INTERNATIONAL SYMPOSIUM ON HEALTH EFFECTS OF LOW DOSES OF IONIZING RADIATION: RESEARCH INTO THE NEW MILLENNIUM

SYMPOSIUM INTERNATIONAL SUR LES EFFETS SANITAIRES DES FAIBLES DOSES DE RAYONNEMENTS IONISANTS: DIRECTIONS DE RECHERCHE POUR LE NOUVEAU MILLÉNAIRE

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THE SOMATIC EFFECTS OF EXPOSURE TO ATOMIC RADIATION: THE JAPANESE EXPERIENCE, 1947-1997

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Fifty years ago, when the Atomic Bomb Casualty Commission came into being, the health consequences of exposure to ionizing radiation were poorly understood. It was known that, under appropriate circumstances in experimental systems, ionizing radiation could be carcinogenic, mutagenic, and teratogenic. However, the applicability of this information to the human species was uncertain, and epidemiologic studies were few in number. Moreover, most of the studies that were available involved individual exposed to radiotherapy with whom the effects of radiation could be confounded with those of the illness being treated. Little was known about the dose-response relationship involved, the relative biological effectiveness of different qualities of radiation, or the factors that could modify risk. Undoubtedly, these uncertainties contributed to the decision of Colonel Ashley Oughterson and the Joint Commission for the Investigation of the Effects of the Atomic Bomb to recommend to Major General Norman Kirk, the Surgeon General of the Army, the need for long term studies of the effects of exposure to atomic radiation in Hiroshima and Nagasaki. This recommendation led President Truman to direct the National Academy of Sciences-National Research Council to undertake the requisite studies. But these uncertainties are echoed in the vagueness of the planning documents that established the Atomic Bomb Casualty Commission. These noted that the areas of concern were "cancer, leukemia, shortened life span, reduced vigor, altered development, sterility, modified genetic pattern, changes in vision, shifted epidemiology, abnormal pigmentation, and epilation" [1]

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The organizational and logistic problems that confronted the newly created research institution were formidable [2]. Japan was a devastated, occupied nation with few resources of its own. As a consequence, the Atomic Bomb Casualty Commission had to be largely self-sufficient. It needed to establish its own clinical facilities, recruit and train staff, and develop the means to meet other needs, such as transportation, essential to the fulfillment of its charge. Nonetheless, within a few years after the initiation of these studies, three radiation-related effects on health had been seen. These were an increased in the occurrence of "radiation cataracts", an increase in the frequency of leukemia, particularly of the acute variety, and an increase in mental retardation among those survivors exposed prenatally. Each of these findings is a story in itself. Briefly the findings arose as follows:

It was known in 1945, largely as an outgrowth of the use of x-irradiation in treating cancer of the brain, that if the eye is within the radiation beam and receives a sufficiently high dose, a characteristic change will occur in the lens that leads to a loss in its translucency. To determine whether similar changes had occurred among the survivors in Hisoshima and Nagasaki, an ophthalmologic survey was initiated in the late summer of

1919. Among the 1,000 survivors examined in the course of the survey, 231 of whom were exposed withing 1,000 m -10 cases of presumed radiation opacities were observed [3]. All were exposed within 550-950 m of the hypocenter and all had epilated, suggesting that their doses has been large, possibly 1 Gy or more. The frequency of radiation cataracts among survivors exposed within 1 km was estimated to be 2.5%., but it was thought that this figure might increase with time. A second, larger survey of 3,700 survivors in 1951-1953 revealed 154 individuals with posterior subcapsular plaques large enough to be visible with an ophthalmoscope [4].

Subsequent studies of the atomic bomb survivors, as well as those of persons whose opacities stem from the therapeutic use of irradiation, suggest that there is an exposure threshold - a dose below which these changes do not occur [5]. This value is not known precisely, although clinical studies following x-irradiation suggest that it may be in the neighborhood of w Gy. The threshold value may, of course, differ for various qualities of irradiation. Based on the atomic bomb survivors, the threshold for y-irradiation, measured in terms of the dose absorbed by the eye, appears to be 0.73 Gy whereas the threshold for neutron irradiation is much lower, under 0.10 Gy. These values, particularly the one for y-irradiation, seem lower than estimates from the clinical studies, but if the neutron dose is weighted to account for its greater biological effectiveness, the estimated minimal dose of radiation is 1.5 Sv. It must be noted, however, that a threshold could be spurious, arising solely because of our inability to detect very small changes, and may not reflect an actual threshold in their occurrence.

The first intimation that leukemia was elevated among the survivors arose through the perceptiveness of a young Japanese physician, Takuso Yamawaki. As early as 1949, he believed that he was seeing more cases of leukemia in his clinical practice than he expected, and he sought the advice of hematologists at the Atomic Bomb Casualty Commission, who confirmed his diagnoses. This finding, the first evidence of a possible increase in any cancer among the survivors, immediately prompted an effort to confirm and extend what apparently was being seen. The task was made difficult, however, by the absence of individual dose estimates, the lack of a systematic case-finding mechanism, and uncertainties about the size of the population at risk. Nevertheless, through clinical examinations, physician referrals, and death certificates, some 19 individuals were identified who had either died from or had the onset of leukemia in the years 1948-1950 among an estimated 98,265 survivors in Hiroshima based on the 1949 census of survivors of the city (and 10 cases among 96,962 survivors in Nagasaki) [6]. When these cases and the survivors were distributed by distance from the hypocenter, a significant increase in the number of cases was seen within 2 km. And, by 1953, when 50 cases of leukemia had accumulated in Hiroshima, Moloney and Kastenbaum [7] were able to show that cases increased in frequency from 1 in 12,625 individuals exposed at 2,500 m or beyond to 1 in 80 if exposure occurred within 1 km. Thus, the risk within 1 km was more than 150-fold greater than that at a distance where the dose was presumably very low. When the cases and individuals at risk were divided into those with a history of epilation, oropharyngeal lesions, or purpura or some combination of these and those without such symptoms, the increase in incidence with declining distance from the

hypocenter was more striking among those individuals with complaints associated with acute radiation sickness. Statistically, the data were consistent with a straight-line relationship between the logarithm of the distance of the survivors from the hypocenter and the logarithm of the incidence of leukemia, a fact suggested by not established in the earlier study.

As the number of cases continued to grow, it was possible to examine the relationship of the type of leukemia to exposure and the gender and age distribution of the affected individuals as well as their distance from the hypocenter. Acute forms were the most common, followed by the chronic myelocytic types, but a paucity of cases of chronic lymphocytic leukemia apparent also was noted. Although age was recorded in terms of the apparent onset of symptoms, rather than age at exposure, the risk of leukemia was clearly greater at younger ages. Finally, because some of these affected individuals had been seen repeatedly in the hematological surveys that had occurred immediately before or shortly after the establishment of the Atomic Bomb Casualty Commission, it was possible to gain some insight into the length of time intervening between exposure and the onset of leukemia. It appeared to lie between 2 and 8 years.

Soon after the introduction of radium therapy, case reports began to appear that suggested that, when this therapy was used on pregnant women (generally to treat a malignancy of the cervix of the uterus), the developing fetus often was seriously affected. Finally, in 1929, two obstetricians, Leopold Goldstein and Dougas Murphy, attempted a more systematic study [8]. Questionnaires were sent to some 1,700 gynecologists and radiologists in the United States seeking to identify women who had received radiation therapy during pregnancy. One hundred and six women were identified, and of these, 74 were delivered of full-term children. Thirty-eight of these children had more or less serious disturbances of health or development, and 16 or the 38 were described by these investigators as "microcephalic idiotic children." Fifteen of these were born to women who had received either radium or x-ray treatments early in pregnancy. This was a number far greater than would have been expected if no causality were involved.

The observations stimulated an investigation of the children exposed *in utero* to atomic radiation. This effort led to the establishment of at least three overlapping samples of individuals exposed prenatally to the atomic bombings of Hiroshima and Nagasaki. These samples are the culmination of a series of actions that occurred between 1950 and 1960. In brief, four avenues of ascertaining information about prenatally exposed survivors were used: the birth records required by Japanese law and maintained by the appropriate city offices in Hiroshima and Nagasaki; the supplementary schedules of the Japanese National Censuses of 1950 and 1960, which sought to identify all survivors then alive: the 1950 sample Census conducted by the Commission: and finally, the fortuitous recognition of a prenatally exposed individual through the Commission's Master File of survivors or some other chance encounter. The nature and time of availability of these sources of data for the years subsequent to 1960 census can contribute to mortality data for the years subsequent to 1960 but have never been a part of either the initial clinical sample or its subsequent revision.

Cognitive function was measured in a number of different ways, varying with the ages of the children at the time of each biennial examination. While they were still young, assessment of the children's intelligence rested largely on the examining pediatricians's clinical impression of their intellectual status relative to their peers, their ability to count and perform simple sentences. Once they were older, however, structured intelligence tests were used. These included two Japanese intelligence tests, the Tanaka B and the Koga, the Bender-Gestalt, and the Goodenough "Draw-a-Man" test.

Analysis of these data has shown that the developing human brain is especially sensitive to radiation-related damage in the period 8 to 15 weeks after ovulation when the cerebral cortex is being established. This damage is manifested as an increased occurrence of severe mental retardation [9] as well as a diminution in the intelligence quotient [10] and school performance [11] among those prenatally exposed survivors not deemed to be mentally retarded clinically. Studies of seizures, especially those without known precipitating cause , also exhibit a radiation effect on those exposed 8-15 weeks after ovulation [12]. Radiation can induce small head size as well as mental retardation but the biologic events that subtend these abnormalities are still unclear. However, magnetic resonance imaging of the brains of some of the mentally retarded survivors has revealed a large region of abnormally situated gray matter, suggesting an abnormality in neuronal migration although some of the loss in cognitive function may be ascribable to cell killing.

Initially, the studies we have described briefly focused on the demonstration of radiation-related effects and not on dose-response relationships because even crude estimates of individual doses were not available. For this purpose, opportunistic samples could suffice but not long afford the basis for a critical assessment of risk. Accordingly, in 1955, the Francis Committee, named after Thomas Francis, an epidemiologist and virologist, urged a reorientation of the studies. They argued that the individual studies had to serve the whole, which only could be done by unifying them through a focus on a common set of survivors. The new research strategy they proposed, termed the "Unified Central Program", included a mortality surveillance, known as the "Life Span Study", a clinical study to assess health and morbidity, termed the "Adult Health Study", and a program of autopsies. The former two center on fixed samples of survivors and suitably age-, gender-, and city-matched comparison persons, whereas the last entails the pathological study of as many deceased individuals from the mortality surveillance as possible. This reorientation began in 1957, and the focus on fixed samples or cohorts has served and continues to serve the studies well.

With the establishment of the Unified Study Program, the development of a leukemia registry, and the evolution of means to assign individual doses of y and neutron radiation, understanding of the leukemogenic effect of atomic bomb exposure improved materially. Today, the incidence of leukemia is known to be related to dose-the higher

the dose the greater the risk- but this increase is not simply proportional to the dose an individual receives. Risk rises slowly to 0.5 Gy and then accelerates.

The frequency of new cases of leukemia among the survivors reached a peak about 1952 and has declined steadily since. It had not, however, completely disappeared as recently as 1985, suggesting a period of risk after exposure of at least 40 rather than the 25 years that has been accepted generally. Moreover, when incidence by dose was examined in relation to age at the time of the bombing and the calendar time of disease onset, it seems that the higher the dose, the greater the radiation effect in the early period, before October 1955, and the more rapid the decline in risk in subsequent years. The leukemogenic effect occurred later among individuals who were older at the time of bombing.

As the number of cases of leukemia continued to grow, it was possible to confirm and extend the earlier findings on the relationship of the different types of this disorder to dose. The radiation-related risk of acute lymphocytic leukemia as well as "the other types" of acute leukemia, such as acute myelogenous leukemia, seemed higher among survivors exposed at younger ages, whereas the frequency of chronic granulocytic leukemia was greater among individuals who were middle-aged or older when exposed. But, it was not clear whether the different types had different dose-response relationships, and as earlier investigators noted, at least one form of leukemia, chronic lymphocytic, did not appear to be radiation-related in the Japanese. However, few cases actually have been seen, and no truly reliable statement of the risk of this form of leukemia among the survivors is possible, although it should be noted that other groups of individuals exposed to above-background levels of ionizing radiation, such as radiation workers, also have not shown a radiation-related increased in chronic lymphocytic leukemia.

Recently, it has been possible to reclassify most of the cases of leukemia occurring among members of the Life Span Study by using the French-American-British system and to reanalyse the accumulated information. This reanalysis has clarified some previously puzzling aspects of the data but also has raised some new questions regarding radiation-related leukemogenesis. For example, it has been recognized for some time that cases of chronic lymphocytic leukemia have occurred only in Nagasaki. This was puzzling. Reclassification, however, reveals that most of these cases are, in fact, instances of adult T cell leukemia, and it has been demonstrated that infection with the human T lymphotrophic virus type 1 associated with this form of leukemia is common in areas of the westernmost major island of Japan, Kyushy, including Nagasaki, but is relatively rare in the western part of Honshu where Hiroshima is located.

An even more recent analysis, based on 231 cases of leukemia occurring between 1950 and 1987 among survivors receiving doses of 4 Gy or less, suggests that the effects of irradiation differ depending on the type of leukemia involved. Preston and his colleagues [13] find the effect of exposure , as measured by the excess absolute risk, to be somewhat more pronounced on the occurrence of acute myelogenous leukemia (1.1 cases/10^4 PYSv) and chronic myelogenous leukemia (0.9 cases) than on acute lymphocytic leukemia (0.6 cases) whereas the excess relative risk is greater for acute

lymphocytic (9.1) and chronic myelogenous leukemia (6.2) than for acute myelogenous leukemia (3.3). This difference in the absolute and relative risks is not unexpected because acute lymphocytic leukemia is less common than the other two subtypes and a smaller absolute risk can give rise to a higher relative risk under these circumstances. Moreover, they find that only acute myelogenous leukemia exhibits a distinct nonlinear dose-response function; there was no evidence of nonlinearity for the other subtypes. If this apparent difference in the dose-response function is real, it would have interesting implications for radiation-related leukemogenesis, but it must be kept in mind that the number of cases of acute lympphocytic leukemia or chronic myelogenous leukemia is small relative to the number of cases of acute myelogenousss leukemia and that the capacity to discriminate among different dose-response functions is correspondingly pooreer. These analyses further confirm earlier observations that survivors exposed before the age of 20 are more likely to develop acute leukemia (notably acute lymphatic leukemia) than older survivors, but the latter are more prome to develop chronic myelogenous leukemia.

Toward the end of the 1950s, largely from the clinical studies of members of the Adult Health Study, evidence began to emerge on an increase in thyroid cancer [14, 15]. And soon thereafter it was apparent that cancers of the breast, lung, and stomach also were elevated among the survivors. Subsequent years have not only confirmed these early findings but have extended the list of radiation-related malignancies to include the esophagus, colon, liver, ovaries, skin, salivary glands, and urinary bladder [16, 17].

Moreover, once individual specific dose estimates became available, more precise estimates of risk could be made. These estimates revealed risk to be a function of age at exposure, the young (those under 20 at time of bombing) having the highest risk, but the differences in risk between males and females was small. Risk of solid tumors collectively was linear with dose, that is, risk increased in direct proportion to the dose (see Table 1).

Over these findings, however, hung one nagging uncertainty. How reliable were the diagnoses on death certificates? Comparison of the death certificate statements with findings at autopsy revealed confirmation rates to be generally high, particularly for cancer, but detection rates were often low [18]. But fortunately in 1957 and 1958, a tumor registry had been established in each of these cities. These registries could and do provide information on the incidence of cancer, and these incidences can be compared with the mortality findings. Such comparison reveals a high correspondence in the risk estimated from the mortality surveillance and that from the registry data [19, 20].

Until relatively recently, it generally has been thought that all of the life-shortening seen among the survivors was attributable to the increased frequency of cancer. However, some 20 years ago, evidence began to emerge, albeit it weak, showing that non-cancer mortality also might be increased [21]. Initially, it was tempting to believe that the apparent increase was spurious, ascribable to errors in causes of death as revealed by death certificate. Although we are still uncertain whether the effect is real or

attributable to some as-yet-unrecognized bias in the data, the evidence that the effect may be real grows. First, careful study of the errors inherent in death certificates fails to account for the increase that has been seen [22]. Second, data emerging from the biennial clinical examinations of the survivors are beginning to mirror the findings seen in the mortality surveillance.

In retrospect, these findings make more interesting an earlier study of the incidence of stroke and coronary heart disease in the years 1958 through 1974 among the survivors participating in the Adult Health study. This investigation reported the incidence of these two circulatory diseases to be significantly higher than anticipated among women in Hiroshima who were exposed heavily-who received a T65 dose of 2 Gy or more. Because an exposure effect was not seen among women in Nagasaki or in men in either city and there was evidence of a higher autopsy rate among heavily exposed women in Hiroshima, which could have led to a higher rate of recognition of stroke or heart disease, there was a reluctance to accept this seeming association as real. Nevertheless, the effect could not be explained by an inadvertent confounding of such known risk factors as smoking, an elevated level of serum cholesterol, or the occurrence of hypertension (high blood pressure), that contribute to the occurrence of cardiovascular disease. This earlier study has been extended to include the years from 1974 through 1985 using the newer doses. The results confirm those found earlier among heavily exposed women in Hiroshima, but now there is also a statistically significant increase in the incidence of "heart disease" among heavily exposed men in Nagasaki. Within the other two gender-city groups (Hiroshima men and Nagasaki women), the association of exposure with risk of stroke or coronary artery disease remains equivocal and is not statistically significant. Although this recent study makes more plausible an association, it does not remove all of the uncertainties. There has been a statistically demonstrable, temporal lowering in the frequency of cerebrovascular disease in postwar Japan, which commonly has been attributed to dietary changes. This has precipitated a concern that the same westernization of the diet (which has presumably contributed to the diminution in cerebrovascular disease) might increase the frequency of cardiovascular disease, although there is little direct evidence to support this apprehension.

As judged by participants in the Adult Health Study, serum cholesterol levels have been rising steadily with time in Japan (some 25 mg-percent, on average, in the past 30 years), and elevated levels of serum cholesterol has been associated with a higher frequency of cardiovascular disease, but there has been no consistent upward trend in the occurrence of myocardial infarction. However, the possibility of a temporal trend makes it more difficult to demonstrate a true radiation effect because the trend itself, if one exists, is so poorly understood. There are other observations that suggest some biological rather than chance basis for these findings. Firs, x-ray examinations of the Adult Health Study participants have revealed the frequency of calcification of the aortic arch and the abdominal aorta to increase with dose, and second, ophthalmic studies have shown retinal arteriosclerosis also to increase in frequency with dose. As yet, however, it has not been possible to integrate these findings into a coherent biological explanation of the apparent

increase with dose of deaths ascribable to causes other than cancer, and it may be some time before this is possible.

Table 1. EXCESS SOLID CANCER DEATHS IN THE LIFE SPAN STUDY COHORT BY DOSE, 1950-1990

Dose, Sv	Subjects	Observed deaths	Expected deaths	Attributable fraction, %
0 (<0.0006)	36,459	3,013	0	0
0.0005-0.1	32,849	2,795	34	1
0.1-0.2	5,467	504	29	6
0.2-0.5	6,308	632	75	12
0.5-1.0	3,202	336	78	23
1.0-2.0	1,608	215	70	33
>2.0	679	83	49	59
Total	86,572	7,578	334	

Adapted from Preston et al. ([16]).

As the studies in Japan have proceeded, each new finding (see Table 2) has raised new questions that demand resolution. Some effects seen among the survivors have not been observed in other exposed populations, and effects have been reported in these other groups that have not been seen in the atomic bomb survivors. The origin of these differences must be resolved if our understanding of the biological effects of ionizing radiation is to be complete. Still, other unsolved problems involve a better characterization of the contribution of host and environmental factors to the occurrence of radiation-related malignancy. A variety of studies from many areas in the world indicates that some cancers aggregate in families, suggesting that genetic or familial factors play a part in their etiology. But it is not known whether those individuals in Hiroshima and Nagasaki who have developed malignancies, presumably related to their exposure to ionizing radiation, come from families who, even in the absence of such exposure, are cancer-prone. If this should be so, how could this information be used to identify those persons with the greater risk? Similarly, it is important to determine more reliably the trend in risk with attained age among the younger survivors who generally have exhibited the higher relative risks thus far.

TABLE 2. A SUMMARY OF THE FINDINGS TO DATE.

A. Significant radiation-related increase

Malignant tumors: Leukemia, cancers of the breast (female), colon, liver, lung, ovary, skin (non-melanoma), stomach, and thyroid.
Lenticular opacities
Small head size, mental retardation, diminished IQ and school performance, increased frequency of seizure (prenatally exposed)
Retarded growth and development (among survivors exposed at young age or prenatally)
Chromosome abnormalities in lymphocytes
Somatic mutation in erythrocytes and lymphocytes

B. Suggestive radiation-related increase

Malignant tumors: cancers of the esophagus and urinary bladder, malignant lymphoma, salivary gland tumors, and, possibly multiple myeloma.
Adult-type malignancies among the prenatally exposed
Impairment of neuromuscular development among the survivors exposed *in utero*
Parathyroid disease
Mortality from diseases other than malignant tumors, specifically cardiovascular disease and liver cirrhosis, at higher doses
Specific (humoral or cell-mediated) changes in immunologic competence

C. No radiation-related increase seen to date

Malignant tumors: chronic lymphocytic leukemia, osteosarcoma
Acceleration of aging
Sterility or infertility among the prenatally or postnatally exposed
F_1: congenital abnormalities, mortality, including childhood cancer, chromosome aberrations and in biochemically identifiable genes

Improving the estimates of cancer risk as well as other radiation-related damage necessarily will remain a central activity of the Radiation Effects Research Foundation through the years immediately ahead, but developing better estimates without an understanding of the underlying molecular and cellular processes that are involved is an empty victory. Not to denigrate the importance of risk analysis; it can be helpful in more ways than just through the quantitative expression of risk. It can identify issues that should be of concern to experimentalists and are addressed more readily in experimental systems than epidemiologically. This method argues for a more dynamic interaction than commonly occurs between epidemiologists and statisticians, on the one hand, and

experimental biologist, on the other. Nevertheless, in the final analysis, intelligent intervention and the amelioration of risk must be based on biological understanding.

Developments in biology have lifted a corner of the curtain that has obscured this understanding. To further these advances, and in particular their application to radiation-related damage, it is not only important that current tissue repositories, which focus primarily on malignant tumors, be supported but that means be found to collect and store tissues on a wider sampling of exposed individuals, most of whom will not die from malignancy. These tissues and cells can serve as the bases for future molecular and cellular studies as newer techniques become available. The Adult Health Study has been, and will undoubtedly continue to be, the primary source of much of this biological material, which argues not only for the continuation of these examinations but means, in turn, that the Foundation must maintain an active laboratory program, one with a staff and facilities capable of using the newer techniques as they evolve.

There are still other ways that the studies in Hiroshima and Nagasaki can contribute to the betterment of human and the quality of life. Over the 30-odd years that the Adult Health Study has continued, an enormous body of data has accumulated pertinent to the process of aging among the Japanese and presumably other ethnic groups. Analysis of these data holds promise of insights into childhood precursors of subsequent cardiovascular disease, for example, or into events premonitory of the occurrence of senile dementia later in life. It can be presumed, therefore, that, in the years ahead, the data of the Foundation will see important uses in the study of variation among individuals in the process of aging.

Future studies of the prenatally exposed undoubtedly will focus on the relationship of exposure to ionizing radiation and aging, including that of the central nervous system. The prenatally exposed survivors are unusual in many respects, not the least of which is the fact that they are the only group of survivors whose life experience subsequent to exposure can be followed from birth to death and, as such, can provide unique insights into the effect of exposure on aging. Obviously such studies must have direction, and recent experimental investigations could provide this.

Numerous events are involved in the process that brings forth a functional brain, any one of which is potentially susceptible to radiation damage and could lead to a different result. Patently, there is a need to confirm and extend the findings on cerebral cortical impairment after prenatal exposure. To do so, however, will entail more neurologically focused clinical examinations that has occurred in the past, including the various techniques now available to image the brain of the still living prenatally exposed atomic bomb survivors. These studies could have value well beyond the immediate assessment of the risk of prenatal exposure to irradiation and could contribute to a deeper understanding of human embryonic and fetal development, to a clearer appreciation of the diversity among individuals in the age at achievement of specific embryonic or fetal landmarks, and to a sharper definition of the developmental ages most vulnerable to exposure to chemical or physical teratogens.

As yet, among the prenatally exposed survivors, there have been no studies directed toward the effect of irradiation on specific, cortical functions. Nevertheless, many of these functions can be investigated with a surprising degree of precision, and the time at which cortical neurogenesis is initiated in these areas, and its duration, often is known reasonably well. Particularly appealing are the various aspects of visual function. Some 30% of the cortex appears to be involved in the processing of visual stimuli, and the mechanisms through which this processing occurs are better understood than for any other cortical area.

Members of the prenatally exposed clinical sample are still examined biennially at the Radiation Effects Research Foundation. This examination emphasizes general health, but a search should also be made for evidence of central nervous system damage. The neurological examination itself does not now but should include tests of motor control and development. Some cognitive tests, such as word association, learning ability, and memory and intelligence, should also be included. But there is the opportunity to do more. In light of experimental findings on other primates, careful studies of auditory and visual acuity, olfaction, and taste should be contemplated. Evidence of an earlier loss in hearing or in vision that normally accompanies aging should also be sought because a lesser initial number of neuronal cells could lead to earlier manifestation of an aging central nervous system.

Cancer among the *in utero* exposed is another area that has yet to be fully exploited. Although this group of individuals has not exhibited a higher likelihood of developing childhood malignancies, possibly because of the small number of individuals involved, evidence has accumulated and continues to accumulate that their risk of adult-onset cancers is elevated (23, 24). However, the number of cases seen thus far remains small, and site-specific analyses are still problematic, but the years immediately ahead should bring a substantial increase in the data available for analysis because these individuals now have entered those ages in life when the incidence of cancer increases dramatically. Experience with the postnatally exposed survivors has shown that, for solid tumors, the increase risk does not manifest itself until those survivors reach the cancer-prone ages. Finally, ambiguities still exist in the doses assigned to specific survivors. These ambiguities obviously need to be resolved if the full value of the studies in Japan are to realized.

Clearly, the fabric of effects of exposure to the bombing of these cities is not fully woven. Some heretofore unsuspected consequences surely will emerge as the studies continue, and others will be better defined. Over half of the survivors are still alive (see Table 3), and what their future holds only can be judged in terms of what the past has revealed. It is obviously of the utmost importance that the studies continue because only thereby will answers be found to such issues as the effect of age at exposure on subsequent risk and the duration of expression of that risk.

TABLE 3. PROJECTED SIZE OF THE LIFE SPAN STUDY COHORT, 1995-2020

	1995	2000	2005	2010	2015	2020
Age at exposure (years)						
0- 9	16,450	15,990	15,290	14,280	12,710	10,390
10-19	14,500	13,540	12,040	9,800	6,780	3,620
> 20	12,800	8,910	5,340	2,710	970	100
Total	43,750	38,440	32,760	26,790	20,460	4,110
Average attained age(years)						
	64.7	67.9	71.3	74.7	78.0	81.3
Average age at the time of the bombings(years)						
	14.7	12.9	11.3	9.7	8.0	6.3

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IN UTERO EXPOSURE TO LOW DOSES OF IONIZING RADIATION AND ITS EFFECT ON THE DEVELOPING NERVOUS SYSTEM

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1. BACKGROUND

Actively dividing cells are known to be more sensitive to ionizing radiation than cells that have completed division or differentiated cells that seldom undergo division (ICRP 1986, United Nations 1986). Prompted partially by this fact, partially by the findings on rodent embryos and fetuses exposed prenatally to ionizing radiation, and partially by the studies of Goldstein and Murphy (1929) of the children born to women who were exposed to uterine irradiation in the course of pregnancy, epidemiological studies have been conducted on individuals who were exposed prenatally (when cellular growth is rapid) to atomic radiation in Hiroshima and Nagasaki. To identify and describe the effects of ionizing radiation on the growth of the embryo and the foetus, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF), have conducted numerous studies on those survivors who were exposed prenatally to atomic radiation in Hiroshima and Nagasaki (Miller et al. 1956, Wood et al. 1967a,b, Blot 1975, Blot et al. 1972, Otake and Schull 1984, Schull and Otake 1986, Otake et al. 1987, 1988, 1993, Schull el al. 1988, Dunn el al. 1990). Documentation of the deleterious effects of exposure to ionizing radiation on the developing human brain rests largely on these studies, which are reviewed here.

Evaluation of data from Hiroshima and Nagasaki on the development of severe mental retardation with or without small head size (Otake et al. 1987), IQ (Schull and Otake 1986, Schull et al. 1988), and school performance (Otake el al. 1988) revealed that exposure to atomic radiation had a significant effect on brain development among the survivors exposed at 8-15 and 16-25 weeks after ovulation. A study of the occurrence of seizures of unknown cause (Dunn et al. 1990) also found a radiation effect at a gestational age of 8-15 weeks. Whether a threshold exists in the effects seen on the developing brain among the prenatally exposed survivors is still uncertain. It is also unclear to what extent microcephaly is a symptom independent of mental retardation and through what mechanism radiation-related damage to the brain arises. However, brain damage is not the only untoward health consequence of prenatal exposure to irradiation. Other studies have shown that the prenatally exposed survivors also have an increased risk of cancer. Yoshimoto et al. (1988) have reported on the cancer risk over a period of 40 years among in utero exposed survivors of the atomic bombings. Their results suggest that susceptibility to radiation-induced cancers may be higher in pre- than in postnatally exposed survivors, but a more recent study by Delongchamp etal. (1997) fails to confirm this apparent effect. Clearly, the dose-response relationship for cancer mortality among the prenatally exposed survivors has yet to be determined reliably. It will not become clear for some years since only now are these survivors entering those years of life when cancer mortality begins to increase dramatically and where the effects of exposure become more apparent.

2. BRIEF DESCRIPTION OF MATERIAL

2.1. The population of prenatally exposed atomic bomb survivors

The first study population of prenatally exposed atomic bomb survivors was established from data collected in the course of the genetic studies conducted at ABCC from 1948 to 1953. Subsequently, a more systematic ascertainment was begun in Hiroshima in 1953 and in Nagasaki in 1955 based on the municipal records of births occurring before 31 May 1946 but after the atomic bombing (6 August 1945 in Hiroshima; 9 August 1945 in Nagasaki) (Schull and Otake 1986). Finally, in 1959, new, so-called clinical samples were established in these two cities. These samples were selected on the basis of the 1950 national census and the ABCC master file, and were drawn from all survivors exposed prenatally within 2000 m of the hypocentre who were residing within the contact area in Hiroshima or Nagasaki on October 1, 1950. The comparison groups, matched by sex and age (trimester), were randomly selected from among distally exposed survivors (3000-4999 m) and non-exposed survivors (> 10,000 m) residing within the same contact area. Collectively, these individuals number 1566 persons (1242 in Hiroshima and 324 in Nagasaki) on whom DS86 doses are available. Of these study subjects, 1473 had their head size measured at least once between the ages of 9 and 19 years. The first clinical examinations were conducted in 1948, with the majority of the study subjects being re-examined at 2 year intervals up until 1964. The population of school children on whom school performance is based consists of prenatally exposed school children enrolled in Hiroshima elementary schools in 1956.

2.2. The 1986 dosimetry system (DS86)

In 1987 it became possible to assign to these survivors individual dose estimates based on the DS86 dosimetry system (Roesch 1987). These estimated doses are individually calculated without using average correction factors; thus better allowing for the scattering of radiant energy that occurs within tissues. Since DS86 foetal absorbed doses are not yet available, the absorbed dose to the mother's uterus has been used as a surrogate in the studies reviewed here. Kerr (1979) has noted that there is little difference between the foetal absorbed dose and the estimated maternal uterine absorbed dose. Parenthetically, it should be noted that the foetal absorbed doses computed under the T65 dosimetry system, used until 1987, were merely estimates of maternal shielded kerma, multiplied by mean correction factors (Milton and Shohoji 1968, Kerr 1979).

3. DEVELOPMENT OF THE BRAIN AND ITS RELATIONSHIP TO GESTATIONAL AGE

Gestational age at the time of exposure is the most important single factor in determining the nature of the insult, to the developing brain, of exposure to ionizing radiation. Different functions of the primate central nervous system are localized in different structures, with differentiation of these taking place at different stages of development and over different time periods. Generally, the embryonic stage in humans is taken to be the period up to week 8 after fertilization, and the foetal stage is the period from the beginning of week 9 after fertilization until parturition. The formation of most human organs is largely complete by week 8 after fertilization. However, development of the cerebral cortex occurs rapidly in the interval from 8 to 15 weeks after fertilization. In fact, Dobbing and Sands (1973) have reported that the

normal number of neurons in the cerebral neocortex of the human adult has generally been achieved at about 16 weeks after fertilization. To reflect the different known phases in the normal development of the brain, the ages of the survivors at the time of exposure have been grouped for analytic purposes.

That is, development has been classified into four periods from the presumed day of fertilization, i.e. 0-7, 8-15, 16-25 and >26 weeks. By the end of 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 period, a rapid increase in the number of neurons occurs. These immature neurons lose their capacity to divide, becoming perennial cells, and migrate from the proliferative zones to the cerebral cortex, their site of function. In the third period, in situ cellular differentiation accelerates, synaptogenesis, which commences at about week 8 after fertilization, increases, and the definitive cytoarchitecture of the brain unfolds. The final period consists mainly of continued cytoarchitectural development, cellular differentiation and synaptogenesis.

4. RESULTS OF EPIDEMIOLOGICAL STUDIES

4. 1. Mental retardation

Mental retardation or mental deficiency customarily implies a failure in intellectual development that results in social incompetence. The severity of retardation is usually assessed by intelligence tests, but this has not always been and there is no unanimity in the designation of different degrees of severity. The International Classification of Diseases, for example, describes mental retardation as mild, moderate, severe or profound depending upon whether the IQ is 50-70, 35-49, 20-34 or under 20, respectively. Given the existing differences in the way in which mental retardation is classified, it is reasonable to ask 'How and by what criteria were the cases of mental retardation described here diagnosed?' The mentally retarded cases discussed in this report were identified on the basis of the clinical assessment of one or more paediatricians at the ABCC clinical facility and not by IQ scores. The criteria they used for the diagnosis of mental retardation were if the child proved 'unable to make simple conversation, to perform simple calculations, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized'. Mentally retarded individuals determined in this way have been defined as severely mentally retarded (Otake et al. 1987), although most would probably be categorized as mildly or moderately retarded by ICD standards.

Since the date of fertilization is uncertain, time 'after ovulation' (taken to be two weeks after the onset of the last menstrual period) is used in the estimation of the developmental age at exposure and in the grouping of the study cases. Thirty cases of severe mental retardation were detected before 17 years of age. Of these, 18 (60%) had small heads, i.e. the circumference of the head was two or more standard deviations (SD) below the age- and sex-specific means of the overall sample between 16 and 19 years of age (see Appendix I of Otake et al. 1987). Fifteen of the 18 cases (83%) were among the survivors exposed at 8-15 weeks after fertilization. Empirically this is the period of maximum radiosensitivity (figure 1). For a radiation dose of > 0.0 1 Gy, a small head was observed in 15 of the 17 severely mentally retarded cases (88%) in the 8-15 weeks group, and in two of the four severely mentally retarded cases (50%) in the 16-25 weeks group.

A threshold can be demonstrated statistically in the occurrence of the cases of clinically identified severe mental retardation among those survivor groups exposed at 8-15 and 16-25 weeks after ovulation, and a linear relationship to the DS86 doses, using the uterine absorbed dose, seems to be indicated. However, whether a threshold exists in the other measures of cortical dysfunction, such as IQ or school performance data, is still statistically unclear.

4.2. Intelligence quotient (IQ)

IQ data were collected in 1955 to 1956 at the Hiroshima and Nagasaki ABCC clinical facilities on the prenatally exposed survivors and 'non-exposed' pre-parturient residents of these cities at the time of the bombing (the latter group were those over 10 000m from the hypocentre). The 1673 examinees with DS86 dosimetry were 10-11 years old at that time. Of the study subjects, 11 were severely mentally retarded of which 8 (73%) had an IQ of less than 70 (ranging from 56 to 64); the remaining three were untestable (Schull et al. 1986, 1988). The average IQ score and 95% confidence intervals (CI) were 63-8 ± 16-7 for those survivors with a small head size accompanied by mental retardation, and 68.9 ± 23.3 for those with mental retardation but without small head size. Alternatively, the average IQ score was 96.4 ± 19.8 for those survivors with small head size but without mental retardation. The average score for the entire study population was 107.8±32.1. Although no significant difference in average IQ was noted between the first two groups, the average IQ of these two groups was significantly less than the average of those individuals with a small head only. No statistically significant difference was observed between the average IQ score of those with a small head without mental retardation and the average IQ of the entire study population.

No evidence of a radiation effect on intelligence was seen among children exposed prior to week 8 or at 26 or more weeks after ovulation. Although no heterogeneity exists among the various dose groups in the variances of IQ scores in children exposed at 8-15 and 16-25 weeks after ovulation, based on Bartlett's test of homogeneity of variances (Bartlett 1937), a significant heterogeneity was seen among the mean values. The diminution in mean scores of children exposed 16-25 weeks after ovulation was not as marked as the diminution at 8-15 weeks in the low dose range (figure 2). When the IQ scores were regressed on the DS86 dose estimates, IQ diminished linearly with increasing dose in the children exposed 8-15 weeks after ovulation. The estimated decrease in IQ score under the linear dose-response model in this group was 29 points (95% CI 8.2 points) per 1 Gy of DS86 uterine absorbed dose when the mentally retarded cases were included in the analysis and 25 points (95%CI ± 9.8 points) when they were excluded (Schull et al. 1988).

4.3. School performance

The school performances described here are based on the school records of 929 first to fourth grade students enrolled at 44 elementary schools in the Hiroshima City in August and September 1956, including a school for the blind and an orphanage. The prenatally exposed children were 10-11 years old at the time, with the majority having completed the fourth grade, and included 14 severely mentally retarded individuals. A significant decline in average school performance was observed in the groups exposed at 8-15 and 16-25 weeks (figure 3), with the tendency most pronounced in the lower grades. As in the case of severe mental retardation and the IQ data, no evidence of a radiation effect was observed in the

children exposed at gestational ages of less than 8 weeks or greater than 26 or more weeks (Otake et al. 1988). The correspondence in achievements in seven mandatory subjects (language, civics, arithmetic, science, music, drawing and gymnastics), taking the first grade for example, was very high, ranging from a correlation coefficient of 0.62 (music and gymnastics) to 0.82 (language and arithmetic). Given the high correlation in the performance in the seven subjects, in the analysis the means of the seven performance scores were evaluated against the DS86 uterine absorbed dose.

Parenthetically, it should be noted that the decision to use the mean was not capricious, and can be justified by a statistical technique known as principal component analysis. This is a way of determining the most important weighted combinations or factors among a series of correlated variables; these factors can then be used to analyse the variability that is observed among individuals. In the present instance, the most important factor, the one that captures the greatest amount of the inter-individual variability (some 75%), is related to the mean, or the average of the seven school scores. Be this as it may, simple regression reveals that the damage to the foetal brain at 8-15 weeks after ovulation is linearly related to the absorbed uterine dose, and this is obtained even with the exclusion of individuals with severe mental retardation. Damage to the foetal brain of the group exposed 16-25 weeks after ovulation appears to be weaker than that observed in the group exposed 8-15 weeks after ovulation when assessed by school performance.

4.4. Seizures

Seizures are often associated with defective development of the brain. Thus, it was suspected that children with radiation-related brain damage might exhibit seizures more frequently than those children without such damage. In the original PE86 sample, these children were first examined in the year 1948 when they were 2 years of age and follow-up for many continued until 1964 (Dunn et al. 1990). The earliest recorded age at onset of a seizure was 9 months postpartum, and the latest was 14 years of age. Of 1183 examinees, 52 cases of seizures were identified based on statements of the child's mother at the time of the routine biennial examinations. Among these 52 cases, in 24 instances there was no identifiable concomitant acute insult, such as fever, trauma, post-vaccination reaction, or anoxia during an acute postnatal event, which might be seen as causal. These 24 cases are considered to be unprovoked seizures. Among survivors exposed 0-7 weeks after ovulation, no record of seizures was noted even in the dose group 0-10Gy or over. Seizures were most frequent among those exposed 8-15 weeks after ovulation. When the 22 children with severe mental retardation were excluded, the test of significance of the increase of seizures was suggestive but only for seizures of unknown aetiology (those without a known precipitating cause) (Dunn et al. 1990). This was observed not only for seizures of unknown cause but for all seizures as well, i.e. for seizures with or without a recognizable cause for their occurrence, such as fever, trauma, or reaction to vaccination (figure 4). The risk ratios for unprovoked seizures, following exposure 8-15 weeks after ovulation, are 4-4 (90% confidence limits: 0-5-40-9) after 0- 10-0-49 Gy and 24-9 (4-1-191-6) after 0-50Gy or more -when the severely mentally retarded cases are included, and 4-4 (0-5-40-9) and 14-5 (0-4-199-6), respectively, when they are excluded.

4.5. Small head size

Exposure to ionizing radiation in early gestation can result in diminished head size as well as mental retardation, but in the case of children with small head size without mental retardation, no evidence other than retardation of growth and development was observed (Tabuchi el al. 1967, Wood et al. 1967a,b). Small head size is defined as a head circumference that is more than two standard deviations below the sex- and age-specific mean for the entire clinical study population. Small head size, as used here, encompasses both microcephaly and craniostenosis. Microcephaly is a condition in which the cranium and cerebral hemispheres are abnormally small and is frequently accompanied by mental retardation and seizures. Since it is generally difficult to determine brain size, retardation of brain development is commonly investigated by measuring head size. Craniostenosis is usually considered separately and is a condition in which the head remains small due to the early closure of the sutures of the calvarium, and although it resembles microcephaly grossly, there is no abnormality in the brain other than diminished size. Radiation has a significant effect on the development of mental retardation with and without microcephaly. The bones forming the cranial vault are known to develop in close relation with the growth of the brain and dura mater. Dobbing (1984) also investigated the relationship between the developing brain and the development of small head size with and without the presence of mental retardation. However, it is still unclear to what extent small head size is a symptom independent of mental retardation and what mechanism underlies radiation-related damage to the brain.

Out of the 1473 cases, 62 had head circumferences 2 SD or more below the age- and sex-specific mean in the total sample at the time of measurement, based on the criterion for small heads at ages 9-19 years. Of the 30 cases of severe mental retardation alluded to in Section 4.1 above, 26 are members of this study group. Of these 26, fifteen (58%) had a small head size. Most (86%) of the individuals with small head sizes were exposed in the first (55%) or second trimester (31%) of pregnancy (figure 5) (Otake and Schull 1993). The frequency of small head size is shown by gestational age group in figure 6. Unlike the situation with respect to mental retardation where no increase is seen in the group exposed 0-7 weeks after ovulation, the frequency of small head size is definitely elevated in this gestational age group.

4.6. Magnetic resonance imaging (MRI) of the brain

Magnetic resonance images of the brain of five mentally retarded cases exposed 8-15 weeks after ovulation have been obtained and the findings follow. A large region of ectopic gray matter was observed in the two individuals exposed in weeks 8 or 9 after ovulation. This is strong evidence that neurons have failed to migrate to their natural functional sites. No distinct ectopic gray matter was observed in the two individuals exposed in weeks 12-13 after ovulation; however, a mild macrogyria, which is indicative of a developmental disorder of the cortical region, was observed. Both individuals also exhibited a mega cisterna magna, and one had a distinctly atypical corpus callosum. Finally, none of the changes observed in these four individuals was seen in the one individual who was studied and was exposed in week 15 after ovulation. Although the brain was small, its cytoarchitecture appeared to be normal (Schull et al. 1991).

4.7. Anthropometric measurements

Review of the relationship between small head size and anthropometric measurements such as height, weight, sitting height and chest circumference, revealed significantly lower values among those with small head size in comparison with those individuals with a normal head size. Data on head size, height and weight at 18 years of age in the clinical sample showed a linear dose-response relationship, with a statistically suggestive decrease with increasing dose ($p < 0.10$) (Otake et al. 1993). Longitudinal data based on repeated measurements of stature from ages 10 to 18 years are shown by sex and dose in figure 7. Using a growth curve model, the relationship between the estimated DS86 uterine absorbed dose and gestational age (weeks), or between the estimated DS86 uterine absorbed dose, the square of this dose, and the gestational age of 455 prenatally exposed atomic bomb survivors, was reviewed to examine retardation of growth and development. Comparisons were made by city, sex, dose and foetal .age. The most significant difference was observed between the two sexes, namely that male children were larger than females. A highly statistical significant growth retardation was observed with increasing uterine dose in all trimesters combined and the first and second trimesters of pregnancy (figure 8). The adolescent spurt in growth and development in Japanese males seems to occur at the age of 14 on average. In view of this, an analysis of growth was made based on a linear dose-response relationship for each of the four measurements of stature on 704 individuals between the ages of 10 and 13 years and on 838 individuals between the ages of 15 and 18 years. Division of the subjects into a pre-growth spurt group and the maturity group increases the number of subjects available for analysis and hence the statistical power of detecting a radiation-related difference. An effect of exposure on growth is apparent between the ages of 10 and 13 years, and it clearly continues between the ages of 15 and 18 years. In the former age group, growth retardation showed a highly significant difference with increasing uterine dose ($p<0.01$) for all trimesters combined, but a suggestive difference ($p<0.10$) for the first trimester; whereas in the latter group, a significant retardation of growth ($p < 0.05$) was observed in both the first and second trimesters.

4.8. Neuromuscular function

The relationship of two neuromuscular function tests, namely grip strength and speed on a repetitive action test, to dose, anthropometric measurements (height, weight, sitting height and chest circumference) and IQ scores was examined with city and sex considered as covariates. The analysis is based on 888 individuals who completed the two tests between 1961 and 1962 (ages 15-16 years) (Yoshimaru et al. 1995).

When the severely mentally retarded cases were included, the grip and repetitive action tests showed the effects of radiation exposure to be statistically significant in the group exposed at 8-15 weeks, and suggestively significant in the 16-25 weeks group. Of these 888 individuals, 572 had their intelligence tested at ages 10-11 years (1955-1956). When the 10 severely mentally retarded cases within this study group were included, the dose-related diminution of IQ scores was significant in both the group exposed at 8-15 weeks and the group exposed at 16-25 weeks after ovulation, as was seen in the larger sample shown in figure 2. The results of an analysis of covariance of the two types of tests (grip and repetitive action) revealed a significant relationship with IQ scores only in the 16 weeks or more group, but not with dose. With the mentally retarded cases excluded, the relationship between the projected grip scores and projected repetitive action scores in the > 16 and < 15 -weeks groups, based on the

standard results obtained using estimates from a covariance analysis of the results of the grip tests and repetitive exercise tests, is shown in figure 9.

4.9. Does a threshold exist?

It is important heuristically and for regulatory purposes to know whether a threshold exists for the radiation effects on the developing brain that have been described. Although no clear threshold is yet available for the prenatally exposed atomic bomb survivors, the efforts to reveal a threshold, if one exists, will now be described. When the two cases of Down's syndrome presumably unrelated to radiation are excluded from the 19 cases of severe mental retardation (18 with small heads and one with a normal head circumference) which were exposed 8-15 weeks after ovulation-the period of maximum radiosensitivity, and a linear threshold model is fitted to the data, the 95% lower limit of the estimated threshold ranges from 0.06 to 0.31 Gy, which suggests the presence of a threshold. But for the 16-25 weeks group, the 95% lower limit of the estimated threshold is 0.28 Gy, irrespective of whether the two cases of mental retardation presumably unrelated to radiation are, or are not, included (Otake et al. 1996). Simple inspection of the data on seizures also suggests the presence of a threshold in the 8-15 weeks group, but the 95% lower limit of the estimated threshold includes zero, so that the presence of a threshold is statistically doubtful (Dunn et al. 1990). The mean IQ scores (Schull et al. 1988) and school performance scores (Otake et al. 1988) seem to be similar to the scores of the control group in the <,O-IOGy dose group, and no excess risk is statistically observed. Alternatively, a significant effect of radiation is seen on head size in the first and second trimesters of pregnancy and in the 0-7 and 8-15 weeks postovulation groups. No increase in risk of small head size was observed in the group exposed in the third trimester or in the group exposed > 16 weeks after ovulation. The estimated threshold obtained from the dose-response relationship for small head size is approximately zero (Otake and Schull 1993). Thus, the apparent lack of a threshold for small head size and the presence of some differences in the period in which foetuses are susceptible to damage suggest that there is an embryological difference in the occurrence of small head size and the occurrence of mental retardation. However, it is still unclear to what extent small head size is a finding independent of mental retardation and by what mechanism radiation-related damage is caused.

5. DISCUSSION

Two important observations emerge from the re-evaluation of the data on the in utero exposed survivors using the absorbed dose estimates based on the new DS86 dosimetry system.

First, a high correlation is observed between the gestational ages at which severe mental retardation and seizures occur, and the diminution in IQ scores and school performance. No cases of severe mental retardation have appeared among individuals exposed at < 8 or >, 26 weeks after ovulation, and no significant difference was observed between the IQ scores or school performance scores and the absorbed doses in these same age groups. Undifferentiated cells that will eventually differentiate into neurons or neuroglial cells exist in the period < 8 weeks after fertilization, but these cells retain their reproductive capacity, and the cells lost in this period can be replaced. The period > 26 weeks after ovulation is largely one of continued architectural and cellular differentiation, and synaptogenesis. In this period, the production of

the neurons of the cerebral cortex is completed and they lose their regenerative capacity, but these cells are known to be more resistant to radiation than undifferentiated cells in the early stage of development.

Secondly, a significant increase in the frequency of severe mental retardation can be observed only in the periods 8-15 and 16-25 weeks after ovulation. In the former period, 80% of the severely mentally retarded cases developed. The dose-response relationship in this group clearly differs from that at later gestational ages. These findings suggest that the mechanism by which radiation affects the growth and development of the cerebrum differs by gestational age at the time of exposure. The period of maximum radiosensitivity is 8-15 weeks after ovulation for normal cerebral histogenesis. According to the reports of Dobbing and Sands (1973) and Rakic (1975), most of the precursors of the neurons that will populate the cerebral cortex complete proliferation by week 16 after ovulation. Migration of immature neurons from the proliferation zone to the cortex occurs in two discrete stages, from weeks 7-10 and from weeks 13-15 after ovulation, most of them completing migration by week 16 after ovulation (Rakic 1975). This suggests that foetal brain damage in the period 8-15 weeks after ovulation arises as a consequence of impaired cell proliferation or cell migration (or both). Neurons of the cerebrum not only develop at specific stages but also have specific functions localized at specific sites. Thus, for the cerebrum to function properly, the neurons need to be produced at a fixed stage of cerebral development and migrate to a fixed site.

The process by which undifferentiated neurons migrate from the proliferation zone to their functional sites is an active one, occurs under a strict time limit, and is assumed to be due to an interaction between cell surfaces. Thus, any damage to the cell surface, even if it is transitory, can upset the delicate timing of migration (Rozovski and Winick 1979, Schull et al. 1991). It has been shown, for example, that doses as low as O.10 Gy can affect neuronal migration and lead to a changing pattern of expression of the neural cell adhesion molecule N-CAM in the rat brain (Fushiki et al. 1993). This depressed immunoreactivity is localized to the matrix cell zone and appears transitory. N-CAM is thought to play a key role during the development of the nervous system and impairment of its synthesis could have profound effects on neuronal migration.

Several uncertainties are involved with the above risk estimates. First, the data are limited. In particular, the number of heavily exposed survivors is small. Secondly, besides radiation, other factors, such as nutritional deprivation, genetic variation, and bacterial and viral infections during pregnancy, can damage the central nervous system of the embryo and foetus, and evidence suggests that the cerebrum and its adnexa are especially sensitive to oxygen deprivation (Winick 1976, Otake el al. 1993). However, it is doubtful whether these concomitants, even if they exist, would have had dose-dependent effects and thus their effects in the present instance are likely to have been additive rather than multiplicative. The morphological features and developmental processes in the histogenesis of the human cerebral cortex are known to be basically the same as in other mammals. It is interesting in this context that the period of high susceptibility of the cerebral cortex to developmental damage noted in epidemiological studies of prenatally exposed atomic bomb survivors is consistent with the findings obtained from the experimental exposure of mice (Hoshino and Kameyama 1988, Kameyama 1989, Konermann 1989, Sienkiewicz et al. 1994).

As yet, the epidemiological data other than severe mental retardation have failed to show a clear threshold for most of the reported effects of exposure to ionizing radiation on the developing human brain. This is troubling since the majority of recognizable abnormalities caused by radiation are probably the result of injury to more than one cell and are not likely, therefore, to have a linear relationship to dose. Moreover, other deterministic effects of exposure, such as the occurrence of lenticular opacities among the atomic bomb survivors, have been shown to have a threshold (see Otake and Schull 1990). Nonetheless, in the recent series of analyses based on DS86 uterine absorbed doses, data pertaining to severe mental retardation with or without small head size, IQ and school performance show radiation to have a definite deleterious effect on the brain only in the case of individuals exposed prenatally at a gestational age of 8-15 weeks or 16-25 weeks. The occurrence of severe mental retardation in these time periods seems to suggest a threshold in the low-dose region. In the 8-15 weeks group, when all of the cases of mental retardation are included in the analysis, the 95% lower limit of the estimated threshold includes zero and it is unclear whether a threshold exists for this group, but when the two probable non-radiation related cases of Down's syndrome (who were exposed to doses of 0.29 Gy and 0.56 Gy) are excluded from the 18 severely mentally retarded cases in this age group, the estimated threshold ranged from 0.46 Gy (95% lower limit: 0.06Gy) to 0.55Gy (95% lower limit: 0.31 Gy), both of which differ significantly from zero (Otake et al. 1996). A regression analysis of IQ and school performance indicates a linear relationship, although the means of the IQ (Schull et al. 1988) and school performance scores (Otake et al. 1988) in the low-dose region seem to resemble those in the control group, particularly for doses of 0.10 Gy or lower. Alternatively, the risk of severe mental retardation among survivors exposed at 16-25 weeks after ovulation is related linear-quadratically or quadratically to the uterine absorbed dose for the population for whom DS86 doses are available. A linear model for this period suggested the presence of a threshold, which has an estimated 95% lower limit in the region of 0.21 Gy (Otake et al. 1987). The estimates do not change with the exclusion of one case with a mentally retarded sibling (DS86 dose: 0 Gy) and one case who had contracted Japanese encephalitis at the age of four (DS86 dose: 0.04Gy). Seizure data also suggest the presence of a threshold only in those exposed at a gestational age of 8-15 weeks, but the 95% lower limit of the estimated threshold includes zero (Dunn et al. 1990).

A variety of dose-response relationships with and without a threshold have been fitted to the data on small head size grouped by trimester of pregnancy or the postovulatory age (weeks after ovulation) at which exposure occurred. A significant effect of radiation on the frequency of individuals with an atypically small head is noted only in the first and second trimesters and for the intervals after ovulation of 0-7 and 8-15 weeks. The risk of small head size increased significantly with dose in the 0-7 weeks group, but no increase of risk is observed for severe mental retardation in this group. No excess risk of a small head size was observed in the third trimester or among individuals exposed at 16 weeks or more after ovulation. The estimated threshold, based on a linear or a linear-quadratic dose-response relationship, is approximatly zero (Otake and Schull 1993). This apparent absence of a threshold and the somewhat different periods of developmental vulnerability suggest an embryological difference in the events culminating in a small head, on the one hand, and mental retardation, on the other. The seizure data provide only suggestive evidence of a radiation-related risk when the severely mentally retarded cases are excluded.

Finally, it is noted that epidemiological studies are unlikely to ever adequately address two biologically important questions, namely, is there a threshold beneath which damage to the developing brain does not occur, and what is the nature of the molecular events involved? A satisfactory answer to the questions of whether a threshold does or does not exist will come only from experimental studies, and such studies are likely to provide the only compelling evidence on the nature of the molecular events involved. Thus, further systematic studies, including animal experiments, on the relationship of gestational age to impaired formation of the cranial bones, the areas of the brain involved and the molecular nature of damage, are essential to a better understanding of the effects of radiation on the developing central nervous system.

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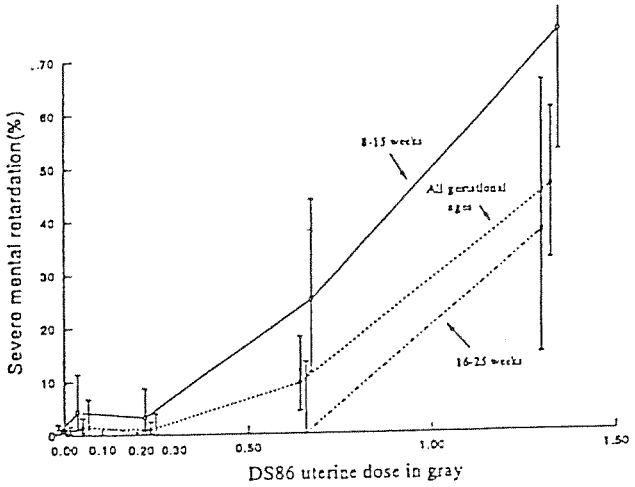

Figure 1. The proportion of severely mentally retarded cases and 90% confidence limits by DS86 uterine absorbed dose and postovulatory age in weeks. (Otake *et al.* 1987.)

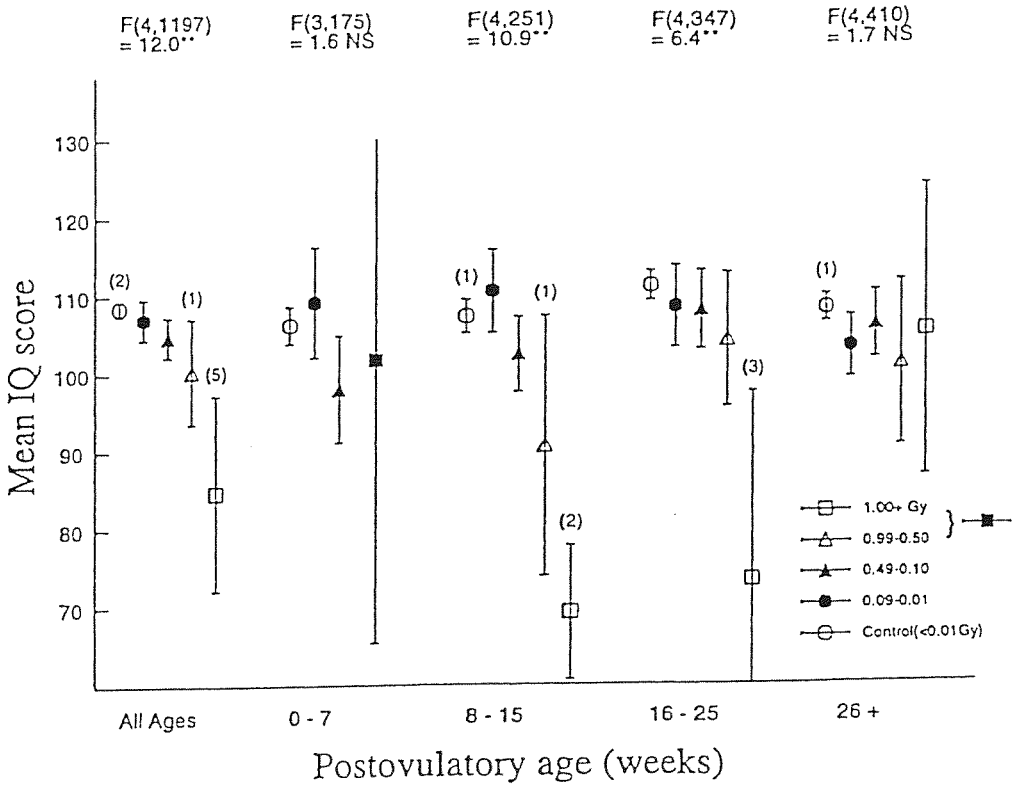

Figure 2. Mean IQ score and 95% confidence limits by DS86 uterine absorbed dose and postovulatory age. The numbers in parentheses are severely mentally retarded cases. The highest IQ score was 64. Note that significance levels are NS is $p \geq 0.10$ and ** $p < 0.01$ (Schull *et al.* 1988.)

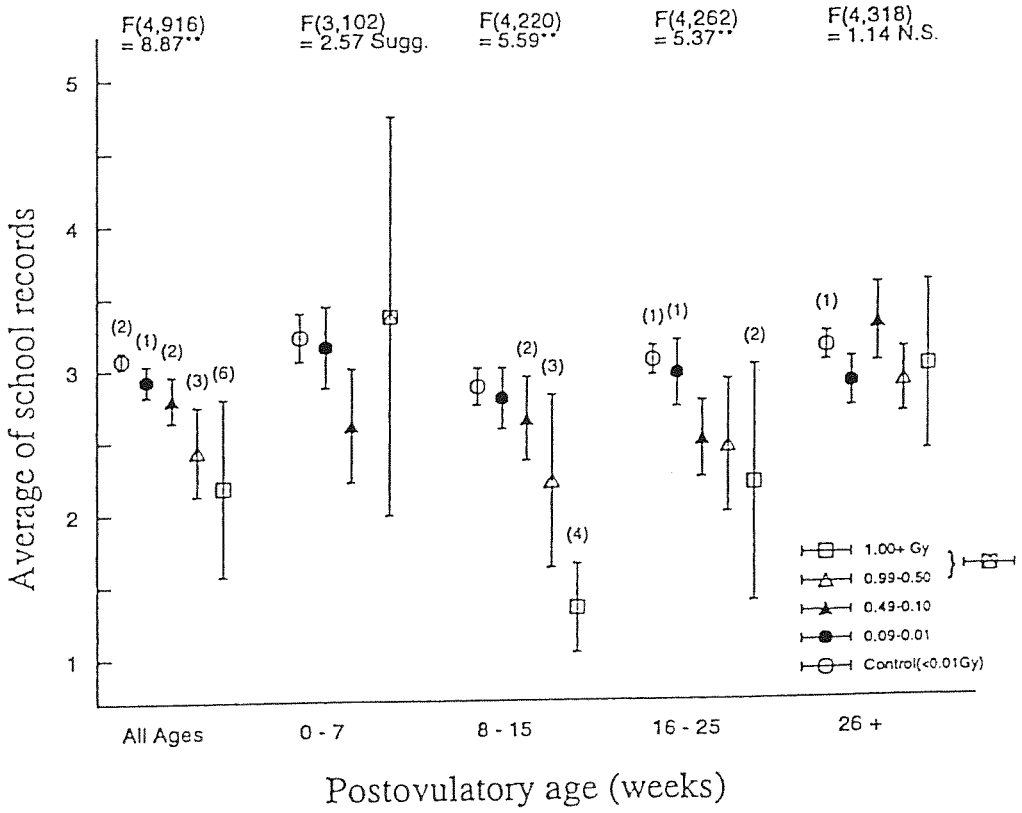

Figure 3. Average school performance score and 95% confidence limits by DS86 uterine absorbed dose and postovulatory age. The numbers in parentheses are severely mentally retarded cases. Note that significance levels are Sugg is $p < 0.10$ and $^{**}p < 0.01$ (Otake *et al.* 1988.)

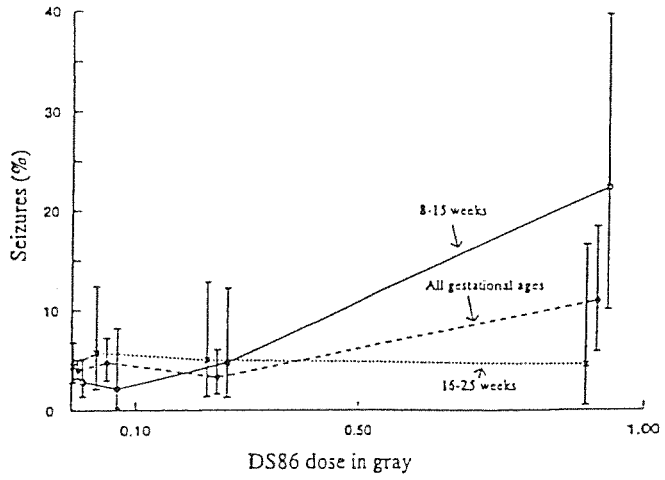

Figure 4. The proportion of seizure cases and 95% confidence limits by DS86 uterine absorbed dose and postovulatory age. (Dunn *et al.* 1990.)

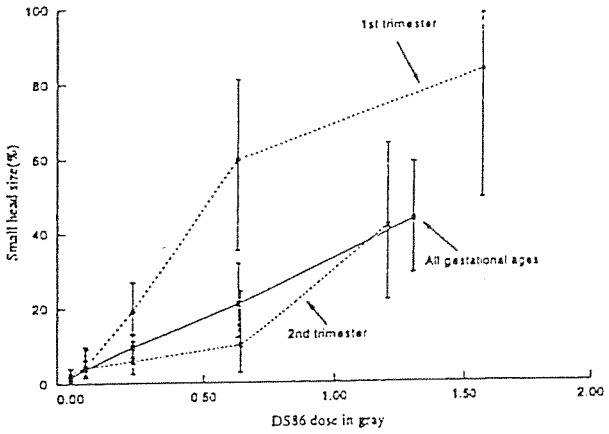

Figure 5. The proportion of small head cases and 95% confidence limits by DS86 uterine absorbed dose and trimester of pregnancy. (Otake and Schull 1993.)

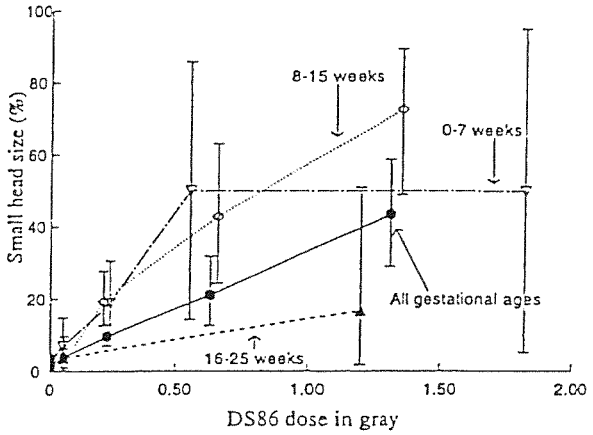

Figure 6. The proportion of small head cases and 95% confidence limits by DS86 uterine absorbed dose and postovulatory age. (Otake and Schull 1993.)

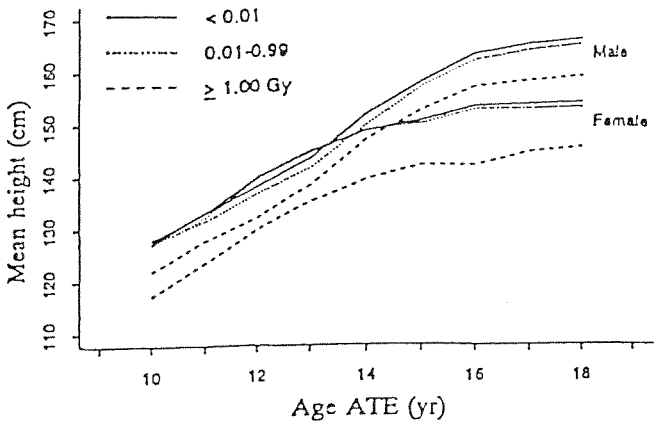

Figure 7. Observed mean stature from 10 to 18 years of age by sex, age at time of examination (ATE) and DS86 uterine absorbed dose. The observed mean values include the severely mentally retarded cases. (Otake *et al.* 1993.)

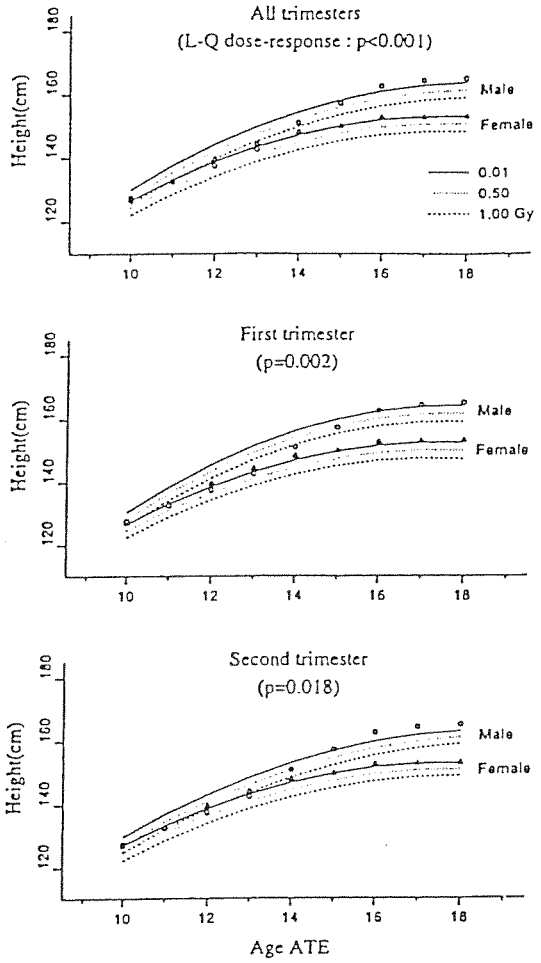

Figure 8. Observed and expected stature based on a linear-quadratic (L-Q) dose-response relationship from 10 to 18 years of age. The observed total means of stature by sex and age at time of examination (ATE) have been plotted as circles and triangles. (Otake *et al.* 1993.)

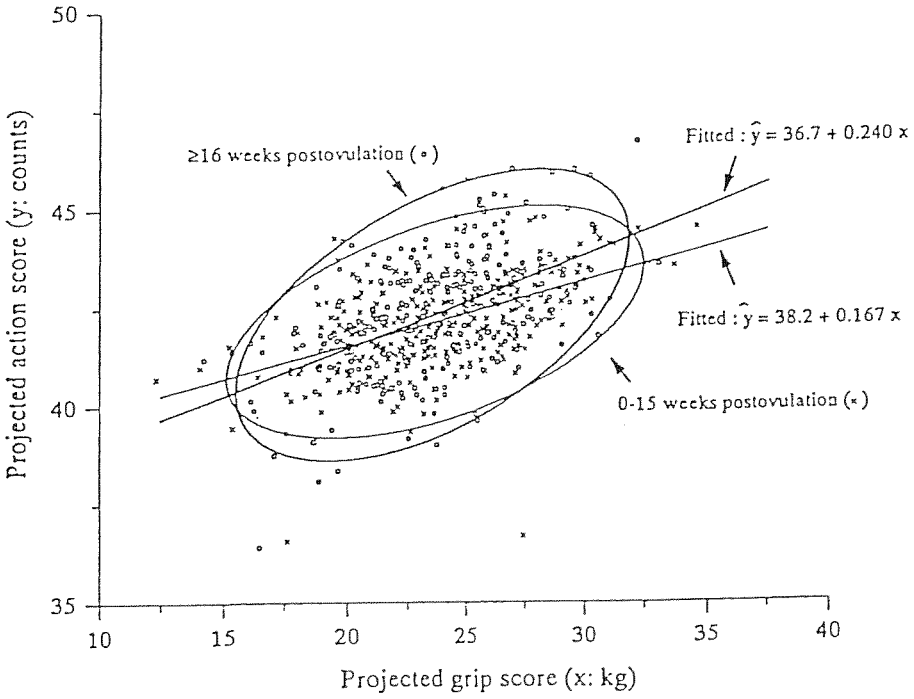

Figure 9. Straight-line relationship and ellipse 95% probability limits 0–15 and ⩾16 weeks postovulation between projected standard scores of grip and repetitive-action tests obtained from the estimated parameters in a multivariate analysis of covariance. (Age ATE, age at time of examination). (Yoshimaru *et al.* 1995.)