in the thyroid doses involved, which were higher than those in Japan? Indeed, how accurate were the thyroid dose estimates? Was the increase due to the difference in exposure, one being ambient and the other primarily ascribable to ingested internal emitters, specifically radioactive iodine? Or was it due to host factors such as the purported endemic iodine deficiency?

Recent studies have addressed most of these concerns, but admittedly questions persist about the reliability and accuracy of the dosimetry. Nonetheless, Jacob and his colleagues (58) have published data on the risk of thyroid cancer among children under the age of 15 at the time of the accident, and have reported that the excess absolute risk (EAR) is 2.3 per 10^4 person-year gray (95% confidence interval: 1.4-3.8). This value lies within the confidence interval stemming from a meta-analysis of the findings from some seven studies of external radiation conducted by Ron and her colleagues (124). Be this as it may, the thyroid cancer seen as a result of the Chernobyl accident appears to differ from spontaneously occurring thyroid cancer in two important respects. First, the disease in children exposed as a result of the accident appears to

have a shorter latency period than that seen in Japan as a result of external radiation, a higher proportion of tumors arising in children under the age of 10, to be more aggressive and to have an almost equal sex ratio. Second, at the molecular level, the radiation-related tumors appear to be different from those that occur spontaneously in that *ret* oncogene activation is much more common (31, 54, 65).

Leukemia -- Mole (83) has argued that an effort to estimate the risk of leukemia among individuals prenatally exposed as a consequence of the Chernobyl accident is likely to be unrewarding. He advances several reasons for this conclusion including uncertain dosimetry, the likelihood that leukemia diagnoses would be made more often after the accident because the possibility would be uppermost in the mind of the examining physician, and the absence of good base line data for the years prior to the accident. Nonetheless a number of publications on the risk of leukemia have appeared, but the findings are ambiguous. Studies of the incidence of childhood leukemia in Finland (3) and Sweden (49) following the accident failed to find evidence of an increased risk. However, a study in Greece, which also failed to find an increased risk of leukemia among children 12 to 47 months of age, does report a significant increase in risk among children exposed in utero (110). The risk is stated to be 2.6 times the incidence of leukemia seen among nonexposed children. These findings were not confirmed by a similar study in Germany (21). Indeed, in the latter instance, the trend with time in the occurrence of childhood leukemia in the in utero exposed following the Chernobyl accident was negative, that is, occurrence declined with time. Ivanov and his colleagues, prompted by the studies just cited, have recently examined the post-Chernobyl occurrence of infant leukemia in Belarus (55). Although they report a weak increasing trend in the occurrence of infant leukemia after 1986, the increase is not statistically significant and there is no indication of a larger excess than that seen in Greece or Germany. They conclude, therefore, that it is difficult to accept radiation as the causal factor given the much greater exposures in Belarus than in either Greece or Germany. Finally, the World Health Organization's International Program on the Health Effects of the Chernobyl Accident (IPHECA) included a component on the risk of leukemia and related blood disorders subsequent to the accident. Although the data as presented by Souchkevitch (134) does not identify age at exposure, this study failed to find a significant

increase in the incidence of childhood leukemia after the accident as compared with the period before 1986 nor was there evidence of any deviation in the usual age distribution.

This issue is likely to remain contentious until the larger, more comprehensive case-control studies of the in utero exposed currently underway in the three affected republics of the Former Soviet Union are completed. However, even in this instance, the results may be ambiguous given the very small ambient dose that could be accumulated in the course of gestation, only a few millisieverts at most. It seems unlikely too that maternal ingestion or inhalation of radionuclides, notably cesium or strontium, would have added significantly to the ambient dose for a variety of reasons but two in particular. First, assuming the source of the exposure is removed, the fetal retention time or biological half-life of cesium is relatively short, about 49 days, and the isotope will be uniformly distributed throughout all organs and tissues of the body. Otherwise put, one would not expect an inordinate dose to the fetal marrow. Second, although the radioactive isotopes of strontium pose a potentially greater hazard since the growth of the fetal and neonatal skeleton is rapid and the hematopoietic system is developing, the estimated lifetime radiation dose to the infant skeleton from a single ingestion of radioactive strontium is small (90). If the dose is indeed small, the sample sizes need to demonstrate an increase in the occurrence of leukemia in childhood will be large despite the probable greater radiosensitivity of the embryo and fetus.

Other childhood cancers -- Michaelis and his colleagues (75) have sought to identify the possible causes of a 1988 incidence peak in infant neuroblastoma in west Germany. Their study involved a case-control design with 1:2 (cases:controls) matching and was restricted to some 80 cases born in 1988 and reported to have a neuroblastoma through March 1992 based on the German Childhood Cancer Registry. Of the 80 original cases, questionnaires were addressed to 73, and 67 responded. Their working hypothesis was that the parents of these children had an excessive intake of ^{137}Cs contaminated food as a result of the accident. However, this hypothesis could not be confirmed — the parents of the cases tended to have eaten less locally grown, contaminated food than the parents of the controls. The relative risk was 0.63 (95% confidence interval: 0.20-1.97).

Experimental studies of carcinogenesis following in utero exposure

An enormous literature exists on the occurrence of malignancy among experimental animals following exposures to ionizing radiation. Much of this literature has been reviewed elsewhere, but of these numerous studies only one seems especially pertinent to the purposes of this chapter, namely, the large beagle study conducted at Colorado State University in the United States in the years following 1967 (5, 6, 7). This conclusion rests on the size of the study population (1,680 animals), the doses employed which ranged from 0 to 0.83 Gy, the perinatal ages at which exposure occurred, and finally, the fact that most of the animals were not sacrificed but permitted to live until death occurred naturally. Thus, in most respects, the parameters of this study mirror those of concern to in utero exposure of the human being. The exposures of moment here occurred at either 8, 28, or 55 days post coitus. Since the gestation time in the beagle is 60-65 days, these ages at exposure correspond approximately to the 5th, 17th, and 33rd post ovulatory weeks in the human embryo or fetus.

These authors note that the fatal cancer rate in their perinatally irradiated dogs was over ten times the expectation in a general canine population and conclude that perinatal irradiation is carcinogenic (5). Among the three prenatal exposure periods, however, the only one that revealed a statistically unequivocal increase in tumor onset rate was the group exposed at 55 days post coitus. Interestingly, while exposure of neonates at 2 days of age or juveniles at 70 days postpartum resulted in an increased risk of benign as well as malignant thyroid neoplasia, including fatal thyroid carcinoma, no statistically significant increase was demonstrable among the prenatally exposed although at face value the prevalence of follicular cell neoplasia was somewhat higher in this group than in the controls (7). Unlike the situation in the human, where papillary carcinomas are the most common radiation-related thyroid malignancy, in the beagles follicular thyroid neoplasia prevailed. No histological difference was noted between the tumors in the irradiated and control dogs.

These findings are in general accord with the epidemiologic evidence, and support experimentally in a relatively large and long-lived animal species that there is an increased risk of malignancy during the early period of life. But this study has another facet of perhaps greater import. The experience of the atomic bomb survivors suggests that the higher risk associated with exposure in the first decade of life may decline with time. However, the evidence supporting this trend is limited since the bulk of the very young survivors of the bombing

are still alive and it will be several decades before enough of their cancer experience has accumulated to be confident of that this apparent trend is real. However, these irradiated beagles may provide one answer to the question of whether the higher risks seen in young dogs persists into adulthood.

THE TERATOGENIC EFFECT OF PRENATAL EXPOSURE TO IONIZING RADIATION

It was evident as early as 1949 that among the prenatally exposed survivors of the atomic bombing of Hiroshima and Nagasaki the prevalence of severe mental retardation was sharply elevated, particularly among those exposed in the earlier months of gestation. No other birth defects have been observed to be increased, despite experimental evidence suggesting a greater frequency of their occurrence following prenatal exposure to ionizing radiation. It is known, however, that many women who were pregnant at the time and exposed to relatively high doses of radiation lost their infants (see 125 for references). Presumably this loss was more likely to have occurred if the embryo or fetus was abnormal, particularly if the abnormality involved some vital center. Ionizing radiation seems most likely to impair those developmental events that are occurring at the time of exposure. Some of these events, for instance, the closure of the primitive neural tube, take place rapidly, in a few days (102), and a failure to find neural tube abnormalities might merely reflect the small number of embryos or fetuses exposed at a vulnerable developmental stage and survived.

EFFECTS ON THE DEVELOPING BRAIN

Three general features of the development and organization of the human brain are important to an understanding of its vulnerability to ionizing radiation (73). These are (a) the brain is an extremely complex organ, with a complicated architecture in which different functions are localized in different structures. Differentiation of the latter takes place at different times and for different durations. This is particularly true of the development of the neocortex, which proceeds over a long time; (b) brain function depends on the disposition and interconnection of structures and cells, and normal structure and function hinge on an orderly sequence of events, each of which must occur correctly in time and space; and (c) the neurons of the central nervous system are not self-renewing. The capacity of neuronal precursors to divide is lost during the populating of the cerebral cortex.

The cells of the different structures of the brain are produced at

different times. If exposure occurs when a certain cell type is being produced, the loss may be permanent (1). Thus each step in the development of the brain is crucially dependent upon the steps that have preceded it and any impingement on this sequence can lead to abnormal development. These abnormalities may occur either during organogenesis, or during the differentiation and growth of the brain mantle. Among the former defects are anencephaly and spina bifida, both failures in the normal formation and elevation of the neural folds and the subsequent proper closure of the neural tube (87, 88, 103), or holoprosencephaly, a failure of the forebrain to divide into two hemispheres. At this time, the undifferentiated neural cells retain their regenerative capacity, and tissue damage can, in theory, be repaired. The closure of the neural tube and the division of the prosencephalic vesicle occur rapidly, within a few days (102) about 4-6 weeks after fertilization.

Disturbances in the production of neurons, and their migration to the cerebral cortex, give rise to malformations of the brain mantle (4, 106, 115, 117). Among such malformations are an absent corpus callosum, or a disorganized cortical architecture which may result in abnormal fissuring of the cerebral hemispheres, or heterotopic grey matter and microcephaly.

Where and how ionizing radiation acts to impair brain function is unknown. However, ionizing radiation could interfere with normal development in a variety of ways (14, 15, 43, 45-48, 151). Damage could arise from the death of glial or neuronal precursors or both, or of immature neurons, or from an impairment of cell migration (32). But abnormality might also reflect an impaired capacity of the neurons to connect correctly (36), or a disoriented dendritic arborization, or a reduced number of dendrites or dendritic spines per cerebral cortical neuron (16-18), or an alteration in the process of programmed cell death, which is essential to the development of the normal brain and its adnexa. Distinguishing between these possible mechanisms of damage, although formidable, is essential to an understanding of the nature of the effects of ionizing radiation.

The causal relationship between irradiation of the embryo and fetus at specific stages of development and the subsequent morphologic and functional damage to the brain, if not the molecular events involved, are well established in a number of experimental animals. Much of this information was summarized in the UNSCEAR 1977 and 1986 Reports (139, 140). But these data give little quantitative insight into effects on the brain in humans, although they can

identify possible ones since, the histological structure of the brain is broadly comparable from one species to another, both in composition and function, and the sequence of developmental events in all mammalian species studied is similar (26, 27). However, the size of the various areas of the cortex devoted to specific functions can and does vary greatly, and so may the target zone associated with specific cortical functions. Finally, although structures in a particular part of the brain are broadly alike in animals of the same and even different species, there is an amazing degree of diversity among individuals within a species.

The evidence from Hiroshima and Nagasaki

Few population-based studies of the effects of prenatal exposure on the developing human embryo and fetus exist. Present knowledge rests mainly on those survivors exposed prenatally in Hiroshima and Nagasaki and to a lesser degree on studies of children who were inadvertently exposed in the course of gestation as a result of maternal radiotherapy, and on comparative embryological studies. However, among these various studies, the size, length of study, variability in dose and post-ovulatory age at exposure make the experiences in Hiroshima and Nagasaki the most important source of information.

Over the years, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF), have established several overlapping samples of prenatally exposed atomic bomb survivors. Since full accounts of the study samples, and the dosimetry can be found elsewhere (e.g., 125), they will not be described here. We turn, therefore, to the estimation of developmental age and the findings.

Developmental age is the single, most important element in determining the nature of the insult to the embryo or fetus stemming from ionizing irradiation. Accordingly, since, as earlier noted, different functions in the human brain are localized into different structures, and since the differentiation of these occurs at different stages of development and over different periods of time, estimated post-ovulatory ages at the time of the bombing (ATB) have been grouped to reflect these known phases in normal development. Post-ovulatory age was estimated using the relationship: Days of pregnancy ATB = 280 - (Date of birth - Date of bombing). The latter dates are 6 August for Hiroshima and 9 August 1945 for Nagasaki, and 280 represents the average duration in days of a pregnancy measured from the onset of the last menstrual period. Fourteen days have been subtracted from the days of pregnancy ATB to account for the time between the

onset of the last menstrual period and ovulation. Four age periods are customarily used: 0-7 weeks, 8-15 weeks, 16-25 weeks and 26 or more weeks after ovulation. These periods correspond to the following embryological events: In the first period, the precursors of the neuronal and glial cells, the principal cells that make up the central nervous system, are mitotically active. In the second, a rapid increase in the number of neurons occurs, these immature neurons lose their capacity to divide, and migrate from the proliferative zones to their site of function in the cerebral cortex. In the third, *in situ* cellular differentiation accelerates, synaptogenesis that commences about the 8th week after fertilization increases, and the final cellular architecture of the brain unfolds. The last period consists mainly of continued architectural development, cellular differentiation, and synaptogenesis.

Effects on brain growth and development

The two most conspicuous effects on brain growth and development that have emerged are an increase in the frequency of severe mental retardation and of small head size without apparent mental retardation. However, an increased frequency of unprovoked seizures has also been observed as well as a statistically significant reduction in intelligence scores and performance in school.

Severe mental retardation

Individuals classified here as severely mentally retarded are those who cannot form simple sentences, perform simple arithmetic calculations, care for themselves, or have been or are institutionalized or unmanageable. Thirty cases of severe mental retardation were observed in the 1,544 individuals included in the revised clinical sample on whom DS86 doses could be computed at the time of analysis (doses were not then available for 55 survivors in this sample).

Three of the retarded children, all in Hiroshima, are known to have, or had, Down's syndrome (one case died in 1952), a fourth, also in Hiroshima, had Japanese B encephalitis in infancy, and a fifth, in Hiroshima had a retarded sibling who was not exposed. It is likely, in these instances, that the mental retardation was merely a part of the former syndrome or secondary to the infection or inherited, but in any event not radiation-related.

When the prenatally exposed survivors exclusive of the three cases of Down's syndrome are distributed over the four post-ovulatory age groupings described above, and the frequency of mentally retarded individuals is examined

as functions of their doses and the post-ovulatory age at which they were irradiated, the following emerges (108):

(i) the highest risk of severe mental retardation is seen when exposure occurred 8-15 weeks after ovulation. This exceptionally vulnerable period coincides with the most active production of cortical neurons and when all or nearly all of the migration of the immature neurons from the proliferative layers to the cerebral cortex takes place;

(ii) within this critical period, damage expressed as the frequency of severe mental retardation increases as the dose to the fetus increases. Some 75% (9 of 12) of fetuses exposed to 1 Gy or more in this period are mentally retarded; this is a risk more than fifty times greater than that in the unexposed comparison group;

(iii) a period of lesser vulnerability appears to exist in the interval 16-25 weeks after ovulation. However, here no increase is seen at doses of less than 0.5 Gy;

(iv) there is no apparent increased risk prior to week 8 or after week 25.

Small head size

A small head in the current context implies a head with a circumference two or more standard deviations below the mean circumference of all of the individuals in the study sample. About 10% of these individuals with small head sizes were mentally retarded. Among the mentally retarded in the 1,598 births in the entire sample, 18 (60%) have been previously reported to have (had) disproportionately small heads (9, 76-78, 137, 148, 149). This value may be low, however, since head circumference was not standardized against body size, and mental retardation is often seen in individuals whose head circumference is disproportionately small for their body size.

Recently, Otake and Schull (107) have re-examined the relationship of small head size to dose among the prenatally exposed population in Hiroshima and Nagasaki using the DS86 doses. The study population consists of the 1,598 individuals (Hiroshima 1,250, Nagasaki 348) used by Otake et al (108) in the analysis of severe mental retardation. DS86 doses (Version 3) are available on 1,566 of these persons (1,242 in Hiroshima and 324 in Nagasaki. Note this represents an addition of 22 cases over the number used in the analysis of severe mental retardation (108). Among these subjects, 1,473 had their head circumference measured at least once in the period from 9 to 19 years of age, and

62 had small heads based on the criterion described above. It should be noted that the criteria differ between males and females for the same chronological age, ranging from a difference of -1.58 to 1.35 cm.

Small head size and post-ovulatory age at exposure:--Within the four post-ovulatory periods alluded to above -- 0-7 weeks, 8-15 weeks, 16-25 weeks and 26+ weeks -- the proportion of individuals with a small head size increases with increasing dose in only the first two periods, and an especially sharp rising trend is seen in the 8-15 week period.

Of the 17 individuals with a small head in the 0-7 week period, 12 without severe mental retardation were exposed to 0.01 Gy or more, and in 1 of the 2 individuals with a small head exposed to >1.00 Gy and 2 of the 4 individuals with a small head exposed to 0.50-0.99 Gy, there was no apparent mental retardation. However, of the 29 individuals with a small head in the 8-15 week period, 26 received a dose of 0.01 Gy or more, and 12 (46.2%) were mentally retarded. Seven of the 8 small head cases who were exposed to >1.00 Gy were retarded. Thus 12 of the 15 individuals with an atypically small head and severe mental retardation occurred at 8-15 weeks after ovulation. In the 16-25 week period, only 1 of the 3 individuals with a small head in the 0.01+ Gy group was mentally retarded and he had been exposed to a dose of more than 1.00 Gy.

The designation "small head size" may cover a variety of possibly different developmental "abnormalities." For example, some of these individuals clearly invite the clinical diagnosis of microcephaly since the head is not only unusually small but often oxycephalic-like. Still others, and they are more common, have a head which is proportionate in all dimensions, but small. Moreover, since head size varies in all populations, some of the individuals with a small head merely represent the lower extreme of normal variability. Based on the criterion for small head size used here, if head sizes are approximately normally distributed, some 2.5% of "normal" individuals would be so classified. Recognizing this fact, Otake and Schull have attempted to estimate the excess number of individuals with small heads ostensibly attributable to exposure to ionizing radiation. Among the 62 individuals with small head size, 37 would be expected normally, and the observed and expected numbers agree well when exposure occurred in the 16th week or later. However, there is a striking excess prior to this time -- where 16 are expected 46 were observed, an excess of 30 cases. If the small head size seen among those 12 individuals with severe mental

retardation is secondary to brain damage, this leaves 18 cases which could represent radiation-related instances of growth retardation without accompanying mental impairment. To explore this possibility the locations of the 47 cases of small head size without mental retardation were determined in a bivariate plot of standing versus sitting height expressed as age and sex standardized deviates based upon the full sample of 1,473 individuals. The individuals with a small head size but no apparent mental retardation were found to be disproportionately represented among the lower values defined by either the 95% or 99% probability ellipse. This suggests that small head size is not an independent teratogenic effect, but is either secondary to mental retardation or to a more generalized growth impairment without clinically recognizable mental retardation.

Intelligence test scores

Intelligence tests differ in the importance given to verbal ability, psychomotor reactions, social comprehension, and so on. Thus, the score attained by an individual will depend to some degree upon the specific test used; however, generally, individuals scoring high on one test obtain high scores on other tests. Most intelligence tests are so constructed that the distribution of test results follows an approximately normal curve, with a mean of 100 and a standard deviation of 12-15 points. As a result, normally some 95% of the population will have scores in the range 70-75 to 125-130, that is, will fall within two standard deviations of the mean. Individuals whose scores lie two standard deviations or more below the mean would commonly be described as retarded. In the Japanese experience, the mean Koga score of some 1,673 tested children was 107.7 (standard deviation 16.08 (126)), and the highest IQ achieved by any of the clinically diagnosed severely mentally retarded children on the test was 64.

Schull et al. (126) have described an analysis of the results of intelligence tests of the prenatally exposed survivors conducted in 1955 by psychometrists in the clinical facilities of the Commission. This analysis of the Koga test scores (66, 138) reveals the following:

(i) there is no evidence of a radiation-related effect on intelligence among those individuals exposed within 0-7 weeks after ovulation or after the 25th week;

(ii) for individuals exposed at 8-15 weeks after ovulation, and to a lesser extent those exposed at 16-25 weeks, the mean test scores, but not the variation in scores about the mean, are significantly heterogeneous among

the four exposure categories; and

(iii) the fact that the mean test score declines significantly with increasing dose without a statistically demonstrable change in the variance of the test scores suggests a progressive shift downwards in all individual scores with increasing exposure.

School performance

As a part of the assessment of the effects on the developing embryonic and fetal brain of exposure to ionizing radiation, the school performances of the prenatally exposed survivors in Hiroshima and a suitable comparison group have been studied (109). The relevant data were collected in 1956 when these children were 10 to 11 years old, and most had recently completed their fourth year of schooling (for details see, 125). The records included information on school attendance, performance in various subjects, their behavior, and physical status.

In the first four years of elementary schooling the Japanese child studies seven different subjects, including the Japanese language, civics, arithmetic, science, music, drawing and handicrafts, and gymnastics. Every student's performance in these subjects is evaluated routinely, and at the end of every school term (there are three in the academic year), a score is assigned for each. Upon the conclusion of the academic year, these scores are summarized into a single value for each subject. The latter varies, normally, in unit steps from +2 to -2. The highest and lowest five percentiles of the class are assigned scores of +2 (very good) and -2 (poor), respectively. The next highest and lowest 20 percentiles are given +1 (somewhat above average) and -1 (somewhat below average), and finally, the middle 50% are given zero (average). Otake et al. (109) have converted these assigned values to a five point scale, giving the highest and lowest scores the values 5 and 1, respectively, and so on.

As a preliminary to determining what measure of school performance should be fitted to the data, the structure of the matrix of correlation coefficients among the seven subjects was examined. These correlations are high, ranging from 0.62 to 0.82, and suggest a strong interdependence of the scores. To determine whether some combination of the scores would provide a more suitable measure of radiation-related damage than the scores individually, summary characteristics of the correlation matrix were computed. These computations revealed that simply averaging the scores would account for 75% of the collective variability. No other combination explains more than 6% of the variability, and all are

associated primarily with a single subject, the second with music, the third with gymnastics and so on.

Achievements in school of the prenatally exposed survivors, as judged by the relationship of the average school performance score, can be summarized as follows:

(i) in the period 8-15 weeks after ovulation scholastic achievement in school diminishes as the absorbed dose increases; and

(ii) a similar diminution is seen in the period 16-25 weeks after ovulation. This trend is stronger, however, in the earliest years of schooling;

(iii) in the groups exposed within 0-7 weeks after ovulation, or 26 or more weeks after ovulation, there is no evidence of a radiation-related effect on academic performance.

Not unexpectedly, given the correlation between average school performance and IQ score ® = 0.54), these results parallel those previously found in prenatally exposed survivors with respect to achievement in standard intelligence tests in childhood.

Seizures

Seizures are a frequent sign of impaired brain development, and therefore, could be expected to affect more children with radiation-related brain damage than children without. Dunn et al. (30) have described the incidence and type of seizures among the prenatally exposed survivors of the atomic bombings, and their association with specific stages of prenatal development at the time of irradiation. Histories of seizures were obtained at biennial routine clinical examinations starting at the age of two years.

Seizures, as here defined, include all references in the clinical records to "seizure", "epilepsy", or "convulsion". All of the medical records of participants in this program of examinations who were coded for seizures were reviewed to characterize the nature of the seizure (its severity, clinical symptomatology, the presence of fever, cause of the seizure, duration), presence of other neurological disease, and any other medical problem. The records were not sufficiently explicit to permit detailed clinical classification; however, sufficient description existed to allow a limited categorization of seizures by etiology for epidemiologic purposes. Cases were classified as febrile, acute symptomatic (seizures due to acute central nervous system insult such as head trauma), and unprovoked. The latter are those cases without a record of fever,

trauma, post-vaccination reaction, or anoxia during an acute, post-natal event. A seizure was so classified if the records revealed no clear statement of exposure to an accompanying infectious, traumatic or fever-producing agent. Strictly neonatal seizures (within the first month post-partum) were difficult to ascertain in this study, which did not begin until the children were two years old. Since neonatal seizures appear to have a different etiology and were most likely under-ascertained, they were routinely excluded.

Fever is the most common cause of a seizure in infancy or childhood. In the event of multiple seizures, however, fever might accompany only one, and then not necessarily the first seizure, and scoring these cases was undoubtedly arbitrary. The convention adopted was the following: if fever accompanied only one of several seizures, making it doubtful that fever was a generally precipitating cause in an individual, the case was scored as unprovoked if no other causal event could be elicited.

Analysis of the data disclosed the following:

(i) No seizures were recorded among individuals exposed 0-7 weeks after ovulation at doses higher than 0.10 Gy.

(ii) In the group exposed to irradiation 8-15 weeks after ovulation, the incidence of seizures was highest among those who received doses exceeding 0.10 Gy and increased with the level of fetal exposure. This was the case for all seizures without regard to the presence of fever or precipitating causes, and for unprovoked seizures.

(iii) When the 22 cases of severe mental retardation were excluded, the increase in seizures was only slightly significant and then only for unprovoked seizures.

(iv) After exposure at later stages of development, there was no increase in recorded seizures.

Other data on the occurrence of seizures following prenatal exposure are sparse. However, two case reports suggest that the post-ovulatory period 8-15 weeks may be a vulnerable time for exposure of the human fetus to radiation with subsequent development of seizures (40). The first involved a male exposed in the second to fourth month of gestation in the course of his mother's radiotherapy (dose unknown) for uterine myomatosis. He subsequently developed epilepsy at the age of 3.5 years. The second was a female, exposed during the 2nd-3rd month, again in the course of treatment of uterine myomatosis in the

mother (dose unknown), who developed epilepsy at two years of age. It warrants noting, however, that seizures have also been reported in rodents following in utero exposure (133).

Recapitulation and interpretation

To summarize, studies of the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki have revealed a significant dose-related increase in the frequency of mental retardation, seizures, and individuals with atypically small heads, and a diminution in intelligence test scores and academic achievement. These effects are most conspicuous in the 8th through the 15th weeks following ovulation; however, there is a significant increase in the number of individuals with small heads in the first two months post-ovulation and some evidence that mental retardation may be more common than expected in the post-ovulatory period 16-25 weeks, particularly at doses of 0.5 Gy or more. Given the correspondence in the period of vulnerability, the severe mental retardation and the reduced intelligence scores and school performance may be manifestations of the same process, in which all the individuals significantly exposed in the relevant stages of pregnancy suffer some dose-related reduction in cortical function.

Interpretation of these findings in mechanistic terms is difficult, and without a clear understanding of the molecular and cellular events that culminate in mental retardation, the role ionizing radiation may play in its origin is elusive. Even the pathological findings or those from neuroimaging of the living brain are still too limited to provide much guidance. The information available can be briefly summarized as follows (for details see 22, 52, 92, 106, 113-117, 127, 147, 153):

(i) Among the mentally retarded who were exposed in the 8^{th} or 9^{th} week following ovulation, in every instance studied, evidence of migrational errors, usually circumventricular heterotopia, has been seen.

(ii) When exposure occurred somewhat later, in the 12^{th} or 13^{th} week, no heterotopias were seen, but indirect evidence of migrational errors exists. This has taken the form of mega cisterna magna, mild macrogyria, and abnormality of the corpus callosum or a poorly developed furrow immediately above the corpus suggesting an error in the development of the band of association fibers, the cingulum, that passes over the corpus callosum. Interestingly, animal experiments suggest the cingulum to be

particularly radiosensitive (118-120).

(iii) Still later in development, at week 15, neither migrational errors nor conspicuous changes in brain structure are seen. Presumably the functional impairment that exists is related to the connectedness that occurs between neurons. There is experimental evidence to show that exposure at this time in the development of the brain in primates leads to a diminished number of connections between neuronal cells (18-20). If all of the connections have functional significance, this diminution must compromise performance in some manner.

Are the developmental errors described in the preceding paragraphs causally related to prenatal exposure to ionizing radiation or are they merely fortuitous? Three lines of evidence suggest causation. First, similar findings have been reported in other individuals who were exposed to ionizing radiation prenatally. For example, Driscoll et al. (29) have described the acute damage to two fetuses, one a male exposed at 16 or 17 weeks of pregnancy and the other a female exposed at 22 weeks to radium therapy in the course of treatment of maternal squamous cell carcinoma of the cervix uteri. Both were alive at the time of hysterectomy, a day following the cessation of treatment in the first instance and six days later in the second. The doses were large - estimated to be about 4.3 Gy at the center of the fetal head and 7.7 Gy at the nearest point inside the cranium in the 16-17 week fetus, and about 16 Gy in the second fetus. In both cases, the brain incurred the greatest damage, but then it was also closest to the source of ionizing radiation. Neuronal cell loss was selective. The primitive post-mitotic migratory cells were promptly killed by the irradiation, paralleling the findings seen in experimental animals. Damage to the cerebellum was less extensive, but noticeable, particularly in the older fetus exposed to 16 Gy. Extensive changes were seen in other organs, notably the bone marrow and lymph nodes.

Second, although migrational errors are often seen associated with well-recognized, inherited, syndromes in which mental retardation occurs (for specific instances, see 23, 43, 72 and for a review, see 4), they appear relatively uncommon in idiopathic (unclassified) mental retardation. Thus, the abnormalities seen among the prenatally exposed survivors in Hiroshima and Nagasaki would not appear to be common findings among the mentally retarded.

Finally, although the prevalence of ectopic grey matter among the mentally

retarded is not reliably known, and it has been reported in other cases of mental retardation not related to irradiation, it is not always a concomitant of mental retardation. Neuroimaging of individuals with the inherited Fragile X syndrome, where varying degrees of mental retardation commonly occur, has not revealed this defect. Autopsy studies have, however, disclosed abnormalities in dendritic spine morphology -- very thin, long tortuous spines with prominent heads and irregular dilatations were noted (147), suggesting a post-migratory developmental error.

Other human studies

Numerous studies and a variety of case reports (see 10, 37, 89, 112, 152, 156 and 79 for a review) have been published that further the understanding of the possible role of ionizing radiation in the origin of brain abnormalities (37, 84). However, few of these studies or reports provide a reliable basis for risk estimation. Generally, there is little information on the exposures or the developmental ages after fertilization at the time of exposure and the sample sizes are often small. An exception is the study of some 998 children born at the Chicago Lying-In Hospital to women who had pelvimetry during the course of their pregnancy (39, 99-101). Since the date at which pelvimetry occurred was recorded, the age of the fetus at exposure could be estimated. While the bulk (87%) were exposed in the second half of pregnancy, 120 or so were exposed prior to the 20th week after the onset of the last menstrual cycle. A variety of endpoints were examined in this group of children, relative to two control groups (born before or after the pelvimetry series was completed), including the occurrence of malignant neoplasms, congenital malformations, and the presence of mental deficiency. Only one statistically significant difference between the exposed and the comparison groups was observed - the frequency of hemangiomas was increased in the pelvimetry group and particularly so when exposure occurred in the second or third trimester (39). Subsequent studies have indicated that this increase was due primarily to flame nevi, and the investigators are inclined to attribute no biological significance to this finding (99). Although the sample is relatively large and the irradiation occurred routinely rather than for medically indicated purposes, the doses are generally small, 0.01 to 0.03 Gy, and as previously indicated, the bulk of the children were exposed in the third trimester (99-101). Unlike those studies where irradiation occurred on a selective basis (e.g., 37), these authors find no evidence of a radiation-related

effect on morbidity or mortality, save the one described above, but the analyses usually pooled all ages at exposure, and the power of the tests, in the statistical sense, is small in light of the expected effect at these doses based on the Japanese studies.

Granroth (38) has examined the association of diagnostic x-ray examinations in Finland with the occurrence of defects of the central nervous system. The data, drawn from the Finnish Registry of Congenital Malformations, reveal a significant increase of abnormalities of the brain, primarily anencephaly, hydrocephaly and microcephaly, among newborn infants prenatally exposed, when contrasted with time-area-matched control subjects. No estimate is given of the fetal absorbed dose. Moreover, as the author notes, the majority of these infants were exposed because of the suspicion of either maternal pelvic or fetal anomaly and, therefore, the exposures were unlikely to have occurred at a time when abnormalities, such as anencephaly, are induced (88). Accordingly, it seems unlikely that the results reflect a teratogenic effect of radiation.

Neumeister (93) has described the findings on 19 children prenatally exposed to doses between 0.015 and 0.1 Gy. No instances of severe mental retardation are recorded, but post-ovulatory age at the time of exposure was not taken into consideration and no suitable comparison group was found. A more recent report, of 73 children, merely states that mental development followed a normal course (94). Meyer et al. (74) failed to find evidence of an increased frequency of severe mental retardation among the offspring of 1,455 women who were exposed to small doses of radiation as a result of diagnostic pelvic examinations. It seems uncertain, however, whether their case-finding mechanism would have identified women who were severely mentally retarded. An increased probability of premature death among such individuals leads to under representation of the mentally retarded later in life. In addition, exposure must commonly have occurred late in pregnancy, after the most vulnerable period.

Other studies, such as those of Nokkentved (96), are similarly inappropriate for the estimation of radiation effects. Nokkentved examined 152 children exposed in the first four months after fertilization to doses ranging from 0.002 to 0.07 Gy. The findings among these children were compared with those in their unirradiated siblings. Only one child, in the exposed group, was found to be microcephalic. There were none among the siblings. Two children in each group were reported to be feebleminded, imbeciles or idiots. Given the

purported doses and sample sizes, these findings are not inconsistent with the experience in Hiroshima and Nagasaki but neither are they compelling.

Chinese investigators (57) have published the results of a study of the effects of prenatal exposure to diagnostic radiation on childhood physical and mental development that addresses some of the limitations previously cited of other studies. The exposed group consisted of 1,026 children who were born in hospitals in Beijing, Shanghai, and Changchun and were between 4 and 7 years of age when recruited. The absorbed dose to the fetus ranged from about 0.012 to 0.043 Gy. However, only 1 child had been exposed prior to the 8th week following ovulation; 13 were exposed in weeks 8-15, 41 in weeks 16-25, and the remainder in the 26th week or subsequently (most actually in the 37th week). The comparison group consisted of 1,191 children matched to the exposed group on sex, age, and hospital of birth. Height, weight and head circumference measurements were obtained, and intelligence was assessed using a Fifty Item Intelligence and Ability Scale developed by the Chinese Academy of Medical Sciences and standardized nationally. No significant difference between exposed and controls emerged in the measurements of physical development or intelligence. At face value, however, the mean intelligence test score was reduced to a modest extent among the exposed, and the distribution of individual scores was slightly shifted toward lower values.

Bohnen and colleagues (11) have described the results of a historical cohort study of 2,980 women pregnant in Rochester, Minnesota between 1917 through 1973. The focus of this study was on the effects of diagnostic irradiation during pregnancy on head circumference at birth. In all some 9,793 pregnancies were studied using the Mayo Clinic Medical Records Linkage System. The authors report that after taking into account sex of the fetus, duration of pregnancy, and congenital head abnormalities there was a significantly decreased head circumference associated with exposures of 0.3 Gy or more in the second or third trimesters. Maximum effects were seen during the mid-gestational and second trimester periods. However, they report no significant effect of radiation when exposure occurred in the first trimester which is at variance with the experience in Hiroshima and Nagasaki but the sample exposed at this age is small.

Finally, and of particular relevance to the effects of chronic exposure, the World Health Organization, through its International Program on the Health Effects of the Chernobyl Accident (IPHECA), has studied some 4,210 children who

were exposed in utero as a result of this accident (134). They were born between 28 April 1986 and 26 February 1987. Ostensibly the cohort includes all such children in the three affected states that were formerly part of the Soviet Union. Individual doses were not available; estimates of exposure were based upon ground contamination with radionuclides. Unfortunately the results are ambiguous and difficult to interpret. Further studies have been proposed but based on the smallness of the dose likely to have been accumulated during critical stages in gestation it seems unlikely that these will be more informative.

Experimental studies

Experimental studies have demonstrated that the radiosensitivity of different components of the brain differs, and substantially so (see, for example, 68, 69). Behavioral changes, possibly analogous to those described above, have been seen in rodents (60, 61, 64, 68, 97, 98, 132, 146) and primates following prenatal exposure (104, 105). Brizzee et al. (17), for example, have reported that exposure of squirrel monkeys on days 89-90 of gestation to cobalt-60 gamma irradiation at doses of 0.5 or 1.0 Gy results in less accurate and poorly coordinated reflexes and neuromuscular coordination. The percentage of correct responses on visual orientation, discrimination, and reversal learning were significantly lower in the exposed animals as contrasted with controls. At doses of 0.10 Gy, no structural or behavioral alterations were seen; however, they conjecture that more sensitive behavioral testing and the use of image-activity computerized microscopic techniques and possibly computer aided mapping of specific neuronal populations will reveal changes (see 67).

These observations are, however, difficult to put into a human perspective. The tests used to measure cortical dysfunction have no obvious human counterparts, the nature of the dose-response relationship is often clouded by the large inherent variability in the endpoints measured, and the like. Nonetheless, three general conclusions seem warranted from the experimental evidence. First, it appears clear that low doses (doses in the range of 0.1 to 0.2 Gy) produce measurable behavioral and anatomic effects. Second, behavioral changes have their structural counterparts in the architecture of the brain. Third, there is a high degree of functional specificity in the information transmitted over neural systems. The strongest human evidence in support of this contention stems from studies of individuals whose corpus callosum was surgically

cut to control intractable seizures. These studies reveal that the ensuing loss of function depends upon the specific callosal regions that are severed (33).

Risk estimates

Qualitative and quantitative estimates of the risk to the brain after prenatal exposure are set forth in Tables 1 and 2. These risks, in sensu strictu, apply only to acute exposures. Little is known about the effects on the developing human embryo and fetus of fractionated or chronic exposures to ionizing radiation. Most of the information available on the effects of dose rate involves the experimental exposure of rodents. Since these findings have been summarized in previous reviews (see, e.g., 69, 130, 131), attention here is restricted to only one or two representative observations. Brizzee and Brannon (16; but see also 59, 62, 70) have examined cell recovery in the fetal brain of rats. Pregnant rats were exposed to cobalt-60 radiation on gestation day 13 to single doses, ranging from 0.25 to 2 Gy in increments of 0.25 Gy, and to split doses of 1 Gy followed nine hours later by a second dose of 0.25 to 1.5 Gy, again in increments of 0.25 Gy. The animals were sacrificed on the 19th day of gestation. The incidence and severity of tissue alterations generally varied directly with dose, and were clearly greater in single dose than in split dose groups with the same total exposure. This reduction in damage with protraction of dose appeared greater for continuous gamma-ray exposure than for serial brief X-ray exposures, and it has been argued that this may indicate a further sparing when the protracted dose is evenly distributed over time (80).

At low doses of radiation, such as those associated with chronic exposure generally, it can be presumed that relatively little, if any cell killing occurs, but this does not preclude other cellular effects. However, there is as yet little or no direct human evidence on the effects of low doses of radiation on the membranal or cytoskeletal properties of either neurons or the radial glial cells which serve as their guidance mechanism.

Uncertainties in the risk estimates

Numerous uncertainties are associated with the risk estimates summarized in Tables 1 and 2. The ones that loom largest include the limited nature of the data, especially on mental retardation and seizures, the appropriateness of the comparison group, errors in the estimation of the tissue absorbed doses and the prenatal ages at exposure, and other factors, such as nutrition and disease, which could play a role. Briefly the import of these is as follows:

Limited nature of the data and the comparison group. Only 21 of the 30 severely mentally retarded individuals in the revised clinical sample received doses of 0.01 Gy or more, and three of these had health problems which could account for their retardation and not be radiation-related (two cases of Down's syndrome and one case of Japanese encephalitis in infancy). Their exclusion does not alter the slope of the dose-response relationship materially (see Table 3); however, with their removal, there are only 18 cases in the critical period without known cause for the retardation other than exposure to ionizing radiation.

As to the comparison group, the atomic bombings resulted in circumstances that could have altered the normal frequency of mental retardation or have interacted non-additively with exposure. However, exclusion of the comparison population does not alter the regression coefficient appreciably (Table 3).

Prenatal age at exposure. The apparent timing of vulnerable events in development can be affected by errors in the determination of prenatal age, and possibly seriously so in specific cases. Gestational age is usually estimated from the onset of the last menstrual period, assuming that 280 days, on average, intervene between the beginning of menstruation and parturition. Post-ovulatory age is then calculated by subtracting two weeks. This method is sensitive to at least two types of errors -- mis-estimation of the onset of menstruation and the tacit assumption that all pregnancies proceed to term. If any terminated prematurely, as must have been true for some of the prenatally exposed survivors, the estimated age of the child at exposure would be incorrect. Another possible source of error arises from the variation between individuals in the prenatal age at which specific developmental events occur (95, 102, 129). This does not seem likely to be a major limitation of the data, but little or no information is available on the probable magnitude of this source of variability.

Estimated tissue absorbed doses. The risk estimates presently available are based on the absorbed dose to the uterus of the mother. This dose could be somewhat higher than that to the developing embryo or fetus in the earlier stages of development, and if so, the effects in the earlier months would be underestimated. Moreover, all estimates of the doses to the survivors of the atomic bombings in Japan are subject to at least three sources of error, specifically those that stem from determinations of dose in air with distance from the epicenter; the attenuation factors for building materials and tissues;

and the locations and positions of the survivors. Some of these can never be evaluated rigorously for all of the individuals concerned, but such errors can influence the shape of the dose-response relationship as well as the parameter values defining that shape (34, 35, 56, 111). Pierce and Vaeth (111) have shown that random dosimetric errors can lead to a 10-15% underestimation of the cancer risk among the survivors, and presumably a similar error could obtain in the estimates described here.

Dose-response function. Within the period of maximum vulnerability, the data on the prenatally exposed survivors can often be satisfactorily approximated by more than one dose-response function, generally a linear or a linear-quadratic model. Given that neuronal death, mismanaged migration, and faulty synaptogenesis could all play a role in the occurrence of cortical dysfunction and that each could have its own different dose-response relationship, there is little or no prior basis for presuming that one or the other of these models describes the biological events involved better. The most appropriate model, therefore, remains a matter of conjecture, and it seems unlikely that epidemiological studies will ever be able to resolve this. This means necessarily that the model to be used in the estimation of risk must rest on a series of considerations, not all of which are biological.

Threshold models can be fitted to the Japanese data, but generally the fit is not demonstrably better statistically than non-threshold models (Table 3). Thus the justification for threshold models rests not on the epidemiological evidence but on experimental findings, and the supposition that teratogenic effects necessarily involve damage to a number of cells. It is arguable, however, whether either of these bases withstands serious scrutiny. First, the experimental data are often contradictory or difficult to place in perspective. For example, Hoshino and Kameyama (50) have reported the frequency of pycnotic cells to be linear with dose at doses below 0.24 Gy, and Wanner and Edwards (145) have reported a measurable, but not statistically significant diminution in brain weight in guinea pigs at exposures as low as 0.04 Gy. And Wagner and his colleagues (143) have demonstrated a statistically significant diminution in the brain weight of guinea pigs exposed to 75 mGy on the 21st day following conception (approximately the 5th to 6th week following conception in the human). The loss in brain weight was approximately 1 mg per 1 mGy. Many of these effects have also been seen in larger animals. As an instance, Hamilton and his

colleagues (42) have reported a significant reduction in brain weight in beagles exposed at 28 or 55 days postcoitus. They noted that among dogs given lower doses and followed for up to 11 years, there was a significant decrease in brain weight at doses of 0.80-0.88 Gy. This decrease was still present after normalization for radiation-induced reductions in body size. Konermann (69) has argued that the lowest effective dose in animals for overt brain damage is generally 0.1 Gy or higher. However, he notes that more subtle changes can be seen at doses as low as 0.025 Gy and that errors in alignment are marginally significant at 0.05 Gy ($P<0.10$). It is not obvious what the occurrence of pycnotic cells or malaligned neurons is measuring, insofar as functional brain damage is concerned. Nor is it clear what a loss in brain weight implies, if the numerical densities of brain cells are increased, as has been reported (119). An increased cell density can mean fewer axons, dendrites, and glial processes between the nerve cells, and fewer intercellular connections could reduce the quality of brain function.

Commonly when a threshold is invoked to account for a series of experimental observations, the threshold is not formally estimated but merely taken to be the lowest dose at which an investigator finds a statistically significant effect in pairwise comparisons with the control. But since statistical power diminishes as the magnitude of the effect decreases, and it is impossible by statistical means to demonstrate "no effect," this is a weak argument. Few experimental studies have the requisite sample size to preclude non-threshold dose-response models, whether linear or linear-quadratic. Indeed, rarely is an explicit dose-response model fitted to the observations; significance is more generally asserted, as previously stated, on the basis of pairwise comparisons often with no allowance for the number of comparisons made. Establishment of a threshold is thus no less difficult in an experimental situation than in an epidemiological one.

Extraneous sources of variation. Alternative, non-radiation-related sources of variation might account for the effects on the developing human brain observed among the prenatally exposed atomic bomb survivors. These include (a) genetic variation; (b) nutritional deprivation; (c) bacterial and viral infections in the course of pregnancy; and (d) embryonic or fetal hypoxemia, since there is substantial evidence to suggest that the cerebrum and its adnexa are especially sensitive to oxygen deprivation. The possible roles these may play

in the present context have been explored elsewhere (79, 80, 82, 108, 125). Suffice it here to state that no fully satisfactory assessment of the contribution of these sources of variation can be made so many years after the event. It is only possible to speculate on their importance. Given the present uncertainties (since most of these extraneous sources of variation would have a greater impact at high than low doses, and thus produce a concave upwards dose-response function), the careful course would be to assume that the dose-response relationship is not materially altered other than additively by these potential confounders.

CONCLUSIONS

Carcinogenesis:

Although the evidence is not seen as compelling to everyone, there is ample reason to believe that in utero exposure does, in fact, increase the risk of a malignancy. This conclusion rests not only on studies of children who received prenatal x-ray exposure for medical diagnostic purposes, but also the experiences of the survivors of the atomic bombing of Hiroshima and Nagasaki exposed in utero, and the findings, particularly with respect to thyroid cancer, emerging from the studies of the Chernobyl reactor accident. Precisely what this increased risk may be is more conjectural. Doll and Wakeford (28) have estimated it to be 6% per sievert, based largely on the Oxford Survey of Childhood Cancer. However, cohort studies suggest a somewhat lower value. There are other puzzling aspects of the Oxford study which have yet to be resolved, and may be unresolvable given the increasing tendency to eschew exposure of a pregnant woman to ionizing radiation. Nonetheless the bulk of the evidence suggests that the developing fetus is sensitive to the carcinogenic effects of exposure to low-LET ionizing radiation and possibly more so than has proven true for individuals exposed as adults.

Teratogenesis:

The human brain is extraordinarily sensitive to ionizing radiation at certain stages in its prenatal development. Present evidence, based largely on the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki, reveals the risk of damage to the brain to be highest for exposures occurring during post-ovulatory weeks 8-15. In the period 16-25 weeks after ovulation, a lesser vulnerability is observed, with little apparent risk for

exposures prior to week 8 or after week 25.

Damage may be manifested as an increase in the frequency of severe mental retardation, of small head size without apparent mental retardation, of unprovoked seizures (those with no known precipitating cause), or reduced intelligence quotient (IQ) scores, or lower scholastic achievement in school. The damage caused by exposure to 1 Gy within the most vulnerable period, 8-15 weeks after ovulation, increases the frequency of mental retardation to about 40% (background frequency: 0.8%), or a loss in intelligence score of approximately 25-30 points, depending upon the sample used to estimate the risk, and whether the mentally retarded are or are not included in that sample. Prenatal exposure to 1 Gy appears to imply a decrement in average school performance score equivalent to the shift of an average individual from the middle 50 percentile of his or her class to the lower 10 percentile, or approximately a 25-fold increased risk of unprovoked seizures. These estimates assume a linear dose-response without threshold. If a linear threshold model is fitted to the same data, the estimated threshold, after the exclusion of those cases of mental retardation of probable non-radiation-related etiology, is about 0.10 Gy, but it warrants noting that a linear-quadratic model without a threshold describes the data equally well. For the period 16-25 weeks, no cases of severe mental retardation were observed at exposures of less than 0.5 Gy. Thus, with some uncertainty, a threshold could be assumed in this case.

Anhang/Appendix W

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Table 1. A brief summary of the estimates of relative risk of childhood cancer from the larger case-control and cohort studies on the risk of cancer following in utero exposure to ionizing radiation.

Reference	Study Years	Ages	Relative Risk (95% confidence interval)	P-value
Case-control studies				
Stewart et al., 1956*	1953-55	< 10	2.05 (1.40, 3.01)	< 0.01
Stewart et al., 1958*	1953-57	< 10	2.06 (1.58, 2.68)	< 0.01
Bithell et al., 1975*	1953-67	< 10	1.47 (1.34, 1.62)	< 0.01
Harvey et al., 1985**	**1930-69**	**< 15**	**2.40 (1.00, 5.90)**	**< 0.04**
Rodvall et al., 1990**	1952-83	< 16	1.38 (0.78, 2.46)	0.27
Cohort studies				
Magnin, 1962	1948-56	< 15	1.00 (0.06, 15.9)	0.99
Griem et al., 1967	1948-66	< 15	1.19 (0.34, 4.19)	0.79
Hagstrom et al., 1969	1945-67	< 15	4.77 (0.33, 69.5)	0.25
Diamond et al., 1973	1947-59	< 10	1.02 (0.51, 2.01)	0.96
Yoshimoto et al., 1988	1950-60	< 15	2.11 (0.15, 30.8)	0.58

* Oxford Survey of Childhood Cancer

** A twin study.

Table 2. The effect on the developing human brain of exposure to ionizing radiation 8-15 weeks after ovulation.

Effect	Risk at 1 Gy	Comments
Severe mental retardation	Increased 50-fold	Risk rises from 0.8% at 0 Gy to 44% at 1 Gy.
Intelligence test score	Decreased 24-33 pts.*	This is a decline of about 2 std deviations.
School performance	Decreased 1.0-1.3 pts.	This is a fall from the class 50 percentile to the lowest 10.
Seizures, unprovoked	Increased 20-fold	Risk rises from 0.9% at 0 Gy to 20% at 1 Gy.

* Note this is not a confidence interval but rather the range of central values established through including the school children known to be mentally retarded and the controls and then through excluding these two groups (see Schull et al. 1988, Table 4b).

Table 3. Quantitative estimates of the risk to the developing human brain from exposure to ionizing radiation 8-15 weeks after ovulation assuming a linear dose-response model unless otherwise stated.

Sample	a*	S_a	b	S_b
Severe Mental Retardation				
All cases	0.747		0.429	0.088
Excluding probable non-radiation related cases	0.738		0.394	0.089
Excluding non-radiation related cases and controls	0.185		0.407	0.088
Controls pooled but non-radiation related cases excluded	0.648		0.396	0.088
Threshold model excluding non-radiation related cases	1.405	0.12<T<0.60	0.743	0.121
Intelligence test scores				
All cases (PE86 subsample)	109.5	0.916	-25.30	3.95
Excluding retarded (PE86 subsample)	109.5	0.905	-21.00	4.50
Excluding retarded and controls (PE86 subsample)	111.6	1.718	-24.15	5.22
School performance (Fourth grade)				
All cases (PE86 subsample; Hiroshima only)	2.88	0.064	-0.95	0.42
Excluding retarded (PE86 subsample; Hiroshima only)	2.86	0.059	-1.280	0.59
Seizures, unprovoked				
Including mentally retarded	0.889		0.201	0.084
Excluding mentally retarded	0.921		0.149	0.101

* a is the risk at 0 Gy, S_a is its standard deviation, b is the risk at 1 Gy, and S_b is its standard deviation.