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Developmental Effects of Irradiation on the Brain of the Embryo and Fetus

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RADIATION PROTECTION

ICRP PUBLICATION 49

Developmental Effects of Irradiation on the Brain of the Embryo and Fetus

A report of a Task Group of Committee 1 of the
International Commission on Radiological Protection

ADOPTED BY THE COMMISSION IN JULY 1986

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PREFACE

At its meeting in Geneva in November 1982, the Commission approved a proposal by its Committee 1 on Radiation Effects to set up a Task Group to carry out a critical evaluation of the data relating to radiation-induced effects on the central nervous system, especially radiation-induced mental retardation, assessing the gestational age at risk and the quantitative risk at low doses; to analyze these effects in the light of what is known about cell survival, proliferation, repopulation and differentiation in the development of the fetal brain; and to identify the needs for future research, where appropriate.

The membership of the Task Group was as follows:

W. J. Schull (Chairman)
J. Dobbing
Y. Kameyama
R. O'Rahilly
P. Rakic
G. Silini

The membership of Committee 1 at the time that this report of the Task Group was completed was as follows:

W. K. Sinclair (Chairman)
S. Abrahamson
G. W. Barendsen
J. I. Fabrikant
S. B. Field
R. J. M. Fry
L.-E. Holm
A. M. Kellerer
J. Lafuma
C. E. Land
B. Modan
K. Sankaranarayanan
W. J. Schull
I. Shigematsu
A. C. Upton
D. Wu

Sir Edward E. Pochin served as the Commission's critical reviewer of the Report.

I. INTRODUCTION

A. Background

1. The developing mammalian brain is substantially more susceptible to teratogenic insults than most other embryonic and fetal structures; presumably this reflects its architectural complexity, its long developmental (and hence sensitive) period, the vulnerability of the undifferentiated neural cell as compared with the developed neuron, the fact that neuronal function is contingent upon position and that neuronal cells do not proliferate in the cortex, but must migrate there over substantial distances, and the inability of the brain to replace lost neurons. Clinical investigations of the effects of post-fertilization pelvic irradiation have demonstrated a damaging effect of such exposure upon the development of the embryonic and fetal brain (e.g. Refs. 5, 36, 68; see Refs. 8 and 73 for recent reviews) and an increased prevalence of severe mental retardation has been seen in children who were prenatally exposed to the atomic bombing of Hiroshima and Nagasaki.[69,70,98,127,131,132]

2. A recent reassessment of these latter data has suggested that the highest risk of forebrain damage occurred in the 8th through the 15th week after fertilization[86,87] (throughout this report prenatal ages are expressed in weeks after fertilization). This corresponds to the time when the most rapid proliferation of neuronal elements and substantial migration of neurons to the neocortex from their proliferative zones near the cerebral ventricles are occurring.[101,117] Before the 8th week, there is apparently little risk of severe mental retardation. In the period of maximum sensitivity, damage, expressed as the frequency of subsequent severe mental retardation, appears to be approximately proportional to the absorbed dose received by the fetus and, over all doses, the risk is five or more times greater in these weeks than in later ones. A linear model is not equally applicable, however, to radiation-related mental retardation after the 15th week, the observed values suggesting that within this latter period a threshold may exist.[86,87] Note that, in this context, a severely mentally retarded individual is one who cannot form simple sentences, perform simple arithmetic calculations, care for himself or herself, or was or is institutionalized or unmanageable.

3. Analysis of intelligence test scores on the prenatally exposed survivors, who were not recognized to be mentally retarded clinically, has revealed a progressive shift downwards in the distribution of these scores with increasing exposure.[120] This shift is observed within the same post-fertilization age groups as those in which severe mental retardation occurs, and suggests that the effects of ionizing radiation on the developing brain may be of a more subtle nature than has heretofore been suspected on the basis of the occurrence of severe mental retardation. These findings, in particular the timing and duration of the period of maximum sensitivity, the possible linearity of the dose–response relationship within this period, the seeming pervasiveness of the effect, and the implications of these for the diagnostic and therapeutic use of ionizing radiation as well as for occupational exposures, have prompted a reevaluation of the role of radiation as a teratogen of the central nervous system.

B. Task Group's Charge from the Commission

4. The Task Group's charge, as set forth in the minutes of the meetings of the International Commission on Radiological Protection, was "to carry out a critical evaluation of the data relating to radiation-induced effects on the central nervous system, especially radiation-induced mental retardation, assessing the gestational age at risk and the quantitative risk at low doses;

to analyze these effects in the light of what is known about cell survival, proliferation, repopulation and differentiation in the development of the fetal brain; to identify the needs for future research where appropriate and to develop a document for the Committee on the subjects mentioned".

II. PRENATAL DEVELOPMENT OF THE PRIMATE BRAIN AND CEREBRAL ADNEXA

5. The brain, one of the most complex organs in the human body, is the culmination of a long and interrelated sequence of molecular, cellular and tissue events, some of which occur before birth and some later. The former, the ones of interest here, are divisible on the basis of the time after fertilization (but before birth) at which they occur. Some are said to be embryonic and some to be fetal. Conventionally, embryogenesis describes the phase of prenatal development in which the establishment of the characteristic configuration of the embryonic body occurs; it is the period from the appearance of the embryonic disk to the end of the 8th week after fertilization. After this time, the embryo is called a fetus. Most of the architectural complexity of the brain evolves in this latter, fetal period through a series of interrelated events. To understand the ways in which ionizing radiation could affect these, one must know their nature and time of occurrence. The paragraphs that follow set forth the normal embryonic and fetal development of the human brain.

A. The Cerebrum and Cerebellum

6. Ectodermal tissue destined to give rise to the central nervous system can be identified in the human embryo as early as 16 days after fertilization.[89] The events which ensue in this tissue are strikingly similar among all vertebrates (see Fig. 1 for their timing in the human; the numbers in the body of the graph represent conventional stages in embryonic development). A neural plate forms, followed by a neural groove that is present in about one quarter of human embryos at 18 days. Shortly thereafter, closure of the groove begins at the level of the brain primordium (fourth somite), and proceeds both cranially and caudally. The three major divisions of the brain (prosencephalon, mesencephalon and rhombencephalon) can be identified by 20 days, before the actual presence of any portion of the neural tube,[76] which begins to form about 22 days after fertilization with open ends that soon close. The closed tube rapidly increases in length (the cell population doubles every 8 h or so) and flexes most pronouncedly at the rostral (head) end in the area of the brain primordium. All of this is accomplished around the 5th week or so following fertilization (see Fig. 2). The lateral walls of the neural tube then quickly thicken and differentiate into four distinct layers or zones: a ventricular, a subventricular, an intermediate (the mantle or migration layer), and, finally, a marginal zone. The primitive forebrain, the prosencephalon, is at this time not much different from the remainder of the neural tube, but this soon changes as two hemispheric vesicles begin to develop. Eventually, these evolve into the cerebral hemispheres (Fig. 3). As these changes take place, two functionally-different populations of cells begin to emerge—the neuronal and neuroglial precursor cells. When and where their divergence occurs is still unknown; however, immunocytochemical methods, utilizing a specific glial cell marker, glial fibrillary acidic protein, have established the presence of at least two cytochemically distinct, mitotically active, but morphologically indistinguishable, classes of cells in the embryonic proliferative zone.[112]

7. At about the 8th week after fertilization, there begins a period of cell multiplication in the

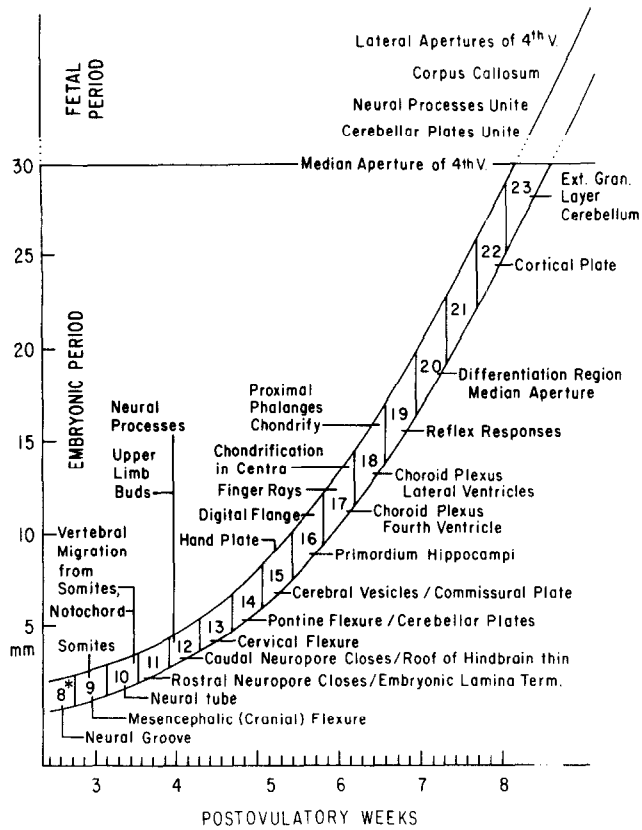

Fig. 1. Major development events in man in the nervous and skeletal systems correlated with stage, age, and average crown rump length. Asterisk at stage 8 indicates presence of notochordal plate. (Adapted from O'Rahilly and Gardner[90])

primitive brain which lasts until about the 16th week. The dividing ventricular and subventricular cells are a mixture of neuronal and glial precursors (here and subsequently the terminology advocated by the Boulder Committee[10] is used). The neuronal precursors undergo their final divisions in these weeks and their differentiation into neurons puts an end to their multiplication. A little before mid-gestation, all neurons in the cerebral cortex have been generated. However, a special variety, the granular or micro-neurons, does not achieve its maximum number until much later. In both the cerebellum and hippocampus, these cells continue to be produced during the first several months after birth.

8. Following their last cell division, neurons migrate to their appropriate positions.[9,101,117] It is now generally believed that this movement of cells is an active one and not a passive peripheral displacement.[109,116,118] Not all of the factors involved in this phenomenon in the human are known;[101,117] however, there is experimental evidence that a modification of cell surfaces or spaces on or near the glial processes, which guide the postmitotic neurons during their movement to their final destination, is involved.[109,112] The cells probably advance by making adhesive contacts at their leading edges, or growth cones, and then pulling themselves forward. Edelman,[35] for example, has shown that cell adhesion molecules, complex glycoproteins whose structure and function are apparently under genetic control (see Refs. 50, 44 and the Glossary), play a central role in these morphogenetic movements, and do so through

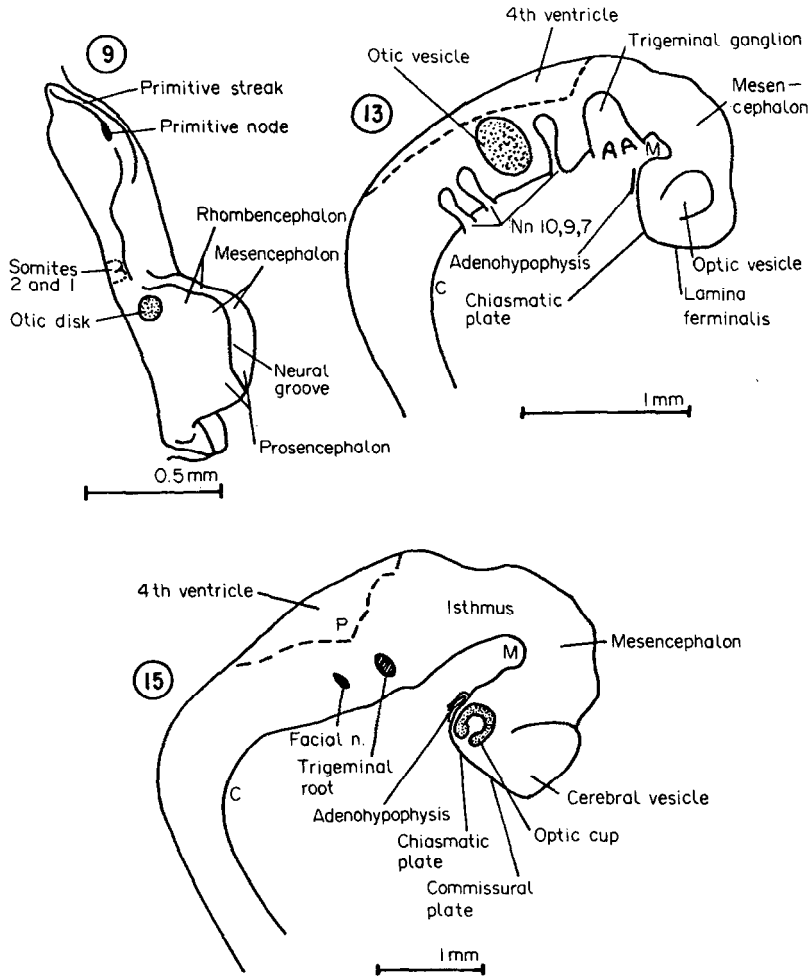

Fig. 2. Right lateral views of the developing brain in man at 3, 4, and 5 postovulatory weeks (stages 9, 13, and 15, respectively). The letters C, M, and P indicate the cervical, mesencephalic (or cranial), and pontine flexures of the developing brain, respectively. The scales are indicated, and it will be noticed that each successive drawing shows some further reduction. The illustrations are based on Born reconstructions of Carnegie embryos (Nos. 1878, 836, and 3952). The lengths of the embryos are 1.38, 4 and 6.7 mm, respectively. (After O'Rahilly and Gardner[90])

local cell surface modulation. The neural cell adhesion molecule, which is present on all neurons (but not on the glia) and facilitates neuron–neuron recognition, is ubiquitous within the vertebrate central nervous system, including the human fetal brain, and another, the neural–glial cell adhesion molecule, apparently binds neurons to glia. Thus, differential adhesiveness appears to play a major role not only in the migratory movement of neuronal cells but also in their establishment of connections.

9. Two waves of neuronal migration take place during the formation of the cerebral cortex (Fig. 4). The first of these commences more-or-less coterminously with the appearance of the cortical plate, that is at about the 7th week, and appears to involve cells from the ventricular zone. This first wave ceases at about the 10th week, when numerous nerve fibers appear in the intermediate zone which, as a result, thickens markedly at that period. The second, much larger, wave begins at about the 11th week and terminates at about the 15th or 16th. This wave consists

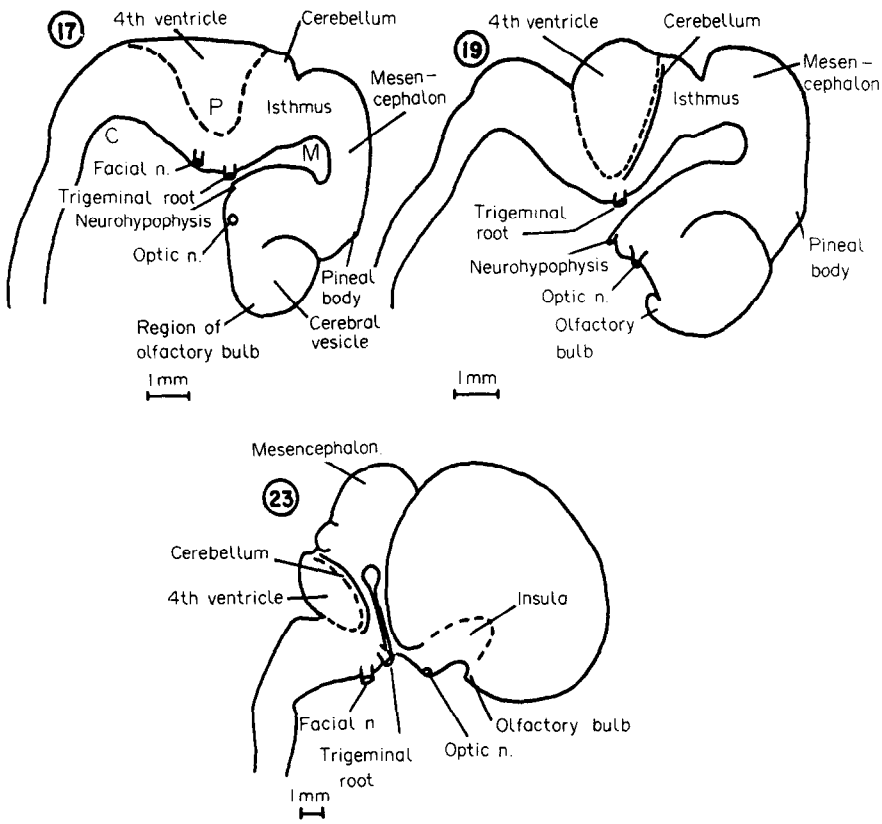

Fig. 3. Right lateral views of the developing brain in man at 6, 7 and 8 postovulatory weeks (stages 17, 19, and 23, respectively). The letters C, M, and P indicate the cervical, mesencephalic (or cranial), and pontine flexures of the developing brain, respectively. The scales are indicated, and it will be noticed that the third drawing is approximately only half the scale of the first two. The illlustrations are based on Born reconstructions of Carnegie embryos (Nos. 6520, 5609, and 417). The crown–rump lengths of the embryos are 14.2, 18 and 32 mm, respectively. (After O'Rahilly and Gardner[90])

of cells produced in both the ventricular and subventricular zones. During this period, as the migratory cells move through a now much denser intermediate zone en route to the cortical plate, they are assisted by the long processes of radial glial cells[109] (Fig. 5). These cells are usually located near the ventricular surface and their elongated processes traverse the entire width of the cerebral wall and terminate at the pial surface. At a later time, after the neurons, and possibly other cells, have stopped migrating, these amitotic radial glia, a transient class, will reenter the mitotic cycle and subsequently some may lose their processes and differentiate into astrocytes.[112] However, at this juncture, they seemingly serve at least two functions, namely, (a) to guide the migrating neurons through the densely packed intermediate zone, and (b) to ensure the faithful projection of the ventricular surface onto the expanding and convoluted cerebral cortex by preventing the lateral intermixing of cells that are generated in different regions.[109,110] Thalamocortical projections appear from the 8th until the 15th week; the last of these are the posterior thalamic radiations from the dorsolateral zone (including the nucleus lateralis posterior) and the posterior zone of the thalamus, and from the geniculate bodies. The last areas of the cortex to show completion of neuronal migration are the cinguli and the anterior insulae.

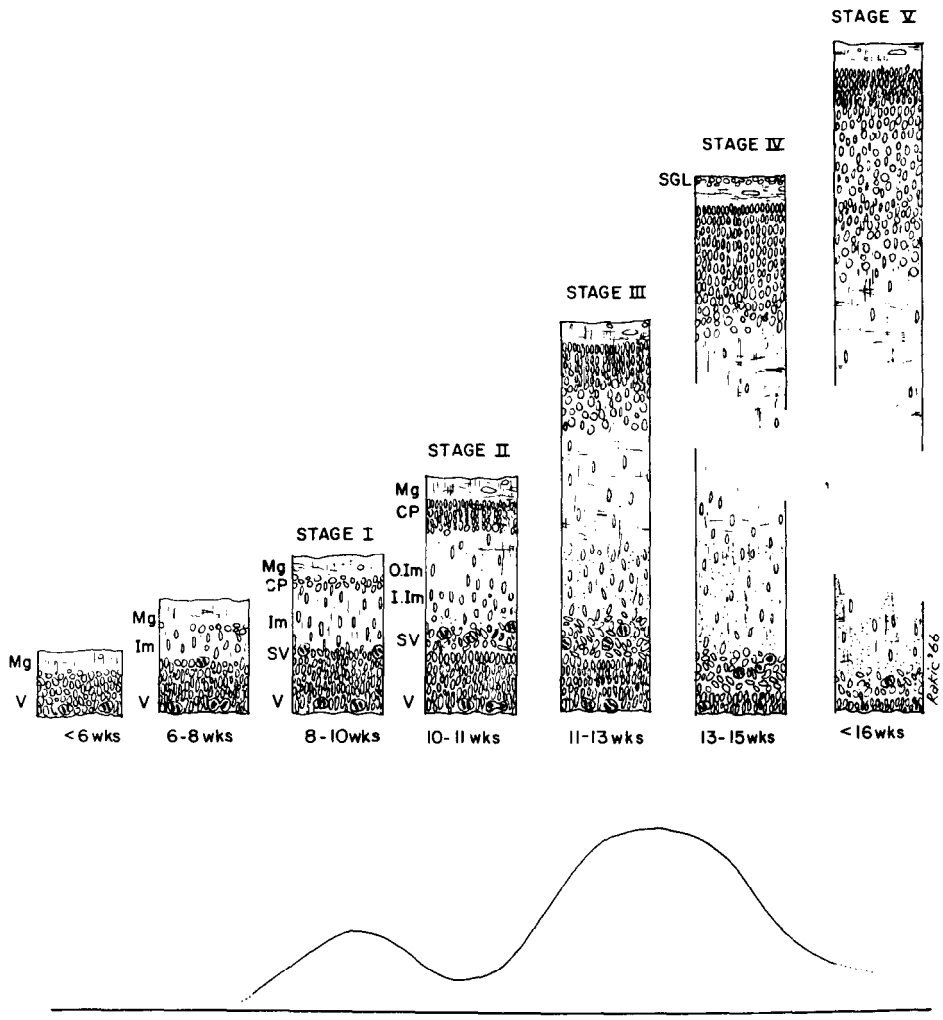

Fig. 4. Semidiagrammatic drawings of the human cerebral wall at various ages after fertilization (listed in weeks below each column). The stages refer to an arbitrarily chosen area midway along the lateral surface of the hemisphere. Because there is a gradient of maturation, as many as three of the five stages of cortical development may be observed in different regions of the neocortex in the same fetal brain. In the two extreme right columns, the intermediate zone is not drawn in full because the thickness of the cerebral wall has increased markedly compared with earlier stages. Thus, the accumulation of cells situated below the cortical plate in the last two stages—the so-called subplate layer—is not illustrated. The curve below the drawings indicates waves of cell migration to the neocortex. Abbreviations: CP, cortical plate; Im, intermediate zone; I.Im, and O.Im, inner and outer intermediate zones; Mg, marginal zone; SGL, subpial granular layer; SV, subventricular zone; V, ventricular zone; wks, age after fertilization in weeks. (From Sidman and Rakic[118])

10. In the human and other primates, no cortical neurons are actually generated in the cortex itself;[111] here they migrate over substantial distances, tens of times their cell diameters. Cell migration in other parts of the central nervous system, or in most other species, does not generally involve comparable distances. For example, the cells that comprise the developing primate spinal cord undergo relatively little migration, and no further division after the 8th week following fertilization in the human.[118]

11. Some of the complexity of the events that can disturb the development of the cerebral

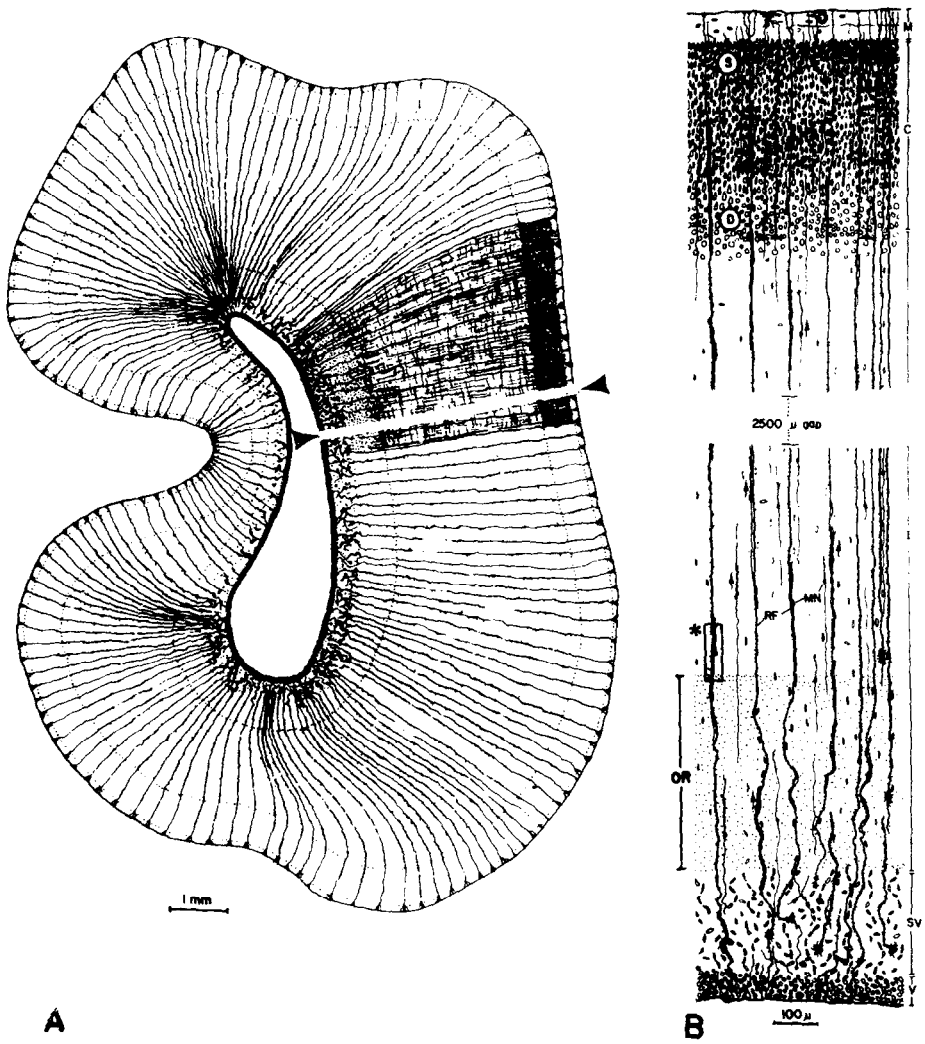

Fig. 5. (A) Camera lucida drawing of a Golgi-impregnated coronal section at the parieto-occipital level of the brain of a 97-day monkey fetus. The radial fibers are inscribed in slightly thicker lines than in the actual specimen to illustrate their arrangement at such a low magnification (scale equals 1 mm). The area delineated by the white strip between the arrowheads is drawn in B at higher magnification. (B) Composite camera lucida drawing of the cerebral wall in the area indicated by the white strip in A, combined from a Golgi section (black profiles) and an adjacent section stained with toluidine blue (outlined profiles). The middle 2 500 microns of the intermediate zone, similar in structure to the sectors drawn, is omitted. The 100 micron scale indicates the magnification. Abbreviations: C, cortical plate; D, deep cortical cells; I, intermediate zone; M, marginal layer; MN, migrating cell; OR, optic radiation; RF, radial fiber; S, superficial cortical cells; SV, subventricular layer; V, ventricular zone. (After Rakic[101])

hemispheres is implied in the way in which the cortical architecture evolves. This occurs in all examined mammalian species from the inside out,[3] but this sequence is particularly sharp in primates.[111] Thus, neurons are settled in such a way that the most superficial ones in the adult brain are the last to leave the proliferative zones and reach their ultimate destinations by passing over the bodies of their predecessors.[111] As stated above, during their journey from the proliferative zones to their final destination in the cortex, migrating neurons are guided by elongated radial glial fibers.[109] Thus, the neurons that have arrived via a particular glial process

remain arranged in vertical columns; the late neurons slide past the already present ones and ultimately arrange themselves peripherally to their predecessors,[101,112] and those that arrive first are displaced to deeper levels by those that arrive later. Ultimately, the more superficially placed neurons will be involved mostly in cortico-cortical connections; the neurons in the middle layers will form mainly local synaptic circuits; whereas the more deeply situated cells will connect with subcortical structures. The cortical plate thickens as the migration proceeds and layers of cells pile one upon the other. After the 18th week, the ventricular zone has been reduced to a thin epithelial lining of the ventricular cavity itself (Fig. 4). The cortical plate is now very much thicker and more clearly stratified; it is from this stratified structure that the isocortex, the laminated, phylogenetically younger part of the cerebral cortex, evolves.[117]

12. Numerous factors other than cell proliferation and migration can influence the achievement of proper brain architecture, and, therefore, the occurrence of neurologic abnormality. Cellular position, for example, is extremely important. Inherited defects in the development of the central nervous system, particularly in the mouse, have provided informative illustrations of the consequences of mismanaged migration.[18,101] Also, as in other embryological systems, overproduction and selective elimination of cells occurs (see, e.g. Ref. 100), and these phenomena seem to obtain wherever it has been possible to count neuronal cells unambiguously.[19] The occurrence of programmed cell loss obscures the importance of radiation-induced cell death. On the one hand, it could be argued that such death may be relatively unimportant in view of the great amount of cell death that goes on normally during brain development; on the other hand, radiation-induced cell death could intrude on a precisely programmed elimination of cells in normal development and, therefore, be very important.

13. Several features of these regressive events are especially pertinent here. First, instances are known of large-scale elimination of early-formed pathways as a result of the selective loss of cells or long axon collaterals. Specifically, the optic nerves in the fetal monkey[100] and in the fetal human have more than twice the number of axons present in the adult. These axons are eliminated mostly in mid-prenatal life. Similarly, the restriction of the callosal projection occurs through the selective elimination of collaterals, but apparently without the death of their parent cells.[51] These transneuronal degenerative processes appear dependent upon successful collateralization of efferent and afferent systems and may not occur after connectivity is well advanced. To the extent then that exposure to ionizing radiation results in the loss of long axon collaterals, it may lead to the removal or reorganization of neural pathways without cell death. Second, it is possible that this degeneration adjusts the magnitude of each neuronal population to the size or functional needs of its projection field, and also eliminates neurons whose axons have grown to the wrong target.[19] Thus, selective neuronal death appears to be an important mechanism for the elimination of developmental errors. Finally, although most early cell deaths in the embryonic and fetal nervous system may be fortuitous, some evidence suggests that certain cell deaths are "programmed" and their function may be to control the size of specific neuronal lineages (see Ref. 19 for a fuller description).

14. During cerebellar development in the human, proliferation of Purkinje cells, Golgi Type II neurons and neurons of the deep cerebellar nuclei occurs largely, if not exclusively, in the ventricular zone (and possibly in the adjacent subventricular layer) up to the 11th week after fertilization.[102] At the 12th or 13th week, however, numerous immature neurons have gathered to form the primordial deep nuclear complex, and part of the Purkinje population has reached the cerebellar cortex by the 13th week after fertilization. These latter cells must have been present as postmitotic cells in the intermediate zone by the 11th week, since the external granular layer does not contribute cells to the cerebellar cortex until after the 15th week or so. Maturation of the Purkinje cells exhibits three clearly differentiable stages.[144] In the first, which

occurs primarily in the 16th to 20th weeks, the cells are relatively smooth, possess few processes and are distributed in a layer several rows deep. During the second stage, which lasts from the 16th through the 28th week approximately, the cells gradually organize into a single row and develop numerous spines. The first morphologically well-defined synapses now appear on the Purkinje cell somatic spines, and afferent fibers become prominent. At this stage, the fetal cerebellar cortex consists of five layers, three of these (the external granular, Purkinje and granular layers) are cellular and are separated by two cell-sparse zones, the molecular layer and the lamina dissecans, which makes its appearance at this time.[102] The Purkinje layer is now numerically stable, although the cells in the granular layers will continue to increase in number throughout gestation and into postnatal life.[102] These granular neurons arise in the transient external granular layer and migrate inwards, with the aid of Bergmann glial fibers, to a destination beneath the Purkinje cell layer. In the third and final stage, the dendritic arbor, that appears and grows prominent from the 18th to 24th week, flattens and the somatic spines disappear. These stages are characteristic of all vertebrates, not solely humans; the latter differs from other species only in the times of onset and termination of these events, and in their absolute and relative duration.[118]

15. Finally, the human brain is anatomically asymmetrical, and this asymmetry develops during intrauterine life. No other species yet studied has been shown to possess so high a degree of cortical asymmetry, and this may be a unique feature of the human brain.[42] Chi and his associates,[24] for example, have shown that asymmetry of the temporal speech region develops *in utero* and, no less importantly, that the smaller homologous area on the right side develops earlier than the larger left-side region. Thus, the lateralization of cerebral function begins early and is associated with microscopic (and occasionally gross) anatomic differences between regions. Different areas of the cortex differ substantially in lamination, cellular size, cell packing densities and distribution of cell types; moreover, there is strong evidence to support the notion that distinct architectonic areas have distinct connectional patterns and functions.

B. The Cerebral Adnexa

16. All nonautonomic neurosensory stimuli—auditory, gustatory, olfactory, tactile and visual—are processed ultimately by some portion(s) of the cerebral cortex. It has been estimated that as much as 30% of the human cortex is involved in the processing of visual stimuli—color, form, movement and the like. Accordingly, no account of the development of the brain is complete without some consideration of the development of the cerebral adnexa and the pathways of their interaction with the cerebral cortex.

(1) *Vision*

17. About 3 weeks after fertilization, the optic primordium and the optic sulcus emerge in the prosencephalic fold.[94] In the 2 weeks that follow, the optic vesicle develops further and its components differentiate. Retinal pigment and the oculomotor nerve make their appearance. The lens vesicle is soon formed, and the lens body appears about 33 days after fertilization, when it consists solely of primary lens fibers. Near the end of the 5th week, the eyelid grooves become discernible. Soon thereafter, the various layers of the retina—the proliferative zone, external neuroblastic layer, transient fiber layer,and the internal neuroblastic layer—become differentiated. Between 40 and 57 days after fertilization, nerve fibers that reach the brain are visible in the retina; the cornea, sclera and vitreous body appear, and secondary lens fibers form. Retinal pigment becomes visible at about the 5th or 6th week.[94] Thus, by the 8th week after fertilization,

most of the major structures of the eye have developed, tissue differentiation has begun and only the iris and a few other structures remain to develop.

18. Studies using tritiated thymidine, a specific precursor of DNA, in nonhuman primates, have demonstrated that all neurons that comprise the visual system are generated (had their last division) before birth,[113] indeed, mostly in the first two-thirds of the prenatal period. No new neurons are added in neonatal life or during adulthood.[106] After their last division, neurons develop their connections. Autoradiographic studies of axonal transport, carried out in nonhuman primates, have shown that the retinal ganglion projections are distributed through the optic chiasma to the lateral geniculate bodies, approximately half to each side.[113] These latter laminated structures, part of the main visual pathway, lie above the superior colliculus. Each eye is represented by three laminae[105] distributed complementarily between the two bodies. Autoradiography has also demonstrated a segregated representation of each eye in the superior colliculus "where fibres from the two eyes terminate in complementary, alternating territories 0.1–0.5 mm wide".[105] Impairment of this developmental process could possibly lead to abnormal neuronal connections and cause defective vision, e.g. ambylopia (see Ref. 105).

(2) *Hearing*

19. The otic primordium appears at about 20 days after fertilization, slightly before the optic disk and in the next 5 weeks all of the components of the auditory system emerge.[94] The geniculate and cochlear ganglia are established; the cochlea, stapes, stapedius, malleus, incus and tympanic membrane become visible, and the labyrinth has largely completed its gross development. Generally, knowledge of the embryonic development of the human ear is much less complete than for the eye. This is especially evident in respect to the middle ear and its relationship to either the inner or the external ear. These deficiencies are probably not of moment in the context of this report, however, for it seems unlikely that ages at exposure in an epidemiological series can be dated with a precision sufficient to identity radiation-related events where the sensitive periods may extend over intervals no greater than a few days or a week.

(3) *Olfaction*

20. As early as 24 days after fertilization, on either side of the frontal prominence of the embryo, a thickening of the surface ectoderm emerges to form the olfactory plate. Soon afterwards, at about 32 days after fertilization, two fast growing ridges, the medial nasal swellings, surround this plate, which then forms the depression known as the olfactory pit. The rostral olfactory elevation on the ventral surface of the cerebral vesicle that gives rise to the future olfactory bulb can be identified in about one out of two human embryos at 33 days after fertilization. The bulb itself is relatively smaller in humans than in macrosmatic mammals. In embryonic development, it has a lumen, but this is eventually replaced with an accumulation of glial cells. The olfactory bulb and all other areas of the brain where efferent fibers from the bulb synapse are termed the rhinencephalon. This structure is commonly divided into an anterior and a posterior olfactory lobe. The former consists of the olfactory bulb itself, the anterior olfactory nucleus, the olfactory trigone, the anterior perforated substance, the olfactory tubercle, the lateral olfactory stria, and Broca's diagonal band. The posterior lobe comprises the cortical areas of the temporal lobe of the cerebrum itself.

C. Summary

21. Development of the primate brain and its adnexa differs from the development of most other organs or organ systems in the following ways.

(a) *Structurally, the brain is one of the most complex organs of the body, with an involved architecture in which different functions are localized in different structures.* Differentiation of these structures 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) *Organizationally, brain function critically depends on the disposition and interconnection of structures and cells and, developmentally, normal structure and function hinge on an orderly sequence of events (cell division; programmed cell death; migration, including the positioning and selective aggregation of cells of the same kind; differentiation, with the acquisition of new membrane properties; and synaptic interconnection), each of which must occur correctly, temporally and spatially.* Impaired cell division will presumably give rise to fewer neurons; disturbances in cell migration may result in ectopic gray matter and areas of dysplasia, and, finally, interference with cellular differentiation or synaptogenesis will give rise to a less developed system of cellular connections. Ultimately, however, these processes have in common the fact that the disruption of any one or combination of them will lead to the loss of nervous function.

(c) *Functionally, the neurons of the central nervous system are not self-renewing.* The mitotic potential of neuronal precursors is exhausted during histogenesis and culminates in differentiated neurons which do not divide. Development of the primate brain in this respect is unlike that in some non-mammalian vertebrates and even some mammals. In all vertebrate species, the majority of neurons are generated during the embryonic period, although production of some additional neurons continues throughout the life span of fish, amphibians and some birds. Autoradiographic studies of the brains of rhesus monkeys, labeled as adults, have failed, however, to disclose a single heavily-labeled cell with the morphological characteristics of a neuron.[106] Presumably, this also obtains in the human. Neuronal loss, therefore, is irreparable, for repair through repopulation cannot occur. Glial division, a common response to injury, may offset the loss of brain weight, but will not result in restoration of neuronal function.

III. DEVELOPMENTAL DISORDERS OF THE CENTRAL NERVOUS SYSTEM

A. General Remarks

22. Malformations of the central nervous system are commonly divided into two groups, namely, the organogenetic, those that occur in the course of major organogenesis, and the histogenetic, those that take place during the differentiation and growth of the brain mantle. Among the former are the dysraphic malformations, such as anencephaly and encephalomeningocele, which represent failures in the normal formation and elevation of the neural folds and the subsequent proper closure of the neural tube.[79,89] The role of the mesenchyme in the closure process is not clearly understood.[80] The forebrain, or holoprosencephalic, defects reflect the failure of the single telencephalic primordium to produce two lateral cerebral vesicles. At this time, the undifferentiated neural cells retain their regenerative capacity and tissue damage can theoretically be repaired. The closure of the neural tube and the division of the prosencephalic vesicle take place relatively rapidly, probably within a few days in humans.[90] These events occur early in embryogenesis, some time in the 4th to 6th week after fertilization. Many of the abnormalities affecting the brain stem may involve vital centers and are, therefore, probably incompatible with life.

23. Disturbances in the production of neurons, and their migration from the periventricular proliferative zones to the cerebral cortical area, give rise to the histogenetic malformations. Recent advances in developmental neurobiology have shown that many of these stem from failures in the normal interactions of cells (neural and non-neural) during the development of the primate brain. Normal interactions hinge upon (a) production of a sufficient number of neurons, (b) their appropriate positioning, (c) establishment of the requisite cell shapes, and (d) formation of synaptic connections.[103] Among such malformations are, for example, an absent corpus callosum, or a disorganized cortical architecture which may later result in abnormal fissuration of the cerebral hemispheres, heterotopic cortical gray matter and microcephaly. The sensitivity to damage of the differentiating neural tissue appears to change with age, but so too does its capacity to replace damaged cells. Thus, it is impossible to say whether the intrinsic or apparent sensitivity of the structures changes as a function of time. At any given time in development, the probability of causing abnormalities, and their severity, changes as the dose of the teratogenic agent changes. In addition, since, for the same dose, damage can vary as a function of the time in development at which the insult occurs, histogenetic defects, unlike the organogenetic ones, can also differ substantially in severity. In very general terms, the sensitive period for histogenetic abnormalities is not only later but undoubtedly much longer, certainly months instead of days. It is reasonable to argue that the longer sensitive period and the limited repair capability must be important reasons why histogenetic malformations are much more common than organogenetic ones.

24. The cells of the different structures of the brain are produced at different times. If the proliferating ventricular and subventricular cells are damaged during periods when a particular cell type is being produced, the loss may be permanent. Thus, a brief insult may lead to preferential damage to a particular region and consequently bring about a permanent functional or behavioral abnormality. One population of neurons can control the number of neurons in another structure with which it shares a common synaptic territory.[43] Several generations of neurons originate in the same restricted location in the proliferative zone, migrate along the same glial fascicles and consequently accumulate in the same radial cortical region.[101] If the guideline, the glial fascicle, is destroyed, or the surface properties of the cells (glial, neuronal, or both) are changed, neurons may fail to migrate, or aggregate at intermediate spots along their migratory route and ectopic gray matter result.[109] Thus, these glial processes appear to be essential not only as guides to the migrating neurons, but also to serve as a mechanism to preserve the topographical, and hence functional, relationship of clonally-related cells.[112]

B. Cerebral Abnormalities

25. The critical period for histogenetic abnormalities of the cerebral cortex occurs when the telencephalic matrix cells undergo their last cellular division, begin to migrate to the cortical plate and start to differentiate into specific phenotypes. Production of neuronal cells and their migration commence at about the 8th week after fertilization and shortly thereafter the cortical plate begins to develop. Cortical neuron production has largely terminated by the 16th fetal week. Subsequently, the laminar cortical architecture becomes apparent and dendritic arborization of the cortical neurons, a process which extends into postnatal life, begins. Loss of the superficial cells of the developing brain, the cortico-cortical ones, can lead to convolutional abnormalities which, since neuronal function follows position, may in turn contribute to the origin of functional and behavioral abnormalities. Migrational errors may lead to convolutional abnormalities, such as lissencephaly, pachygyria, and certain types of polymicrogyria.

26. Disorders such as the dyslexias appear to be due to aberrations in specific cortical areas.[40] Galaburda and Kemper,[41] for example, have described a severely dyslexic child with neuronal migration defects in the speech region of the left hemisphere. Specifically, they found small focal wartlike accumulations of ectopic neurons in Layer I and scattered focal cortical dysplasias; these architectonic aberrations were confined to the left hemisphere. Other cases with comparable structural abnormalities have been described subsequently. It has been speculated that the abnormal cytoarchitecture and the aberrant myelinated fiber bundles seen in these disorders may be the result of an injury to the medial geniculate nuclei and the nucleus lateralis posterior at the time when normally the posterior thalamic radiations from the dorsolateral and the posterior zones of the thalamus and the geniculate nuclei develop, that is, at the end of neuronal migration to the cortex.[63]

27. Similarly, auditory, olfactory and visual anomalies could be the consequence of damage to the specific cortical areas involved in these sensory functions rather than to the end organs themselves.

C. Cerebellar Abnormalities

28. The most common histogenetic abnormality of the cerebellum is a hypoplasia with deranged cortical structure that stems from injury to the external granular matrix. Although some cell classes such as Parinsi cells and Golgi Type II cells are generated early in the cerebellar anlage, other and more numerous cells such as the granular neurons are generated late. Thus, overall, cerebellar growth starts later, proceeds more slowly, and, therefore, ends later than that of the rest of the brain. This bimodal and protracted growth may account for the differential susceptibility of the cerebellum to growth restriction.[102] This was also suggested by the finding of a net increase in the number of cells of the forebrain.[25,26,46] However, the biochemical method used in these studies fails to distinguish between cell types and, therefore, does not establish which cells are primarily affected. In all major respects, development of the human cerebellum resembles that in other mammals, provided account is taken of the different timing of birth relative to brain development. A diminution in the number of granular neurons which may be produced perinatally is probably less of a developmental handicap than a loss of Purkinje cells which, if it occurs, would do so early in the second gestational trimester; however, the loss of a small number of granular cells may result in reduced motor skill or fine-grain clumsiness in children. Because of its unique developmental sequence, in which two populations of neurons are generated at opposite sides of the cortical plate and migrate in a subsequent phase to bypass each other, the cerebellum is the most frequent site of genetic abnormalities[1,7] and can be easily altered by various cytostatic agents and ionizing radiation.[2]

D. The Brain Adnexa

29. Abnormalities that involve the brain adnexa could arise from maldevelopment of the end-organs themselves (e.g. the eyes or ears), of the processing of the signals transmitted from these organs to the brain, or both. Failures in signal processing could be the consequence of a defect in the optic or auditory nerves, or as previously suggested, in the various cortical areas involved in auditory, olfactory and visual function. Defects in the optic tract, for instance, would be manifested as aberrations in the field of vision, with their nature and extent depending upon the severity of the damage. Total destruction of the retina or the optic nerve would, of course, result in blindness. Damage to the optic chiasm, the primordium of which can be identified as early as the 4th week after fertilization, could give rise to total or unilateral blindness depending upon

the location and severity of the lesion. Radiation-induced damage to the lens might be manifested as a lenticular opacity or the presence of polychromatic granules. Damage to the iris could be severe and culminate in a coloboma, or mild and manifested as heterochromia or other pigmentary disturbance. Rhinencephalic damage could, if severe, produce anosmia, and if less severe, an inability to perceive specific classes of odors, a selective anosmia. Whether prenatal damage of the nature described can be ameliorated postnatally is unclear; however, if such amelioration is possible, the effects of prenatal irradiation will be more difficult to assess.

IV. IONIZING RADIATION AS A CENTRAL NERVOUS SYSTEM TERATOGEN

30. Ionizing radiation could interfere with the development of the central nervous system in a variety of ways.[8,11,45,47] First, radiation effects could arise from the death at mitosis of glial or neuronal precursors or both, or the killing of postmitotic, but still immature, neurons. Second, such effects could stem from an intrusion on migration, either through an alteration, directly or indirectly, of the cell surface phenomena that are involved, or through the death of the glial cells that guide the migrating neurons. Radiation could alter the surface properties of the glial or neuronal cells or both, indirectly, e.g. through somatic mutation. It is not clear whether neuronal and glial cells are equally radiosensitive; however, disturbances of myelin formation, a mature glial function, have not been described in experimental situations following irradiation. Third, abnormality might reflect an impaired capacity of the neurons to connect correctly. Development of neuronal connections, or synaptogenesis, is a multifactorial phenomenon; it involves timing, space, possibly diffusible agents, and surface-mediated competition. Irradiation could lead to disoriented dendritic arborization, or a reduced number of dendrites or dendritic spines per cerebral cortical neuron. Finally, programmed cell death, essential to the development of the normal brain and its adnexa, could also be accelerated or otherwise altered by ionizing radiation.

A. Effects of Radiation Exposure

31. There is abundant information on the biological effects caused by prenatal exposure of mammals to ionizing radiation. These data, largely experimental, afford little quantitative insight, however, into central nervous system effects that may arise in human beings, although they do serve to identify possible ones. Much of this evidence has been summarized in a recent publication of the United Nations Scientific Committee on the Effects of Atomic Radiation entitled *Biological Effects of Prenatal Irradiation* (Ref. 130; see also Refs. 129, 142). Therefore, in the paragraphs that follow, no effort is made to give an exhaustive account and the remarks are restricted to selected findings.

(1) *Evidence from experimental animals*

32. The limitations of the human data make inevitable the use of other animal species for both descriptive and experimental studies, and this gives rise to speculation about their possible relevance to the human.[32] There are, of course, species differences in brain development, attributable partly to the differing complexity of the ultimate adult organ, but especially to the different rates of brain growth and the different timing of birth in relation to brain developmental events.[29] In general, the histological structure of the brain is similar, both in composition and function, from one species to another; and so, too, is the sequence of

developmental events in all mammalian species studied. However, the process of brain development which occurs in the human from fertilization to about the second birthday is qualitatively similar to that seen in the rat within the first 6 weeks following fertilization. For example, the transition from the major phase of multiplication of the neuronal precursors to that of glial multiplication, which occurs shortly before mid-gestation in man, occurs at about the time of birth in the rat.[25] In general, therefore, the newborn rat is neurologically much less mature than the human infant; whereas many other species, including the guinea pig and the nonhuman primate, are more neurologically mature at birth, the spectrum ranging from the late-maturing mouse and rat to the early-maturing guinea pig, with nonhuman primates much closer to the guinea pig than to the human (Fig. 6).

33. It is difficult to compare the brain of a newborn rat, which has not yet begun to myelinate, with that of a newborn human, which has, or with the brain of a newborn guinea pig in which myelination has been completed. In order to examine the radiation effects observed in laboratory animals and their relation to human observations, it is the timing of an environmental insult, in relation to brain developmental events, that strongly dictates the consequences of that insult; therefore, it is necessary to apply the experimental procedure at comparable stages in brain growth, rather than at comparable gestational ages. The duration of exposure must also match the different time scales, but if these factors are taken into account, even the small laboratory species can provide some, at least qualitative, information of relevance to the human. Some apparent qualitative differences between rats and humans, which have been interpreted as evidence that some events occur concurrently in the rat which are sequential in the human, may result from a failure to take into account the relatively far more rapid rate of development in the rat.

34. None of these remarks is intended to deny the existence of true species differences nor that some neurologic effects of ionizing radiation may be more appropriately studied in one animal

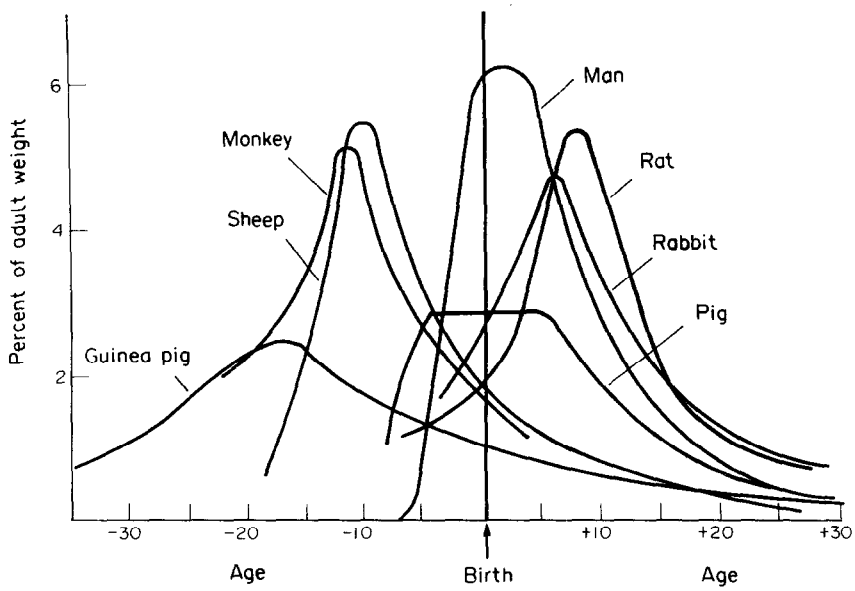

Fig. 6. The temporal pattern of brain growth of 7 mammalian species expressed as first-order velocity curves of the increase in weight with age. Rates are expressed as weight gain as a percentage of the adult weight for each unit of time. The units of time for each species are as follows: guinea pig, days; rhesus monkey, 4 days; sheep, 5 days; pig, weeks; man, months; rabbit, 2 days; rat, days. (After Dobbing and Sands[25])

surrogate than another. The complexity of the nonhuman primate brain obviously makes it valuable for many experimental purposes and the protracted span of development of the primate brain increases the resolution of temporal sequences in neurogenesis; but the use of rats and mice can much more conveniently and quickly lead to a better understanding of human teratogenesis than has sometimes been supposed. Although extrapolations must be made with care, it is clear that the use of animals is vital to progress in understanding the effects of ionizing radiation. At the same time, direct evidence, especially that of a quantitative nature, must be continually sought from human studies and will eventually be the most convincing.

(a) *Primates*

35. There is a paucity of data on the prenatal effects of irradiation of brain tissues in nonhuman primates.[13,91,104] Ozzello and Rugh[91] have, however, described the acute pathologic changes in nine rhesus monkeys exposed to absorbed doses of 2 to 4 Gy at fetal ages ranging from 110 to 160 days. The prenatal period is, on the average, 168 days in the rhesus; thus, exposures at 110 days would correspond to about 25 weeks of prenatal age in the human, if maturity at birth was the same, but, in view of the greater maturity of the rhesus brain at birth, the correspondence may be with an even later stage of human development (Fig. 6). They report no gross anomalies, but note that "the irradiation in all cases occurred after the completion of organogenesis when gross congenital anomalies can no longer be induced". They do describe a marked general depression of mitotic activity, a limitation of extramedullary hematopoiesis in the liver and spleen, and a severe necrosis of the lymphocytes in the thymus as well as depletion of lymphocytes in the spleen and lymph nodes. They allude to studies of the central nervous system, but do not report any results. However, their findings certainly suggest that at exposures of 2 Gy or more the fetus exhibits the hematopoietic signs of acute radiation illness. It has been speculated that some of the brain damage seen at these higher exposures in humans may reflect a hypoxia stemming from the hematopoietic depression associated with acute radiation sickness.[57]

36. Rugh *et al.*[104] studied two *Macaca mulatta* prenatally exposed to doses of 3 and 2 Gy at 60 and 80 days of prenatal life, respectively. These post-fertilization ages would correspond to about the 14th and 18th week in the human if, again, the same maturity existed at birth. At autopsy, at 23 months post-partum, the brain of the younger animal, which received the higher dose, was grossly "abnormal, definitely microcephalic, about half the volume of the control, and the cord some 2.5 cm shorter". The older, less heavily exposed animal differed little, if at all, from the control with regard to brain and cord measurements, convolutions and sulci. These investigators did note, however, that "some of the sulci of the x-irradiated brain are shallower than normal, and several show minor deviations from the control". They further stated that, "On observation one gathered the impression that both x-irradiated monkeys were nervous, easily stimulated to excessive activity, and showed unpredictable behavior when compared with the control".

37. Brizzee and his colleagues[12] examined the effects of prenatal ionizing radiation on the visual cortex and hippocampus of newborn squirrel monkeys (*Saimiri sciureus*) exposed, whole-body, to a dose of 2 Gy (^{60}Co) at 0.004 Gy per second on approximately the 75th day of gestation. The prenatal period in this species of monkey has been estimated to be about 147 days, so these exposures would correspond to about the 19th week in the human, subject to the previously-stated caveats associated with extrapolations of age after fertilization. They examined such endpoints as the depth and number of cortical neurons, the number of glial cells in the cortical region, and the number of apical, basal and oblique dendrites in the Meynert neurons. At this phase of development, the hippocampus, a submerged gyrus that forms the

larger part of the olfactory cerebral cortex, seems significantly more vulnerable to radiation than the motor and visual areas of the cerebral cortex. They further reported the number of dendritic spines per linear unit of dendritic shaft was significantly lower in irradiated than in control animals in all three classes of dendrites (apical, basal and oblique). They concluded that, "These observations, . . . , indicate a regional and neuronal vulnerability based on a reduction of dendritic spine numbers in the large pyramidal neurons in both sensory and motor areas of the cerebral cortex, rather than cell loss from these regions". At these prenatal ages it appears, therefore, that irradiation causes, either directly or indirectly, damage to synaptogenesis, rather than cell death.

38. In more recent publications,[14,92,93] these investigators have reported that visual acuity is significantly lower in squirrel monkeys receiving 0.5 and 1 Gy prenatally (at 80–90 days after fertilization) and significant differences exist in foveal cone density. At 1 Gy, the histological structure of the cortex was altered and a thinning was seen in the foveal striate cortex. They further noted that nervous activity (as studied between birth and 3 months of age) was less accurate and complete at both doses in comparison with controls. Specifically, the time for the performance of reflexes and neuromuscular coordination was increased, as was the percentage of incorrect responses in tests of visual orientation, discrimination and reversal learning.

39. It is noteworthy that in many, if not all, of these studies, irradiation of the primate fetus occurred after the cessation of most, if not all, neuronal migration to the cerebral cortex, and, thus, after what appears to be the period of maximum sensitivity of the cortex to radiation damage insofar as the human fetus is concerned. Of course, migration does continue to occur even in the post-natal period, in the hippocampus and cerebellum (see, e.g., Refs. 110, 112).

(b) *Nonprimates*

40. The neurological effects of exposure *in utero* to ionizing radiation on experimental mammals other than primates have been summarized elsewhere.[129,130]

41. Animal studies suggest that disturbances in cell kinetics may occur at doses slightly lower than 0.1 Gy, and that the vulnerability of the cell to radiation damage is functionally related to its stage in the mitotic cycle.[64–66] Wanner and Edwards[138] have shown that guinea pigs exposed prenatally, on the 21st day after fertilization, to doses as low as 0.10 and 0.15 Gy have significantly lower brain weights, after adjustment for body size, and a significantly increased number of microcephalic offspring. Study of the embryonic brain soon after irradiation showed extensive cell death in the ventricular zone, and at birth there was a deficiency in DNA and cholesterol similar in proportion to the diminution in brain weight.[139] This deficit in brain weight was not made up in postnatal growth. They suggest, therefore, that the lost weight results from the death of proliferating ventricular cells, the neuronal precursors, which are normally rapidly dividing at this time in this species. D'Amato and Hicks[33] have found that rats exposed *in utero* on the 16th to 18th fetal day to about 10 R exhibited alterations in the migration of neuronal cells to all layers of the cortex. At exposures of 10 and 20 R, there was no evidence of cell killing in the proliferative–migratory system, but at higher exposures, such as 30 and 40 R, neuronal death did occur. However, cortical volume was not always measurably diminished; the missing neurons were apparently replaced by neuroglia or neuropil, the network of axons, dendrites and synapses. The significance of these findings in relation to other histological or functional end-points is not completely understood. Studies with higher doses have also shown that germinal and mantle layer cells and those actively migrating may be selectively destroyed. However, even those seemingly normal cells in the cortex that survive exposure may be aberrant in several respects; they have fewer primary dendrites and the amount of branching seen is less, suggesting that the capacity to connect with incoming axons has been reduced. D'Amato and

Hicks noted that, "Around the time of birth, the threshold exposure dose (sic) for producing effects was about 10 R, but in fetal life, judging from the effects of 20 or 10 R, it lay below 10 R".

(2) *Evidence from man*

(a) *Hiroshima and Nagasaki: The prenatally exposed*

42. (i) General information on the sample. Few population-based studies of the effects of *in utero* exposure on the developing human embryo and fetus exist. Among these, however, the size, length of study, and variability in dose and post-fertilization age at exposure, make the experiences in Hiroshima and Nagasaki the most important. These populations were exposed at a variety of developmental phases and, therefore, presumably a variety of sensitivities.

43. Over the years, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation, have established several overlapping samples of individuals prenatally exposed to the atomic bombing of Hiroshima and Nagasaki. The earliest observations, those of Plummer[98] and Yamazaki and his colleagues,[143] for example, were based on opportunistic samples and made no systematic attempt to be complete. Indeed, they were restricted in the method of ascertainment and in structure; often only one city or a limited prenatal age distribution was involved. About 1955, however, there occurred the first effort at the construction of an exhaustive clinical sample of the prenatally exposed survivors. This gave rise to what has been termed the PE-86 sample. Its members were ascertained through a variety of sources, but primarily birth registrations, interviews of women who were enrolled in the genetics program in the years 1948–1954 and were possibly pregnant at the time of the bombing, the National Census of 1950, and earlier ad hoc censuses conducted by the city authorities and the Atomic Bomb Casualty Commission. No attempt was made to match the more distally exposed or the nonexposed, by sex or prenatal age at the time of the bombing, with those survivors exposed within 2 000 m.

44. In 1959, this sample was revised,[16] and it is this latter group of individuals which has been the basis of most subsequent analyses (see, e.g., Refs. 70, 131, 132). This revision was motivated by two considerations. First, the earlier (1955) sample contained a disproportionate number of prenatally exposed survivors who were thought to have received doses of less than 0.01 Gy and, since the clinical facilities and personnel were limited, their examination strained resources and seemed unproductive in view of their probable exposures. A limitation of the sample size, therefore, was in the interests of clinical efficiency, at the loss presumably of little or no information. Second, the First and Second Special Censuses, conducted in 1950 and 1951 by the ABCC, appeared to offer a better basis for the selection of a nonexposed comparison group than had previously obtained. This new sample, known as the Revised PE-86 sample, differs in several important respects from the unrevised one. *It includes no survivors prenatally exposed at distances between 2 000 and 2 999 m.* Exposed individuals are limited to those survivors prenatally exposed within 2 000 m (the proximally exposed), or between 3 000 and 5 000 m (the distally exposed). *Nonexposed persons include only those individuals who were beyond 10 000 m at the time of the bombing and were enumerated in the First or Second ABCC Sample Censuses.* Finally, *the survivors within the 3 000–5 000 m zone, as well as the nonexposed, were matched as to sex and age (by trimester of pregnancy) with those exposed within 2 000 m.* These steps reduced the clinical burden substantially, but resulted in little change in the number of persons within 2 000 m. Both samples include virtually all individuals who received "substantial exposures", those with tissue absorbed doses of 0.5 Gy or more, and differ primarily in the number and ascertainment of individuals in the dose range 0–0.01 Gy.

45. In retrospect, this redefinition of the sample had two undesirable consequences. First, through the exclusion of individuals in the 2 000–2 999 m range, it removed some survivors

who, according to subsequent dosimetric evaluations, may have experienced doses above 0.01 Gy. Second, and more important in the present context, it diminished greatly the information on intelligence testing. These tests were done in 1955, before the selection of the present nonexposed portion of the sample, and were not repeated later. Many of the nonexposed in the Revised Sample were never tested.

46. In the analyses which follow, both samples are used. The data on severe mental retardation are restricted to the Revised Sample, since it involves the only individuals on whom extensive clinical observations are available in both cities. Insofar as the intelligence tests are concerned, attention is focused on the earlier, unrevised sample, to bring the largest practicable number of observations to bear on the issue of possible brain damage more subtle than severe mental retardation. However, analyses of the intelligence tests have been made on the Revised Sample as well, and these lead to very similar conclusions (see Ref. 120).

47. (ii) Dose estimates. Recently published analyses of the effects have used estimated fetal absorbed doses based on the revised T65 (see Glossary) values for kerma,[77,61] and the body attenuation factors proposed by Kerr,[60] assuming a relative biological effectiveness for neutrons of one. Specifically, the tissue gamma dose was taken to be equal to 0.42 times the gamma kerma plus 0.077 times the neutron kerma, while the tissue neutron dose was taken to be equal to 0.14 times the neutron kerma, and the total tissue dose to be the sum of the two individual tissue doses. There is evidence that within the T65 system of dosimetry,[77] low doses have been systematically underestimated, whereas high ones have been overestimated.[58] Such dose errors can lead to spurious curvilinearity.[38,39] Although both the T65 values and organ shielding factors are under review,[61,67] they presently provide the only basis, applicable to all survivors (shielded and unshielded), to estimate absorbed dose in fetal tissue. This is likely to remain so for some further time. At this juncture, it is difficult to predict precisely the effects of the proposed dosimetric changes.

48. (iii) Pathological findings. Four of the members of the revised sample who have died have come to autopsy; two were mentally retarded and two were not. All were exposed, but only one, a mentally retarded individual, received a dose in excess of 0.01 Gy. Of the two with normal intelligence, one, a male, exposed 21 weeks after fertilization, died at 9 years of age from granulocytic leukemia; autopsy disclosed extensive brain hemorrhages which were thought to be the final cause of death. The brain had a normal weight of 1 440 g, and the architecture was normal. The death of the other, a female, at age 29 was ascribed to "cardiac insufficiency". She had been exposed in the 24th fetal week. Autopsy revealed multiple bilateral pulmonary infarcts and evidence suggestive of autoimmune disease; however, the clinical data available on this individual were too scanty to pursue this possibility further. Cut sections of the cerebrum, cerebellum, brain stem, and spinal cord showed no abnormality on either gross or microscopic examination. The brain had a normal weight of 1 450 g; there was no gross or histologic evidence of edema, which would have increased brain weight.

49. Both of the mentally retarded had brain weights substantially below normal. One of these individuals, an overweight female, exposed to less than 0.01 Gy in the 31st week after fertilization, had a body mass index (defined as weight in kilograms divided by the square of the height in meters) of 28.6, and died, at age 20, of congestive heart failure. Autopsy disclosed severe edema and congestion of both lungs as well as marked, diffuse fatty infiltration of the liver. Multiple transections of the brain, which weighed 1 000 g, revealed the usual pattern of gray and white matter and no evidence of edema. The other mentally retarded individual, a male, with a brain weighing 840 g, died at age 16, of acute meningitis. He had been exposed in the 12th fetal week.[84,141] His mother's estimated tissue kerma (T65DR) was 3.75 Gy. He was bilaterally microphthalmic, had microcorneae and bilateral hypoplasia of the retina,

particularly in the macular area. Posterior subcapsular opacities were present in both eyes. Coronal sections of the cerebrum revealed massive ectopic gray matter around the lateral ventricles. Histologically, there was an abortive laminar arrangement of nerve cells within the heterotopic gray areas, imitating the normal laminar arrangement of the cortical neurons. The cerebellum and hippocampi were normal histologically. Ectopic gray matter was not observed in any of the other three cases, including the second mentally retarded individual, as previously stated.

50. (iv) Findings related to brain growth and development. Only two conspicuous effects on brain growth and development have emerged thus far in the study of atomic bomb survivors exposed prenatally in Hiroshima and Nagasaki. These are some cases of severe mental retardation and some of small head size without apparent mental retardation. Additionally, groups within the survivors have shown significantly reduced IQ scores. The severe mental retardation and the reduced IQ scores 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 IQ, thus increasing the number of those classified clinically as being severely retarded. This increase would be dose-related and, if the shift of IQ had no clear dose threshold, might, in turn, show no threshold. While this is a plausible, and perhaps likely, explanation on biological grounds, the data (see paragraph 56) do not exclude an alternative explanation in which there is a dose-dependent probability that a few individuals suffer a large shift in IQ, while, by a different process, others suffer a small shift with high probability.

51. (v) Findings related to severe mental retardation. First, 30 of the 1 599 pregnancies included in the revised clinical sample terminated in a child with severe mental retardation and, second, 18 of these, or 60%, had disproportionately small heads, that is, a head with a circumference more than two standard deviations below the mean observed among the 1 599 births.[6,69,70,71,127] Of those pregnancies that terminated in a mentally retarded child (Table 1; data on the cities separately will be found in Refs. 86, 87) no fewer than 19 (and 17 of the 21 who received exposures of 0.01 Gy or more) were exposed in the 8th through the 15th week after fertilization.[86] This is many times the expectation based on the assumption of no effect of fetal age at exposure. In this context, to reiterate, severe mental retardation implies an individual unable to form simple sentences, to solve simple problems in arithmetic, to care for himself or herself, or is (was) unmanageable or institutionalized. *There is no evidence of a radiation-related increase in mental retardation either in the interval from fertilization through the 7th week, or after the 25th week [Table 1, and Figure 7].*

52. Table 2 gives the intercepts and slopes obtained when a linear model, without threshold, is fitted to the data in Table 1 with and without the inclusion of the 0–0.01 Gy group (the "controls"), and when the controls are pooled over all prenatal ages. Within the most vulnerable age group (irradiated at the 8th through the 15th week following fertilization), the rate of increase in incidence of severe mental retardation with dose is about 0.4 Gy^{-1} with an estimated standard error of about 0.09 Gy^{-1} (see Table 2).

53. Three of the severely mentally retarded children, all in Hiroshima (estimated fetal absorbed doses: 0, 0.11, and 0.36 Gy), are known to have, or have had, Down's syndrome and a fourth, also in Hiroshima (estimated fetal absorbed dose 0.02 Gy), Japanese encephalitis in infancy. It is conceivable that, in these instances, the mental retardation was merely a part of the former syndrome or secondary to the infection, but in either event not radiation-related. Nevertheless, the main conclusions stand: virtually the same regression coefficients were obtained when these four children were excluded from the analysis.

54. (vi) Findings related to small head size. As previously stated, the small head sizes to which reference has been made were two or more standard deviations below the mean head size

Table 1. Incidence of severe mental retardation in individuals exposed prenatally to the atomic bombing of Hiroshima and Nagasaki.[a] Data for the two cities have been combined and the cases distributed by gestational age at exposure and fetal absorbed dose, based on the T65 revised dosimetry.[b] (Source of data: Radiation Effects Research Foundation TR 1-83, Table 1a)

	Dose categories (Gy)[c]				
Ages	<0.01	0.01–0.09	0.10–0.49	0.50–0.99	1.00+
All gestational ages:			Cities combined		
Subjects	1085	292	169	34	19
Retarded	9	4	4	6	7
Percent	0.8	1.4	2.4	17.6	36.8
0–7 Weeks:					
Subjects	210	55	26	2	2
Retarded	1	0	0	0	0
Percent	0.5	0.0	0.0	0.0	0.0
8–15 Weeks					
Subjects	257	69	50	13	9
Retarded	2	3	4	4	6
Percent	0.8	4.3	8.0	30.8	66.7
16–25 Weeks					
Subjects	312	86	45	15	5
Retarded	2	1	0	2	1
Percent	0.6	1.2	0.0	13.3	20.0
26+ Weeks					
Subjects	306	82	48	4	3
Retarded	4	0	0	0	0
Percent	1.3	0.0	0.0	0.0	0.0

[a] Note that the frequency distribution by gestational age in this table is slightly different from that given in the *Br. J. Radiol.* **57**, 409–14 (1984) due to differences in grouping; these differences have little effect on the risk estimates. The data for the two cities are separately presented elsewhere.[86,87]

[b] The tissue gamma dose is taken to be equal to 0.42 times the gamma kerma plus 0.077 times the neutron kerma; the tissue neutron dose is taken to be equal to 0.14 times the neutron kerma; and the total tissue dose is taken to be the sum of the two individual tissue doses.

[c] The mean doses within these dose categories over all gestational ages are 0, 0.04, 0.23, 0.72, and 1.61 Gy, respectively.

of all of the individuals in the revised study sample. About 10% of these individuals with small head sizes were also mentally retarded. Among the mentally retarded, as stated above, 18 out of 30 (60%) had small head sizes.[131,132] It should be noted that head circumference was not standardized against body size and, since mental retardation is often seen in individuals whose head circumferences are disproportionately small for their body sizes, the value just cited may be spuriously low. It is commonly thought that the development of the bones forming the vault is closely associated with the development of the brain and dura, and it is known that in fetal life these bones move with the growing brain. It is not clear, therefore, how independent this seeming abnormality may be of the severe mental retardation. However, as noted above, glial cells retain their proliferative ability and could replace lost tissue mass, as D'Amato and Hicks[33] have observed experimentally. If so, brain volume could remain the same and head size develop normally, but cortical function would be diminished.

55. Recently, Ishimaru, Nakashima and Kawamoto[52] reexamined the data on head circumferences obtained on the clinical sample when the prenatally exposed were 18 years old. They found that head size diminishes linearly, and significantly so, with estimated T65 dose. It is important to note that height also diminished with increasing dose and that the correlation of

Table 2. The relationship of mental retardation to absorbed fetal dose. (Source of data: Radiation Effects Research Foundation TR 1-83)

Gestational age	Cities combined					
	a ($\times 10^{-2}$)	s_a	b [Gy^{-1}]	s_b [Gy^{-1}]	Deviance	P
All gestational ages	0.768	0.253	0.174[a]	0.041	3.78	0.29
8–15 weeks	0.917	0.567	0.404[a]	0.078	1.11	0.77
16–25 weeks	0.601	0.415	0.101	0.059	3.25	0.36
Relationship of mental retardation to dose: "controls" excluded						
8–15 weeks	2.189	2.242	0.378[a]	0.089	0.61	0.74
16–25 weeks	0.409	1.055	0.106	0.068	3.20	0.20
Relationship of mental retardation to dose: "controls" combined over all age groups						
8–15 weeks	0.863	0.278	0.406[a]	0.077	1.11	0.77

The deviance, which is a measure of the goodness-of-fit of the model to the data, has three or two degrees of freedom depending upon whether the zero dose group is or is not included in the modeling. The P value is the probability (two tailed) of exceeding the deviance by chance under the null hypothesis. The variable a is the estimated number (intercept) of cases of mental retardation (per 100 individuals) in the zero dose group and s_a its standard error; bD is the increase in the frequency of mental retardation, with dose D, expressed in grays (100 rad) and s_b is its standard error. Note that with the binomial distribution the deviance takes the form $2[\text{Sum } z \ln(z/\hat{u}) + \text{Sum } (n-z)\ln\{(n-z)/(n-\hat{z})\}]$ where the z's are the observed values, $\hat{u}$ the estimates of the p's under the complete model, that is when the p's are all different and match the data completely, and the $\hat{z}$'s are the estimates of the p's under the fitted model.

[a] Significant at the 0.001 level.

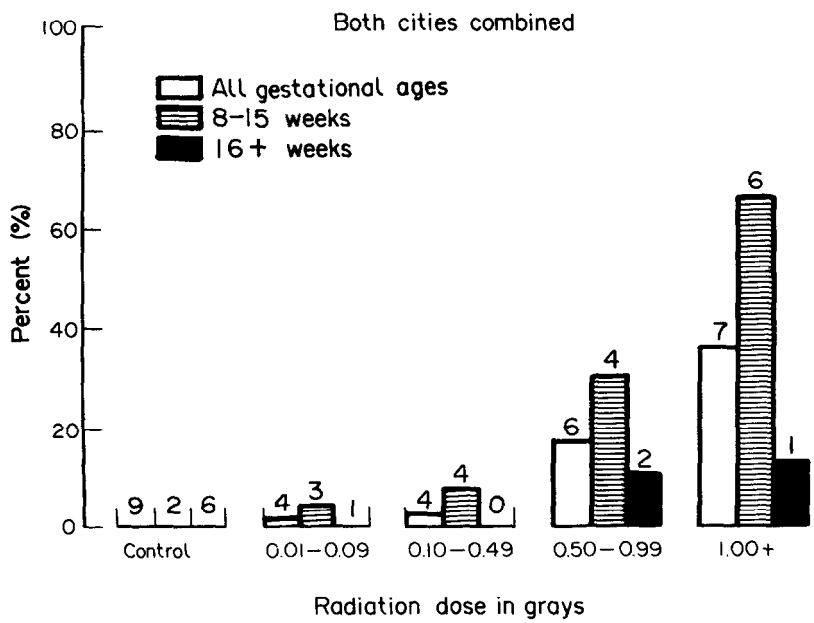

Fig. 7. The frequency of mental retardation among the *in utero* exposed in Hiroshima and Nagasaki by dose and prenatal age. Cities pooled. The numbers above the histograms are the numbers of cases observed. Mean doses for the five exposure categories are 0, 0.04, 0.23, 0.72, and 1.61 Gy, respectively. (From Otake and Schull[86])

body size with head circumference was not taken into account. Prenatal age at exposure, which was treated as a continuous variable, was not significantly related to head circumference, nor was city. They do not state how gestational age was computed, but presumably the estimates were based on the last menstrual period. No other malformations have been shown to be unequivocally increased in survivors exposed *in utero*.[69,98]

56. (vii) Findings related to intelligence tests. Schull and Otake[120] reported on an analysis of Koga intelligence test scores, (Ref. 59, 1972) obtained in 1955 on survivors exposed prenatally. These results, with some additional data, are summarized in Tables 3a and 3b. Table 3a relates to the whole data base, whereas Table 3b excludes those of the individuals tested who had also been classified clinically as severely retarded in the studies described in paragraphs 51–53. This dual presentation reflects the alternative explanations in paragraph 50. The data are also shown in Figs. 8a and 8b.

57. A number of conclusions can be drawn from these Tables and Figures:

(1) There is an apparent dose-related reduction in mean IQ for the groups irradiated in the periods 8–15 weeks and 16–25 weeks after fertilization.
(2) The effect is still apparent when the seriously retarded are excluded from the population analyzed.
(3) No such effect is apparent for the periods 0–7 weeks or from 26 weeks to birth.

Table 3a. Mean intelligence score (Koga) by fetal or embryonic age at exposure and tissue absorbed dose based upon the T65DR estimate of tissue kerma and Kerr's organ dose estimates. All individuals on whom intelligence test data are available are tabulated, including those diagnosed as severely mentally retarded clinically. See footnotes to Table 1

Dose category (Gy)		Age in weeks after fertilization				
		0–7	8–15	16–25	26-term	Total
Less than 0.01	*N*	200	229	341	433	1203
	mean	107.0	108.4	110.7	108.2	108.8
	s.d.	14.54	15.76	15.54	15.46	15.43
0.01–0.09	*N*	49	78	96	99	322
	mean	102.1	111.8	106.5	103.7	106.3
	s.d.	15.41	17.35	16.57	16.40	16.82
0.10–0.49	*N*	16	32	28	35	111
	mean	108.9	102.0	107.6	104.9	105.3
	s.d.	15.24	16.88	10.66	15.98	15.01
0.50–0.99	*N*	2	7	13	4	26
	mean	98.5	83.1	97.0	114.5	96.1
	s.d.	19.09	25.53	25.78	10.50	24.60
1.00+	*N*	2	5	2	3	12
	mean	95.0	82.6	71.5	108.0	89.2
	s.d.	42.43	16.52	16.26	8.89	21.92
All	*N*	269	351	480	574	1674
	mean	106.1	107.7	109.2	107.3	107.7
	s.d.	15.03	17.19	16.21	15.67	16.08

Significance of the differences among dose means within an age group

Weeks after fertilization	$F_{(df1,df2)}$	Signif.
0–7	$1.582_{(4,264)}$	n.s.
8–15	$9.075_{(4,346)}$	<0.001
16–25	$6.291_{(4,475)}$	<0.001
26-term	$2.094_{(4,569)}$	0.08
All	$10.155_{(4,1669)}$	<0.001

Table 3b. Mean intelligence score (Koga) by fetal or embryonic age at exposure and tissue absorbed dose based upon the T65DR estimate of tissue kerma and Kerr's organ dose estimates. All individuals on whom IQ data are available are included except those diagnosed as severely mentally retarded clinically. See footnotes to Table 1

Dose category (Gy)		Age in weeks after fertilization				
		0–7	8–15	16–25	26-term	Total
less than 0.01	*N*	200	228	341	432	1201
	mean	107.0	108.6	110.7	108.3	108.8
	s.d.	14.54	15.40	15.54	15.30	15.30
0.01–0.09	*N*	49	78	96	99	322
	mean	102.1	111.8	106.5	103.7	106.3
	s.d.	15.41	17.35	16.57	16.40	16.82
0.10–0.49	*N*	16	32	28	35	111
	mean	108.9	102.0	107.6	104.9	105.3
	s.d.	15.24	16.88	10.66	15.98	15.01
0.50–0.99	*N*	2	5	11	4	22
	mean	98.5	92.4	103.5	114.5	102.5
	s.d.	19.09	24.39	22.32	10.50	20.91
1.00+	*N*	2	4	1	3	10
	mean	95.0	87.8	83.0	108.0	94.8
	s.d.	42.43	13.67	—	8.89	19.38
All	*N*	269	347	477	573	1666
	mean	106.1	108.3	109.5	107.4	107.9
	s.d.	15.03	16.48	15.80	15.56	15.77

Significance of the difference among dose means within an age group

Weeks after fertilization	$F_{(df1,df2)}$	Signif.
0–7	$1.582_{(4,264)}$	n.s.
8–15	$4.999_{(4,342)}$	<0.001
16–25	$2.930_{(3,473)}$	0.03
26-term	$2.221_{(4,568)}$	0.06
All	$5.099_{(4,1661)}$	<0.001

Qualitatively, these findings are consistent with the interpretation that there is a dose-related shift in IQ and that this could explain the increase in clinically classified cases of severe retardation. They do not exclude the possibility of two separate effects, as indicated in paragraph 50. The statistical uncertainties in the data, and the known problems of obtaining a high consistency in intelligence testing, prevent quantitative statistical analysis of these data from refining these qualitative conclusions.

58. (viii) Other possible causes for the observed mental effects. Alternative explanations for the mental effects observed have been suggested. These include (1) genetic variation, (2) nutritional deprivation, (3) bacterial and viral infections in the course of pregnancy, and lastly (4) an increased embryonic or fetal hypoxaemia secondary to radiation damage to the haematopoietic system of the mother and (or) her developing child, since there is substantial evidence to suggest that the cerebrum and its adnexa are especially sensitive to oxygen deprivation. Assessment of the possible contribution of each of these potential confounders would be a formidable task.

59. Numerous genetic forms of severe mental retardation are known.[81] Most are recessively inherited and infrequent, but collectively they have a significant impact on the frequency of this condition. Rare, recessively inherited disorders are functionally related in occurrence to the frequency of consanguineous marriages. At the time these survivors were conceived, such

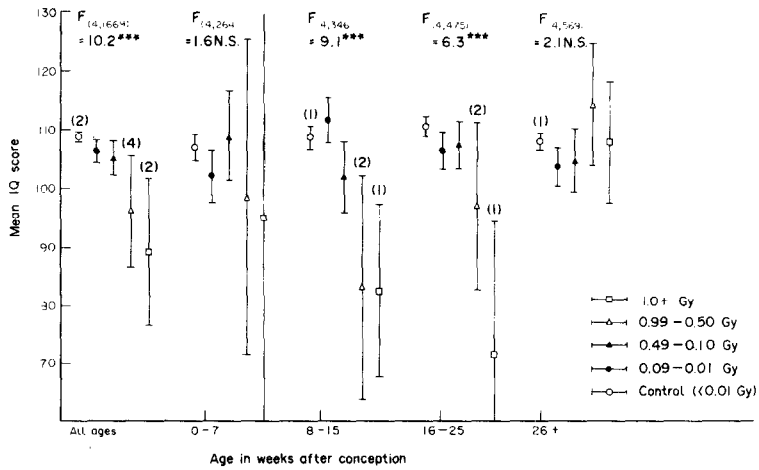

Fig. 8a. The mean scores by prenatal age at exposure with their 95% confidence intervals by gestational age groups and absorbed fetal dose categories. The numbers in parentheses refer to the number of tested, severely mentally retarded cases in each gestational age category. The 95% confidence limits have been obtained from the standard deviations in Table 3a by dividing by the square root of N and multiplying by 2. N is the number of cases in each group. F-values are reproduced from Table 3a and *** indicates significance at the <0.001 level. (After Schull and Otake, unpublished data)

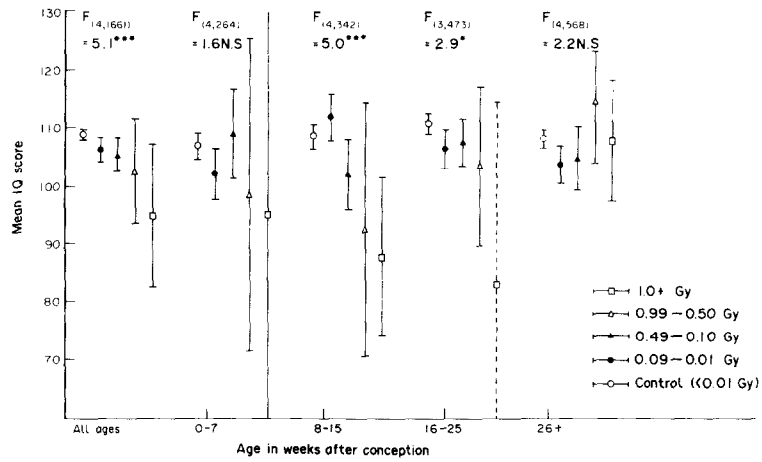

Fig. 8b. The mean scores by prenatal age at exposure with their 95% confidence intervals by gestational age groups and absorbed fetal dose categories. The severely mentally retarded cases in each gestational age category have been excluded. The 95% confidence limits have been obtained from the standard deviations in Table 3b by dividing by the square root of N and multiplying by 2. N is the number of individuals in each group. The 16–25 week, 1.0+Gy, group includes only one individual. In this case, the 95% confidence interval is calculated as twice the standard deviation for all individuals included in Table 3b. F-values are reproduced from Table 3b; *** indicates significance at the <0.001 level and * indicates significance at the <0.5 level. (After Schull and Otake, unpublished data)

marriages were common in Hiroshima and Nagasaki, but especially so in the latter.[122,123] This difference in inbreeding could, in principle, contribute some, possibly even most, of the inter-city difference, not only in the frequency of severe mental retardation but also in average intelligence test score, since this too varies with inbreeding.[123] However, it is improbable that genetic differences contribute importantly to the shape of the dose–response curve in either city or in the various post-fertilization age groups.

60. The role of maternal malnutrition on the subsequent mental performance of the child is

controversial, and evidence, epidemiological or experimental, of the possible interaction of such malnutrition with radiation damage is virtually nonexistent. Marasmic infants, underweight at birth, who die of malnutrition during the first year of life, are known to have brains that are smaller in wet and dry weight than normal, and the total RNA, total cholesterol, total phospholipids and total DNA contents are proportionally reduced; DNA synthesis is slowed, cell division curtailed and a reduced number of brain cells are seen.[114,136,137] Marasmic infants of normal birthweight tend not to show these effects. There is no report of underweight, marasmic infants among survivors exposed *in utero*.[20] The Dutch famine study,[124] too, failed to show an effect of famine in early life on human behavior, although social class distinctions were still clearly visible.

61. If the impairment seen stems largely from effects on neuronal number or migration, it seems unlikely that maternal malnutrition would restrict fetal growth as markedly in the second trimester as in the later, supposedly less protected, stages of gestation. Moreover, if, as Dobbing and Sands[27,31] observe, malnutrition interferes primarily with the growth and establishment of synaptic connections, the effects of malnutrition will be largely postnatal, since this phase of brain growth occurs predominantly after birth.

62. Other possible confounders include bacterial and viral infections, and an embryonic or fetal hypoxemia secondary to radiation damage to the hematopoietic system of the mother and (or) her developing child. Mothers whose embryos or fetuses received absorbed doses of 0.5 Gy or more received 1 Gy or more themselves, and many experienced some degree of acute radiation illness (see paragraph 35). One of the consequences of such illness is a hematopoietic depression that may persist for some time before a recovery occurs, if the individual survives. Red blood cell counts may fall to 50 or 60% of the normal value, and hemoglobin values to 6–8 g%. Whether this would have given rise to an embryonic or fetal hypoxemia is uncertain. Two lines of evidence suggest, however, that it may not. First, since the fall in red cells and hemoglobin is a gradual one, some form of cardiac or ventilatory compensation may occur. Moreover, women with sickle cell anemia, who commonly have hemoglobin values in this low range, do not have an increased frequency of severely mentally retarded children, although their reproductive performance is impaired in other respects.[99] Second, studies of the families of women with high-affinity hemoglobins have failed to show a disturbed segregation ratio.[21] This suggests that the reversal of the usual gradient in oxygen affinity between mother and fetus is not lethal in late pregnancy when beta-chain synthesis begins (the affinity mutants mostly involve the beta-chain). It can be argued too that even if a hypoxemia occurred, it would have been only at the higher maternal exposures, and should, therefore, contribute to a nonlinear dose–response relationship. Any hypoxemia resulting from direct damage to the fetus would be inextricably confounded with a possible maternal effect and should enhance the likelihood of a nonlinear dose–response relationship.

63. (ix) Other possible data to be extracted from the Japanese experience. Over the years, studies of the survivors exposed *in utero* to the atomic bombing of Hiroshima and Nagasaki have focused on two separate end points, namely severe mental retardation and small head size. This preoccupation has resulted in a dichotomization of processes which must certainly be continuous and a failure to look at these in their entirety. Moreover, virtually all, if not all, prior efforts to assess central nervous system damage in the survivors exposed *in utero* have involved either cross-sectional analysis or the cumulative frequency of occurrence of a particular end point. However, the manifestations of central nervous system impairment may include, for example, reduction in the rapidity of learning as well as an absolute decrement in ultimate performance.

64. There are data, substantial in number and variety, which bear on these issues and have not

been analyzed comprehensively heretofore. They include information on convulsions, on photophobia, diplopia and other aberrations of vision, on the achievement of developmental landmarks such as the age when the child sat, talked and walked, on school attendance and performance, on neuromuscular skill (grip and repetitive action tests) and the like. It is important that these data be examined as expeditiously as practicable.

(b) *Exposure in utero: Other human data*

65. Numerous studies, ostensibly aimed at an understanding of the possible role of ionizing radiation in the origin of central nervous system abnormalities have been published,[36,68] but few, aside from the Japanese experience, provide a reliable basis for risk estimation. Generally, there is little information on the exposures, or on the ages after fertilization at the time of exposure. However, Granroth,[37] in Finland, has examined the association of diagnostic x-ray examinations with the occurrence of defects of the central nervous system. The data, drawn from the Finnish Registry of Congenital Malformations, reveal a significant increase in central nervous system abnormalities, primarily anencephaly, hydrocephaly and microcephaly, among newborn infants exposed *in utero*, 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 clinical suspicion of either maternal pelvic or fetal anomaly and, therefore, the exposures were unlikely to have occurred at a time when dysraphic abnormalities, such as anencephaly, are induced.[79] Accordingly, it seems unlikely that the results reflect a teratogenic effect of radiation.

66. Neumeister[82] has described the findings on 19 children exposed *in utero* to doses between 0.015 and 0.1 Gy. No instances of severe mental retardation are recorded, but developmental age at the time of exposure was not taken into consideration. Meyer and colleagues[72] failed to find evidence of an increased frequency of severe mental retardation among 1 458 women who were exposed to small doses of radiation *in utero* as a result of diagnostic pelvic examinations of their mothers. It seems uncertain, however, whether their case-finding mechanism would have identified women who were severely mentally retarded, and, of course, the increased probability of premature death among such individuals would lead to underrepresentation of the 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 Oppenheim *et al.*[88] and Nokkentved,[83] are similarly inappropriate for the estimation of radiation effects.

(c) *Exposure of the infantile and juvenile brain*

67. Because maturation of the brain in the human species continues beyond birth, some notion of the possible effects on the central nervous system of prenatal exposures to ionizing radiation, especially in the later weeks of gestation, may be gained from data on exposures of the infantile and juvenile brain. It is clear that ionizing radiation used therapeutically in the treatment of brain tumors or acute leukemia can have deleterious effects, as measured by conventional intelligence testing, at these ages (e.g. Refs. 34, 48, 78, 107, 119). Meadows and her colleagues[78] stated that, "Significant reductions were found in overall IQ score for the majority of children, younger patients being most affected". The exposures involved in these instances are high, tens of Gy, and most, possibly all, of the individuals involved were also receiving chemotherapy.

68. X-ray induced epilation was extensively used between 1910 and 1959 for treatment of tinea capitis; indeed, it has been estimated that more than 200 000 children worldwide received this form of treatment. Albert and his colleagues,[1] in their study of one such group of patients, reported an increased number of cases of mental illness, including psychosis, personality

disorders and psychoneurosis, among 1 908 individuals with tinea capitis treated by x rays, as contrasted with 1 801 with tinea capitis treated by other means. It has been estimated that, in the Adamson–Kienbock treatment regimen used in these instances, the brain received 1.5–1.75 Gy at its surface, decreasing to 0.7 Gy at the base. More recently, Omran and his associates[97] described the results of psychiatric and psychometric evaluations of 109 of these cases treated by x-ray therapy and 68 treated chemotherapeutically. They found more patients with deviant Minnesota Multiphasic Personality Inventory (MMPI) scores among those who had been irradiated than in those chemotherapeutically treated, and the former were judged more maladjusted by their MMPI profiles. Hence, there is evidence that exposure to ionizing radiation can modify personality traits, but interpretation of these data is difficult since x-ray and chemotherapeutic treatments differ in aspects other than radiation exposure, and because a variety of emotional disturbances are associated with protracted hospitalization of the young. However, Ron and her coworkers (Ref. 108; see also Refs. 1, 97, 121) have reported a similar finding among individuals treated for tinea capitis who were not on adjuvant therapy nor hospitalized and received similar radiation doses, possibly 1.3 Gy, on the average. They have stated that, "The irradiated children had lower examination scores on scholastic aptitude, intelligence quotient (IQ) and psychologic tests, completed fewer school grades, and had an increased risk for mental hospital admissions for certain disease categories". No estimate was apparently made of the diminution in intelligence test score per unit exposure.

B. Effects of Dose Fractionation

69. Little appears to be known about the effects on the developing embryo and fetus of chronic or fractionated exposures to ionizing radiation. Given the complexity of brain development and the differing durations of specific developmental phenomena, it is reasonable, however, to assume that dose fractionation will have some effect. The hippocampus, which is involved in memory, and the cerebellum continue to have limited neuronal multiplication, and migration does occur in both organs. Changes continue in the hippocampus and cerebellum into the first and second years of life. Continuing events such as these may show dose-rate effects differing from those associated with the multiplication of the cells of the ventricular and subventricular areas of the cerebrum, or the migration of neurons to the cerebral cortex.

70. Most of the information that is presently available on the effects of dose rate involves the experimental exposure of rodents, and must be interpreted with due regard to the differences between species in developmental timing and rates relative to birth. Brizzee and Brannon (Ref. 7, see also Ref. 56), for example, have examined cell recovery in the fetal brain of rats. Timed-pregnancy rats were exposed on gestation day 13 to single doses of cobalt-60 radiation, ranging from 0.25 to 2 Gy in increments of 0.25 Gy, and to split doses of 1 Gy followed 9 hours later by a second dose of 0.25 to 1.5 Gy, again in increments of 0.25 Gy. The pregnant animals were killed 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. These authors observed that, "The presence of a threshold (shoulder) zone on the dose–response curve in the split-dose animals suggests that cell recovery occurred in some degree in the interval between the two exposures".

71. Some insight into the nature of the developmental effects to be anticipated from chronic exposure to ionizing radiation may come from behavioral toxicology and the exposure of embryos and fetuses to environmental pollutants, notably the heavy metals.[133–135] Fetal methylmercury poisoning, for example, has been seen in Japan and Iraq, to mention but two

sites. In Minamata (Japan), where the bay and its marine life were contaminated by methylmercury, 23 of 359 children born between 1955 and 1959 showed symptoms of cerebral palsy, a proportion 10 to 60 times higher than normally expected. The pattern of brain damage is different in individuals exposed *in utero* to that seen in adult exposures. Tissue destruction tends to be more uniform. Fetal exposure reduced brain weight in severely poisoned children to one-half or less of normal, and abnormal cells could be seen distributed throughout the brain. Severe, permanent central nervous system damage leading to behavioral and other neurological disorders was also seen in Iraq, where methylmercury-contaminated grain, intended to be planted, was used as food. These incapacitating consequences were often observed in children of mothers whose most common symptom of methylmercury poisoning during pregnancy was a mild, transient paresthesia. Such observations suggest that the embryo and fetus are much more sensitive to methylmercury than the mother, but it should also be noted that methylmercury accumulates to higher concentrations in the blood and tissues of the embryo and fetus than in those of the mother.[53,140]

72. The fetal alcohol syndrome offers another possible paradigm. Central nervous system abnormalities, particularly mental retardation and small head size, are also the most pronounced effects of heavy intrauterine exposure to alcohol.[125] The average IQ of individuals with fetal alcohol syndrome is about 65, although scores may vary from 16 to 105;[126] also, the severity of the mental retardation correlates with the severity of the dysmorphic features in the individual. Clarren and his colleagues (Ref. 22; see also Ref. 49) have noted that areas of ectopic gray matter in the frontal and temporal white regions of the cerebral hemispheres and leptomeningeal neuroglial heterotopias, both evidences of abnormal cell migration, are common findings among infants with fetal alcohol syndrome. This appears true not only among those infants born to the chronic alcoholic mother, but also among those born to women who describe themselves as infrequent drinkers who have occasional episodes of intensive drinking. The minimum amount of alcohol necessary to produce a harmful effect on the fetal central nervous system is unknown; indeed, neither the exact risks of steady drinking at any level nor those of binge drinking are known.[23] To date, however, adverse effects have not been reported at less than two drinks in a day (generally taken to be the equivalent of less than 30 ml of absolute alcohol).

73. It is generally assumed that the teratogenic effect of alcohol, insofar as central nervous system abnormalities are concerned, is initiated during the first trimester, but this follows more from *post hoc ergo propter hoc* reasoning than from observation. Given the commonly chronic nature of the exposure, it is not surprising that the sensitive period is imperfectly known. Renwick and Asker,[115] using an argument based upon the seasonality in prevalence of fetal alcohol syndrome on the one hand, and ethanol use on the other, suggested that the damage may be as late as the 18th to the 20th prenatal week of age. Since they apparently measure gestation from the last menstrual period (Ref. 115, see p. 102), this corresponds to the 16th to the 18th week after fertilization and suggests that the vulnerable periods for alcohol use and exposure to ionizing radiation may be similar. It should be noted, however, that leptomeningeal heterotopias of the kind observed in fetal alcohol syndrome have not been reported in either humans or other primates exposed to ionizing radiation, although heterotopic gray areas have been seen, as previously described. These leptomeningeal heterotopias are continuous with the molecular layer of the cortex and are thought to be persistences of its subpial granular layer.[15] If so, they arise somewhat later, probably after the 24th week.[15,145] The aberration in migration that occurs appears less a failure of the neurons to move from the periventricular proliferative areas than an inability to recognize when to stop; the cells commonly migrate beyond their normal sites of final differentiation.

V. PERIODS OF MAXIMUM SENSITIVITY

74. The period of maximum sensitivity or vulnerability is understood as that period in development during which defined teratological effects are most likely to be produced. This does not imply that some malformations can be produced only at certain times, but rather that a given dose is more effective at some stages[129] and that the duration of the period of effectiveness may be broadened by increasing the dose. The causal relationship between irradiation of the embryo and fetus at specific stages of gestation and the nature of the subsequent organ damage are well established in a number of experimental animals. In the human, the evidence is less direct and rests partly on observations from Hiroshima and Nagasaki, partly on observations on children following the therapeutic use of radium or x rays, and partly on comparative embryological considerations. On the basis of the data presently available, only a limited and tentative temporal pattern of radiation injury involving the brain can be deduced. Table 4 sets forth the weeks following fertilization at which major developmental features of the brain evolve, and the possible damage that could ensue if the normal pattern of orderly differentiation and development did not occur (see also Refs. 8, 28, 145).

Table 4. A tentative temporal pattern of radiation injury to the brain

Postovulatory weeks	Developmental features	Possible damage
3–4	Formation of neural tube	Dysraphic abnormalities
4–10	Formation and fusion of cerebellar plates	Cerebellar agenesis or hypoplasia
3–12	Early multiplication of cells in ventricular zone	Small head size
6–16	Neuronal migration	Heterotopic gray matter
8–15	Cortical histogenesis	Mental retardation
24–33	Thalamocortical innervation	Abnormal cortical differentiation
24–38	Involution of subpial granular layer	Marginal heterotopias

VI. RISK ESTIMATES IN HUMANS

A. General Remarks

75. Quantitative risk estimates for radiation damage to the brain after prenatal exposure of human beings are of importance for their practical implications to radiological protection. However, the human data on which to base such estimates are limited and imperfect. Two types of observations are available, namely (1) the frequency of severe mental retardation recognized clinically, and (2) the diminution of intelligence as measured by conventional intelligence tests. Each has its own limitations. Although cognizant of these and other difficulties inherent in the interpretation of the available information, until such time as more direct measures of brain damage, such as cell death or impaired cell migration, are available, these observations are the only ones on which risk estimates can be based. Anecdotal clinical evidence is of little assistance and experimental data on infrahuman species are compromised for reasons adduced elsewhere in this report. The latter data, though important qualitatively, provide an uncertain basis for quantitative estimates of prenatal risks in the human.

76. One of the most important problems in estimation of the risk to the developing brain of exposure to ionizing radiation is the shape of the dose–response relationship. As stated, many of

the data that have helped to identify the teratogenic effects of radiation have limited applicability, for the doses are either too poorly known or too invariant to permit discrimination between different plausible models. The information on the atomic bomb survivors represents one of a very few sets of data that may be relevant. But even here, the multiplicity of ways in which irradiation could affect the normal development of the brain and culminate in mental impairment makes it hard to assess the reasonableness of an observed dose–response relationship. This seems likely to remain true until the different causes of an intellectual deficit of an organic nature can be distinguished one from another.

77. Paragraph 116 of *ICRP Publication 26*[54] recommends that the conditions of occupational exposure of women diagnosed to be pregnant should be limited to those in which it is most unlikely that annual exposures would exceed 3/10 of the dose-equivalent limits (Working Condition B). As discussed in the Commission's statement from its 1983, Washington, meeting,[55] the methods of protecting pregnant women at work should provide a standard of protection for the fetus broadly comparable with that provided by protection of members of the general public. If under Working Condition B, as would be expected, substantial irregularities in the dose rate do not occur, the dose received by the fetus over the critical 2 months (from 8–15 weeks post fertilization) would not be expected to exceed about 1 mSv. The Commission has recommended[55] that specific operational arrangements should be made to avoid irregularities in the rate at which the dose could be received and to keep the dose to the fetus as low as reasonably achievable. In the paragraphs that follow, estimates of risk are discussed in the context of these recommendations.

B. Cerebrum

78. Recent reevaluation of the Japanese atomic bomb survivor data has provided a new perspective on the periods of sensitivity of the developing brain to radiation-related damage, and the possible nature of the dose–response relationship. These findings have been described in some detail in paragraphs 50–55; briefly, and as they specifically concern risk estimation, they are as follows.

79. The period of maximum vulnerability to radiation appears to be the time from approximately the beginning of the 8th through the 15th week after fertilization, that is, within the interval when the greatest proliferation of neurons and their migration to the cerebral cortex occur. A period of lesser vulnerability occurs in the succeeding period, from the 16th through the 25th week after fertilization. The latter accounts for about a fourth of the apparently radiation-related cases of severe mental retardation. The least vulnerable period is the initial 7 weeks after fertilization, during which no radiation-related cases of severe mental retardation occur. Within the period of maximum vulnerability, the simplest statistical model consistent with the data appears to be a linear one without threshold. The slope of this relationship, based on the supposition that the occurrence of mental retardation is binomially distributed, as estimated by the maximum likelihood method using the Generalized Linear Interactive Modeling (GLIM) statistical package, corresponds to an increase in frequency of severe mental retardation of $0.40\ Gy^{-1}$ (CI: 0.25–0.55). Thus, the frequency of severe mental retardation rises from about one case per hundred individuals exposed to less than 0.01 Gy to approximately 40 cases per hundred at an exposure of 1 Gy. Uncertainties in assigning some exposures to a defined stage of pregnancy have been found to have little effect on this risk estimate.[87]

80. To determine whether a threshold is consistent with these data, and to estimate its value, the data in Table 1 with respect to the events in the 8th through the 15th weeks after fertilization have been analyzed with the 0–0.01 Gy group excluded. The results are shown in Table 2. The

slope does not change appreciably with the exclusion of this group, which suggests that the data are internally consistent. It is possible to compute the largest threshold that would be consonant with the observations; this is taken to be that one which would not make the residual chi-square (a measure of the unexplained variation) improbably large at the 5% level. The value that emerges is 0.10 Gy; thus, these data cannot exclude a threshold lying between 0 and 0.10 Gy. For the second period of vulnerability, the dose–response relationship appears curvilinear, and threshold values below approximately 0.5 Gy cannot be excluded.

81. The data on intelligence tests suggest the same two gestational periods of vulnerability to radiation, the first period showing the greater sensitivity. However, the form of the dose–response relationship has not been well established by the data available so far.

82. Intelligence has been variously described as the ability to manage oneself and one's affairs prudently; to combine the elements of experience; to reason, compare, comprehend, use numerical concepts and combine objects into meaningful wholes; to have the faculty to organize subject-matter experience into new patterns; or to have the aggregate capacity to act purposefully, think rationally and deal effectively with one's environment. Given such differences in definition, it is natural that the bases of measurement should vary. Intelligence tests differ one from another 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 type of test used; generally, however, individuals scoring high on one type of test tend to obtain high scores on other tests. Most intelligence tests are so structured that the distribution of test results follows an approximately normal curve, with some 95% of the population falling within two standard deviations of the mean. Individuals whose scores lie, consistently, two standard deviations or more below the mean would commonly be described as retarded; more specifically, within the United States, individuals with scores below 25 are said to be profoundly retarded; those in the 25–39 range, severely retarded; those with scores of 40–54, moderately retarded; and those between 55–69, mildly retarded. This classification is similar to that proposed by the World Health Organization. In the Japanese experience, the highest IQ achieved by any of the severely mentally retarded children on the Koga test was 68.

83. Under the operational arrangements recommended by the Commission (see paragraph 77) the dose received by the fetus over the most critical 2 month period (8–15 weeks after fertilization) would be expected not to exceed about 1 mSv. Assuming a linear dose–response relationship without threshold, the corresponding risk to the fetus is estimated not to exceed 4×10^{-4} (Table 2). Furthermore, the data cannot exclude a threshold lying between 0 and 100 mGy of low-LET radiation. If such a threshold does exist, and exceeds 1 mGy, there would be no risk to the fetus under the operational arrangements referred to above. Exposure in these conditions during weeks 16 to 25 post fertilization might add a risk not exceeding about 1×10^{-4}, if no threshold exists for this period (but see paragraph 80), yielding a total risk not exceeding about 5×10^{-4} from exposure throughout pregnancy, since no retardation appears to be induced by exposures before 8 or after 25 weeks after fertilization. In the absence of radiation exposure, the risk of severe mental retardation at Hiroshima and Nagasaki was 8×10^{-3} (Table 2).

C. Cerebellum

84. At present, there is no evidence of radiation-related cerebellar damage without concomitant damage to the cerebrum in the survivors of the atomic bombing of Hiroshima and Nagasaki exposed prenatally. It may be difficult to identify such damage for several reasons. First, Purkinje cells, the only efferent neurons in the cerebellum, are proliferating and migrating

in the same developmental period as the neuronal cells that will populate the cerebral cortex, and thus damage to precursors or differentiated Purkinje cells would occur at the same time and may be inseparable from damage to those cells that will give rise to the cerebral cortex. Second, the granular neurons, the most numerous nerve cells in the cerebellum, retain their proliferative abilities after birth and could, in theory, repopulate areas of the developing cerebellum damaged by radiation. To the extent that this occurs, granular cell damage might be mitigated. Estimates of the risk of damage to the cerebellum following prenatal exposure, based on fixed or progressive neurological deficit, are presently not possible.

D. Mid-Brain and Brain Stem

85. Overt damage to these parts of the central nervous system has not been reported. Estimates of the risk of damage to the mid-brain or brain stem following prenatal exposure are, therefore, presently impossible.

E. Uncertainties

86. Numerous uncertainties are associated with these estimates of risk. These include the limited nature of the data, the appropriateness of the comparison group, errors in the estimation of the tissue absorbed doses and the prenatal ages at exposure, correlative neuroanatomy, the spectrum of severity of mental retardation, the subjective nature of intelligence testing, and other confounding factors in the post-bomb period, including nutrition and disease.

87. *The limited data and the appropriateness of the comparison group.* Only 21 of the 30 severely mentally retarded individuals in the revised clinical sample received fetal absorbed 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). As earlier noted, their exclusion does not alter the slope of the dose–response relationship materially; however, with their removal, there are only 18 cases without known cause for the retardation other than exposure to ionizing radiation.

88. As to the comparison group, the atomic bombings resulted in exceptional circumstances that could have altered the normal frequency of severe mental retardation or have interacted with exposure nonadditively. However, exclusion of the comparison population does not appreciably alter the regression coefficient.

89. *Errors in the estimation of fetal absorbed dose.* All estimates of doses to individuals in the Japanese cohort are subject to at least three sources of error, namely those that stem from (a) the air dose curves themselves, (b) the attenuation factors for tissues, materials, positions, and the like, and (c) the assertions as to the locations of the survivors. Some of these, notably the assertions of the locations of the survivors, can never be evaluated rigorously for all of the individuals concerned. Errors of this nature can affect inferences on the overall shape of the dose–response relationship as well as parameter values defining that shape. It should also be noted that the fetal absorbed doses used here are, in fact, estimates of the doses to the uterus, and must be somewhat higher than those to the developing embryo or fetus. This discrepancy will undoubtedly vary with the size of the latter. Most of the factors indicated above are likely to be altered when the dosimetry revisions are complete. Therefore, it must be emphasized that present estimates of risk based on the T65 dosimetry should be considered tentative. However, these changes should not affect the periods of maximum sensitivity, since the timing of vulnerable events in development is independent of estimates of dose.

90. *Errors in the estimation of 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. Postovulatory age is usually estimated from the onset of the last menstrual period, and adjustment is then made for the difference between that date and the probable date of fertilization (usually taken to be 2 weeks later). Women with irregular menstrual cycles or who miss a menstrual period for any of several reasons, notably lactational amenorrhea, illness or malnutrition, could erroneously identify the onset of their last cycle. Japanese women nursed their infants longer during that period than presently prevails, so lactational amenorrhea may have been more common. Some were undernourished, due to the economic stringencies that obtained during and following the war, and infectious diseases were more frequent in the surviving populations.

91. Another possible source of error stems from racial and inter-individual variability in the prenatal age at which specific developmental events occur. 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.

92. *The spectrum of severity of mental retardation.* Clinical diagnoses of severe mental retardation are subjective, and although pediatricians, neurologists and clinical psychologists would agree if the retardation is sufficiently severe, less agreement would occur for the less severely affected. Moreover, aspects of behavior, other than apparent intelligence, influence the diagnosis, such as hyperactivity or self-destructive tendencies. The Japanese survivors were examined repeatedly, and usually by different physicians. The clinical records reveal an agreement of clinical opinion; however, the examining physician's assessment could have been influenced by the findings and statements of another physician at a prior examination. Examinations were, however, done without prior knowledge of the individual's exposure, and therefore, presumably this error would be randomly distributed with respect to dose and prenatal age.

93. *The subjective nature of intelligence testing.* Intelligence tests are not free of cultural factors, and thus extrapolations over time, social status or geography are uncertain. Repeated tests of the intelligence of the same individual will differ and, therefore, have limitations as descriptors of individual ability.

VII. RESEARCH NEEDS

94. There are substantial limitations on the information that is presently available to interpret observations such as those that stem from the Hiroshima and Nagasaki experiences. In view of the outstanding importance of radiation-related mental changes, these limitations must be redressed by further research. First, there is a need to identify reliably, in the human, the ages after fertilization at which environmental insults, chemical or physical, are effective.[30,74] Second, there is a need for substantially more detailed quantitative information on the normal development of the human brain at all levels, from the morphological to the molecular, including quantitative studies of neuronal and neuroglial proliferation, development of synaptic complexity and dendritization, and myelination. Such studies are essential to understanding teratologic effects of chemical, physical or pharmacologic agents. Little is known, for example, about the inter-individual variability in developmental stages at fixed times after fertilization for phases in embryonic and fetal development, or about ethnic variability in the age at achievement of specific embryonic or fetal landmarks.[85] Although the rudiments of the embryonic nervous system can be identified some 18 days after fertilization, and much is now known about its development in the first 8 weeks of embryonic life, truly detailed information is

still lacking. At 5 weeks after fertilization, no fewer than 100 morphologically separate features of the brain can be identified, but the subsequent changes in each of these as development progresses have not been studied.[95,96] For the period 8–15 weeks post-fertilization, when maximum sensitivity to the induction of radiation-related mental retardation apparently occurs, even less has been documented morphologically or quantitatively. Given the difficulty of obtaining embryonic and fetal material at these ages, existing embryological collections warrant greater utilization. Third, further research into the anatomic, biochemical, metabolic, and pathologic bases of mental retardation is patently needed to differentiate among mechanisms. Much must be learned about the embryonic and fetal development of normal neurochemical and metabolic activity, such as the elaboration and metabolism of neurotransmitters and the evolution of surface membrane activity. Fourth, there is a need for improved noninvasive objective tests of cortical function that could provide evidence indicative of the loss or impairment of specific groups of cells in the proliferative zones. Such tests will help to detect teratogen-related damage more subtle and regionally specific than that which culminates in severe mental retardation or diminished performance on intelligence tests. It should be noted, however, that such tests, even though physically noninvasive, could be psychologically invasive so that the greatest care must be given to their conduct. Fifth, it is clear that dose–response relationships that evolve from the limited epidemiological data presently available must ultimately be confirmed experimentally in animals. Special value in this field relates to information available from primates. Sixth, and finally, certain radiobiological variables warrant fuller study. Information from nonhuman primates would be particularly valuable. However, it is unlikely that much information would come from limited studies of either low dose-rates or fractionated exposures, since the sample sizes needed would be extremely large. Understanding will, therefore, depend mainly upon a better knowledge of the biological processes involved. Studies on small animals could contribute importantly here, particularly as to the relative sensitivities of the stages and components involved in radiation-related damage to the central nervous system.

GLOSSARY

In this document the definitions of the Boulder Committee[10] have been adopted. Prior to this effort at standardization and revision, based on the application of newer techniques of study, the idiosyncratic use of terms like neuroblast, spongioblast, matrix cell, mantle layer and the like made synthesis of different embryological and neuroembryological studies difficult. Some investigators, for example, have used the expression postmitotic neurons but others contend that all neurons are postmitotic, that is to say, a neural cell does not become a neuron until it has lost its mitotic potential. Neurons can, of course, be morphologically immature or mature.

Marked structural differences exist in the wall of the cerebral hemispheres. To describe these architectonic differences, terms such as cortex and mantle are used. Thus, the outer later of gray matter of the brain is described as the mantle; whereas the word cortex is applied to gray matter structured in accordance with certain principles; it must be multilayered, the layers themselves must be organized columnarly, and finally, there should be tangential as well as radial connections.[75] Prominent among the cortical areas are the archicortex, isocortex (neocortex) and the paleocortex.

Amblyopia: a dimness of vision; the partial loss of sight.

Archicortex: a ring of gray matter around the choroid fissure on the medial side of the brain. It is

the first part of the cerebral cortex to differentiate. Initially it is a region localized in the medial wall between the choroid plexus and the sulcus of the corpus callosum. As the hemisphere grows, it migrates through the medial wall to the inferior horn of the lateral ventricle. Phylogenetically, it is the oldest part of the cortex.

Cell adhesion molecules: adhesion among cells of vertebrate tissues plays a central role during development, and adhesive interactions between nerve cells and their neurites are believed to be an important factor in the assembly of nervous tissue and the interconnections of different parts of the nervous system. Two different types of cell–cell adhesion have been identified, one calcium-dependent and the other not. Calcium-independent cell–cell adhesion in nervous tissue appears to be mediated by a glycoprotein, termed the neural cell adhesion molecule (N-CAM), distinguished by an unusually large amount of sialic acid. It seems to be an integral part of the cell membrane, and the purified protein has a molecular weight between 200 000 and 250 000 daltons on sodium dodecyl sulfate polyacrylamide gel electrophoresis. It is fractionable, and at least one 65 000 dalton polypeptide manifests most, if not all, of the antigenic determinants of intact N-CAM. The limited quantities of this protein normally present in tissue has made its complete chemical characterization difficult, and, as yet, it has not been sequenced.

Cingulum: a well-marked band of associated fibers in the medial portion of each cerebral hemisphere, passing from near the region of the anterior perforated substance backward over the upper surface of the corpus callosum in the medullary substance of the collosal gyrus.

Commissure: a bundle of fibers that connects symmetric parts of the brain across the midline; they ensure the integration of the two hemispheres as a functional unit.

Corpus callosum: the principal commissure of the cerebral cortex; it connects the nonolfactory areas of the left cortex with those of the right. It is through the fibers of this commissure that one hemisphere gains access to the information unilaterally represented in the cortex of the other.

Cortical plate: concentrations of neurons beneath the marginal layer, appearing between 7 and 8 postovulatory weeks and being the precursor of the six-layered cerebral cortex.

Dysraphic: pertaining to incomplete closure of the neural tube.

Embryo: the human organism in its early stages of development; that is, from fertilization until approximately 8 weeks.

Fetus: the human organism from 8 weeks of life to the time of birth.

Geniculate bodies: an eminence produced by the underlying lateral geniculate nucleus, a group of nerve cell bodies; it is related to the central visual pathway.

Gyrus: the gyri are prominent rounded elevations, or convolutions, on the surface of the cerebral hemispheres.

Insula: a triangular area of the cerebral cortex which forms the floor of the lateral cerebral fossa, which is, in turn, a depression on the floor of the cranial cavity.

Intermediate zone: this zone is the third to form; its early cellular occupants are immature neurons that are destined never to divide again and have migrated to it from the ventricular zone. In the cerebrum, cells migrate through this intermediate layer to form a cortical plate at the junction of the intermediate and marginal zones.

Isocortex: the laminated, phylogenetically younger part of the cerebral cortex which reaches its highest development in the human.

Lamina dissecans: a cell-sparse layer between the Purkinje and inner granular layers of the cerebellum seen at the five-layer stage; it has been recognized only in primates (and possibly in the blue whale). The lamina dissecans appears at about the 20th week of development and disappears some 12 weeks later. Its function is not known.

Lissencephaly: lack of convolutional pattern in the cerebral cortex due to a defect in development.

Macrosmatic: having the sense of smell strongly or acutely developed.

Marginal zone: this zone is recognizable soon after the formation of the ventricular one; it is a cell-sparse layer composed of the outermost cytoplasmic parts of the ventricular cells. It contains no primary cell type of its own and the nuclei of the ventricular cells do not enter it.

Mental retardation: in the context of this document, severe mental retardation implies an individual who is unable to perform simple calculations, to make simple conversation, to care for himself or herself, or was or is institutionalized. Such individuals are generally found to have an intelligence test score which is less than 70 on conventional tests.

Mesencephalon: the slightly narrowed midportion of the developing brain that coincides with the curvature known as the cephalic flexure.

Neocortex: that portion of the gray matter covering the cerebral hemispheres showing stratification and organization characteristic of the most highly evolved type.

Neuroglia: a highly branched cell that makes up the supportive structure of nervous tissue.

Neuron: the nerve cell with its processes, collaterals and terminations; it is regarded as the structural unit of the nervous system. Under normal circumstances, the neuron is a nonproliferating cell.

Pachygyria: unusually thick convolutions of the cerebral cortex, related to defective development.

Paleocortex: the ventrolateral area of the cerebral cortex. Phylogenetically this is the oldest portion of the cerebral cortex, and consequently differs most from the isocortex. It lies in the area adjacent to the corpus striatum and includes the primary olfactory cortex.

Pia (or pial surface): the delicate fibrous membrane closely enveloping the brain and spinal cord.

Polymicrogyria: the presence of numerous abnormally narrow cerebral convolutions.

Prosencephalon: the forebrain, i.e. the part of the brain that develops rostral to the cephalic flexure. It comprises the diencephalon (interbrain) and the telencephalon (endbrain), and the latter gives rise to the right and left cerebral vesicles, i.e. the future cerebral hemispheres.

Purkinje cell: a large neuron of the cerebellar cortex situated on the boundary between the molecular and granular layers of the cerebellum with an extensive dendritic tree; it derives its name from Johannes Purkyně, a Bohemian anatomist and physiologist, who is credited with the first description of this layer of the cerebellum. These cells are the sole output channels of the cerebellar cortex, and excitatory and inhibitory impulses converge on them from many sources.

Rhinencephalon: the olfactory bulb and all other areas of the brain where efferent fibers from the bulb synapse; commonly taken to include the bulb, the anterior olfactory nucleus, the olfactory trigone, the anterior perforated substance, the olfactory tubercle, the lateral olfactory stria, Broca's diagonal band, and the cortical areas of the temporal lobe of the cerebrum.

Rhombencephalon: the hindbrain, i.e. the part of the brain that develops caudal to the cephalic flexure. It includes the pons and medulla oblongata; it gives rise to the cerebellum, and is continuous with the spinal cord.

Rostral: relating to any anatomical structure resembling a beak.

Subventricular zone: the subventricular zone is located at the junction of the ventricular and intermediate zones; its cellular occupants are small and round or oval and are distinguishable from the cells of the intermediate zone by their proliferative activity. The subventricular cells are unlike the ventricular ones in that they remain stable in position without the to-and-from nuclear displacement during the mitotic cycle that characterizes the ventricular cell. This zone gives rise to special classes of neurons and to all macroglial cells, with the possible exception of the ependymal cells. Subventricular cells fall into two classes based on size and morphology; both classes proliferate.

Sulcus: one of the grooves, or furrows, on the surface of the brain.

Superior colliculus: the more cephalic of the two pairs of rounded eminences in the roof of the mesencephalon, the midbrain. It is primarily concerned with visual reflexes.

Telencephalon: the endbrain, i.e. the terminal part of the prosencephalon. It gives rise to the right and left cerebral vesicles, i.e. the future cerebral hemispheres.

Thalamus: a large ovoid mass of gray substance, with a flattened inner or medial surface, which serves as a relay station for sensory stimuli to the cerebral cortex; it also has important integrative and nonspecific functions.

T65 dosimetry: a system of gamma ray and neutron exposures assigned to each individual survivor of the atomic bombing of Hiroshima and Nagasaki based upon the stated distance from the hypocenter and shielding (see Refs. 4, 77 for a fuller explanation).

Ventricular zone: the ventricular zone contains only ventricular cells; the latter are simply mitotic and intermitotic forms of a single pseudostratified columnar epithelial cell. The ventricular cells are the ultimate progenitors of all neurons and macroglial cells of the central nervous system, and the zone itself becomes attenuated and eventually disappears as its cells become transformed.

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