SOURCES AND EFFECTS OF IONIZING RADIATION

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NOTE

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ANNEX H

Radiation effects on the developing human brain

CONTENTS

INTRODUCTION

1. The developing human brain has been shown to be especially sensitive to ionizing radiation. Mental retardation has been observed in the survivors of the atomic bombings in Japan exposed *in utero* during sensitive periods [M2, M3, O1, P1, T1, W1, W2], and clinical studies of pelvically irradiated pregnant women have demonstrated damaging effects on the fetus [G1, I1, M1, Z4]. The sensitivity of the brain undoubtedly reflects its structural complexity, its long developmental (and hence sensitive) period, the vulnerability of the undifferentiated neural cells, the need for cell migration to functional position and the inability of the brain to replace most lost neurons.

2. Previous UNSCEAR reports have considered the general developmental effects of prenatal irradiation. In the UNSCEAR 1977 Report [U4], mainly animal data were considered. In the UNSCEAR 1986 Report [U2], more recent animal data and, to the extent possible, data on effects in humans were considered in order to derive risk estimates. The risks of effects, including mortality and the induction of malformations, leukaemia and other malignancies and mental retardation, were assessed to be 0.4 Gy^{-1} at the time of peak sensitivity and 0.1 Gy^{-1} in less sensitive periods. These values were derived on the assumption

that the induction of effects is linear with dose. In the UNSCEAR 1988 Report [U1], these findings were summarized with the further statement that the risk estimates "may need substantial revision downward (particularly in the low-dose ranges)" and that "the Committee intends to review this in the near future". These points are considered in the further study outlined in this Annex.

3. The most significant point to investigate is whether the revised dosimetry system (DS86) [R1] for the survivors of the atomic bombings in Japan alters the interpretation of results previously gained and, therefore, requires the risk estimates to be changed. In particular, it will be necessary to establish whether it should be assumed that there is linearity of the dose-response and whether there may be thresholds of doses for effects at particular stages of fetal development.

4. In this Annex the emphasis is on reviewing the results of the study of the survivors of the atomic bombings in Japan. The results of other human epidemiological investigations and of pertinent experimental studies provide supplementary information, and these have been considered as well.

I. THE HUMAN BRAIN

A. DEVELOPMENT

5. The brain is the culmination of a long and interrelated sequence of molecular, cellular and tissue events. Some of these occur before birth and some after. Those occurring before birth are classifiable on the basis of the time after fertilization at which they occur as either embryonic or fetal. Conventionally, embryogenesis describes the phase of prenatal development from the appearance of the embryonic disk to the end of week 8 after fertilization. After this

time, the developing organism is called a fetus. Most of the structural complexity of the brain evolves in the fetal period through a series of interconnected events involving the production of neuronal cells, their migration from the periventricular proliferative zones to the cortex, their further differentiation, their growth in size and complexity of structural and molecular organization, and the establishment of primary neuritic processes that contribute to the emerging fields of

connection. The details of these developmental events have been described elsewhere [C6, C7, I1, M8, M9, O15, R2, R6, R10, R11, S17, U2] and will not be reviewed in depth here. In this Annex, discussion will be limited to certain general principles of brain development that have emerged largely in the last several decades and to recent experimental and epidemiological findings that bear on an understanding of the mechanisms through which prenatal exposure to ionizing radiation can lead to brain dysfunction.

6. One of the first differentiation events in the very early embryo is the appearance of discrete neural precursors, the neuroblasts, which separate from a defined region of the primitive ectoderm. These cells are aggregated around the ventricles of the developing brain, and their descendants will populate the cortex. The mechanisms that operate within this ventricular zone to determine the ultimate fate of immature cortical cells are not well understood. However, evidence accumulates that in early corticogenesis there is a cooperation among the cells in the proliferative zone. For example, recent studies have shown that the neuroblasts in the proliferative zone are physiologically coupled by gap junctions into clusters of 15-90 cells [L4]. This has been demonstrated through the use of a low molecular weight dye, Lucifer yellow, that can be injected into a single cell and can easily pass through gap junctions from one cell to another. To distinguish between coupling through gap junctions and coupling through cytoplasmic bridges, possibly stemming from membrane fusion, the investigators also injected into single cells horseradish peroxidase (HRP), which does not pass through gap junctions because of its molecular size but can pass through cytoplasmic bridges. The injected HRP was invariably restricted to a single cell, indicating that the coupling was not due to cytoplasmic bridges. Similarly, experiments designed to decrease the conductance of gap junction channels and thus increase membrane resistance showed that the membrane resistance of cells within clusters was increased, but there was no increase in membrane resistance among non-coupled neurons in the cortical plate. The coupled cells, identified by the cell to cell diffusion of Lucifer yellow, form columns within the ventricular zone. The clusters themselves allow direct cell-to-cell interaction at the earliest stages of corticogenesis, and these interactions could participate in determining the fates of the developing neurons. This behaviour suggests an interdependency of the fate of these cells such that the death of one, whatever the cause, could lead indirectly to the impairment of the developmental potential of others. Once migration commences, however, the number of cells within the clusters decreases, and apparently the individual immature neurons divorce themselves from the clusters, since they can no longer be shown to be dye-coupled.

7. It is important to note here that experimental studies currently suggest that each cortical neuron has not only a designated date of birth but also a definite functional address (see, e.g. [R16]). Since cerebral neuronal cells proliferate in specific peri- or circumventricular zones, proper function implies migration. The event (or events) that initiates the movement of post-mitotic, undifferentiated neurons from the proliferative zones to their normal sites of function is still unknown. However, once initiated, the movement of cells extends over weeks in aggregate, although an individual cell may reach its destination in a matter of days at the most. The migratory process itself is an active, timed phenomenon dependent to a large degree on an interaction between the surface membranes of the neurons and their guidance cells, on matrix materials such as cytotactin and on the subsequent morphological shaping of the two different families of cells, neurons and neuroglia. Not all of the factors involved in this phenomenon are known; however, there is experimental evidence that a modification of cell surfaces or spaces on or near the glial processes, which guide the neurons during their movement, is involved [F1]. The cells probably advance by making adhesive contacts at their leading edges, or growth cones, and then pulling themselves forward. Edelman [E2], for example, has shown that specific molecules, known as cell adhesion molecules, whose structure and function are apparently under genetic control, play a central role in these movements and that they do so through local alteration of the cell surface. It has also been demonstrated experimentally that within the optic tectum the growth cones are able to read gradients of surface-associated information in the process of axonal path-finding [B15]. Thus, any damage to the surface membranes or impairment of these molecular processes, however transitory, could impair the timing of migration. It is known, for example, that blockade of the cell surface adhesion molecules with appropriate antibodies prevents proper migration of external granule cells in cerebellar slices in culture [C9, H12, L3] and would presumably also do so in vivo.

8. Two waves of neuronal migration take place [R15]. The first of these commences at about week 7 after fertilization and appears to involve cells from the inner area of proliferation, the ventricular zone. (Here and elsewhere, unless specifically stated otherwise, time is expressed in weeks following fertilization, estimated from and therefore assumed synonymous with time of ovulation.) The intermediate zone through which they pass is then sparsely structured and contains few impediments to their movement. This wave ceases at about week 10, when numerous nerve fibres appear in the intermediate zone, which thickens markedly. The second wave, numerically much the larger, begins about week 10, normally terminates about week 15 or so and involves cells from a zone

further from the lumen than the zone from which the earlier migrants came. This time the migratory cells must traverse a denser intermediate zone and move past those earlier formed neurons that have already migrated, are positioned and have formed connections. The later-formed neurons are assisted on their way to the cortical plate by the long processes of specialized cells, the radial glia. At a subsequent time, the radial glia will begin to divide anew and become differentiated into astrocytes. However, at this juncture, they seemingly serve two functions: first, to guide the migrating neurons through the densely packed intermediate zone and secondly, to ensure the faithful mapping of the ventricular surface onto the expanding and convoluted cerebral cortex by preventing or minimizing the intermixing of cells generated in different regions of the proliferative zone. While the majority of young neurons do migrate along these radial pathways, some mixing of these clonally related cells occurs. Walsh and Cepko [W8], using a retroviral marking method *in vivo*, have shown that in the rat some labelled cells appear to migrate up different radial glial fibres and even along the ventricular surface, perpendicular to the fibres themselves. The latter form of migration could cause a wide dispersion of related cells and suggests that the pathways for neuronal migration are far more complex than the simple routes offered by radial glia. It is not yet clear how common this occurrence is, whether it is species-dependent or whether all of the labelled cells are indeed clonal or reflect an inhomogeneous distribution of the viral label [K13]. However, these authors, using a new method to identify the functional specification of the progenitors in the cortex, have recently confirmed their earlier findings and argue that this widespread and numerically significant dispersion of neuronal clones implies that the functional specification of cortical areas occurs after neurogenesis [W14]. O'Rourke et al. [O14] have confirmed these observations with time-lapse confocal microscopy.

9.   The cellular and molecular mechanisms of cell migration are not yet well understood, and little attention has heretofore been paid to cell membrane properties and changes in ionic concentration during cell movement. Only recently, for example, has it been recognized that migrating neurons in the developing central nervous system express voltage-sensitive ion channels before they reach their final destination. These channels appear to play a transient but specific developmental role in directing the migration of immature neurons. Thus, Komuro and Rakic [K14] have shown, using laser scanning confocal microscopy, that in the mouse cerebellum, granular neurons will not migrate until they have begun to express N-type (conotoxin-sensitive) calcium channels on their plasmalemmal surface. If these specific channels are inhibited by the addition of conotoxin to the tissue

culture medium, the neurons will not migrate; however, the inhibition of other calcium channels, as well as those of sodium and potassium, had no effect on the rate of granule cell migration. Accordingly, they speculate that "the early expression of conotoxin-sensitive calcium channels in postmitotic cells may be an essential prerequisite to both the initiation and the execution of their movement".

10.   Once migration has ceased, the fate of the migrating cells will ultimately depend on their abilities to connect with other neuronal cells; formation of these axonal pathways is a competitive phenomenon, and those cells that do not form the connections that allow stimuli to be passed from one cell to another will die and disappear. How these growing neurons find their targets has been one of the central problems of neurobiology for the last 40 or so years. It is now generally believed that the answer lies in chemo-affinity, that is to say, that the biochemical specification of growing axons is crucial in leading them to their appropriate targets [S15]. The precise nature of this process is unclear, and competing theories exist. Some speculate that there is a structural or strict chemospecificity in which the ultimate pattern rests on the complementary recognition of mutually specific cell surface markers, but this implies the existence of a very large number of such markers, much larger than has yet been identified. Others argue that the pattern arises through a regulatory or dynamic modulation of a relatively small number of specificities (see, e.g. [E2]). Evidence in support of this latter notion can be found in the fact, as previously stated, that late-formed neurons must migrate past those that have already migrated, are positioned, and have formed connections. Chuong et al. [C9] have shown that modulation of the neural cell adhesion molecule (N-CAM), which is present on all neurons (but not on the glia), or of the neuralglial cell adhesion molecule (Ng-CAM), which binds neurons to glia or glial molecules such as cytotactin, is implicated in the differential adhesiveness and regulation of this passing movement. N-CAM exists in two forms, an adult and an embryonic, which differ in their degree of sialylation. The embryonic form, E-N-CAM, is highly sialylated, whereas the adult form is not. In the cerebellum, E-N-CAM is never expressed in the germinal zone of neuroblasts destined to form or forming the external granular layer. It is, however, expressed by the granule cells during their migration but ceases to be demonstrable when these cells have reached their final position in the internal granular layer. Other cerebellar cell types do express E-N-CAM as histogenesis unfolds, but they, too, cease to do so with the overt cessation of cerebellar histogenesis [H14]. These findings suggest that E-N-CAM is only characteristic of growing and moving cellular structures.

11. Establishment of the proper axonal pathways entails cooperativeness as well as competition. It has been shown that in the developing mammalian telencephalon there exists a special group of early arising neurons, the subplate or transient pioneer neurons, that are instrumental in the laying down of the first axonal pathways and may be essential to the establishment of permanent subcortical projections [K4, M13]. These subplate neurons will disappear in postnatal life after the adult pattern of axonal projections is well established. It is also known that in the development of the central nervous system in some invertebrates, the grasshopper for instance, if the pioneer cells are prevented from differentiating through heat shock, the sensory growth cones that would have migrated along the pathways established by the pioneers are blocked and fail to reach the central nervous system [K4]. While the death or failure of a pioneer cell to differentiate may not always preclude the establishment of a specific pathway, since the function of the pioneer may be assumed by another cell, it is clear that in some instances the pathway will not develop if the pioneer cell is prevented from differentiating. Moreover, at least in some insect species, where the geometry of a specific neuronal pathway may be quite complex and involve sharp angles, it has been shown that other specialized cells contribute to the delineation of the pathway. These cells have been called "landmark" cells, and their presence and proximity apparently signal the pioneer to change course. Finally, as knowledge of the embryology of the brain increases and recognition of the functional specificity and diversity that exists among neurons grows, it becomes more plausible to assume that the loss of relatively small numbers of neuronal cells could have an effect on brain development out of proportion to the actual number of cells that are killed or whose differentiation is impaired.

12. Some cerebral neurons, presently thought to be relatively few in number, do not have their origin in the circumventricular proliferative zones but arise elsewhere and migrate into the cerebrum. It has been shown, for example, that those neurons that secrete the hormone that releases the luteinizing hormone, the one responsible for stimulating production of the sex hormones testosterone and oestrogen, actually have their origin in the olfactory placode. These neurons, known as LHRH cells, begin to migrate from their sites of birth in the placode through the olfactory bulb and into the cerebrum at about gestational day 12 or 13 in the mouse, following the terminal nerve (nervus terminalis). Most of the migration is completed by gestational day 16, and the cells, which are ciliated and morphologically distinguishable from other neurons, are diffusely distributed through the cerebrum [S9, W7]. These events in the human would be occurring at about 12-14 weeks after fertilization.

13. Many areas of the mammalian brain are characterized by repeated ensembles of anatomically and physiologically distinguishable nerve cells. Among such ensembles are those of the barrels and columns seen in the somatosensory cortex, the pattern of glomeruli in the olfactory bulbs and the columns of the visual cortex. Understanding the development of these neuronal assemblages has an important bearing on the nature of critical periods, the manner in which neural information is stored and the age-dependent neuronal response to injury. Progress in this understanding has been slow for lack of suitable study techniques, and it has not been clear whether the initial assemblages persist or whether they are lost or gained as the brain develops. Recently, LaMantia et al. [L2] have been able to show that with regard to the glomerular pattern in the olfactory bulbs, the brain is gradually constructed by the addition of new glomeruli to a persisting population, without apparent losses from the original population. Customarily regressive phenomena (cell death, synaptic loss and axon elimination) are known to play an important role in the development of the brain, but their findings suggest that these regressive events must proceed during the construction of olfactory neural circuits, if they occur at all in this region of the brain. However, LaMantia et al. [L2] note that the olfactory system has several extraordinary features that may lead to an exaggeration in the elaboration of these functional units in the olfactory bulbs. These findings suggest a need to reconcile the observation that some portions of the brain evolve through ongoing construction with the commonly accepted notion of development through the selection of useful circuits from a larger initial repertoire (see, e.g. [E2]).

14. Three general features of the development and organization of the human brain and its adnexa are important to an understanding of the nature of its vulnerability to malformation or maldevelopment, namely:

(a) 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 the latter takes place at different times and for different durations. This is particularly true of the development of the neocortex, which proceeds over a long time;

(b) brain function critically depends on the disposition and interconnection of structures and cells, neuronal and glial, and 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 proper-

tics; and synaptic inter-connection), each of which must occur correctly in time and space. Both cooperation and competition are involved in many of these events;

(c) the neurons of the cerebrum are not self-renewing. The capacity of neuronal precursors to divide is exhausted during the populating of the cerebral cortex and culminates in differentiated neurons that do not undergo further division.

Proper cortical function depends ultimately not only on the quantity of neuronal cells but their quality as well, and the latter depends, in turn, upon a variety of cellular and molecular processes, some intrinsic to these cells but some not. This has been particularly well illustrated through studies of the genetic disease, ataxia-telangiectasia (see [B17]).

15. *Summary.* The majority of neurons in the developing central nervous system migrate from the site of their last cell division to their final, functional position. The processes of acquisition of this position, the endowing of neurons of the six cortical layers of the cerebrum with their laminar identities and the parcellation of the neocortex into over 40 functionally distinct areas remain poorly understood and pose a major problem for neurobiology [S18]. Understanding these phenomena and the plasticity of the brain, i.e. its capacity to continually remodel itself, is also central to understanding how exposure to ionizing radiation impinges on the cytoarchitectonic structure of the central nervous system and its functioning.

B. DEVELOPMENTAL DEFECTS

16. Malformations of the brain may occur either in the course of major organogenesis, or take place during the differentiation and growth of the brain mantle. Among the former defects are 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 [M11, M15, O4], and holoprosencephaly, which reflects the failure of the forebrain to divide into hemispheres or lobes. 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 [O5]. These events occur early in embryogenesis, 4-6 weeks after fertilization.

17. Disturbances in the production of neurons and their migration to the cerebral cortex give rise to malformations of the brain mantle [S1, S2]. 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 [R3, R4, R5]. Among such malformations are, for example, an absent corpus callosum or a disorganized cortical architecture, which may later result in abnormal fissuring of the cerebral hemispheres, heterotopic cortical grey matter and microcephaly.

18. The sensitivity of the differentiating neural tissue to damage changes with age, and so does its capacity to replace damaged cells. It is therefore 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. Moreover, for a given dose, damage can vary as a function of the time in development at which the insult occurs, and therefore defects that arise in the growth and differentiation of the brain mantle, unlike those that arise in the course of organogenesis, can also differ substantially in severity. Broadly stated, the sensitive period for such abnormalities is months instead of days. The longer sensitive period and the limited repair capability must be important reasons why these malformations are much more common than organogenetic ones [D7]. The complexity of the origin of these defects is illustrated by the relationship between brain function and cellular repair that characterizes the human genetic disorder, ataxia-telangiectasia [B17, C13, C14]. In addition to the neurological defects ataxia-telangiectasia is also associated with immunodeficiency, an elevated incidence of lymphoreticular neoplasms and *in vivo/in vitro* cellular radiosensitivity [C13]. Recent molecular studies suggest that the primary defect in ataxia-telangiectasia may center on the misrepair of DNA double strand breaks (see Annex E, "Mechanisms of radiation oncogenesis") and given the dramatic neurological dysfunction that characterizes the disorder it may be concluded that DNA repair is critical for neuronal development and maintenance.

19. 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 certain cell type is being produced, the loss may be permanent. Thus, a brief insult may lead to the preferential damage to a particular region and consequently cause a permanent functional or behavioural abnormality.

20. The period of maximum sensitivity or vulnerability to developmental disorders 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 [U4] and that the duration of the period of effectiveness may be broadened by increasing the dose. Table 1, adapted from Williams [W10], sets forth the weeks after fertilization at which major developmental features of the brain evolve. By extension, it would be possible to suggest the damage that could ensue if the normal pattern of orderly differentiation and development did not occur (see also [J2, Z2]).

1. Cerebral and cerebellar abnormalities

21. The critical period for abnormalities in the development of the cerebral cortex occurs when the telencephalic matrix cells undergo their last cellular division, begin to migrate to the cortical plate and differentiate into specific phenotypes (see, e.g. [K8]). The production of neuronal cells accelerates and their migration to the cortical plate commences at about week 8 after fertilization. Cortical neuron production has largely terminated by week 16 after fertilization. Subsequently the laminar cortical structure becomes apparent and dendritic arborization, a process that extends into postnatal life, begins. Migrational errors involving the superficial cortico-cortical cells of the developing brain, or the loss of some of these cells, can lead to convolutional abnormalities [C2, G7], which since neuronal function follows position, may in turn contribute to the origin of functional and behavioural abnormalities.

22. Disorders such as the dyslexias (severe inabilities to read) appear to be due to aberrations in specific cortical areas [G5, K2]. Galaburda et al. [G6], for example, have described a severely dyslexic child with small focal wartlike accumulations of ectopic neurons in layer I and scattered focal cortical dysplasias; these aberrations were confined to the speech region of the left hemisphere. Other cases with comparable structural abnormalities have been described subsequently.

23. 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 or to specific sensory fibres in the corpus callosum [G9]. In the case of olfaction, at least, damage can apparently arise through a failure of the LHRH cells to migrate into the cerebrum, since anosmia is a part of the syndrome of hypogonadism and hypergonado-trophism known to be associated with migrational errors in these cells [S9].

24. Hypoplasia with deranged cortical structure stemming from injury to the external granular matrix is the most common abnormality of the cerebellum. Although some cell classes, e.g. the Golgi Type II cells, are generated early in the cerebellar anlage, other and more numerous cells, such as the granular neurons, are generated late. 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 [R3]. In all major respects, the development of the human cerebellum resembles that in other mammals, when allowance is made for the different timing of birth relative to brain development [D6]. 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 [C1].

2. Abnormalities of the brain adnexa

25. Abnormalities involving the brain adnexa arise from either maldevelopment of the end-organs themselves, the eyes or ears, for example, (see [O11] for a description of the early normal development of these organs), or in the processing of the signals transmitted from these organs to the brain, or both [O6]. Failures in signal processing could be the consequence of a defect in the optic or auditory nerves or in the various cortical areas involved in auditory, olfactory and visual function.

26. Defects in the optic tract, for instance, could be manifested as aberrations in the field of vision, their nature and extent depending on the severity of the damage. Total destruction of the retina or the optic nerve would result in blindness. Damage to the optic chiasm could give rise to total or unilateral blindness, depending on the location and severity of the lesion. Damage to the iris could culminate in a coloboma or be manifested as heterochromia or other pigmentary disturbance. Neither of these latter defects have been seen, however, among the prenatally exposed survivors of the atomic bombings [K12].

27. Rhinencephalic damage could, if severe, produce anosmia, and if less severe, an inability to perceive specific classes of odours, a selective anosmia. Whether such prenatal damage to the brain adnexa can be subsequently ameliorated is unclear; however, some experimental evidence, based on the exposure of only a portion of the brain, suggests that the undamaged areas can compensate for the loss of function in the damaged regions. If such amelioration is possible, the effects of prenatal irradiation will be more difficult to assess. Special neurons in the nose are capable of

detecting a myriad of odors and communicating these to the brain. These neurons, unlike most others, when they age and die, are replaced with new ones derived from a population of progenitor cells in the nasal epithelium. These new neurons will acquire chemosensitivity and form synaptic connections in the olfactory bulb of the brain. This process occurs continuously, but despite this constant change the sense of smell is normally quite stable. Whether this would be true following exposure to ionizing radiation is not known.

28. *Summary.* The cells of the different structures of the brain are produced at different times, and hence the sensitivity of these structures to damage changes with age at exposure. A brief insult that might at one stage of embryogenesis have little or no effect can, at another stage in development, lead to preferential damage to a particular region and consequently cause a permanent functional or behavioural abnormality. At any given time, the probability of causing abnormalities and their severity change as the dose of the teratogenic agent changes. For a given dose, however, defects that arise in the growth and differentiation of the brain mantle, unlike those arising in the course of organogenesis, can differ substantially in severity, since the sensitive period for such abnormalities is months instead of days. The longer sensitive period and the limited repair capability must be important reasons why these malformations are much more common than organogenetic ones [D7].

II. RADIATION EFFECTS

29. Cells that are actively dividing are more responsive to radiation than those that only divide occasionally, or cannot divide. Given the number of proliferating cell populations in the embryo or fetus, it is to be expected that their tissues would be especially prone to radiation injury. This damage could take a variety of forms, ranging from necrotic to apoptotic death (see, e.g. [G11, H10]) to the impairment of the cell membrane without death. Apoptosis, that is, programmed cell death, is the most common form of cell death in the body and is particularly important in embryo- and fetogenesis in the shaping and reshaping of tissues and organs. It differs from death due to necrosis in a number of ways. Normally the cell dies quickly, within four hours or so, rather than through a process that extends over a much longer period, as in necrosis. Moreover, in apoptosis the cell membrane remains intact as death occurs, whereas in necrosis the integrity of the membrane is rapidly lost. Inoue et al. [I6] have demonstrated that radiation-induced cell death in the external granular layer of the cerebellum of newborn mice is of an apototic nature.

30. Where and how exposure to ionizing radiation at critical developmental junctures acts to impair brain function is unknown at the moment. However, ionizing radiation could interfere in a variety of ways [B3, B4, H1, H2, Y2]:

(a) 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;

(b) such effects could result from an intrusion on cell migration either through an alteration of the cell surface phenomena that are involved, through the death of the glial cells that guide the migrating neurons or through infringement on gap-junction-mediated intercellular communication [F1]. It is not clear whether neuronal and glial cells are equally radiosensitive; however, disturbances of myelin formation, a mature glial function, have been described in brain stem fibre tracts in experimental situations following irradiation and appear more severe after exposure to neutrons than to x rays [G7];

(c) abnormality might reflect an impaired capacity of the neurons to connect correctly. The development of neuronal connections, or synaptogenesis, is a multifaceted phenomenon; it involves timing, space, surface-mediated competition and, possibly, diffusible agents;

(d) irradiation could also lead to disoriented dendritic arborization, or a reduced number of dendrites or dendritic spines per cerebral cortical neuron [B5, B6];

(e) programmed cell death, which is essential to the development of the normal brain and its adnexa, could also be accelerated or otherwise altered by ionizing radiation.

If cell death is not the sole mechanism through which irreparable damage occurs and if ionizing radiation can contribute to one or more of the levels or sites at which neuronal variation can arise, then there are numerous possible effects. Edelman [E2], for example, has identified seven major levels of neuronal variation, and within each of these there is commonly more than one site at which variation can be envisaged (see Table 2). Relatively few of these sites or levels of variation have been studied from a radiobiological perspective.

31. Distinguishing between the possible alternative mechanisms of damage and sites of altered variation, although formidable, is essential to more complete

understanding of the nature of the effects of ionizing radiation. How rapidly this understanding will be attained is unknown, but there are promising developments. For example, the study of neuron-specific proteins such as neuron-specific enolase, a cytosolic form of the glycolytic enzyme enolase (phosphopyruvate hydratase), may provide a means to discriminate between cortical dysfunction stemming from radiation-related neuronal death or necrosis, on the one hand, and errors in migration, on the other [I4]. Enolase is a dimeric enzyme composed of various permutations of three immunologically distinct subunits (alpha, beta and gamma). Immunohistochemical studies, using antibodies to the gamma subunit, have localized alpha-gamma and gamma-gamma dimers specifically within neuronal and neuroendocrine tissues. It is this specificity of distribution that makes neuron-specific enolase a useful marker not only for neuronal damage but also for neuroendocrine tumours. Coquerel et al. [C8], for example, have shown that the level of neuron-specific enolase in the cerebrospinal fluid increases as the necrosis volume increases and that at birth, the cerebrospinal fluid level of this enzyme is highly prognostic of infants who will subsequently exhibit confirmed brain damage. It has also been reported that cerebrospinal fluid as well as serum levels of neuron-specific enolase are elevated in non-febrile seizure disorders but not in cases of simple febrile convulsions [K10]. It is, however, not yet clear whether similar elevations occur in well-recognized migrational disorders, such as schizencephaly, a rare abnormality of the brain in which clefts extend across the cerebral hemispheres; if they do not, this enzyme might provide a simple tool for separating cortical functional errors associated with neuronal ectopias from abnormalities stemming from neuronal death.

32. Progress in the understanding of brain organization and function entails not only the use of newer tools but also the formulation of testable propositions [F5, K5]. One such organizational notion is the radial unit hypothesis of Rakic [R12, R13], who argued that the cortex is a collection of ontogenetic columns, each arising from a specific proliferative unit and clonal in nature. Substantial data support this contention. Mountcastle [M12], for example, showed that the neurons within a single column in the somatosensory cortex are responsive to a specific modality and receptive field of stimulation. Other sensory and association areas in the cortex behave similarly. It is thought that those columns innervated by a single thalamic nucleus (subnucleus or cell cluster) serve as a basic processing module. If this perception of cortical organization (and indirectly function) is correct, the loss of a few cells, conceivably even a single cell, could result in the loss, or compromise, of specific somatosensory or association abilities, if the loss occurs in the formative periods for these processing modules.

33. This radial unit thesis can only explain how neurons acquire proper positions; it does not define what initiates or governs their subsequent differentiation, including the course of synaptogenesis, nor does it necessarily establish when the specification of functional areas of the cortex occurs [W14]. Moreover, it does not provide answers to questions such as what prompts the shift from symmetric division of the neuronal stem cell, with one stem cell giving rise to two others, to asymmetric division, with one stem cell producing another stem cell and also an undifferentiated neuron that divides no further? If a single progenitor in the proliferative zone can produce more than one cell phenotype, how does this happen? What mechanism or mechanisms switch on the migratory process? How does the migrating neuron dissociate itself from its guidance mechanism when it nears its functional site? What further clues does it need to position itself properly within its functional domain?

34. The causal relationship between irradiation of the embryo and fetus at specific stages of development and the subsequent morphologic and functional damage to the brain, if not the molecular events involved, are well established in a number of experimental animals. There is abundant information on the biological effects caused by prenatal exposure of mammals to ionizing radiation. Much of this evidence has already been summarized in the UNSCEAR 1986 Report [U2]. These data give, however, little quantitative insight into effects on the brain in humans, although they serve to identify possible effects.

35. The limitations of the human data make studies on other species inevitable, if the risks of exposure are to be understood. There are, of course, differences in the brain development of different species. These are attributable partly to the differing complexity of the adult organ, but especially to the different rates of brain growth and the different time of birth in relation to developmental events in the brain [D1]. In general, the histological structure of the brain is comparable from one species to another, both in composition and function, and the sequence of developmental events in all mammalian species studied is also similar. However, the sizes of the various cytoarchitectonic areas of the cortex devoted to specific functions can and do vary greatly. For example, the primary visual cortex occupies 1/5 of the neocortical surface in monkeys but only 1/30 of it in humans, and Broca's language area exists only in the human species. This suggests that the target zone associated with specific cortical functions differs in different species and that the extrapolation of experimental observations on subhuman forms must take account of these dissimilarities. Finally, although structures in a particular part of the brain are broadly alike in animals of the same and even different species, as previously stated, at the finer level of

axonal and dendritic ramifications and connections there is a considerable degree of diversity among individuals within a species.

36.   In order to examine the radiation effects observed in laboratory animals and to relate them to human observations, the timing of an insult, in relation to the developmental events in the brain that dictate the consequences, must be considered [D6, D7]. Experimental procedures must be applied at comparable stages in brain growth rather than at comparable gestational periods. The duration of exposures must also match the different time-scales, but if these factors are taken into account, even the small laboratory species can provide at least some qualitative information of relevance to the human. The complexity of the non-human primate brain obviously makes it valuable for many experimental purposes, and its protracted span of development 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, the use of experimental 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.

37.   In this Chapter the primary epidemiological study of the prenatally exposed survivors of the atomic bombings in Japan is reviewed. These results are supplemented by additional but much more limited epidemiological investigations of other exposed individuals. Experimental studies may be particularly important to clarify mechanisms of actions. Some comments on recent findings from this field conclude this Chapter.

A.   PRENATAL EXPOSURE TO ATOMIC BOMBINGS

38.   Few population-based studies of the effects of prenatal exposure on the developing human embryo and fetus exist. Present knowledge rests mainly on the observation of those survivors exposed prenatally during the bombings of Hiroshima and Nagasaki and, to a lesser degree, on studies carried out on children who were prenatally exposed to radium or x rays in the course of radiotherapeutic treatment of their mothers and on comparative embryological studies. Among these, however, the size, length of study, variability in dose and post-ovulatory age at exposure make the experiences in Hiroshima and Nagasaki the most important source of data.

39.   Over the years, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation

Effects Research Foundation (RERF), have established several overlapping samples of individuals prenatally exposed to the atomic bombings of Hiroshima and Nagasaki. These samples, the studies and the findings are described in some detail in this Annex because of their inherent importance and to illustrate the breadth and consistency of the effects that have emerged.

40.   *Study samples.* The earliest observations, those of Plummer [P1] and Yamazaki et al. [Y3], were based on opportunistic samples and made no systematic attempt to be complete. They were restricted in the method of ascertainment and in structure; often only one city or a limited prenatal age distribution was involved. In 1955, however, the construction of an exhaustive clinical sample of the prenatally exposed survivors was started. This gave rise to what has been termed the PE-86 Sample. Its members were ascertained through a variety of sources but primarily through birth registrations, interviews with women who were enrolled in the genetics programme in 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 ABCC. No attempt was made to match, by sex or prenatal age at the time of the bombing, the more distally exposed or the non-exposed with those survivors exposed within 2,000 meters.

41.   In 1959, this sample was revised [B7] according to the following considerations:

(a)   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 clinical facilities and personnel were limited, examination of these individuals strained resources and seemed unproductive in view of the probable exposures. In the interests of clinical efficiency, sample size was limited, at the loss, presumably, of little or no information;

(b)   special censuses conducted in 1950 and 1951 by the ABCC appeared to offer a better basis for the selection of a comparison group of non-exposed individuals than had previously obtained.

42.   This new sample, known as the Revised PE-86 Sample, or the Clinical Sample, differs in several important respects from the unrevised one:

(a)   it includes no survivors prenatally exposed at distances between 2,000 and 2,999 meters;

(b)   exposed individuals are limited to those survivors prenatally exposed within 2,000 meters (the proximally exposed) or between 3,000 and 5,000 meters (the distally exposed);

(c)   non-exposed persons include only those individuals who were beyond 10,000 meters at the

time of the bombing and were enumerated in the special censuses;

(d) the survivors within the 3,000-5,000 meter zone, as well as the non-exposed, were matched for sex and age (by trimester of pregnancy) with those exposed within 2,000 meters.

These steps reduced the clinical burden substantially but resulted in little change in the number of persons within 2,000 meters. Both samples include virtually all individuals who received substantial exposures (those with estimated 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. It is this group that has been the basis of most subsequent analyses (see, e.g. [M3, W1, W2]).

43. The data on severe mental retardation are restricted to the Clinical Sample, since it involves the only individuals on whom extensive clinical observations are available in both cities. In so far as intelligence tests and school performance data 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. The intelligence tests were conducted and the school performance data obtained in 1955, that is, before the definition of the revised sample.

44. *Dose estimates.* The analyses of the effects of prenatal exposure to ionizing radiation to be described in the paragraphs to follow all employ the estimated absorbed dose to the mother's uterus based on the DS86 dosimetry ([R1]; see also [H5, K3]), unless otherwise specifically noted. Estimates of the absorbed doses to the fetus itself are not yet available and may not be for some time. Parenthetically, it should be noted that the organ absorbed doses computed under the DS86 system are actually age-specific population averages rather than individual-specific estimates, since the mean dose to an organ depends not only on the energy spectrum of the gamma rays and neutrons involved but also on the size of the organ. This will vary with the size of an individual survivor, which is not known. The organ doses estimated are, therefore, based on a "reference" man or woman, a hypothetical individual whose size approximates that of the average Japanese man or woman at the time of the bombings. The doses are derived from a mathematical phantom that simulates the human body by a series of simple geometric shapes: ellipsoids, elliptical cylinders and cones, or parts of these. The size of the phantom can be adjusted to represent individuals of different ages or genders. Six different phantoms were used: an infant, a juvenile and an adult for each of the two sexes. When one of these phantoms is used in concert with a computer program that models the transport of neutrons or photons through the body by Monte Carlo

methods, an estimate of the average absorbed dose in an organ can be calculated.

45. The element of uncertainty introduced by this method of estimating doses is presumably not serious except, possibly, in the case of a pregnant woman. Here the difficulty arises because the reference woman used in the DS86 calculations was assumed not to be pregnant, as was certainly true of the vast majority of women survivors. However, in the pregnant woman the size of the uterus changes dramatically as pregnancy advances, and as the uterus enlarges, the other organs of the abdomen are shifted from their normal position and compressed. Thus the estimated dose to the uterus based on the reference woman describes the actual dose to the uterus more poorly in the later stages of pregnancy than in the early ones, before the uterus has undergone much change in size, and it may therefore be a poorer surrogate later in pregnancy. Although the error in the dose this may introduce is presumably small, given the energy spectrum involved, it should be noted, nonetheless, that to the extent that doses are overestimated, the risk to the embryo or fetus will be underestimated, or conversely if the doses are underestimated.

46. *Developmental age.* One of the most important factors, aside from dose, in determining the nature of the insult to the embryo or fetus resulting from exposure to ionizing radiation is the developmental age. Accordingly, since, as previously stated, different functions in the human brain are localized in different structures and since the differentiation of these takes place at different stages of development and over different periods of time, the estimated post-ovulatory ages at exposure (here taken to be synonymous with developmental age) have been grouped so as to reflect these known phases in normal development. Post-ovulatory age has been estimated to be 280 days less the number of days between the bombing and the birth. The average duration of a pregnancy, measured from the onset of the last menstrual period is taken to be 280 days. Fourteen days are subtracted from the days of pregnancy at time of bombing to account for the time between the onset of the last menstrual period and ovulation (and fertilization of the oocyte). Four age periods have been used: 0-7 weeks (0-55 days), 8-15 weeks, 16-25 weeks and 26 or more weeks after ovulation.

47. At the post-ovulatory age of 0-7 weeks (0-55 days), the precursors of the neurons and neuroglia, the two principal types of cells that give rise to the cerebrum, have emerged and are mitotically active. At 8-15 weeks, a rapid increase in the number of neurons occurs; they lose their capacity to divide, becoming perennial cells, and migrate to their functional sites. At 16-25 weeks, differentiation *in situ* accelerates,

synaptogenesis that began about week 8 increases, and the definitive cytoarchitecture of the brain unfolds. At 26 or more weeks, architectural and cellular differentiation and synaptogenesis of the cerebrum continue, with, at the same time, accelerated growth and development of the cerebellum.

48. Experimental studies [H11] have shown that irradiation at about day 16 in the rat (roughly week 28 in the human) will produce gross distortions of the leaf-like gyri, or folia, of the cerebellar cortex, as well as deficiencies in the granular and molecular layers of the cerebellum. The defects in these layers are even more common when exposure occurs shortly after birth, although the folial changes are not. In the rat, when irradiated between day 19 and day 21 (about week 31 to week 35 in the human), disordered cerebellar migration is a common occurrence [C12, H20].

49. **Effects on brain growth and development.** So far, only two conspicuous effects on brain growth and development have emerged in the study of prenatally exposed survivors of the atomic bombings of 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 an increased frequency of unprovoked seizures and significantly reduced intelligence scores and performance in school. The severe mental retardation and the reduced intelligence scores and school performance may be manifestations of the same process, in which all the individuals significantly exposed in the relevant stages of pregnancy suffer some dose-related reduction in cortical function, thus increasing the number of those classified clinically as being severely retarded.

1. Severe mental retardation

50. Individuals classified here as severely mentally retarded are those who cannot form simple sentences, perform simple arithmetic calculations, care for themselves, or have been or are institutionalized or unmanageable. Thirty cases of severe mental retardation were observed in the 1,544 individuals included in the Clinical Sample for whom DS86 doses can be computed (doses were not available for 55 survivors in this sample at the time of this analysis). Details of exposures and clinical findings for the 30 cases of severe mental retardation are given in Table 3.

51. Three of the severely mentally retarded children, all in Hiroshima (estimated uterine absorbed doses 0, 0.29 and 0.56 Gy; post-ovulatory ages 36, 13, and 12 weeks, respectively), are known to have or to have had Down's syndrome (one child died in 1952). A fourth child, also in Hiroshima (estimated uterine

absorbed dose 0.03 Gy; post-ovulatory age 20 weeks) had Japanese B encephalitis in infancy, and a fifth, in Hiroshima, had a retarded sibling (dose 0 Gy; post-ovulatory age 20 weeks). 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.

52. When the prenatally exposed survivors, exclusive of the three cases of Down's syndrome, are distributed over the four post-ovulatory age groupings described in paragraph 47 and the frequency of mentally retarded individuals is examined in the light of their estimated doses and the post-ovulatory age at which they were irradiated, the following emerges (see Table 4 and Figure I) [O1]:

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

(b)   within this critical period, damage expressed as the frequency of subsequent severe mental retardation increases as the dose estimated to have been received by the fetal tissues increases. Some 75% (9 of 12) of fetuses exposed to 1 Gy or more in this period are mentally retarded; this is an incidence more than 50 times greater than that in the unexposed comparison group;

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

(d)   there is no apparent increased risk before week 8 or after week 25. Whether the seeming absence of an effect in the first two months after ovulation is real, or merely reflects the fact that embryos exposed at that stage of development commonly fail to survive to an age at which mental retardation can be recognized, is unclear. However, experimental studies (see, e.g. [H11, H13]), have also failed to find effects on the developing mouse or rat nervous system at doses as high as 3 Gy in the first 8 days after fertilization, a period of time corresponding to the first 8 weeks or so in the human.

2. Small head size

53. The small head sizes to which reference has been made were two or more standard deviations below the mean head size 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 in the 1,598 births in the entire sample [B2, M2, M3, M4, T1], 18 persons (60%) have been previously reported to have or to have had disproportionately small heads [W1, W2]. This value may be spuriously low, since 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. 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 severe mental retardation nor what small head size may imply about the nature of the radiation-related damage. It is tempting to believe that the smaller head arises as a result of fewer neurons (because of cell death), but this may not be so. Reyners et al. [R14] have found that in the rat at low doses of x-radiation (0.09-0.45 Gy), the numerical densities of neurons and glial cells are actually increased, although the size of the cells is significantly reduced. The authors suggest that the brain has undergone a "miniaturization" rather than necrosis. However, as previously noted, glial cells retain their proliferative ability and could replace lost tissue mass, as D'Amato et al. [D2] observed experimentally. If so, brain volume could remain the same and head size develop normally, but cortical function would be diminished.

54. Recently, Otake and Schull [O13] re-examined the relationship to radiation exposure of small head size among the prenatally exposed population in Hiroshima and Nagasaki, using the estimated DS86 doses. The study population consisted of the 1,598 individuals (Hiroshima 1,250, Nagasaki 348) used by Otake et al. [O1] in the analysis of severe mental retardation. DS86 doses were available on 1,566 of these persons (1,242 in Hiroshima and 324 in Nagasaki; this represents an addition of 22 cases to the number described in [O1]). Among these subjects, 1,473 had their head circumference measured at least once in the period from 9 to 19 years of age.

55. As stated above, an individual with a small head size is defined as someone with a head circumference less than 2 standard deviations below the mean observed at his or her specific age at measurement. It should be noted that often, in the past, these individuals have been described as microcephalic. This term seems inappropriate, however, for two reasons: first, microcephaly denotes a clinically recognizable smallness of the head, which is often misshapen as well, and secondly, the clinical diagnosis generally is applied to individuals whose head is even smaller in circumference (often 3 standard deviations or more

below the mean) than the criteria used here. Accordingly, either of two terms, "atypically small head" or "small head size" would seem to be more appropriate to describe the individuals satisfying the criteria described above.

56. Of the 30 cases with severe mental retardation described elsewhere [O1], 26 were included among the 1,473 study subjects. Three of the four lost cases died before 1954, that is, before they were 9 years of age. The one remaining case, a non-exposed individual, survives, but she did not have a physical examination between 9 and 19 years of age.

57. Among the sample of 1,473 individuals, 62 had small heads according to the criterion previously described. It should be noted that the criteria are different for males and females of the same chronological age; the differences range from -0.98 to 1.34 cm.

58. *Small head size and trimester of exposure.* The frequency of individuals with small head sizes, with and without severe mental retardation, is shown in Table 5 by trimester at exposure and estimated DS86 uterine absorbed dose. Figure II gives the proportion of small head sizes by trimester at exposure. As is evident from Figure II, the incidence of individuals with small head sizes in the first trimester unquestionably increases with increasing estimated dose; it also increases in the second trimester, but to a lesser extent. Hardly any increase is observed in the third trimester. Of the 26 mentally retarded individuals, 15 (58%) had small heads (Table 5). About 24% of the 62 individuals with small head size (determined by age-specific criteria) among the 1,473 clinical subjects from both cities were mentally retarded. This rate increases to 29% (13/45) when only those survivors exposed to 0.01 Gy or more are considered. These rates, it will be noted, are greater than that (10%) previously reported by Wood et al. [W1, W2].

59. Almost all of the individuals with small head sizes were exposed in the first or second trimester, 55% in the former and 31% in the latter. The risk of an atypically small head and severe mental retardation observed among individuals exposed in the second trimester to an estimated 0.01 Gy or more is 57% (8/14), but only 19% (5/27) in the first trimester. Alternatively stated, among individuals with an atypically small head and severe mental retardation, the bulk, 62% (8/13), were exposed in the second trimester.

60. *Small head size and post-ovulatory age (weeks) at exposure.* The proportion of individuals with small head size for the four post-ovulatory periods, namely, 0-7 weeks, 8-15 weeks, 16-25 weeks and ≥26 weeks, is also shown in Table 5. The proportion of indivi-

duals with small head size increases with increasing estimated dose in only the first two periods, and an especially sharp rising trend is seen in the 8-15 week period (Figure 11).

61. In the 17 individuals from both cities with a small head in the 0-7 week period there was no apparent mental retardation. Twelve of these individuals were exposed to an estimated dose of 0.01 Gy or more. One of two (50%) of the individuals exposed to ≥1.00 Gy had small head size and two of four (50%) exposed to 0.50-0.99 Gy had small head size. There were 29 individuals with small head size in the 8-15 week period, 26 of whom received an estimated dose of ≥0.01 Gy; 12 of them (46.2%) were severely mentally retarded. Seven (87.5%) of the eight small head cases who were exposed to ≥1.00 Gy had severe mental retardation. Thus, 12 (80%) of the 15 individuals with an atypically small head and severe mental retardation occurred at the most radiosensitive period, 8-15 weeks after ovulation. In the 16-25 week period, only one (33.3%) of the three individuals with small head in the >0.01 Gy group was mentally retarded, and he had been exposed to a dose of more than 1.00 Gy.

62. The rubric "small head size" may, indeed probably does, cover a variety of different developmental "abnormalities". Among the individuals with small head size and severe mental retardation, for example, some clearly invite the clinical diagnosis of microcephaly, since the head is not only unusually small but misshapen, often pointed or oxycephalic-like. Still others, and they are more common, have a head size that is proportionate in all dimensions, albeit small. Moreover, since head size varies in all populations, it can be assumed that some of the individuals here designated as having small head size merely represent the lower extreme of normal variability. Indeed, based on the criterion for small head size used here, if head sizes are approximately normally distributed, some 2.5% of "normal" individuals would be so classified.

63. Since the mean intelligence quotient (IQ) and its standard deviation among the 47 individuals having small head size without severe mental retardation approximate the values seen in the entire clinical sample, it is conceivable that a significant fraction of these individuals are the "normals" alluded to above. Accordingly, Otake and Schull [O13] attempted to estimate the excess number of individuals with small heads ostensibly attributable to exposure to ionizing radiation (see Table 6). Among the 62 individuals with small head size, some 37 would be expected normally, and the observed and expected numbers agree reasonably well when exposure occurred in the 16th week or later. However, there is a striking excess prior to this time, where 16 are expected but 46 were actually

observed, an excess of 30 cases. If it is assumed that the small head size among those 12 individuals with severe mental retardation is secondary to brain damage, this leaves 18 cases that might represent radiation-related instances of growth retardation without accompanying mental impairment. But can these latter individuals be distinguished from those expected by chance? To explore this possibility, the locations of the 47 cases of small head size without mental retardation were determined in a bivariate plot of standing versus sitting height expressed as age- and sex-standardized deviates based upon the full sample of 1,473 individuals. The individuals with a small head size but no apparent mental retardation were found to be disproportionately represented among the lower values defined by either the 95% or 99% probability ellipse (see Figure 4 in [O13]). Three individuals were outside the 99% ellipse, but only one of these three received an estimated dose of known biological consequence. Specifically, the DS86 uterine absorbed doses in the mother were 0, 0.04 and 0.49 Gy. These observations suggest that small head size is not an independent teratogenic effect but is either secondary to mental retardation or to a more generalized growth impairment without clinically recognizable mental retardation (see [O16]).

3. Intelligence test scores

64. 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.

65. 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 specific test used; generally, however, individuals scoring high on one test tend to score high on other tests. It is important to note, however, that even with the same test an individual's score is not an immutable value, as retesting has shown. Thus, a change of a few points in a particular child's score may not be clinically significant, but a change of only a few points in the mean score for a population of children can have important public health implications, resulting in a higher proportion of socially dysfunctional individuals. Most intelligence tests are so structured that the distribution of test results follows an

approximately normal curve, with a mean of 100 and a standard deviation of 12-15 points. Thus, normally some 95% of the population will have scores in the range 70-75 to 125-130, that is, will fall within two standard deviations of the mean. Individuals whose scores lie, consistently, two standard deviations or more below the mean would commonly be described as retarded. In the Japanese experience, the mean Koga score of some 1,673 tested children was 107.7 (standard deviation 16.08) [S4], and the highest IQ achieved by any of the clinically diagnosed severely mentally retarded children was 64 [O1].

66. Schull et al. [S4] have described an analysis of the results of intelligence tests of the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki conducted in 1955 by trained psychometrists. This analysis of the Koga test scores [K1, T2], which also used estimates of the DS86 uterine absorbed dose, reveals the following (see Figure III):

(a)   there is no evidence of a radiation-related effect on intelligence among those individuals exposed at 0-7 weeks or >26 weeks after ovulation;

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

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

67.   While intuitively it is reasonable to assume that achievement on intelligence tests is related to the quality of brain function, and that the diminished performance described above reflects some functional impairment, the biological basis (or bases) of that impairment is far from clear. Performance on intelligence tests can be affected by factors other than ionizing radiation, such as motivation, socialization at home and in school, and physical impairment (defective vision or hearing, for example). Of necessity, since information on these extraneous sources of variability does not exist, they must be assumed to be part of the random error in the analyses of such tests, but the possibility that they change systematically with dose cannot be ignored, although there is no evidence that this is so.

68.   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 mental retardation.

4.   School performance

69.   As a part of the continuing assessment of the effects on the developing embryonic and fetal brain of exposure to ionizing radiation, the school performances of prenatally exposed survivors of the atomic bombing of Hiroshima and a suitable comparison group have been studied [O2].

70.   The Japanese place strong emphasis on school performance and school attendance [B9]. As a consequence, the Japanese child rarely misses school without good cause and places high value upon achievement in school. If a child's attendance record is correlated with illness and performance with innate ability, attendance might be correlated with exposure as a consequence of more (or less) frequent illness, and performance might reflect the nature of the developmental events that took place when exposure occurred. Accordingly, with the approval and assistance of the Municipal Board of Education in Hiroshima and the written consent of the parents of those prenatally exposed, their school records were microfilmed in 1956. At that time these children were 10-11 years old, and most had recently completed their fourth year in elementary school. The records themselves include information on school attendance, performance in various subjects, behaviour and physical status.

71.   The attendance records of the public schools of Japan indicate the actual number of days of school and the total number of days of school missed by a specific child, the number of days tardy and the number of days the child left school prematurely. The days missed are further subdivided into absences because of illness and absences for other reasons, such as death or illness of another member of the child's family. The ratio of the days missed through illness to the total days of school affords a crude measure of the health of a given child.

72.   With some 250 school days per academic year, the typical child in these years failed to attend school fewer than 5 days a year. On average, school absences for illness tend to increase generally with dose among the four post-ovulatory age groupings, when the clinically recognized mentally retarded cases are included in the sample analysed. Absences also tend to diminish in number as the child advances in school. This continues to be true when the mentally retarded, who are more prone to illness, are excluded, but the overall effect of radiation on attendance becomes more equivocal. When one turns to age-specific categories, it is observed that (a) the number of absences continues to diminish in all age groupings as the child advances in school; and (b) the largest and most consistent effect of radiation, with and without respect to sex, involves the age group exposed 8-15 weeks after ovulation.

73. In the first four years of elementary schooling the Japanese child studies seven subjects: the Japanese language, civics, arithmetic, science, music, drawing and handicrafts, and gymnastics. Every student's performance with respect to these subjects is evaluated routinely, and at the end of every semester (there are three in the academic year) a score is assigned for each. At the end of the academic year, these scores are summarized into a single value for each subject. The latter varies, normally, in unit steps from +2 to -2. The highest and lowest five percentiles of the class are assigned scores of +2 (very good) and -2 (poor), respectively. The next highest and lowest 20 percentiles are given +1 (somewhat above average) and -1 (somewhat below average), and finally, the middle 50% are given zero (average). Otake et al. [O2] have converted these assigned values to a five-point scale (5, 4, ..., 1), giving the highest and lowest scores the values 5 and 1, respectively, and so on. Some scores for some individuals were either missing or illegible in the copies of the original records; all of the information that was available was used in these instances.

74. Before determining what measure of school performance should be fitted to the dose data, given the interdependence of the various school performance scores, the investigators examined the structure of the matrix of correlation coefficients among the seven subjects previously enumerated. The correlations were high, ranging from 0.62 to 0.82, suggesting a strong interdependence of the scores. Accordingly, to determine whether some combination of the scores would provide a more suitable measure of radiation-related damage than the scores individually, summary characteristics of the correlation matrix were computed. These computations revealed that assigning approximately equal weights to the scores and summing the product of the score and its weight would account for 75% of the collective variability. More mathematically stated, the vast majority of the variability was explained by the first eigenvector, which since it weights subjects equally, is tantamount to the mean of the individual subject scores. No other combination of the scores explained more than 6% of the variability, and all were associated primarily with a single subject, the second with music, the third with gymnastics, etc.

75. Achievements in school of the prenatally exposed survivors, as judged by the relationship of the average school performance score in these subjects, can be summarized as follows (see Figure III):

(a) for 8-15 weeks after ovulation, scholastic achievement in school diminishes as the estimated absorbed dose increases;

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

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

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

5. Seizures

76. Seizures are a frequent sequela of impaired brain development and could therefore be expected to affect more children with radiation-related brain damage than children without. Dunn et al. [D3] have described the incidence and type of seizures among the prenatally exposed survivors of the atomic bombings and their association with specific stages of prenatal development at the time of irradiation. Histories of seizures were obtained at biennial routine clinical examinations starting at the age of 2 years.

77. Seizures, as here defined, include all references in the clinical records to "seizure", "epilepsy" or "convulsion". All of the medical records of participants in this programme of examinations who were coded for seizures were reviewed to characterize the nature of the seizure (i.e. its severity, clinical symptomatology, presence of fever, cause of the seizure, duration), the presence of other neurological disease, developmental landmarks, school performance, and any other medical problem. The records were not sufficiently explicit nor were electroencephalographic findings available to permit detailed clinical classification. However, there was enough description to allow a limited categorization of seizures by aetiology for epidemiologic purposes. Starting with all seizures, cases were classified as febrile, acute symptomatic (seizures due to acute central nervous system insult, such as head trauma) and unprovoked.

78. Cases of unprovoked seizures are those seizures without a record of a concomitant acute insult, that is, a known precipitating cause of a seizure, e.g. fever, trauma, post-vaccination reaction, or anoxia during an acute postnatal event. A seizure was so classified if the medical records revealed no clear statement of exposure to an accompanying infectious, traumatic or fever-producing agent. Strictly neonatal seizures (within the first month post-partum) were difficult to ascertain in this study, which did not begin until the children were 2 years old. Since neonatal seizures appear to have a different aetiology and were most likely underascertained, they were routinely excluded.

79. Fever is the most common precipitating cause of seizure in infancy or childhood. In the event of multiple seizures, however, fever might accompany only one seizure, and then not necessarily the first, and scoring these cases was undoubtedly arbitrary. The investigators adopted the following convention: if fever accompanied only one of several seizures, making it doubtful that fever was a generally precipitating cause in an individual, the case was scored as unprovoked.

80. No seizures were recorded among individuals exposed 0-7 weeks after ovulation at estimated doses higher than 0.10 Gy. In the group exposed 8-15 weeks after ovulation, the incidence of seizures was highest among those who received doses exceeding 0.10 Gy and increased with the level of fetal exposure. This was the case for all seizures without regard to the presence of fever or precipitating causes, and for unprovoked seizures. When the 22 cases of severe mental retardation were excluded, the increase in seizures was only slightly significant, and then only for unprovoked seizures. After exposure at later stages of development, there was no increase in recorded seizures.

81. Other data on the occurrence of seizures following *in utero* exposure are sparse, and there is little to which these observations can be compared. However, two case reports suggest that the period between 8 and 15 weeks may be a vulnerable time for exposure of the human fetus to radiation, with subsequent development of seizures [G10]. The first individual was a male exposed in the second to fourth month of gestation in the course of his mother's radiotherapy (dose unknown) for uterine myomatosis. He then developed epilepsy at the age of 3.5 years. The second was a female exposed during months 2 and 3, again in the course of maternal treatment for uterine myomatosis (dose unknown); she developed epilepsy at 2 years of age.

82. *Summary.* To summarize paragraphs 50-81, studies of the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki have revealed a statistically demonstrable dose-related increase in the frequency of mental retardation, seizures, individuals with atypically small heads, diminution in intelligence test scores and academic achievement. These effects are most conspicuous in weeks 8-15 following ovulation; however, there is a significant increase in the number of individuals with small heads in the first two months post-ovulation (12 of 81) and some evidence that mental retardation may be more common than expected in post-ovulatory weeks 16-25, particularly at doses estimated to be 0.5 Gy or more, where 3 (12.5%) of 24 children were retarded.

6. Pathologic and other findings of brain abnormalities

83. The biology of mental retardation remains enigmatic, and without a clear understanding of the molecular and cellular events that culminate in this functional defect, the role ionizing radiation may play in its origin is elusive. Despite important recent advances in diagnostic methods, causation is unknown in the great majority of cases of mental retardation. Often (10%-20% of cases) the brain appears normal by all standard methods of neuropathologic examination. Even more frequently the structural changes that are seen are mild and non-specific: the brain may be small, the grey matter may be aggregated abnormally in the subcortical areas, the columnar arrangement of cells may be unusual or the neurons may be more tightly packed than customary. However, two observations are common: a dysgenesis of dendritic spines on the cortical pyramidal neurons and impaired growth of dendritic trees of pyramidal neurons, affecting both basal and apical dendritic branches [H18]. These findings suggest defects in the geometry of the cerebral cortex, which form a plausible, but obviously not established, basis for the mental retardation. They further suggest that the difference between the normal brain and the retarded one may be as much quantitative as qualitative. But the brain is a structure that undergoes major postnatal developmental changes, including the pruning and rearrangement of synapses, and these continue into adolescence. Since this postnatal growth may modify errors that arose prenatally or perinatally, neuropathologic abnormalities seen in the cortex may depend on the age at which the individual was studied. Catch-up growth has been observed in some instances in experimental animals, but the prevalence of this in the human is unknown. Postnatal growth changes may merely lead to mismatched connections and a brain with the normal numbers of synapses, which have not, however, been incorporated into functional units.

84. Whether the cases of mental retardation seen among the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki represent malformations or instances of maldevelopment is not clear. The issue is more than semantic; it strikes at the mechanism of damage. This mechanism can be perceived as involving a dose-related large effect on a small number of individuals, i.e. as a malformation, or as a small effect on a large number of individuals, i.e. as maldevelopment, or, conceivably, as a mixture of the two. In maldevelopment, mental retardation reflects a dose-proportional effect on a variable that is continuously distributed. Otherwise stated, exposure results in a shifting downwards of the distribution of capacities for intelligence and results in some individuals whose capacity falls below that associated

with clinical judgments of retardation. An analogy
involves small-statured individuals, some of whom are
small because of a single gene effect, such as the
achondroplastic dwarfs, and others merely represent
the lower end of the normally occurring variation in
stature. Other analogies could be drawn, such as sper-
matogenesis or haematopoiesis.

85. Pathological findings are still too limited to
provide an unequivocal answer to the origin of mental
retardation following exposure to ionizing radiation.
The information available from studies performed is
presented here.

86. Four individuals of the Clinical Sample who died
have been submitted for autopsy; two were mentally
retarded and two were not. Of the two with normal in-
telligence, a 9-year-old male exposed in week 20 after
ovulation to a dose estimated to be less than 0.01 Gy,
died from granulocytic leukaemia; autopsy disclosed
extensive brain haemorrhages, which were thought to
be the final cause of death. His brain had a normal
weight of 1,440 g and a normal structure. The death of
the other, a 29-year-old female, was ascribed to car-
diac insufficiency. She had been exposed in fetal
week 24 to an estimated dose of less than 0.01 Gy.
The autopsy revealed multiple bilateral pulmonary
infarcts and evidence suggestive of autoimmune dis-
ease (the clinical data were too scanty, however, to
pursue this possibility). Cut sections of the cerebrum,
cerebellum, brain stem and spinal cord showed no
abnormality on gross or on microscopic examination.
The brain had a normal weight of 1,450 g; there was
no evidence of edema, which would have increased
brain weight.

87. Both of the mentally retarded individuals had
brain weights substantially below normal. One of these
individuals, a 20-year-old overweight female (MF
400133) exposed in week 31 after ovulation to an esti-
mated dose of less than 0.01 Gy, died of congestive
heart failure. Her body mass index (defined as weight
in kilograms divided by the square of the height in
meters) was 28.6; a body mass index of 27 or greater
is commonly used to define obesity. 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 grey and white matter
and no evidence of edema. Her mental retardation was
presumably not related to her exposure, given the very
low dose involved. The other mentally retarded indivi-
dual, a male (MF 142623), died of acute meningitis at
the age of 16 years [N3, Y1]. If he had been carried
to the normal termination of a pregnancy, he would
have been exposed 12 weeks after ovulation, but given
his birth weight (1,950 g), he was undoubtedly pre-
mature. His weight suggests that he was actually

exposed at week 8 or 9, since a full-term Japanese
infant would weigh about 3,200 g. The estimated
absorbed dose to the uterus of his mother was 1.2 Gy,
and his brain weighed 840 g. He was bilaterally
microphthalmic and 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 heterotopic grey matter around the lateral
ventricles. Histologically there was an abortive laminar
arrangement of nerve cells within the heterotopic grey
areas, imitating the normal laminar arrangement of the
cortical neurons. The cerebellum and hippocampi were
histologically normal, but both mamillary bodies were
missing. These bodies, which can be seen in recon-
structions at 6 weeks after conception but are not
externally recognizable in their double form until
somewhat later, are thought to function as a part of
the limbic system, which controls emotions and moti-
vations, and interestingly this boy was not only
retarded but severely emotionally disturbed. Hetero-
topic grey matter was not observed in any of the other
three cases, including the second mentally retarded
individual.

88. Heterotopic masses are collections of nerve cells
in abnormal locations within the brain. They are due
to an arrest in the migration of the immature neurons.
They may be single, multiple, unilateral, bilateral,
periventricular or located deep within the white matter.
The most common locations are subependymal and
just below the neocortex. They may be isolated or
associated with other anomalies in brain development,
such as schizencephaly, a rare abnormality of the brain
in which clefts extend across the cerebral hemispheres.
Individuals with isolated heterotopias can be clinically
asymptomatic; when symptomatic, they often present
with seizures in infancy or early childhood, but
seizures have also been reported associated with other
neurological defects, such as homonomous hemi-
anopsia, the loss of vision in one half of the visual
field in one or both eyes [O12]. Seizures have also
been seen accompanied by the partial or complete
absence of the corpus callosum [B13]. Most hetero-
topias are probably microscopic, but if sufficiently
large (0.5 cm or so), they can be readily visualized
with either computed tomography or magnetic reson-
ance imaging [B13, O12]. The incidence of isolated
heterotopias, either asymptomatic or symptomatic, is
not known.

89. Ectopic grey matter is commonly seen in rodents
following exposure to ionizing radiation. Hicks et al.
[H9] reported such occurrences more than three
decades ago and argued that they arose from surviving
cells that retained the capacity to divide but did so in
an abnormal environment. More recently, Donoso et
al. [D8] found that all rats exposed to 1.25 Gy of

x-radiation on gestational day 15 developed ectopic areas beneath the corpus callosum and adjacent to the caudate nucleus. It is presumed that these isolated islands, or rosettes, of neuronal cells arise through faulty repair of radiation-related damage to the ependymal wall of the lateral ventricles, leading to an encirclement of mitotic cells. Subsequent divisions of these cells result in neuroblasts migrating in all directions. Structurally, the rosettes are not laminated but contain neurons with the shapes and sizes characteristic of cortical pyramidal cells. At 4 weeks of age, these cells are immature and seldom seen in the layered cortex above the corpus callosum. At 4 months of age, however, the immature cells are no longer present in the ectopias, and the ectopic pyramidal cells resemble those in the cortical layer. Donoso et al. [D8] found the number and distribution of spines on the ectopic pyramidal cells to be lower than for the layered cortical neurons. They further found that, whereas the number of apical spines decreased with age in the control animals, this did not occur in the ectopic zones. Synapses in the layered and ectopic cortex were morphologically indistinguishable. Since synaptogenesis in the rat is largely a postnatal phenomenon, and synapses were seen in the ectoectopic areas, these areas may have retained some functional activity.

90. The brains of five of the mentally retarded individuals exposed to the atomic bombings, all during week 8-15 after ovulation, have been examined using magnetic resonance imaging techniques [S8]. Although the number of individuals that have been studied is small, several different anomalies of development have been seen, and these correlate well with the embryological events transpiring at the time the individuals were exposed.

91. Two individuals, both males (MF 404259 and 471693), exposed during weeks 8 and 9 after ovulation, showed ventricles somewhat larger than normal and areas of heterotopic grey matter adjacent to the lateral ventricles. One of these individuals (MF 404259) exhibited an underdeveloped area in the left temporal region, an anterior commissure somewhat wider than normal and a thickened nucleus accumbens sept. Formation of the caudate lenticular bridge also appeared to be poor. It is noteworthy that this is the period when the first wave of neuronal migration develops, the one that proceeds without the support of the radial glial fibres. The findings in these two cases are strikingly similar but not identical to those on the autopsied case described earlier. However in these two instances, unlike the autopsied case, both mamillary bodies are clearly visible in the images. While this fact could be attributable to variation in developmental age, it could also suggest that the estimated ages at exposure are not exact.

92. Ectopic grey matter occurs in other instances of mental retardation not related to exposure to ionizing radiation, but its prevalence among mentally retarded individuals is not reliably known, and it may vary with the type and severity of the retardation. Thus, for example, Rosman and Kakulas [R20] have contrasted the brains of six mentally retarded individuals with muscular dystrophy with those of six dystrophic patients without mental defect. The average brain weight of the deficient group was significantly less than that of the controls. Grossly visible malformations of cerebral development were present in three of the deficient patients, four showed pachygyria and all six had significant microscopic heterotopias. There were no gross lesions in the control subjects, and significant microscopic heterotopias were present in only one of the patients whose intelligence was considered to be normal. A similar comparison of individuals with multiple neurofibromatosis (von Recklinghausen's disease) with and without mental retardation found the cortical architecture to be grossly or microscopically abnormal among the mentally retarded but not among those who were not retarded [R19]. These architectural abnormalities included random orientation of neurons, a disarray of normal cortical lamination and heterotopic neurons within the cortical molecular layer. Among the retarded individuals they also commonly saw (three out of five cases) small heterotopias in the deep cerebral white matter (defined as more than 10 mm from the cortico-white matter junction). These were not seen in the individuals of normal intelligence. However, subcortical heterotopias were present in all instances of the disease.

93. Ectopic grey matter is not invariably associated with mental retardation. The neuro-imaging of individuals with the inherited fragile X syndrome, where varying degrees of mental retardation commonly occur, has not revealed this defect. Of 27 individuals who have been studied, eight were found to be abnormal [W13]. Seven of these individuals exhibited only a mild enlargement of the ventricles, but in one a moderate, generalized dilation was seen. Autopsy studies have, however, disclosed abnormalities in dendritic spine morphology; very thin, long, tortuous spines with prominent heads and irregular dilatations were noted [W13]. This suggests a developmental error occurring after migration was completed.

94. Two individuals, both females (MF 401081 and one unregistered case not included in the clinical sample), exposed at 12-13 weeks after ovulation, that is after completion of the initial wave of migration and late in the second, exhibit no evidence of conspicuous migrational errors but do show a faulty brain structure. There is an enlargement of the prominently rounded elevations of the brain, the gyri. These elevations are separated by furrows or trenches, the sulci, and the

latter are shallower than normal. Both individuals have a mega cisterna magna, that is, an enlargement of the subarachnoid cistern that lies between the under surface of the cerebellum and the posterior surface of the medulla oblongata. One of the cases (the unregistered one) studied at this time exhibited a corpus callosum (the network of nerves that provides communication between the two halves of the brain) markedly smaller than normal and a poorly developed furrow immediately above the corpus, suggesting an aberration in the development of the band of association fibres, the cingulum, that passes over the corpus callosum. Interestingly, animal experiments suggest the cingulum to be particularly radiosensitive [R14, R17]. Indirectly, these findings suggest errors in migration.

95. Still later in development, a male exposed to an estimated dose of 1.5 Gy at week 15 exhibited neither migrational errors nor conspicuous changes in brain structure (MF 143818). It is therefore presumed that the functional impairment that exists must be related to the degree of connectedness between neurons. There is experimental evidence to show that exposure at this time in the development of the brain in primates leads to a diminished number of connections between neuronal cells [B6]. If all of the connections can be presumed to have functional significance, then the diminution must compromise performance in some manner.

96. Are the developmental errors described in the preceding paragraphs causally related to prenatal exposure to ionizing radiation, or are they merely fortuitous, characteristics of mental retardation generally? Two lines of evidence suggest causation. First, although the data are limited, similar findings have been reported in other individuals who were exposed to ionizing radiation prenatally. For example, Driscoll et al. [D5] have described the acute damage to two fetuses, one a male exposed at 16 or 17 weeks of pregnancy and the other a female exposed at 22 weeks to radium therapy in the course of treatment of maternal squamous cell carcinoma of the cervix uteri. Both were alive at the time of hysterectomy, a day following the cessation of treatment in the first instance and six days later in the second. The doses were large, estimated to be about 4.3 Gy at the centre of the fetal head and 7.7 Gy at the nearest point inside the cranium in the 16-17 week fetus, and about 16 Gy in the second fetus. In both cases, the brain incurred the greatest damage, but then it was also closest to the source of ionizing radiation. Neuronal cell loss was shown to be selective. The primitive post-mitotic migratory cells were promptly killed by the radiation, and in this respect the findings parallel those seen in experimental animals. Damage to the cerebellum was less extensive but still noticeable, particularly in the older fetus exposed to 16 Gy. Extensive changes were seen in other organs, notably the bone marrow and lymph nodes.

97. Thus the findings of Driscoll et al. as well as those of other investigators (see, e.g. [M19]), clearly indicate that if the dose is sufficiently high, severe damage to the brain can occur at stages in gestation consistent with those seen in the survivors of the atomic bombings in Japan. Unfortunately, the ages at exposure are described in terms of weeks of pregnancy, but if it is assumed that this implies time from the onset of the last menstrual period, as is commonly the case, then, measured from the moment of ovulation, these fetuses were 14-15 and 20 weeks of development at the time of exposure. However, dose-response extrapolations to the situation among the prenatally exposed survivors of the atomic bombings must be guarded. The doses were three to eight times higher than the highest received by any one of the survivors of the atomic bombings, and well above the presumed whole body fetal LD_{50}. Moreover, the Japanese studies are based upon live-born children surviving at least to an age where a clinical diagnosis of mental retardation could be made. Given the extensiveness of the damage in the cases described by Driscoll et al., it is questionable whether these fetuses would have survived gestation and parturition.

98. Second, although migrational errors are often seen associated with well-recognized, often inherited, syndromes in which mental retardation occurs (for specific instances, see [D9, H19, M20], and for a review [B16]), they appear relatively uncommon in idiopathic (unclassified) mental retardation. Crome [C10], for example, describes the findings at autopsy on 282 institutionalized mentally defective individuals. He points out rather carefully the limitations of the sample of individuals he studied and does not argue that his findings are representative of "the large number of mentally retarded individuals in the community or special hospitals". Among 191 individuals with unclassified mental retardation, he identified about 500 main abnormalities (each individual was counted as many times as main diagnoses occurred). About half of these abnormalities involved either dilation of the ventricles or a small brain (based on weight). However, smallness was defined as anything under 90% of the average, which implies that some 40% or so of a random sample of individuals would be diagnosed as having an abnormally small brain. Of more immediate interest and relevance to the prenatally exposed is the frequency of macrogyria (or pachygyria) and ectopic grey matter, since these are the primary findings reported in the Japanese studies. Crome identified only two cases (among 500-odd diagnoses) of pachygyria and two of "ectopic nodules of grey matter". Another, smaller series of autopsies of mentally retarded individuals in Finland revealed three cases of pachygyria or agyria among 80 individuals [P3]. Finally, a study of retarded individuals in Denmark reported 34 cases of microgyria or pachy-

gyria among 175 autopsies [C11]. Thus, the abnormalities seen among the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki would not appear to be common findings among the mentally retarded.

99. *Summary*. A variety of anatomical abnormalities of the brain have been seen among the prenatally exposed, mentally retarded survivors of the atomic bombings of Hiroshima and Nagasaki and in other embryos or fetuses also exposed to ionizing radiation. Although the data are limited, these gross anatomical effects have thus far been seen only at doses in excess of 0.5 Gy. Some of these abnormalities have been observed among mentally retarded individuals who were not exposed to radiation, but they appear to be less common. The abnormalities commonly correlate well with the embryological events occurring at the time of exposure, suggesting a causal relationship. However, the observations are essentially descriptive and subject to different interpretations; they suggest but cannot establish the nature of the cellular or molecular events that are impaired. Further similar studies are obviously needed.

B. OTHER HUMAN STUDIES

1. Prenatal exposure

100. Numerous studies and a variety of case reports (see, e.g. [B1, D5], and [M19] for a review) have been published that further the understanding of the possible role of ionizing radiation in the origin of brain abnormalities [G1, M1]. However, few of these studies or reports provide a reliable basis for risk estimation. Generally, there is little information on the exposures or on the developmental ages after fertilization at the time of exposure, and the sample sizes are often small. An exception to this is the study of some 998 children born at the Chicago Lying-In Hospital to women who had pelvimetry during the course of their pregnancy [O3, O8, O9]. The pelvimetric procedure was standard and resulted in an estimated dose of 0.005 Gy to the fetus. Since the date at which pelvimetry occurred was recorded, the age of the fetus at exposure could be estimated. While the bulk (87%) were exposed in the second half of pregnancy, 120 or so were exposed prior to the day 140 after the onset of the last menstrual cycle. A variety of end-points were examined in this group of children, relative to two control groups (born before or after the pelvimetry series was completed), including the occurrence of malignant neoplasms and congenital malformations, and the presence of mental deficiency. Only one statistically significant difference between the exposed and the comparison groups was observed: the frequency of haemangiomas was increased in the pelvimetry group,

particularly when exposure occurred in the second or third trimester [G8]. Subsequent studies have indicated that this increase was due primarily to flame nevi, and the investigators are inclined to attribute no biological significance to their finding [O8]. Although the sample ascertained by Oppenheim et al. [O3, O8, O9] is relatively large (about 1,000 first-born children) and the irradiation occurred routinely rather than for medically indicated diagnostic purposes, the doses are generally small, 0.01-0.03 Gy, and as previously indicated, the bulk of the children were exposed in the third trimester. Unlike those studies of individuals where irradiation had occurred on a selective basis (e.g. [D4]), these authors find no evidence of a radiation-related effect on morbidity or mortality, save the one described above, but the analyses usually pooled all ages at exposure, and the power of the tests, in the statistical sense, is small in light of the expected effect at these doses, based on the Japanese studies.

101. Granroth [G2] has examined the association of diagnostic x-ray examinations in Finland with the occurrence of defects of the central nervous system. The data, drawn from the Finnish Registry of Congenital Malformations, reveal a significant increase in abnormalities of the brain, primarily anencephaly, hydrocephaly and microcephaly, among newborn infants prenatally exposed, when contrasted with control subjects matched by time and area. 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 anomaly or fetal anomaly, so the exposures were unlikely to have occurred at a time when abnormalities such as anencephaly are induced [M11]. Accordingly, it seems unlikely that the results reflect a teratogenic effect of radiation.

102. Neumeister [N1] has described the findings on 19 children prenatally exposed to doses estimated to be between 0.015 and 0.1 Gy. No instances of severe mental retardation are recorded, but post-ovulatory age at the time of exposure was not taken into consideration and no suitable comparison group was found. A subsequent report, on 73 children, merely states that mental development followed a normal course [N7]. Meyer et al. [M5] failed to find evidence of an increased frequency of severe mental retardation among 1,455 women who were prenatally exposed to small doses of radiation 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. An increased probability of premature death among such individuals leads to underrepresentation of the mentally retarded later in life. In addition, exposure must commonly have occurred late in pregnancy, after the most vulnerable period.

103. Other studies, such as those of Nokkentved [N2], are similarly inappropriate for the estimation of radiation effects. Nokkentved examined 152 children exposed in the first four months after fertilization to doses ranging from 0.002 to 0.07 Gy. The findings among these children were compared with the findings among their unirradiated siblings. Only one child, in the exposed group, was found to be microcephalic. There were no cases of microcephaly among the siblings. Two children in each group were reported to be retarded. Given the purported doses and sample sizes, these findings are not inconsistent with the experience in Hiroshima and Nagasaki.

104. Recently, Chinese investigators [H8, H17] published the results of a study of the long-term effects of prenatal exposure to diagnostic x-radiation on childhood physical and mental development that addresses some of the limitations, previously cited, of other studies. The exposed group consisted of 1,026 children who had been born in hospitals in Beijing, Shanghai and Changchun and were between the ages of 4 and 7 years when recruited. The absorbed dose to the fetus ranged from about 0.012-0.043 Gy; these doses were estimated using a thermoluminescent dosimeter in a human fetus phantom exposed to x rays from the posterior-anterior, lateral and axial views with typical exposure factors. Only one child, however, was exposed before week 8 following ovulation; 13 were exposed in weeks 8-15, 41 in weeks 16-25 and the remainder in week 26 or subsequently (most of them in week 37 or thereafter). The comparison group was comprised of 1,191 children matched to the exposed group by sex, age and hospital of birth. Height, weight and head circumference measurements were obtained, and intelligence was assessed using a 50-item intelligence and ability scale developed by the Capital Institute of Pediatrics of the Chinese Academy of Medical Sciences and standardized nationally. No significant difference between exposed and controls emerged in the measurements of physical development. The mean intelligence test score was reduced to a modest but statistically significant extent among the exposed group as compared to the non-exposed group (mean IQ: 100.35 and 101.71, respectively), and the distribution of individual scores was slightly shifted towards lower values. However, when possible confounding factors were taken into account, this difference was no longer statistically significant, nor was a significant difference found when attention was focused on those cases exposed between 8 and 15 weeks after conception. Given the small doses and the small sample size in the critical period, it is not surprising that these authors found no significant effects.

105. Ragozzino et al. [R21] have described the outcome of 9,970 pregnancies recorded for 2,980 women in the Rochester, Minnesota, metropolitan area

in the United States in the years 1935-1960. The health status of the children was followed for more than 20 years in 70% of the entire cohort. This was possible because of the linkage system for medical records, which facilitated the retrospective determination of radiation absorbed dose and the comprehensive, long-term follow-up of mothers and offspring. Absorbed dose to the fetus for examinations in which the uterus was in the primary radiation beam was estimated for five intervals of gestation by multiplying calculated fetal dose at conception by a scale factor based on average maternal anterior-posterior dimension at different gestational ages. Fetal absorbed dose was expressed as the total absorbed dose in the first trimester, as the total dose absorbed by mid-gestation and as the absorbed dose accumulated throughout gestation. For purposes of analysis, the doses were classified into three categories, namely, 0 Gy, 0-3 mGy, and >3 mGy. Among the 8,014 children where the data were complete, 63 cases of mental retardation were recorded. The relative risk in the highest dose group, based on the mid-gestation total absorbed dose, was not statistically significant; the value was 1.1 (95% CI: 0.06-5.39). Data were not reported on the occurrence of seizures.

106. Results are also now available from a 5-year clinical-physiological study of children who were born after the Chernobyl accident whose mothers lived in contaminated areas at the time of pregnancy [T6, T7]. The critical periods for cerebro- and corticogenesis (8-15 and 16-25 weeks) for 370 of these children occurred in May, June and July of 1986, but the doses accumulated in these periods are not clear. However, the findings of Ilyin et al. [I5] suggest that they were probably a few tens of milligray at most.

107. Some delay in myelination, accompanied by slight psychomotor disorders, was seen in 14.5% of children exposed in the critical period of cerebrogenesis, but in only 7.5% of children born in the first half of 1988. EEG studies of these children showed a delay in normal alpha rhythm formation, with significant input of slow waves and later formation of zone differentiation. This was found in 16%-18% of children examined at 2 and 5 years of age. For the critical group of children, symptoms associated with an increase in intracranial pressure were seen, as revealed by special function studies. This was found in 18%-35% of cases, more frequently among children 2-3 years old.

108. The occurrence of seizures, confirmed by repeated EEG examinations, was observed in 14 of 342 children [T6, T7]. However, seven of these children were excluded since they had other proved causes of symptomatic seizures. For the other seven there were no other apparent causes than radiation exposure.

Seizures were observed more frequently in the group exposed at 8-15 weeks (13.4%) than in the group exposed at 16-25 weeks (8.2%); in the comparison group, the frequency of seizures was only 3.0%-3.2%. Insofar as the developmental period of vulnerability is concerned, these findings are consistent with those that have been reported for the prenatally exposed survivors in Hiroshima and Nagasaki. No cases of microencephaly, Down's syndrome or any gross CNS defect were observed in the study group.

109. *Summary.* Aside from the observations on the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki, there are few other population-based studies of the effects of prenatal exposure on the developing human embryo and fetus. Those that have been published often provide no information on the doses received by the embryo or fetus or on the developmental ages after fertilization at which exposure occurred. Moreover, the sample sizes are often small and the power of the statistical tests inadequate in the light of the expected effect based on the Japanese experience. These caveats notwithstanding, the information provided by those studies that are available is broadly consistent with the Japanese data and not clearly contradictory.

2. Exposure of the infantile and juvenile brain

110. Because maturation of the human brain continues beyond birth, possible late-stage effects of prenatal exposure of the brain to ionizing radiation (especially in the later weeks of gestation) may be similar to effects from exposures of the infantile and juvenile brain. It is clear that ionizing radiation used therapeutically in the treatment of brain tumours or acute leukaemia at these ages can have deleterious effects, as measured by conventional intelligence testing (e.g. [E1, H3, M10, R7, S3]). Meadows et al. [M10] stated that "significant reductions were found in overall intelligence score for the majority of children, younger patients being most affected". The exposures involved in these instances were high, tens of gray, and most of the individuals involved were also receiving chemotherapy. It is also important to bear in mind that protracted hospitalization of the young often denies them the opportunity to socialize with their contemporaries and the intellectual interactions this affords. Neuropsychologic and other effects of therapeutic irradiations of children are discussed in Annex I, "Late deterministic radiation effects in children".

111. X-ray induced epilation was extensively used between 1910 and 1959 for the treatment of tinea capitis. It has been estimated that more than 200,000 children worldwide received this form of treatment. Albert et al. [A1], in their study of one group of children treated for tinea capitis, reported a higher

incidence of mental illness, including psychosis, personality disorders and psychoneurosis, among 1,905 children treated for this disease by x rays than among 1,501 children 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.

112. Subsequently, Omran et al. [O7] described the results of psychiatric and psychometric evaluations of 109 children with tinea capitis treated by x-ray therapy and 65 treated with chemotherapy. They found more patients with deviant Minnesota Multiphasic Personality Inventory 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, because x-ray treatment and chemotherapy treatment differ in aspects other than radiation exposure and because a variety of emotional disturbances are associated with protracted hospitalization of the young. However, Ron et al. [R8] (see also [A1, O7, S5]) have reported a similar finding among individuals treated for tinea capitis who were not on adjuvant therapy nor hospitalized and who received similar radiation doses, possibly 1.3 Gy, on the average. Ron et al. [R8] 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". Apparently no estimate was made of the diminution in intelligence test score per unit exposure. The increased frequency of cases of cortical dysfunction reported by these authors and in the studies described in the preceding paragraph are not known to be associated with demonstrable anatomic changes in the brain.

113. Studies of children exposed during the first few months of life to absorbed doses in the brain of 1.0-5.2 Gy as a result of therapy for haemangiomas of the head, face and neck also reveal impaired subsequent brain development (see, e.g. [T3, T4, T5]). These investigators assessed brain function using not only conventional clinical and neurological examinations but also electroencephalography, electromyography, rheoencephalography and a variety of psychological tests. More than half of the children exposed to doses ranging from 0.46 to 1.3 Gy exhibited functional central nervous system changes. These were commonly manifested as memory and emotional defects. At somewhat higher doses (2.3-3.4 Gy), damage was more pronounced and included structural-functional asymmetries that could be demonstrated electroencephalographically. Long-term follow-up has re-

vealed some amelioration of these effects in some instances. At doses of 4.2-5.2 Gy, arrested physical and endocrinological growth was seen, accompanied by a reduction in head size with deformity. Mental retardation combined with epileptoid phenomena was also seen. No amelioration occurred with time in these cases. Generally, it was found that the older the child at the time of exposure, the higher the dose required to produce a specific effect.

114. Studies have been made in the former Soviet Union of the late consequences of radiation therapy for brain tumours, using concentrated beams in fractionated exposures [M25]. Observations after 5-10 years disclosed a number of asthenoneurotic cerebrasthenic syndromes, combined with hypertension, vestibular and atactic insufficiency, and residual hemiparesis in some children. Psychological studies have revealed passive attention instability, active attention exhausti-bility, rapid loss of interest due to fatigue and memory and intellect reduction; some children exhibited overt emotional disorders. In nearly half of the cases studied, however, some amelioration of these effects occurred, and after 5-7 years there was an apparently satisfactory social and school adaptation. Seven individuals developed an epileptoid syndrome after 10 years, and nine had a lowered convulsion preparedness threshold, based on electroencephalogram (EEG) tests.

115. Long-term observations have also been made on 89 Soviet children treated with ^{60}Co gamma rays for haemangiomas of the skin in the first 6 months and the first 2 years after birth [T4, T5]. Local doses were estimated to be 15-28 Gy, but exposure of the brain was non-uniform, varying from 1 to 3 Gy. A retardation in the development of motor and motorstatic functions, as evidenced by psychomotor performance or partial-speech, was seen in 11 children. By 5-6 years of age, almost a quarter of the children (22 per cent) exhibited an encephalopathy syndrome, often with evidence of minor organic damage to the central nervous system. Among the symptoms they exhibited were headache, difficulty in falling asleep, increased fatiguability of the neuromuscular system, vegetative-vestibular disorders (vegetative as used here and subsequently implies the autonomic nervous system) and a reduction in memory and associative abilities. Eight children had psychovegetative disorders and lowered IQ. After puberty, during adolescence and youth, satisfactory or good social adaptation occurred in some instances, but neuropsychic dysadaptational periods were seen. EEG tests disclosed an epileptoid syndrome, as well as a lowering of the convulsion preparedness threshold in seven individuals, including two with epileptiform seizures (radiation dose 22-26 Gy). These neuropsychic organic and functional changes were most pronounced in children exposed at 1-6 months and 1-3 years of age.

C. EXPERIMENTAL STUDIES

116. As noted in paragraph 2, previous UNSCEAR reports (see, in particular, [U2, U4]) have considered the general developmental effects of prenatal irradiation as revealed by experimental studies. It is not the intent of this Annex to re-examine the voluminous literature, but to comment on certain recent findings that deal specifically with the development of the brain. Mole [M19] reviewed this literature and the basis it affords for predicting malformations after irradiation of the developing human.

117. Experimental studies have demonstrated that the relative sensitivity of different components of the brain to ionizing radiation differs, and possibly substantially so. Reyners et al. [R17, R18], for example, have shown that the cingulum bundle, a myelinated substructure of the corpus callosum, is an especially sensitive indicator of exposure to x-radiation. Changes in this structure occur at doses as low as 0.1 Gy, that is, at doses too low for the effects to be readily explicable in terms of mitotic cell death, and suggest a disordered sequence of morphogenetic events. More recently, using 600 keV neutrons from a Van de Graaff accelerator, Reyners et al. [R22] have shown a significant effect on brain weight at doses as low as 10 mGy. This diminished brain weight is accompanied by a significant reduction in the size of the cingulum bundle. Reyners et al. concluded from their studies that "the threshold dose for detectable effects to a developing brain may be lower than 35 mSv, in particular for acute exposure to high energy transfer particles during the period of corticogenesis." Lent et al. [L1] have shown that mice exposed to 2 or 3 Gy of gamma radiation on gestational day 16 are invariably acallosal. It is not clear, however, whether these changes in the cingulum and the corpus callosum are conspicuously detrimental to the animal nor is it known why the cingulum appears to be so radiosensitive, more so than the entire corpus callosum.

118. Until relatively recently, most experimental studies have focused on changes in brain morphology or weight (e.g. [A3, H7, S13]) following exposure to ionizing radiation rather than changes in brain function. There are exceptions to this statement. Studies conducted almost three decades ago have revealed that seizures occur in rodents following prenatal exposure. Sikov et al. [S12, W11], for example, reported an increased frequency of seizures among the offspring of albino rats exposed at 15 days of gestation to a dose of 0.5 or 1.9 Gy. These seizures were described as focal in onset, with rapid progression from face to forelimb and hind limbs, and then quickly becoming generalized. They were said to be equivalent to the typical Jacksonian seizure in man, in which the attack usually proceeds from the distal to the proximal limb

musculature. No increase in seizures was seen when exposure occurred on day 10 of gestation, and no effort was made to define a dose-response relationship at 15 days of age. Other neurological deficits were noted, such as gait defects, forced circling and hypersensitivity to some sensory stimuli, which manifested itself as exaggerated myoclonic jerks. Although some of these effects were seen in rats exposed on day 10, they were more common among the rats exposed on day 15 and at the higher dose.

119. However, behavioural studies of rodents following prenatal irradiation have now revealed that a variety of behaviours are correlated with cortical morphology. Norton [N5, N6], for example, has reported that cortical thinning is associated with changes in an animal's angle of stride, negative geotaxis and continuous corridor activity, as well as with other behavioural measures. She has further shown that some behavioural tests exhibit a clear dose-response relationship to doses as low as 0.25 Gy (the lowest dose used in her experiment), although several behavioural parameters were not altered by radiation. Jensh et al. [J4, J5] have described similar findings in the Wistar rat at doses of 0.2 Gy and higher, but they concluded that all of the parameters they had studied had thresholds at or above 0.2 Gy. Kimler et al. [K6] have shown that the organ most sensitive to radiation-induced alterations changes: it is the pituitary gland at gestational day 11 and the primitive cortex of the brain at days 13-17, with a peak of sensitivity at day 15. They further noted that a spectrum of related functional and morphological deficits can be produced even by low-dose in utero irradiation (0.25 Gy), with the specific end-point showing the greatest change being determined by the day on which exposure occurs. Finally, Minamisawa et al. demonstrated an effect of aggressive behaviour in adult male mice following fetal exposure to gammarays [M24]. These anatomical and behavioural experi-mental results accord surprisingly well with what has been seen in the human (for a comparison see [S24]).

120. Still other neurophysiologic effects, with different critical periods, have been identified. Recent-ly, for example, it has been shown that mice irradiated prenatally on day 18 (corresponding, roughly, to week 33 in the human) suffer a significant loss in spatial memory [S16]. The integrity of spatial memory ap-pears to depend on the proper development of the hip-pocampus, a primitive, anatomically distinct part of the cortex lying beneath the cerebral hemispheres. This structure arises relatively late in the development of the human brain, but damage to it results in a recog-

nized cognitive defect characterized by severe amnesia and includes deficits in learning mazes. Moreover, there is evidence that associates a reduction in the pyramidal cells within the hippocampus with memory impairment.

121. Analogous behavioural changes have been seen in primates following prenatal exposure [O10]. Brizzee et al. [B12], for example, have reported that the exposure of squirrel monkeys on days 89 and 90 of gestation to ^{60}Co gamma-radiation at doses of 0.5 or 1.0 Gy results in less accurate and poorly coordinated reflexes and neuromuscular coordination. The percentage of correct responses in tests on visual orientation, discrimination and reversal learning were significantly lower in the exposed animals than in the controls. At doses of 0.1 Gy, no structural or behavioural alterations were seen; however, the authors conjecture that more sensitive behavioural testing and the use of computerized microscopic techniques (and, possibly, the computer-aided mapping of specific neuronal populations [K9]) will reveal changes.

122. It is difficult to put these observations into a perspective suitable to the purposes of this Annex: the tests used to measure cortical dysfunction have no obvious human counterparts, the nature of the dose-response relationship is often clouded by the large inherent variability in the end-points measured, and so forth. Moreover, abscopal effects either in the experimental animal, the human or both cannot be excluded. Sloviter et al. [S11], for example, have shown that adrenalectomy of adult male rats results in a nearly complete loss of hippocampal granule cells 3-4 months after surgery. The hippocampus, as previously stated, is involved in learning, memory and a variety of other behaviours and is known to be the target of adrenal steroids. How widespread this phenomenon may be is not known, nor is it clear that radiation-related damage to the adrenals would effect similar changes. However, damage to the adrenals from prenatal exposure has been seen in the human [D5, Y1].

123. *Summary.* Three general conclusions seem warranted from the experimental evidence. First, it appears clear that low doses (that is, doses in the range of 0.2 Gy or so) produce measurable beha-vioural and anatomic effects. Secondly, behavioural changes have their structural counterparts in the architecture of the brain. Thirdly, there is a high degree of functional specificity in the information transmitted over neural systems.

III. RISK ESTIMATES

124. Quantitative risk estimates for radiation damage to the brain after prenatal exposure of human beings are of importance because they have practical implications for radiation protection. However, the human data on which to base such estimates are limited and imperfect. The data on the survivors of the atomic bombings of Hiroshima and Nagasaki provide the primary basis for the risk evaluation. As described in Chapter II, four types of observation are available from these data:

(a) the frequency of severe mental retardation recognized clinically;
(b) the diminution of intelligence, as measured by conventional tests;
(c) scholastic achievement in school;
(d) the occurrence of unprovoked seizures.

Each has its limitations, and there must be an awareness, when interpreting the available information, of these limitations and other difficulties. However, until 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. Unquantified clinical descriptions are of little assistance, and experimental data, though important qualitatively, provide an uncertain basis for quantitative estimates of prenatal risks in humans.

125. One of the most important problems in estimating the risk to the developing brain from exposure to ionizing radiation is the shape of the dose-response relationship. As stated, much of the data that have helped to identify the teratogenic effects of radiation have limited applicability, for either the doses are 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 radiation could affect the normal development of the brain and culminate in cortical dysfunction makes it hard to assess the reasonableness of an observed dose-response relationship. This limitation will remain until the different causes of a neurological deficit of an organic nature can be distinguished one from another.

126. As stated in paragraph 84, it is presently unclear whether the cases of mental retardation seen among the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki represent malformations or instances of maldevelopment. Their origin can be perceived either as involving a dose-related large effect on a small number of individuals or as a small effect on a large number or, conceivably, a mixture of the two. Since the suggested shift of the IQ curve towards lower values must increase the frequency of

mentally retarded individuals with increasing dose, the fall in IQ and the increase in severely mentally retarded individuals with dose may be interrelated. Indeed, the observed increase in mental retardation in the critical 8-15 week period and the shift in mean IQ in this same interval of time can be shown to be mathematically compatible. This fact has led the International Commission on Radiological Protection (ICRP) to conclude that the shift in IQ "appears to be a deterministic effect, probably with a threshold determined only by the minimum shift in IQ that can be clinically recognized" and to assert further that "the observed shift of 30 IQ units per Sv is best suited to describe the risk" of radiation-related mental impairment [12]. The Commission also concluded that "if both observations (alluded to above) are correct, the most likely interpretation is that the dose required to cause an IQ change large enough to make an otherwise normal individual mentally retarded would be high, while the dose that would bring an individual with potentially low IQ over the borderline may be a few tenths of a Sv".

127. It should be noted that ICRP interpretation of the data stemming from the studies in Japan has not gone unchallenged, most notably by Mole [M23]. He argues that the neuroembryology and plasticity of the brain do not support this interpretation, that the correlation between the shift in IQ and the occurrence of severe mental retardation reflects the way in which IQ tests are constructed and is not indicative of a common underlying biologic process, and that the data are actually better described by a threshold model, with the threshold being in the neighborhood of 0.5 Gy.

128. Mole contends that the interpretation of the damage to the developing brain depends upon the choice between two competing proposals about the mechanism of construction of the primitive cerebral cortex. One of these hypotheses, the radial column hypothesis, argues that the development of the cerebral cortex arises through the radial migration of neurons from their sites of birth to predetermined destinations in the cortex, forming, as they move, radial columns with specific functions (see, in particular, [R12, R13]). The other hypothesis (see [W8, W14]) asserts that the migration of neurons is not limited to outward radial movement but can occur in other directions and over longer distances than envisaged by the radial column hypthesis. He argues that ICRP in favoring the radial column hypothesis has erred in denying the plasticity of the human brain. This argument is specious for at least two reasons. First, the hypotheses stated briefly above are not competitive but supplemental; it is not a matter of the choice of one and the rejection of the other. Evidence

clearly exists for both mechanisms of migration. This should not be unexpected, since collectively they afford an explanation for both the known plasticity of the human brain and the necessity that some cortical functions be rigidly encoded. This does not deny plasticity, but asserts that cortical function is a complex process some portion of which is conservative. Secondly, ICRP, while favoring the radial column hypothesis, does not assert that all migration of neuronal cells must conform to this hypothesis. They do note, however, that the radial column hypothesis provides a basis for presuming that some small local lesions could have lasting effects on mental function.

A. RISK FROM ACUTE EXPOSURE

129. Re-evaluation of the data on the survivors of the atomic bombings of Hiroshima and Nagasaki 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 previously. The main points that specifically concern risk estimation are the following:

(a) the period of maximum vulnerability to radiation appears to be the time between 8-15 weeks after ovulation, that is, the interval when neurons are produced in greatest number and when they migrate to the cerebral cortex;

(b) a period of lesser vulnerability occurs in the succeeding period, 16-25 weeks after ovulation. This period accounts for about a quarter of the apparently radiation-related cases of severe mental retardation;

(c) the least vulnerable period is 0-7 weeks after ovulation, during which no radiation-related cases of severe mental retardation occur.

However, as previously stated, within the 0-7 week period, a higher proportion of exposed embryos fail to survive gestation, and it may be that brain-damaged embryos are less likely to survive to an age where their handicap can be recognized clinically. Moreover, a significant increase in the incidence of individuals with an atypically small head, presumably due to generalized growth retardation, does occur in these weeks.

1. Mental retardation

130. In fetuses exposed to radiation in the period 8-15 weeks after ovulation, the prevalence of severe mental retardation at estimated mean doses to the mother's uterus of 0, 0.05, 0.23, 0.64 and 1.38 Gy, was 0.8%, 4.5%, 1.8%, 20% and 75% (Table 4). Within this period of maximum vulnerability, it is difficult to

know, a priori, what the appropriate dose-response model should be, since mental retardation could arise through a variety of different biological or genetic events, ranging from cell killing to mismanaged neuronal migration to errors in synaptogenesis or to some combination of these events. Each of these processes could have its own unique, but currently unknown dose-response relationship. Accordingly the Committee has elected not to fit a specific model or models but to cite the risks as they have been observed empirically.

131. Although the Committee does not believe that a linear dose-response model has much, if any, biological credence, prudence suggests the need to examine such a model, since presumably it would maximize the estimated risk at low doses. Within the most vulnerable age group (irradiation at 8-15 weeks after ovulation), the incidence of severe mental retardation at 1 Gy is 0.39, with a standard error of about 0.09 Gy^{-1}.

132. In fetuses exposed to radiation in the period 16-25 weeks after ovulation, the prevalence of severe mental retardation at estimated mean doses to the mother's uterus of 0, 0.05, 0.23, 0.64 and 1.38 Gy was 0.6%, 1.8%, 0%, 0% and 37.5% (Table 4). Thus, the only demonstrably increased risk occurs at doses estimated to be 1 Gy or more.

2. Small head size

133. A variety of dose-response relationships, with and without a threshold, have been fitted to the data on head size grouped by trimester and post-ovulatory age (weeks) at exposure. A significant radiation-related effect on the incidence of individuals with a small head was noted only in the first and second trimesters and for the 0-7 week and 8-15 week periods after ovulation. It is worth noting that these findings are similar to those of Miller and Blot [M3], when allowance is made for the difference in dosimetry (they used the T65 maternal kerma) and some subsequent small changes in the data. They observed "a progressive increase with dose in the frequency of the abnormality (small head circumference) among persons whose mothers were exposed before the 18th week of pregnancy". When exposure occurred in the first trimester, the risk of an atypically small head suggests a possible linear-quadratic dose-response relationship. Both linear and quadratic terms are significant, but the quadratic term is negative. The results of fitting a linear-quadratic model to the 0-15 week period after ovulation suggest a linear dose-response relationship (Figure II). No excess risk for small head size is seen in the third trimester or among individuals exposed at 16 weeks or more after ovula-

tion. The estimated threshold, based on either a linear or a linear-quadratic dose-response relationship, is zero or nearly so. This apparent absence of a threshold and the somewhat different periods of developmental vulnerability suggest an embryological difference in the events culminating in small head size, on the one hand, and severe mental retardation, on the other.

134. The relationship of small head size to exposure to ionizing radiation and gestational weeks was evaluated using four physical measurements of growth and development: standing height, weight, sitting height and chest circumference. These variables are highly correlated. Accordingly, the four measurements were evaluated as a set, using a multivariate analysis with estimated DS86 dose and gestational week as covariates and sex and small head size as categorical factors. A retardation in growth is observed among individuals with a small head, with or without severe mental retardation, when their physical measurements are compared with those of individuals with a "normal" head size.

135. In order to investigate the possibility of growth retardation using the four physical measurements simultaneously, a multivariate analysis of covariance was attempted, using data for individuals 10-12 and 16-18 years old, for whom comparatively large numbers of observations were available. The retardation of growth with increasing radiation dose is observed at almost all ages, as judged by the negative estimates of the dose parameters associated with the four measurements. However, a statistically significant retardation of growth and development, after adjusting for confounding factors based on sex, small head and gestational age, is noted only at 17 years of age with or without inclusion of severe mental retardation and at 18 years of age with the severe mental retardation cases included. At 16 years of age there is a suggestive retardation of growth among individuals with small head size and severe mental retardation (p < 0.10). At all other ages, no statistically significant retardation of growth is observed; however, as previously noted, at these ages too, growth seems to diminish as the radiation dose increases. It must be borne in mind that where a statistically significant effect of radiation on growth is not seen, the pubertal growth spurt and its variability in age of onset could increase the generalized variance of the measurements, diminishing the sensitivity of the statistical tests. This conjecture is not supported, however, by a test of the homogeneity of the generalized variances, since these cannot be shown to be significantly heterogeneous.

136. Post-ovulatory age is statistically significant and negative for all coefficients associated with the four physical measurements, except for chest circumference at 10 years of age, with or without the inclusion of

individuals with severe mental retardation in the analysis. Individuals with small heads, with or without the inclusion of the cases with severe mental retardation, exhibit a highly significant retardation of growth and development with gestational age at exposure, as judged by the four physical measurements. Why this should be true is not obvious. But since the measurements decline as gestational age increases, it suggests that there may have been some selection for body size in the earlier gestational ages. Expressed in another way, individuals who survived exposure in the early stages of gestation may have represented healthier pregnancies, on average, that were therefore destined to give rise to larger children and young adults. If this were true, it would be reasonable to assume that no gestational age effect would be observed if the comparisons were restricted to those sample members who were either not exposed or exposed to estimated doses of less than 0.01 Gy. When the data are so restricted, however, the effect of gestational age remains, and its origin is unclear.

3. Diminution in intelligence and academic performance

137. The observations on intelligence tests and school performance suggest the same two post-ovulatory age periods of vulnerability to radiation. The period 8-15 weeks again shows the greatest sensitivity, although with the data available so far, it has not been possible to establish the form of the dose-response relationship unequivocally. However, within the post-ovulatory age group most sensitive to the occurrence of clinically recognizable severe mental retardation (exposure 8-15 weeks after ovulation) the diminution in IQ under the linear model is 21-33 points at 1 Gy, based on the new dosimetry and the specific set of observations used.

138. A linear-quadratic model does not generally provide a better fit to the intelligence test data (see Table 7), nor does it reveal persuasive evidence of curvilinearity in the dose response in the most critical post-ovulatory age group. However, the significance of the effect at 16-25 weeks after ovulation is more equivocal with a linear-quadratic model than with a linear one. Regression coefficients obtained in fitting linear and linear-quadratic models to school performance results are shown in Table 8.

139. The effects of diminished mental capacity considered here result from damage to the cerebrum in prenatally exposed individuals. Although experimental studies [A2, C12, H20] and case reports [B1, D5] have established that the cerebellum is sensitive to radiation damage, no evidence has emerged from the studies of the prenatally exposed survivors in Hiro-

shima and Nagasaki of such damage, and for several reasons it may be difficult to identify. First, Purkinje cells, the only efferent neurons in the cerebellum, are proliferating and migrating in the same developmental period as the neuronal cells that populate the cerebral cortex, so damage to precursors or differentiated Purkinje cells would occur at the same time and might be inseparable from damage to those cells that give rise to the cerebral cortex [Z1]. Secondly, 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 that were 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 neurologic deficit, are presently not possible. No evidence of damage to the mid-brain or the brain stem following prenatal exposure has been reported; accordingly, radiation risks to these parts of the central nervous system cannot be estimated.

4. Seizures

140. The risk ratios for unprovoked seizures, following exposure at weeks 8-15 after ovulation are as follows: after doses of 0.1-0.49 Gy, 4.4 (90% CI: 0.5-40.9); after doses of ≥0.5 Gy, 24.9 (90% CI: 4.1-192, mentally retarded included); 14.5 (90% CI: 0.4-200, mentally retarded excluded). Table 9 gives the results of fitting a linear response model to the grouped dose data including and excluding the severely mentally retarded.

141. It is not clear which of these sets of risk ratios, that based on the inclusion or that based on the exclusion of the mentally retarded, should be given the greater weight. The answer hinges ultimately on the mechanisms underlying the occurrence of seizures and mental retardation following prenatal exposure to ionizing radiation, and these are presently unknown. If seizures can arise by two independent mechanisms, both possibly dose-related, one of which causes seizures and the other of which causes mental retardation in some individuals who are then predisposed to develop seizures, the mentally retarded must necessarily be excluded if one is to explore the dose-response relationship associated with the first mechanism. If, however, mental retardation and seizures arise from a common brain defect, which manifests itself in some instances as mental retardation and in other instances as seizures, then the mentally retarded should not be excluded.

142. At present the only evidence suggesting a common radiation-related developmental defect is the occurrence of ectopic grey matter in some instances of

both disorders. However, even this evidence is difficult to put into perspective, because while it is known that ectopic grey matter occurs among some of the radiation-related instances of mental retardation, the observation of ectopia in individuals with seizures is based on other studies. As yet, there has been no investigation of the incidence of ectopic grey matter among the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki who have seizures but no mental retardation.

143. A search for a threshold in the occurrence of seizures (see Table 10) discloses the following: the central values of the threshold for all seizures range between 0.11 and 0.15 Gy in the most critical period, that is, 8-15 weeks after ovulation, and the estimates are even lower for unprovoked seizures (0.04-0.08 Gy). In all of these instances, however, the lower 95% bound on the threshold includes zero, so the data provide no compelling evidence for a threshold.

B. RISK FROM FRACTIONATED OR CHRONIC EXPOSURE TO NEUROTOXINS

1. Ionizing radiation

144. Little is known about the effects on the developing human embryo and fetus of fractionated or chronic 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 reducing the dose rate or dose fractionation will have some effect. The hippocampus, for example, 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.

145. Most of the information available on the effects of dose rate involves the experimental exposure of rodents. Since these findings have been summarized in previous reviews (see, e.g. [K11, M19, U2, U4]), attention here is restricted to only one or two representative observations. Brizzee et al. [B10] (see also [J1]) have examined cell recovery in the fetal brain of rats. Pregnant rats were exposed to ^{60}Co radiation on gestation day 13 in single doses, ranging from 0.25 to 2 Gy in increments of 0.25 Gy, and in 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 animals were disected and examined on the day 19 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. The 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". This reduction in damage with the protraction of dose seems greater for continuous gamma-ray exposure than for serial, brief x-ray exposures, and it has been argued that this may indicate a further sparing when the protracted dose is evenly distributed over time [M19]. If true, this obviously has important regulatory implications.

146. Recently, Vidal-Pergola et al. [V1] reported results of fractionated prenatal doses on postnatal development in Sprague-Dawley derived rats. Their experiment consisted of exposing pregnant females to single doses of 0.5 or 1.0 Gy, or to two doses of 0.5 Gy 6 hours apart. Offspring were subjected to four behavioural tests (negative geotaxis, reflex suspension, continuous corridor activity and gait) on postnatal days 7-28. The rats were then sacrificed, and the brains were removed and processed for histology. For all four behavioural end-points, the fractionated dose produced an effect that was intermediate between the 0.5 and 1.0 Gy doses and that, by linear interpolation, could be expressed as equivalent to a single dose of about 0.7 Gy. Measurements of the upper four layers, the lower two layers and the total thickness of the sensorimotor cortex in the dose-fractionated group revealed significantly less damage than was seen at a single dose of 1.0 Gy but more than that seen at a single dose of 0.5 Gy. Reyners et al. [R22] have examined the effects of protracted exposures to low doses of gamma rays on Wistar rats from day 12 to 16 post conception and found a significant reduction in brain weight at an accumulated dose as low as 160 mGy.

147. Newly developed techniques for the culturing of neuronal cells *in vitro* make such cell studies more practical now than in the past. For example, the means exist to culture cells from a snippet of the embryonic forebrain of the mouse (see, e.g. [F2, H15, H16]). These cells, when dissociated and plated in a monolayer, will form structures with a well-defined lumen and dispose themselves radially around the latter much like the proliferative zones seen in the fetal brain. The cells will divide, become post-mitotic, as evidenced by the presence of neural filament protein, and actually migrate to the periphery of the globular aggregate. At about 5-7 days after the formation of the aggregates, they collapse, presumably for want of a supporting structure, and although the cells will continue to divide and migrate, they no longer have a well-defined architecture. No studies

have been published describing the effect of exposure to ionizing radiation on this sequence of events in these cultures. However, even a week could be long enough to determine whether radiation does alter, even transitorily, the surface properties of these neuronal cells, much as Feinendegen et al. reported for haematopoietic stem cells [F3, F4]. The measurements on the haematopoietic stem cells are essentially indirect, but given the existence of specific monoclonal antibodies to a variety of the neuronal cell adhesion molecules and cytoskeletal proteins, a more direct test of alterations in the neuronal or glial cell membrane or the cytoskeleton of the neuronal cell is possible. If such studies are to be informative, however, it will be necessary to demonstrate that the changes seen *in vitro* parallel changes *in vivo* and are not merely the consequence of the experimental manipulations.

2. Neurotoxic chemicals

148. Some insight into the nature of the developmental effects to be anticipated from chronic radiation exposure may come from toxicological effects in embryos and fetuses exposed to toxic chemicals [W3, W4, W5]. 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. 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 behavioural and other neurological disorders was also seen in Iraq, where seed grain contaminated with methylmercury 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 paraesthesia. 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 [I3, W6].

149. The fetal alcohol syndrome offers another possible paradigm. Abnormalities of the central nervous system, particularly mental retardation and small head size, are also the most pronounced effects of heavy intra-uterine exposure to alcohol [S6]. The average IQ of individuals with fetal alcohol syndrome is about 65, although scores may vary from 16 to 105 [S7]; also, the severity of the mental retardation correlates with the severity of the dysmorphic features in the individual. Clarren et al. [C3, C4] (see also

[H4]) have noted that areas of ectopic grey matter in the frontal and temporal white regions of the cerebral hemispheres and leptomeningeal neuroglial heterotopias, both evidences of abnormal cell migration, are common among infants with fetal alcohol syndrome. This appears true not only among those infants born to chronically alcoholic mothers, but also those born to women who describe themselves as infrequent drinkers who have occasional episodes of intensive drinking.

150. It is generally assumed that the teratogenic effect of alcohol, insofar as abnormalities of the central nervous system are concerned, is initiated during the first trimester, but this has not been well established. Given the commonly chronic nature of the exposure, it is not surprising that the sensitive period is imperfectly known. Renwick et al. [R9], using an argument based upon seasonality in the prevalence of fetal alcohol syndrome, on the one hand, and ethanol use, on the other, suggested that the damage may occur as late as weeks 18-20 of gestation. Since they apparently measured gestation from the last menstrual period [R9], this corresponds to 16-18 weeks after ovulation and suggests that the vulnerable periods for alcohol use and exposure to ionizing radiation may be similar. It should be noted, however, that lepto-meningeal 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 grey matter has been seen, as previously described. These leptomeningeal neuroglial heterotopias are seen as a sheet of neural and glial tissue that covers a part of the brain surface and may partially incorporate the pia mater. They are apparently continuous with the molecular layer of the cortex and may represent a persistence of its subpial granular layer [B8]. If so, they arise somewhat later, probably after week 24 [B8, Z2]. 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.

151. Further insight into the effects of ionizing radiation on the developing human brain is to be found in the neurotoxic effects of prenatal exposure to lead (see, e.g. [M22, S19, S20]). Although the toxic effects of this metal are many and varied, four findings appear especially pertinent to this Annex. First, the effects of prenatal exposure to lead on the development of the central nervous system appear to be linear over a wide range of doses. For example, the decline in performance on the Bayley Mental Development Index, which has a mean of 100 and a standard deviation of 16, is 2-8 points per 10 μg of lead per deciliter of blood [M22]. But the epidemiological data do not allow a threshold to be established with con-

fidence. Linearity does not seem to be true for all neurotoxic effects, however. The lead-related impairment of peripheral nerve conductance, for example, appears to follow a quadratic dose-response curve, suggesting that a threshold may exist for this effect [S21]. In this instance neurotoxicity apparently requires the recruitment of several nerve fibers if a dysfunctional state is to obtain. This suggests that the shape of the dose-response relationship is intimately related to the developmental biology of the end effect measured. Secondly, since there are no absolutely lead-free societies, it is not possible to compare lead-free situations with those involving very low levels of lead exposure in order to determine whether there are non-monotonic regions in the empirical dose-response relationship. This situation is similar to that involving exposure to ionizing radiation. Thirdly, there is substantial evidence supporting the notion that lead toxicity involves molecular interactions of this metal with calcium and sodium [S19]. Given the ubiquity of exposure to lead, its effect on the transmembranal influx of calcium and the possible role of N-type calcium channels in neuronal migration, this suggests the need, in the case of ionizing radiation, to explore carefully the molecular and cellular mechanisms that may subtend radiation damage. Finally, in so far as lead provides a paradigm for the potentiation of radiation-related effects on the central nervous system through other toxic exposures, it is important to recognize that evaluation of the mother at the time of pregnancy may not predict the actual exposure of the embryo or fetus to a neurotoxin. In the case of lead, there is evidence that bone stores of this metal can be mobilized during pregnancy and cause rapid changes in internal exposure.

152. Brock et al. [B11], as well as others, have shown that chemically induced injury to the postnatal mammalian brain is often manifested by alterations in the cytoarchitecture of specific neuroanatomical regions. More importantly, they have shown that these anatomic changes are accompanied by quantitative changes in the proteins associated with specific cell types. Thus, for example, the organometallic compound tri-methyltin, which preferentially destroys the neurons of the limbic system, depresses the concentration of the synaptic vesicle proteins synapsin 1 and p38 but increases that of glial fibrillary acid protein (GFAP) in a dose-related manner. This suggests a widespread astrocytic response to the chemical, since GFAP is the major protein of intermediate filaments in astrocytes. Presumably trimethyltin stimulates astrocyte division and, possibly, other glial elements as well. Whether this also occurs in the prenatal brain is not clear; however, it is known that the radial glial cells that provide guidance during migration of the immature neurons to the cortex will ultimately develop into astrocytes and, possibly, oligodendroglial cells [C5]

once their guidance function ceases. Astrocytes have
many neuronal characteristics, such as neurotransmitter
receptors, ion channels and neurotransmitter uptake
systems. Moreover, it has been shown that cultured
astrocytes express certain neuropeptide genes prefer-
entially and specifically for the brain region from
which the cultured cells were derived, suggesting that
the peptides synthesized in astrocytes may play a role
in the development of the central nervous system
[S10].

153. *Summary.* The information available on exposure
of the developing human brain to protracted doses of
ionizing radiation is still too limited to permit esti-
mates of risk at low dose rates; however, the animal
data that are available suggest that the risk is lower
but the degree of attenuation is uncertain. Moreover,
it is difficult to extrapolate this information to the
human case because of the differences in duration of
the relevant neuroembryologic events. Data on expo-
sure to neurotoxic chemicals have provided some
insight into the molecular and cellular events asso-
ciated with such exposures, which may be pertinent to
radiation-related brain damage.

C. UNCERTAINTIES

154. Estimates of risks from prenatal radiation
exposure of the developing human brain have been
derived only from the high-dose-rate, acute exposures
of survivors of the atomic bombings of Hiroshima and
Nagasaki. Many uncertainties are associated with these
risk estimates. They include the limited nature of the
data, especially on mental retardation and seizures, the
appropriateness of the comparison group, errors in the
estimates of the tissue absorbed doses and in the
estimates of prenatal ages at exposure. Moreover, there
are other confounding factors that would play a role.
Socio-economic circumstances in the final year of the
war and immediately thereafter were stringent, affect-
ing both the availability of food and the resources to
treat disease. Thus, maternal nutrition and health status
and the possibility of intercurrent disease could
contribute to higher risks than might be seen other-
wise.

155. *Sample size and comparison group.* Only 21 of
the 30 severely mentally retarded individuals in the
Clinical Sample received fetal absorbed doses esti-
mated to be 0.01 Gy or more, and three of these had
health problems that could account for their retarda-
tion, making it unrelated to radiation (two cases of
Down's syndrome and one case of Japanese encephal-
itis in infancy). With their removal, there are only 18
cases in the critical period without known cause and
might be attributable to exposure to ionizing radiation
or other factors.

156. As to the comparison group, the atomic bomb-
ings resulted in exceptional circumstances that could
have altered the normal frequency of severe mental
retardation or have interacted non-additively with
exposure. However, comparison of the frequency of
mental retardation among children whose mothers
were present in the city at the time of the bombing but
received an estimated dose of less than 0.01 Gy with
the frequency of severe mental retardation among
children whose mothers migrated into these cities after
the bombing reveals no difference.

157. *Estimation of prenatal age.* The apparent timing
of vulnerable events in development can be affected
by errors in the determination of prenatal age, possibly
seriously so in specific cases. Gestational age is
usually estimated from the onset of the last menstrual
period, assuming that 280 days, on average, intervene
between the beginning of menstruation and parturition.
Post-ovulatory age is then calculated by subtracting
two weeks. This method is sensitive to at least two
types of errors, namely, misestimation of the onset of
menstruation and that associated with the tacit assump-
tion that all pregnancies proceed to term. If any
terminated prematurely, as must surely have been true
for some of the sample of prenatally exposed survivors
in Hiroshima and Nagasaki, the estimated age of the
child at exposure would be incorrect. Prematurity is
generally determined by an infant's size and weight at
birth, but these measurements were not routinely made
and recorded in the months immediately following the
bombings. At the initial physical examination of these
survivors the mother was asked about the child's
weight at birth. The trustworthiness of her recollec-
tions is uncertain, however, since a subsequent mail
survey often revealed large discrepancies between the
weight obtained at interview and that given in the
survey. 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 formerly nursed their infants longer,
so lactational amenorrhea may have been more com-
mon. 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. Another possible source of error
may arise from variations between individuals in the
prenatal age at which specific developmental events
occur [M7, N4, S17]. 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.

158. *Dosimetry.* All estimates of doses in the study
of survivors of the atomic bombings in Japan are sub-
ject to at least three sources of error: (a) determina-
tions of dose in air with distance from the epicentre,

(b) the attenuation factors for building materials and tissues and (c) the locations and positions of the survivors. Some of these, notably (c), 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 [G3, G4, J3, P2]. Pierce et al. [P2] have shown that random dosimetric errors can lead to a 10%-15% underestimation of the cancer risk among the survivors, and presumably a similar error could obtain in the estimates described here. Nevertheless, there remain troublesome inconsistencies in the DS86 system, notably with regard to neutrons in Hiroshima. Straume et al. [S22], for example, using all of the available measurement data on thermal neutron activation including new measurements for ^{36}Cl, suggest that thermal neutron activation at about 1 km in Hiroshima was 2 to 10 or more times higher than that calculated based on DS86. The implications of this discrepancy with regard to risk estimates is not wholly clear, since it must be noted that low-energy neutron activation contributed little to the dose in Hiroshima. It is not presently known whether the fast neutrons, those with energies in the range ~0.1 to 1 MeV, which comprised the bulk of the neutron dose in Hiroshima, have been similarly underestimated. However, Preston et al. [P5] and Sasaki et al. [S23] have attempted to determine the possible impact of this discrepancy on risk estimates. Preston et al., based on several different assumptions regarding the neutron RBE, found that the cancer risk estimates might be in error by 2% to 20%; whereas Sasaki and his colleagues, using a series of in vitro experiments, found that the difference in chromosome aberration frequencies between the two cities is explicable if the neutron dose in Hiroshima was as large as 5% of the total dose in Gy rather than the estimate of 2% or less provided by the DS86 dosimetry.

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

160. First, the experimental data are often contradictory. Some of the disparity in results may reflect the choice of experimental animal; some investigators have used inbred strains of mice or rats and others outbred lines. Some may reflect the choice of the endpoint measured. However, Hoshino et al. [H6] have reported the frequency of pycnotic cells to be linear with dose, even at doses below 0.24 Gy, and Wanner et al. [W9] reported a measurable, but not statistically significant, diminution in brain weight in guinea pigs at exposures as low as 0.04 Gy. More recently, Wagner et al. [W12] demonstrated a statistically significant diminution in the brain weight of guinea pigs exposed to 0.075 Gy on day 21 following conception (this corresponds to approximately week 5 or 6 following ovulation in the human). The loss in brain weight was approximately 1 mg mGy^{-1}. Studies of beagles exposed on the day 26 post-ovulation have shown a similar linear decrease in brain weight over a range of doses extending from 0.16 Gy to 3.6 Gy [H7]. Konermann [K7] has argued that the lowest dose in animals causing overt brain damage is generally 0.1 Gy or higher. This is consonant with other experimental studies. However, he noted that more subtle changes, such as the alignment of the small and medium-sized pyramidal neurons in the inner pyramidal cell layer of the mouse cortex, can be seen at doses as low as 0.025 Gy and that errors in alignment are marginally significant at 0.05 Gy (p < 0.10). It is not obvious what the occurrence of pycnotic cells or malaligned neurons is measuring in so far as functional brain damage is concerned. Nor is it clear what a loss in brain weight implies if the numerical densities of brain cells are increased, as has been reported [R14]. An increased cell density can, of course, mean less neuropil (fewer axons, dendrites and glial processes between the nerve cells), and it is reasonable to assume that fewer intercellular connections could reduce the quality of brain function.

161. Secondly, Müller et al. [M14], in a study of x-ray irradiation of preimplantation stages in the mouse, have shown that exposure at the single-cell stage can produce malformed fetuses, although the risk of death of the fetus is greater. They not only noted that the single-cell stage is characterized by a high radiation sensitivity but also asserted that their observations are best described by a linear-quadratic dose-response function without a threshold in this (their) special case. This conclusion, they contended, is consistent with theoretical considerations, since the exposure of a single cell differs from the exposure of polycytic stages in development, where the high capacity of embryonic cells to replace damaged cells and the need for a number of cells to be affected if a malformation is to ensue argues for a threshold. However, the fact that they found teratogenic effects following the exposure of a single cell, whereas most

other experimental studies have focused on later
critical stages in development and have commonly
found no evidence of a radiation-related effect,
suggests that the mechanisms involved in their
findings may be quite different from those of others.
Indeed, Pampfer and Streffer [P4], in a study of
female mice irradiated with neutrons (7 McV) or
x rays when the embryos were at an early zygote
stage, interpreted their results as suggesting that the
reactions of preimplantation embryos to irradiation
could be more complex than the simple all-or-none
response generally considered. In these experiments,
the most commonly encountered malformation was
gastroschisis, but omphaloceles and anencephalies
were also observed [M21]. The proportion of
malformed fetuses increased with dose in a linear-
quadratic manner for both radiation qualities. These
investigators estimated the relative biological
effectiveness of neutrons in the induction of external
malformations to lie between 2 and 3, increasing
somewhat as the reference x-ray dose increased.

162. *Extraneous variations.* Alternative, non-radia-
tion-related explanations can be found to cause or con-
found the effects to the developing human brain
observed in the study of survivors of the atomic
bombings in Japan. These include (a) genetic varia-
tion, (b) nutritional deprivation, (c) bacterial and viral
infections in the course of pregnancy, and (d) embryo-
nic or fetal hypoxemia, since there is substantial
evidence to suggest that the cerebrum and its adnexa
are especially sensitive to oxygen deprivation. There
were also exposures to other potentially noxious
physical or chemical agents, including the blast wave,
the fumes associated with the extensive conflagration
that followed the bombing, and the volatilization of
chemicals, such as lead, the fires produced. The
possible roles some of these may play in the present
context have been explored elsewhere [M6, M16, O1],
but the roles of others can only be a source of
speculation, since no relevant data are available.

163. Mole [M18], in particular, has contended that the
radiation-related depression of fetal haematopoiesis
may have played an important role in the occurrence
of severe mental retardation among the prenatally
exposed survivors in Hiroshima and Nagasaki by
reducing oxygen transport to the fetal brain. While the
abscopal effect to which he alludes cannot be estab-
lished unequivocally, it remains a contention to bear
in mind in interpreting the human data. However, the
issue of the oxygenation of the developing embryonic
and fetal brain is a complex one, involving not only
blood volume and concentration of haemoglobin, as
Mole suggests, but also the specific haemoglobin
present, since this affects the binding and unloading of

oxygen. The earliest haemoglobins present in the
developing individual, the embryonic ones, are
produced in the yolk sac, but from about week 8
through week 28 after fertilization, the major site of
erythropoiesis in the fetus is the liver and not the bone
marrow [B14]. If a depression in erythropoiesis
occurred at this time, it would have to entail damage
to the haematopoietic cells in the liver or, to a lesser
extent, perhaps, the spleen. The single case of fetal
marrow irradiation at 21 weeks to which Mole alluded
has little relevance, therefore, despite the fact that the
marrow was apparently normal. The site of erythro-
poiesis does gradually shift from the liver and spleen
to the bone marrow in the last half of gestation,
making bone marrow depression a more important
threat to the fetus at this later stage of development.
This is not the time when the brain appears especially
vulnerable. It is, of course, not known whether signi-
ficant damage to the liver does or does not occur at
the doses and times of relevance in the human case;
however, studies of prenatal exposure of rats at
comparable stages of development, 10 and 15 days of
gestation, failed to show an alteration in liver weight
as a percentage of body weight, although spleen
weight did decrease [S13]. It would be reasonable to
presume, nonetheless, that haematopoietic cells in the
liver have the same sensitivity to radiation as those in
the marrow itself and that a diminution in their
number might not be reflected in liver weight. At
about 9 weeks of gestation, the bulk (90%) of the
haemoglobin to be found in fetal red cells is fetal
haemoglobin, and even at birth this haemoglobin still
accounts for 80% of the haemoglobin present. Fetal
haemoglobin has a substantially enhanced alkaline
Bohr effect, which in concert with the fall in pH of
maternal blood as it passes through the placenta
facilitating maternal oxygen unloading, maximizes
oxygen transport to the fetus. Finally, the incidence of
hypoxia-producing complications of late pregnancy
does not appear to be significantly different among
pregnancies terminating in a mentally handicapped
child from that seen in general [D10].

164. No fully satisfactory assessment of the contri-
bution of the sources of variation alluded to above can
be made so many years after the event. It is only pos-
sible to speculate on their importance. Given the
present uncertainties (since most of these extraneous
sources of variation would have a greater impact at
high than at low doses, and thus produce a concave
upwards dose-response function), the careful course
would be to assume that the dose-response relationship
is not materially altered other than additively by these
potential confounders. This would have the effect of
overestimating the risk at low doses, which are of
greatest concern in radiation protection.

IV. FUTURE PERSPECTIVES

165. Numerous events are involved in the processes that bring forth a functional brain, any one of which is potentially susceptible to radiation damage. There is clearly a need to confirm and extend the findings on cerebral cortical impairment following prenatal exposure to ionizing radiation described in the earlier paragraphs. To do so, however, will entail not only more neurologically focused clinical examinations, including the various non-invasive techniques now available to image the living brain, but a concerted effort, national and international, to identify groups of individuals prenatally exposed to ionizing radiation that might be able to contribute information. Such studies will have value well beyond the immediate assessment of the risk of prenatal exposure to radiation; they can contribute to a deeper understanding of human embryonic and fetal development, to a clearer appreciation of the diversity among individuals in the age at which specific embryonic or fetal landmarks are achieved, and to a sharper definition of the developmental ages most vulnerable to exposure to chemical or physical teratogens. Some methods of investigation which might be profitably exploited in future research studies are considered in this Chapter.

166. *Epidemiological studies.* The prenatally exposed survivors of the atomic bombing of Hiroshima and Nagasaki are unusual in many respects, not the least of which is the fact that they are the only group of survivors whose life experience subsequent to exposure can be followed literally from birth to death and who can thus provide unique insights into the effect of the exposure on central nervous system aging. As yet, however, there have been no studies directed at determining the effect of radiation on specific cortical functions. Nevertheless, many of these functions can be investigated with a surprising degree of precision, and the time at which cortical neurogenesis is initiated and its duration, are often reasonably well known. Particularly appealing as subjects of study are the various aspects of visual function. Some 30% or so of the human cortex appears to be involved in the processing of visual stimuli, and the mechanisms through which this processing occurs are better understood than for any other cortical area. Similarly, it has long been known that the brain exhibits weak electrical activity, which can be measured. Its recording is not painful or invasive, and other studies have revealed measurable radiation-related alterations in the normal record of these electrical potentials.

167. Future investigations of central nervous system impairment should look for damage not only to the cerebrum but also to the cerebellum and brain stem, to the extent that effects on the latter can be dissociated from effects on the former. Methods of visualizing the living brain such as magnetic resonance imaging (MRI) or positron emission tomography (PET) might give subclinical evidence of radiation-related central nervous system damage. If there are metabolic differences between neuronal and non-neuronal cells, PET scans, since they can measure some metabolic functions, could give evidence of impaired migration or of sites in the brain that are non-functional but seem to be histologically normal. Individuals with intractable seizures, for example, often have regions of the brain that show no functional activity yet appear grossly normal. Similarly, recent advances in MRI, which does not involve exposure to ionizing radiation, have made possible some functional measurements of brain activity, and further developments can be anticipated. Singly and collectively, these techniques hold great promise for furthering the understanding of the function and physiology of the brain in the healthy as well as the diseased state.

168. Of particular import have been the recent developments in MRI that allow functional parameters to be added to the information content of the images themselves (see, e.g. [M17]). Although these newer uses of MRI have not been applied to the study of functional damage to the brain following prenatal exposure to ionizing radiation, their promise seems great. High-resolution MRI, together with neurological findings has demonstrated, for example, that selective bilateral damage to the hippocampal formation is sufficient to cause significant, permanent memory impairment [S14]. Also, neuropsychological studies of patients with confirmed hippocampal damage suggest that the hippocampus is essential in the establishment of long-term memory. This role of the hippocampus appears to be a time-limited one, however, and ultimately the role is transferred to the neocortex [Z3]. Where practical, the use of these non-invasive but highly informative techniques should be encouraged in clinical as well as experimental studies. They could be the means not only of determining the functional impairment associated with grossly visible changes in the brain but also of identifying damage that cannot be related to gross morphological changes.

169. Radiation-related damage to the brain could also be evaluated by simpler means. Cognitive tests, such as those measuring word association, learning ability, memory and intelligence, could be informative. Moreover, in the light of experimental findings on other primates, careful studies of auditory and visual acuity and olfaction and taste should be useful. These might include the audiometric assessment of the left and right ears and the conventional appraisal of visual acuity. Smell and taste could be evaluated through exposure to a battery of tastes or aromas at different

concentrations. Evidence of premature loss of hearing or vision should be sought, since a lesser initial number of neuronal cells could lead to earlier manifestation of an aging central nervous system.

170. Still other neurophysiologic effects, with different critical periods, can be envisaged. Recently, for example, it has been shown that mice irradiated prenatally on day 18 (corresponding to about week 35 in the human) suffer a significant loss in spatial memory. The integrity of spatial memory appears to depend on the proper development of the hippocampus. This structure arises relatively late in the development of the human brain, but damage to it results in a recognized cognitive defect characterized by severe amnesia and evidenced by deficits in learning mazes. There is evidence that associates a reduction in the pyramidal cells within the hippocampus with memory impairment. Here even simple pencil-and-paper mazes might be informative.

171. Prenatal exposure to a nuclear accident might give rise to a dysfunctional child, either because of organic damage to the developing brain or because of the disturbed psychosocial milieu into which the child is born. The frequency, severity and pathogenesis of these psychosocial disorders have been poorly studied. If their origins are to be understood, the children found to be abnormal need to be studied to ascertain ways in which the children, families, and community and culture interact to cause psychosocial dysfunction and to form perceptions of risk. A child's perception of risk is not independently formed, but is inculcated, at least in part, by the attitudes of his or her age peers

and family, and their attitudes are shaped, in turn, by community and culture. Thus, to understand the origin of psychosocial disorders arising out of a nuclear accident, it is essential to understand the workings of the larger milieu. Without this understanding, purely pragmatic ameliorative or preventive efforts are likely to be unproductive and ultimately self-defeating because they arouse expectations than cannot be fulfilled.

172. *Experimental studies.* Although no animal species is an ideal model for human brain development, experimental studies will and must continue to play an important role in understanding the effects of prenatal exposure on the developing human brain. Such studies can serve to confirm epidemiological findings in humans, to provide data on possible dose-response relationships and to afford insight into molecular and cellular mechanisms that is not easily available from human investigations. It warrants noting, as well, that extrapolations to the human being of molecular and cellular mechanisms revealed by animal experimentation are likely to be better than extrapolations based upon gross, phenotypic end-points, although the latter are often a necessary first step in the detection of radiation-related effects. Numerous questions of a mechanistic nature exist for which answers are not now available. For example, what initiates migration? How does the migrating neuron know that it has reached its destination, which is the point at which it disengages from its radial glial pathway? Recent advances in neuromolecular biology and the ability to culture specific neuronal cells *in vitro* hold promise for providing answers to these fundamental questions.

CONCLUSIONS

173. The human brain is relatively sensitive to ionizing radiation at certain stages in its prenatal development. Data from Hiroshima and Nagasaki, as well as from a few other studies, indicate that there can be consequences to the central nervous system from exposure to radiation at these stages. The abnormalities that have been observed correlate well with animal experiments and with current knowledge of the developmental embryology of the brain. It should be noted, however, that these findings do not represent a major public health problem. There were about 100,000 deaths at Hiroshima and Nagasaki, and somewhat more than 285,000 survivors. Among these survivors there were possibly as many as 10,000 pregnant women whose greatest immediate risk was the loss of their pregnancy. Although the observations on loss of pregnancy are limited, this risk appears to

have been markedly elevated among those women in the first eight weeks of pregnancy, but it was also greater than normal among women in the 8-15 week interval [C15]. Nonetheless, the epidemiological data do indicate substantial risk of abnormalities in the central nervous system following high doses at certain periods of pregnancy. The risk is highest for exposures occurring during post-ovulatory weeks 8-15, that is, when the greatest number of neurons are produced and when they migrate to their functional sites in the cerebral cortex. During weeks 16-25 after ovulation, a lesser vulnerability is observed, with little apparent risk for exposures before week 8 or after week 25.

174. Among the prenatally exposed survivors of the atomic bombings of Hiroshima and Nagasaki who have been under clinical scrutiny, there are 30 cases of

severe mental retardation, some of which are probably not radiation-related, 30 with small head size without apparent mental retardation, 52 with seizures, of which 24 appear to be unprovoked (those with no clinically identifiable precipitating cause) and some with reduced intelligence quotient scores or with lower scholastic achievement in school.

175. Both severe mental retardation and lower intelligence test scores are observed to occur following prenatal exposures during the two sensitive periods of development previously described. These effects are mutually consistent if radiation is seen as operating on a continuum of qualities of brain function. The damage caused by exposure to 1 Gy within the most vulnerable period, namely 8-15 weeks after ovulation, increases the frequency of mental retardation to about 40% (background frequency: 0.8%), and lowers IQ by 25-30 points, which is consistent with the observed increase in mental retardation. The specific value of the IQ decrement depends on the sample used to estimate the risk and on whether the mentally retarded individuals are included in that sample. Prenatal exposure to 1 Gy in the most critical period appears to cause a decrement in average school performance score equivalent to the shifting of an average individual from the 50th percentile to the lower 10th percentile and increases the risk of unprovoked seiz-

ures by a factor of approximately 25. For the period 16-25 weeks, no cases of severe mental retardation were observed at exposures of less than 0.5 Gy. Thus, albeit with some uncertainty, a threshold could be assumed for that period. As to unprovoked seizures, at estimated doses in the range of 0.1 to 0.49 Gy the relative risk is 4.4; whereas at doses of 0.5 Gy or greater the relative risk is 14.5 when the cases of mental retardation are excluded from the data.

176. The risks cited in the preceding paragraphs assume the dose to have been an acute one. It is reasonable to assume, however, that these risks would be smaller for chronic exposure over the same critical periods, and this assumption is supported by the experimental animal information that is available. However, there are numerous potential confounding factors, and the human data are still far too limited to provide quantitative estimates of the possible reduction in risk at low doses.

177. The limitations in the data presently available and the uncertainties in the risk estimates have been pointed out. Definite risk estimates cannot be obtained at doses lower than 0.5 Gy or at low dose rates. The above estimates are therefore obviously provisional until additional evidence from further investigations can be obtained.

Table 1
Temporal pattern of brain development
[W10]

Post-ovulatory age	Important developmental events
3 weeks	Neural folds close to form neural tube Cervical region begins to form Cranial and cervical flexures appear Cranial and spinal motor nuclei develop
4 weeks	Paired optic vesicles evert; cranial and spinal nerves emerge Spinal ganglia develop and axons enter central nervous system Closure of neural tube
5 weeks	Diencephalic nuclei develop Pineal and hypophysis evert Eversion of cerebral vesicles Orbit and lens induced by the optic primordia Choroid plexus develops and cerebrospinal fluid fills neural tube Basal ganglia and amygdala develop Major cerebral arteries form Canalization and development of caudal spinal cord; posterior commissure develops Beginnings of the cerebellum and cerebellar nuclei appear Thinning of the roof of the 4th ventricle allows cerebrospinal fluid to flow out
6 weeks	Neural retina develops Olfactory nerves grow to base of brain; secretory vesicles appear in choroid plexus Beginnings of hippocampus and olfactory apparatus appear
7 weeks	Neocortical primordia appears Olfactory bulb everts Formation of pigmented retinal epithelium and ciliary body
8-11 weeks	Cortical plate appears in neocortex First synapses in the molecular and subplate regions of the neocortex Neurons migrate from the proliferative zones; optic nerve pathways form Proliferative zone of 3rd ventricle is exhausted Cortical plate of cerebellum appears Anterior commissure develops Cortical plate of the hippocampus appears Sylvan and hippocampal fissures form Skeletal muscle innervated and joint cavities appear Basal foramina and subarachnoid spaces open
12-15 weeks	Corpus callosum forms Cavum septum pellicidum formed Migration of neurons to neocortex in full swing Cortical wall triples in thickness Corticospinal fibers dessucate Purkinje cell migration complete, inward migration of external granule cells begins
16-20 weeks	Germinal zones of lateral ventricles are depleted Last wave of neocortical migration Prominence of subventricular germinal zone and first wave of glial migration Thalamocortical afferents invade the depths of the cortical plate, synapses appear and large pyramidal neurons begin to differentiate Cerebral subarachnoid spaces are open to the sagittal sinus Active phase of natural nerve cell death
20-24 weeks	Neuronal migration to neocortex complete Granule cells of cerebellum and dentate gyrus of hippocampus continue to proliferate and migrate Radial glial cells release ventricular attachments and migrate into cortex as protoplasmic astrocytes Primary gyri and sulci form Myelination begins Retinogeniculate, brain stem auditory and visual motor, and sensory lemniscal pathways are among the first to develop
25 weeks to end of term	Granule cell migration continues Glial proliferation continues Appearance of glial fibrils and acidic glial fibrillary protein signal increasing capacity for glial response to injury Secondary gyri and sulci form Maturation of supragranular neocortical layers begins Myelination of internal capsule begins Robust growth of dendrites and axons, and synaptogenesis

Table 2
Sites and levels of neuronal variation
[E2]

Genetic traits and developmental primary processes	Variations in cell division, migration, adhesion, differentiation, death
Cell morphology	Variation in cell shape and size; variation in dendritic and axonal arborizations (spatial distribution, branching order, length of branches, number of spines)
Connection patterns	Variations in number of inputs and outputs; connection order with other neurons; local versus long-range connections; degree of overlap of arbors
Cytoarchitectonics	Variation in number or density of cells; thickness of individual cortical layers; relative thickness of supragranular, infragranular and granular layers; position of somata; variation in columns; variation in strips or patches of terminations; variation in anisotropy of fibers
Transmitters	Variations between cells in a population; between cells at different times
Dynamic response	Variations in synaptic chemistry and size of synapse; in electrical properties; in excitatory/inhibitory ratios and locations of synapses; in short- and long-term synaptic alteration; in metabolic state
Neuronal transport	
Interactions with glia	

Table 3
Severely mentally retarded individuals exposed *in utero* to the atomic bombings in Japan
[O1]

File number	Date of birth	Date of death	Cause of death	Sex	Post-ovulatory age at exposure (weeks)	Absorbed dose in uterus (Gy)		Koga IQ score 1955-1956	Small head size	Significant clinical findings
						Total	Neutron			
					Hiroshima					
245977	5.3.1946	14.1.1953	Malignant neoplasm of liver	F	8	1.4	0.01		Yes	Neo-natal jaundice
404239	1.3.1946			M	8	0.14	0		Yes	
246116	28.2.1946			M	8	0.87	0	64	Yes	
400590	25.2.1946			M	9	1.36	0.01		Yes	
471693	24.2.1946			M	9	0.69	0		Yes	
401141	12.2.1946			M	10	1.02	0		Yes	
400210	15.2.1946	21.1.1952	Ill-defined, unkown	F	11	2.22	0.01		Yes	
857279	11.2.1946			M	11	0.05	0		No	
401023	6.2.1946	28.6.1952	Accidental drowning	F	12	0.56	0		Yes	Down's syndrome
444522	4.2.1946			F	12	1.39	0.01		Yes	
401081	27.1.1946			F	13	1.64	0.01	56	Yes	
404032	23.1.1946			F	13	0.29	0		Yes	Down's syndrome
245763	15.1.1946	30.8.1958	Tuberculosis	M	15	0.61	0		Yes	
241728	11.1.1946			F	15	0.06	0		Yes	
312021	5.1.1946			F	16	0	0		Yes	
400716	12.12.1945	18.2.1970	Renal failure	M	19	1.23	0.01	64	No	
226683	12.12.1945	19.9.1956	Heart failure, epilepsy	M	20	0	0		No	Retarded sibling
433800	8.12.1945			F	20	0.03	0		No	Encephalitis at age 4
440463	22.11.1945			M	22	1.0	0	59	Yes	
440056	29.10.1945			M	26	0	0	60	No	
400133	22.9.1945	26.3.1966	Heart failure, epilepsy	F	31	0	0		No	
403929	18.8.1945			M	36	0	0		Yes	Down's syndrome
					Nagasaki					
050968	22.4.1946			F	1	0	0		No	Possible birth trauma
078487	27.2.1946			M	9	1.16	0	62	No	Neurofibromatosis
142623	6.2.1946	14.3.1962	General symptoms, meningitis	M	12	1.18	0		Yes	
152396	26.1.1946			M	13	0	0		No	
143818	15.1.1946			M	15	1.46	0		Yes	
151845	15.1.1946			F	15	0	0	56	No	
078481	2.11.1945			F	25	1.79	0	60	No	
257021	25.9.1945			F	31	0	0		No	Congenital lues

Table 4
Severe mental retardation in individuals exposed *in utero* to the atomic bombings in Japan [a]
[O1]

Post-ovulatory age	Evaluation categories	Dose categories (Gy) [b]					
		< 0.01	0.01-0.09	0.10-0.49	0.50-0.99	≥ 1.0	Total
Hiroshima							
0-7 weeks	Number of subjects	145	35	24	5	1	210
	Number retarded	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
8-15 weeks	Number of subjects	209	41	50	13	9	322
	Number retarded	0 (0%)	2 (4.9%)	1 (2.0%)	3 (23.1%)	6 (66.7%)	12 (3.7%)
16-25 weeks	Number of subjects	243	47	46	14	7	357
	Number retarded	2 (0.8%)	1 (2.1%)	0 (0%)	0 (0%)	2 (28.6%)	5 (14.0%)
≥ 26 weeks	Number of subjects	227	57	47	4	2	337
	Number retarded	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)
All ages	Number of subjects	824	180	167	36	19	1226
	Number retarded	4 (0.5%)	3 (1.7%)	1 (0.6%)	3 (8.3%)	8 (42.1%)	19 (1.5%)
Nagasaki							
0-7 weeks	Number of subjects	60	6	7	0	1	74
	Number retarded	1 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)
8-15 weeks	Number of subjects	46	3	7	2	3	61
	Number retarded	2 (4.3%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)	5 (8.2%)
16-25 weeks	Number of subjects	65	8	11	2	1	87
	Number retarded	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (1.1%)
≥ 26 weeks	Number of subjects	72	4	14	1	2	93
	Number retarded	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)
All ages	Number of subjects	243	21	39	5	7	315
	Number retarded	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)	4 (57.1%)	8 (2.5%)
Both cities							
0-7 weeks	Number of subjects	205	41	31	5	2	284
	Number retarded	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
8-15 weeks	Number of subjects	255	44	57	15	12	383
	Number retarded	2 (0.8%)	2 (4.5%)	1 (1.8%)	3 (20.0%)	9 (75.0%)	17 (4.4%)
16-25 weeks	Number of subjects	308	55	57	16	8	444
	Number retarded	2 (0.6%)	1 (1.8%)	0 (0%)	0 (0%)	3 (37.5%)	6 (1.4%)
≥ 26 weeks	Number of subjects	299	61	61	5	4	430
	Number retarded	3 (1.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.7%)
All ages	Number of subjects	1067	201	206	41	26	1541
	Number retarded	8 (0.7%)	3 (1.5%)	1 (0.5%)	3 (7.3%)	12 (46.2%)	27 (1.8%)

[a] Three cases of Down's syndrome have been excluded.
[b] DS86 uterine absorbed dose; mean doses within dose categories for total sample are 0, 0.05, 0.23, 0.64 and 1.38 Gy, respectively.

Table 5
Small head size in children exposed *in utero* to the atomic bombings in Japan
[O13]

Post-ovulatory age	Evaluation categories	Dose categories (Gy) [a]					
		< 0.01	0.01-0.09	0.10-0.49	0.50-0.99	≥ 1.0	Total
Hiroshima							
First trimester	Number of subjects	222	57	52	9	3	343
	Number with small head size	7 (3.2%)	3 (5.3%)	12 (23.1%)	5 (55.7%)	2 (66.7%)	29 (8.5%)
	Number mentally retarded [b]	0, 0	0, 1	0, 1	2, 0	2, 0	4, 2
Second trimester	Number of subjects	317	62	57	17	10	463
	Number with small head size	3 (0.95%)	3 (4.8%)	4 (7.0%)	2 (11.8%)	3 (30.0%)	15 (3.2%)
	Number mentally retarded [b]	0, 1	1, 1	1, 0	1, 0	3, 1	6, 3
Third trimester	Number of subjects	229	61	46	7	2	345
	Number with small head size	5 (2.2%)	2 (3.3%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	8 (2.3%)
	Number mentally retarded [b]	2, 1	0, 0	0, 0	0, 0	0, 0	2, 1
Nagasaki							
First trimester	Number of subjects	88	9	15	1	3	116
	Number with small head size	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (100%)	3 (100%)	5 (4.3%)
	Number mentally retarded [b]	0, 1	0, 0	0, 0	0, 0	1, 0	1, 1
Second trimester	Number of subjects	80	9	12	3	2	106
	Number with small head size	2 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100%)	4 (3.8%)
	Number mentally retarded [b]	0, 2	0, 0	0, 0	0, 0	2, 0	2, 2
Third trimester	Number of subjects	74	7	15	1	3	100
	Number with small head size	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Number mentally retarded [b]	0, 1	0, 0	0, 0	0, 0	0, 1	0, 2
Both cities							
First trimester	Number of subjects	310	66	67	10	6	459
	Number with small head size	7 (2.3%)	3 (4.6%)	13 (19.4%)	6 (60.0%)	5 (83.3%)	34 (7.4%)
	Number mentally retarded [b]	0, 1	0, 1	0, 1	2, 0	3, 0	5, 3
Second trimester	Number of subjects	397	71	69	20	12	569
	Number with small head size	5 (1.3%)	3 (4.2%)	4 (5.8%)	2 (10.0%)	5 (41.7%)	19 (3.3%)
	Number mentally retarded [b]	0, 3	1, 1	1, 0	1, 0	5, 1	8, 5
Third trimester	Number of subjects	303	68	61	8	5	445
	Number with small head size	5 (1.7%)	2 (2.9%)	2 (3.3%)	0 (0.0%)	0 (0.0%)	9 (2.0%)
	Number mentally retarded [b]	2, 2	0, 0	0, 0	0, 0	0, 1	2, 3
Hiroshima							
0-7 weeks	Number of subjects	135	36	25	4	1	201
	Number with small head size	5 (3.7%)	3 (8.3%)	5 (20.0%)	2 (50.0%)	0 (0.0%)	15 (7.5%)
	Number mentally retarded [b]	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0
8-15 weeks	Number of subjects	187	41	48	12	7	295
	Number with small head size	3 (1.6%)	1 (2.4%)	11 (22.9%)	5 (41.7%)	4 (57.1%)	24 (8.1%)
	Number mentally retarded [b]	0, 0	1, 1	1, 1	3, 0	4, 0	9, 2
16-25 weeks	Number of subjects	232	45	38	13	5	333
	Number with small head size	2 (0.9%)	2 (4.4%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	5 (1.5%)
	Number mentally retarded [b]	0, 1	0, 1	0, 0	0, 0	1, 1	1, 3
≥ 26 weeks	Number of subjects	214	58	44	4	2	322
	Number with small head size	5 (2.3%)	2 (3.5%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	8 (2.5%)
	Number mentally retarded [b]	2, 1	0, 0	0, 0	0, 0	0, 0	2, 1
Nagasaki							
0-7 weeks	Number of subjects	60	7	7	0	1	75
	Number with small head size	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (100%)	2 (2.7%)
	Number mentally retarded [b]	0, 1	0, 0	0, 0	0, 0	0, 0	0, 1
8-15 weeks	Number of subjects	46	4	9	2	4	65
	Number with small head size	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	4 (100%)	5 (7.7%)
	Number mentally retarded [b]	0, 2	0, 0	0, 0	0, 0	3, 0	3, 2

Table 5 (continued)

Post-ovulatory age	Evaluation categories	Dose categories (Gy) [a]					
		< 0.01	0.01-0.09	0.10-0.49	0.50-0.99	≥ 1.0	Total
16-25 weeks	Number of subjects	65	8	12	2	1	88
	Number with small head size	2 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
	Number mentally retarded [b]	0, 0	0, 0	0, 0	0, 0	0, 1	0, 1
≥ 26 weeks	Number of subjects	71	6	14	1	2	94
	Number with small head size	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
	Number mentally retarded [b]	0, 1	0, 0	0, 0	0, 0	0, 0	0, 1
Both cities							
0-7 weeks	Number of subjects	195	43	32	4	2	276
	Number with small head size	5 (2.6%)	3 (7.0%)	6 (18.8%)	2 (50.0%)	1 (50.0%)	17 (6.2%)
	Number mentally retarded [b]	0, 1	0, 0	0, 0	0, 0	0, 0	0, 1
8-15 weeks	Number of subjects	233	45	57	14	11	360
	Number with small head size	3 (1.3%)	1 (2.2%)	11 (19.3%)	6 (42.9%)	8 (72.7%)	29 (8.1%)
	Number mentally retarded [b]	0, 2	1, 1	1, 1	3, 0	7, 0	12, 4
16-25 weeks	Number of subjects	297	53	50	15	6	421
	Number with small head size	4 (1.4%)	2 (3.8%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	7 (1.7%)
	Number mentally retarded [b]	0, 1	0, 1	0, 0	0, 0	1, 2	1, 4
≥ 26 weeks	Number of subjects	285	64	58	5	4	416
	Number with small head size	5 (1.8%)	2 (3.1%)	2 (3.5%)	0 (0.0%)	0 (0.0%)	9 (2.2%)
	Number mentally retarded [b]	2, 2	0, 0	0, 0	0, 0	0, 0	2, 2
All ages	Number of subjects	1010	205	197	38	23	1473
	Number with small head size	17 (1.7%)	8 (3.9%)	19 (9.6%)	8 (21.1%)	10 (43.5%)	62 (4.2%)
	Number mentally retarded [b]	2, 6	1, 2	1, 1	3, 0	8, 2	15, 11

[a] DS86 uterine absorbed dose; mean doses within dose categories for total sample are 0, 0.05, 0.23, 0.63 and 1.30 Gy, respectively.

[b] Number of mentally retarded with small head size followed by number of mentally retarded with normal head size.

Table 6
Expected and observed incidence of small head size in individuals exposed *in utero* to the atomic bombings in Japan
[O13]

Post-ovulatory age	Number of subjects	Number with small head size	
		Expected [a]	Observed [b]
0-7 weeks	276	7	17 (0, 17)
8-15 weeks	360	9	29 (12, 17)
16-25 weeks	421	11	7 (1, 6)
≥ 26 weeks	416	10	9 (2, 7)
All ages	1473	37	62 (15, 47)

[a] Estimated from assumed 2.5% deviance in the normal distribution.

[b] Number with and without severe mental retardation given in parentheses.

Table 7

Regression coefficients obtained in fitting models to intelligence test scores and uterine absorbed dose for individuals exposed *in utero* to the atomic bombings in Japan
[S4]

Post-ovulatory age	Regression model	Regression coefficient [a]			Significance level of	
		a	b	c	b	c
Clinical subsample, all cases included						
0-7 weeks	Linear	106 ± 1.2	-2.7 ± 5.3			
8-15 weeks		108 ± 0.99	-29.0 ± 4.2		$p < 0.01$	
16-25 weeks		111 ± 0.89	-20.4 ± 4.4		$p < 0.01$	
≥ 26 weeks		107 ± 0.80	-4.2 ± 5.0			
All ages		108 ± 0.47	-15.8 ± 2.4		$p < 0.01$	
0-7 weeks	Linear-quadratic	107 ± 1.2	-34.0 ± 13.5	16.4 ± 6.5	$p < 0.05$	$p < 0.05$
8-15 weeks		108 ± 1.0	-25.8 ± 11.1	-2.9 ± 9.2	$p < 0.05$	
16-25 weeks		111 ± 0.91	-3.6 ± 9.3	-16.8 ± 8.2		$p < 0.05$
≥ 26 weeks		107 ± 0.82	-10.1 ± 12.8	7.1 ± 14.2		
All ages		109 ± 0.48	-20.7 ± 4.8	4.2 ± 3.6	$p < 0.01$	
PE-86 subsample, all cases included						
0-7 weeks	Linear	106 ± 0.94	-1.7 ± 5.1			
8-15 weeks		110 ± 0.92	-25.3 ± 4.0		$p < 0.01$	
16-25 weeks		110 ± 0.76	-21.4 ± 4.2		$p < 0.01$	
≥ 26 weeks		108 ± 0.68	-4.7 ± 5.0			
All ages		109 ± 0.40	-15.7 ± 2.2		$p < 0.01$	
0-7 weeks	Linear-quadratic	107 ± 0.97	-24.1 ± 12.5	12.1 ± 6.1	$p < 0.10$	$p < 0.05$
8-15 weeks		110 ± 0.97	-33.6 ± 9.7	6.1 ± 6.6	$p < 0.01$	
16-25 weeks		110 ± 0.77	-6.9 ± 8.8	-14.9 ± 8.0		$p < 0.10$
≥ 26 weeks		108 ± 0.71	-11.9 ± 12.5	8.8 ± 14.0		
All ages		109 ± 0.42	-20.2 ± 4.6	3.7 ± 3.3	$p < 0.01$	
Clinical subsample, retardation cases excluded						
0-7 weeks	Linear	106 ± 1.2	-2.7 ± 5.3			
8-15 weeks		108 ± 0.98	-25.0 ± 5.1		$p < 0.01$	
16-25 weeks		111 ± 0.89	-9.8 ± 5.7		$p < 0.10$	
≥ 26 weeks		107 ± 0.79	-4.4 ± 5.0			
All ages		108 ± 0.47	-10.2 ± 2.6		$p < 0.01$	
0-7 weeks	Linear-quadratic	107 ± 1.2	-34.0 ± 13.5	16.4 ± 6.5	$p < 0.05$	$p < 0.05$
8-15 weeks		108 ± 1.0	-26.1 ± 12.2	1.2 ± 11.7	$p < 0.05$	
16-25 weeks		111 ± 0.92	-5.9 ± 15.6	-6.2 ± 23.3		
≥ 26 weeks		108 ± 0.82	-10.8 ± 12.7	7.7 ± 14.0		
All ages		109 ± 0.48	-19.0 ± 4.8	8.1 ± 3.8	$p < 0.01$	$p < 0.05$
PE-86 subsample, retardation cases excluded						
0-7 weeks	Linear	106 ± 0.94	-1.7 ± 5.1			
8-15 weeks		110 ± 0.91	-21.0 ± 4.5		$p < 0.01$	
16-25 weeks		110 ± 0.76	-13.3 ± 5.2		$p < 0.01$	
≥ 26 weeks		108 ± 0.68	-4.9 ± 5.0			
All ages		108 ± 0.40	-11.0 ± 2.5		$p < 0.01$	
0-7 weeks	Linear-quadratic	107 ± 0.97	-24.1 ± 12.5	12.1 ± 6.1	$p < 0.10$	$p < 0.05$
8-15 weeks		110 ± 0.94	-29.3 ± 9.9	6.3 ± 6.7	$p < 0.01$	
16-25 weeks		110 ± 0.79	-5.1 ± 15.0	-12.8 ± 22.0		
≥ 26 weeks		108 ± 0.70	-12.5 ± 12.4	9.3 ± 13.9		
All ages		109 ± 0.41	-17.8 ± 4.6	5.9 ± 3.4	$p < 0.01$	$p < 0.10$

[a] The regression coefficient a is the estimated IQ score at zero dose (intercept); b is the increase in IQ score per unit dose (Gy^{-1}); c is the increase in IQ score per unit dose squared (Gy^{-2}).

Table 8
Regression coefficients obtained in fitting models to average school performance and uterine absorbed dose for individuals exposed *in utero* to the atomic bombings in Japan
[O2]

Post-ovulatory age	Regression model	Regression coefficient [a]			Significance level of	
		a	b	c	b	c
First grade						
0-7 weeks	Linear	3.09 ± 0.08	0.23 ± 0.32			
8-15 weeks		2.86 ± 0.06	-1.15 ± 0.22		p < 0.01	
16-25 weeks		3.03 ± 0.05	-0.97 ± 0.24		p < 0.01	
≥ 26 weeks		3.11 ± 0.05	0.23 ± 0.36			
All ages		3.03 ± 0.03	-0.70 ± 0.14		p < 0.01	
0-7 weeks	Linear-quadratic	3.18 ± 0.08	-2.68 ± 0.89	1.38 ± 0.40	p < 0.01	p < 0.01
8-15 weeks		2.87 ± 0.06	-1.21 ± 0.58	0.06 ± 0.48	p < 0.05	
16-25 weeks		3.05 ± 0.05	-1.53 ± 0.72	0.67 ± 0.80	p < 0.05	
≥ 26 weeks		3.10 ± 0.05	0.84 ± 0.79	-0.82 ± 0.95		
All ages		3.05 ± 0.03	-1.51 ± 0.27	0.70 ± 0.20	p < 0.01	p < 0.01
Second grade						
0-7 weeks	Linear	3.09 ± 0.09	0.36 ± 0.34			
8-15 weeks		2.86 ± 0.06	-1.27 ± 0.22		p < 0.01	
16-25 weeks		3.05 ± 0.05	-0.96 ± 0.24		p < 0.01	
≥ 26 weeks		3.16 ± 0.05	0.01 ± 0.36			
All ages		3.05 ± 0.03	-0.76 ± 0.14		p < 0.01	
0-7 weeks	Linear-quadratic	3.17 ± 0.09	-2.14 ± 0.98	1.19 ± 0.44	p < 0.05	p < 0.01
8-15 weeks		2.86 ± 0.06	-1.14 ± 0.57	-0.12 ± 0.48	p < 0.05	
16-25 weeks		3.06 ± 0.05	-1.79 ± 0.72	0.97 ± 0.80	p < 0.05	
≥ 26 weeks		3.15 ± 0.05	0.21 ± 0.80	-0.28 ± 0.97		
All ages		3.07 ± 0.03	-1.64 ± 0.27	0.76 ± 0.20	p < 0.01	p < 0.01
Third grade						
0-7 weeks	Linear	3.11 ± 0.10	0.12 ± 0.38			
8-15 weeks		2.86 ± 0.06	-1.17 ± 0.25		p < 0.01	
16-25 weeks		3.02 ± 0.06	-1.01 ± 0.25		p < 0.01	
≥ 26 weeks		3.10 ± 0.05	-0.06 ± 0.37			
All ages		3.02 ± 0.03	-0.74 ± 0.15		p < 0.01	
0-7 weeks	Linear-quadratic	3.21 ± 0.10	-3.04 ± 1.08	1.50 ± 0.48	p < 0.01	p < 0.01
8-15 weeks		2.86 ± 0.06	-0.90 ± 0.62	-0.25 ± 0.54		
16-25 weeks		3.02 ± 0.06	-1.17 ± 0.77	0.19 ± 0.85		
≥ 26 weeks		3.10 ± 0.05	-0.13 ± 0.81	0.10 ± 0.98		
All ages		3.05 ± 0.03	-1.57 ± 0.29	0.73 ± 0.21	p < 0.01	p < 0.01
Fourth grade						
0-7 weeks	Linear	2.78 ± 0.11	-1.72 ± 0.84		p < 0.05	
8-15 weeks		2.88 ± 0.06	-0.95 ± 0.42		p < 0.05	
16-25 weeks		3.03 ± 0.05	-1.09 ± 0.26		p < 0.01	
≥ 26 weeks		3.13 ± 0.05	-0.35 ± 0.32			
All ages		3.02 ± 0.03	-0.89 ± 0.18		p < 0.01	
0-7 weeks	Linear-quadratic	2.82 ± 0.11	-4.42 ± 2.88	5.66 ± 5.78		
8-15 weeks		2.89 ± 0.07	-1.52 ± 0.98	0.90 ± 1.39		
16-25 weeks		3.05 ± 0.06	-1.88 ± 0.75	0.95 ± 0.84	p < 0.05	
≥ 26 weeks		3.13 ± 0.05	-0.44 ± 0.78	0.11 ± 0.88		
All ages		3.03 ± 0.03	-1.52 ± 0.45	0.82 ± 0.54	p < 0.01	

[a] The regression coefficient a is the mean school score at zero dose (intercept); b is the increase in mean school score per unit dose (Gy^{-1}); c is the increase in mean school score per unit dose squared (Gy^{-2}).

Table 9
Regression coefficients obtained in fitting a linear model to seizures and uterine absorbed dose for individuals exposed *in utero* to the atomic bombings in Japan
[O3]

Post-ovulatory age	Regression model	Regression coefficient [a]		Significance level of b
		a	b	
All seizures				
0-7 weeks [b]	Linear	4.55	-0.046 ± 0.34	
8-15 weeks [b]		2.51	0.18 ± 0.087	p < 0.05
8-15 weeks [b,c]		3.87	0.15 ± 0.084	p < 0.10
16-25 weeks [b]		4.73	0.001 ± 0.052	
≥ 26 weeks [b]		3.89	0.024 ± 0.064	
All ages [b]		3.97	0.054 ± 0.037	p < 0.10
0-7 weeks [d]	Linear	4.62	-0.058 ± 0.12	
8-15 weeks [d]		2.61	0.11 ± 0.11	
8-15 weeks [c,d]		3.70	0.083 ± 0.10	
16-25 weeks [d]		4.39	0.016 ± 0.067	
≥ 26 weeks [d]		3.62	0.029 ± 0.071	
All ages [d]		3.88	0.026 ± 0.040	
Febrile seizures				
0-7 weeks [b]	Linear	4.06	-0.041 ± 0.34	
8-15 weeks [b]		1.80	-0.018 ± 0.071	
8-15 weeks [b,c]		2.21	-0.023 ± 0.073	
16-25 weeks [b]		2.79	-0.030 ± 0.048	
≥ 26 weeks [b]		1.81	0.033 ± 0.052	
All ages [b]		2.46	-0.012 ± 0.015	
0-7 weeks [d]	Linear	4.10	-0.050 ± 0.30	
8-15 weeks [d]		1.96	-0.018 ± 0.081	
8-15 weeks [c,d]		2.21	-0.028 ± 0.017	p < 0.10
16-25 weeks [d]		2.83	-0.036 ± 0.11	
≥ 26 weeks [d]		1.84	0.033 ± 0.056	
All ages [d]		2.61	-0.013 ± 0.021	
Unprovoked seizures				
0-7 weeks [b]	Linear	-	-	
8-15 weeks [b]		0.89	0.20 ± 0.084	p < 0.01
8-15 weeks [b,c]		1.71	0.18 ± 0.083	p < 0.05
16-25 weeks [b]		1.98	0.042 ± 0.054	
≥ 26 weeks [b]		1.89	-0.019 ± 0.070	
All ages [b]		1.45	0.074 ± 0.033	p < 0.05
0-7 weeks [d]	Linear	-	-	
8-15 weeks [d]		0.921	0.15 ± 0.10	p < 0.10
8-15 weeks [c,d]		1.50	0.13 ± 0.099	
16-25 weeks [d]		1.58	0.067 ± 0.065	
≥ 26 weeks [d]		1.69	-0.018 ± 0.065	
All ages [d]		1.30	0.052 ± 0.035	p < 0.10

[a] The regression coefficient a is the number of seizures per 100 individuals at zero dose (intercept); b is the increase in frequency of seizures per unit dose (Gy^{-1}).
[b] Cases of severe mental retardation included in sample.
[c] Pooled controls. Data for controls (> 0.01 Gy) over all gestational ages were used.
[d] Cases of severe mental retardation excluded from sample.

Table 10
Regression coefficients and estimated thresholds obtained in fitting a linear model to seizures and uterine absorbed dose for individuals exposed *in utero* to the atomic bombings in Japan
[O1]

Post-ovulatory age	Regression model	Regression coefficient [a]		Significance level of b	Threshold [b] (Gy)
		a	b		
All seizures					
8-15 weeks [c]	Linear with threshold	2.71	0.26 ± 0.13	p < 0.05	0.15
8-15 weeks [c,d]		3.94	0.25 ± 0.14	p < 0.10	0.20
All ages [c]		4.08	0.10 ± 0.06	p < 0.10	0.23
8-15 weeks [c]	Linear with threshold	2.70	0.17 ± 0.16		0.11
8-15 weeks [d,c]		3.72	0.17 ± 0.20		0.17
All ages [c]		3.93	0.06 ± 0.07		0.23
Unprovoked seizures					
8-15 weeks [c]	Linear with threshold	0.90	0.26 ± 0.11	p < 0.01	0.08
8-15 weeks [c,d]		1.72	0.25 ± 0.11	p < 0.05	0.11
All ages [c]		1.44	0.09 ± 0.04	p < 0.05	0.04
8-15 weeks [c]	Linear with threshold	0.91	0.19 ± 0.13	p < 0.10	0.04
8-15 weeks [d,c]		1.49	0.17 ± 0.12		0.04
All ages [c]		1.28	0.07 ± 0.04	p < 0.10	0.04

[a] The regression coefficient a is the number of seizures per 100 individuals at zero dose (intercept); b is the increase in frequency of seizures per unit dose (Gy^{-1}).
[b] 95% CI in parentheses.
[c] Cases of severe mental retardation included in sample.
[d] Pooled controls.
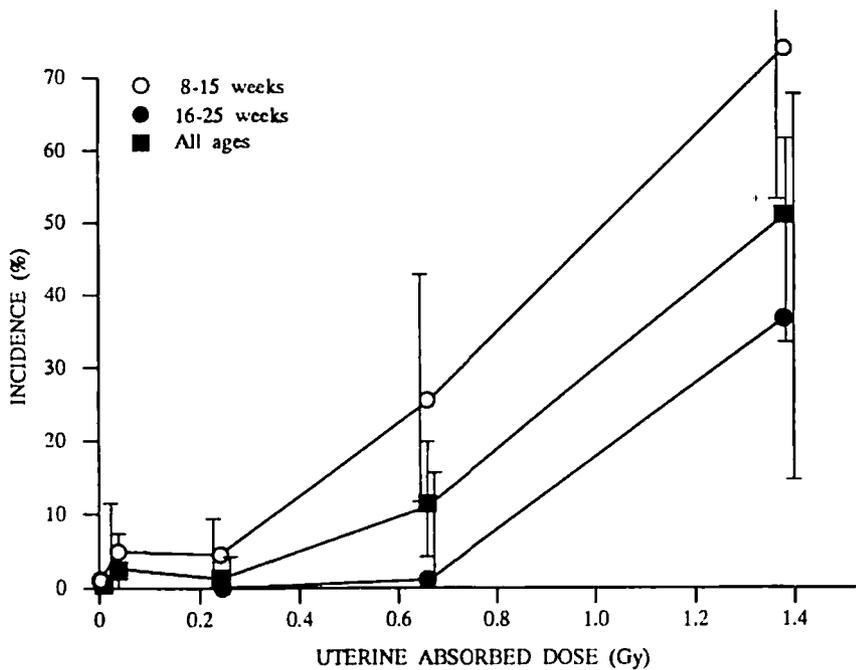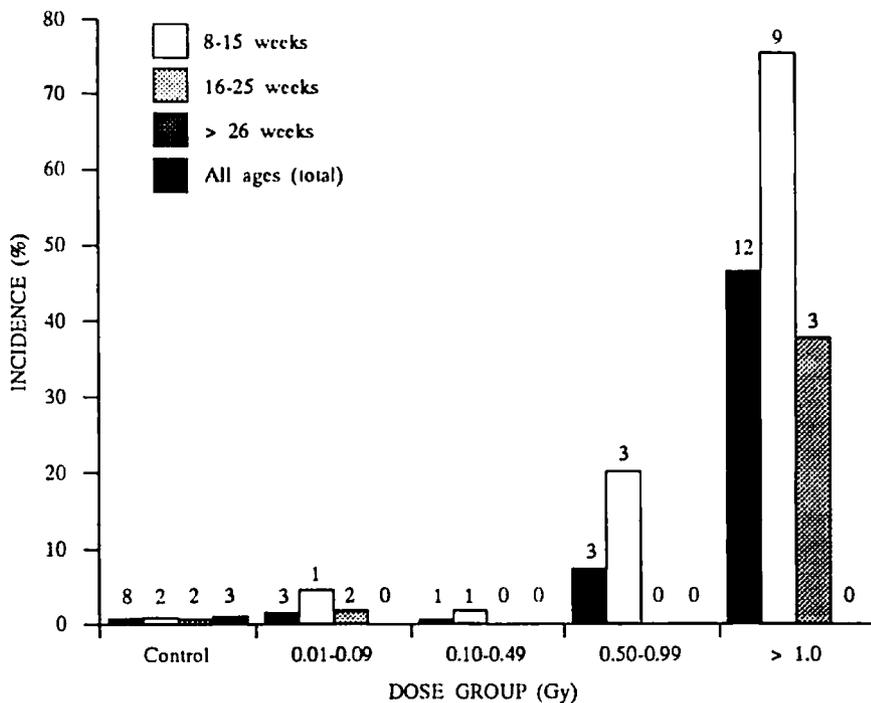[e] Cases of severe mental retardation excluded from sample.

Figure I.
Incidence of severe mental retardation in individuals exposed *in utero* to the atomic bombings
in Japan. Number of cases indicated in upper figure. Total number of cases is 27; one case in controls
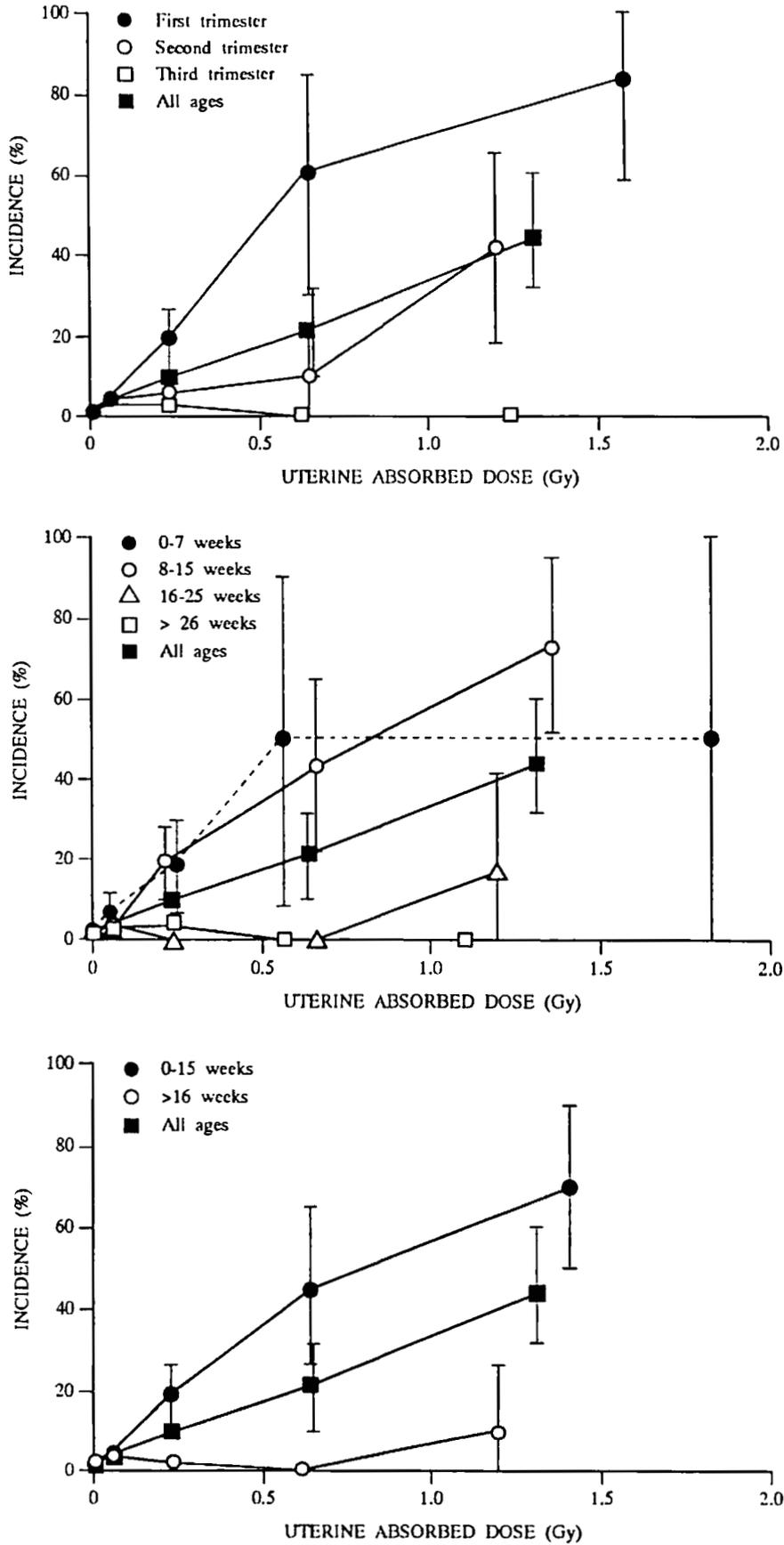exposed at 0-7 weeks not shown; three cases of Down's syndrome excluded.
[O1]

Figure H.
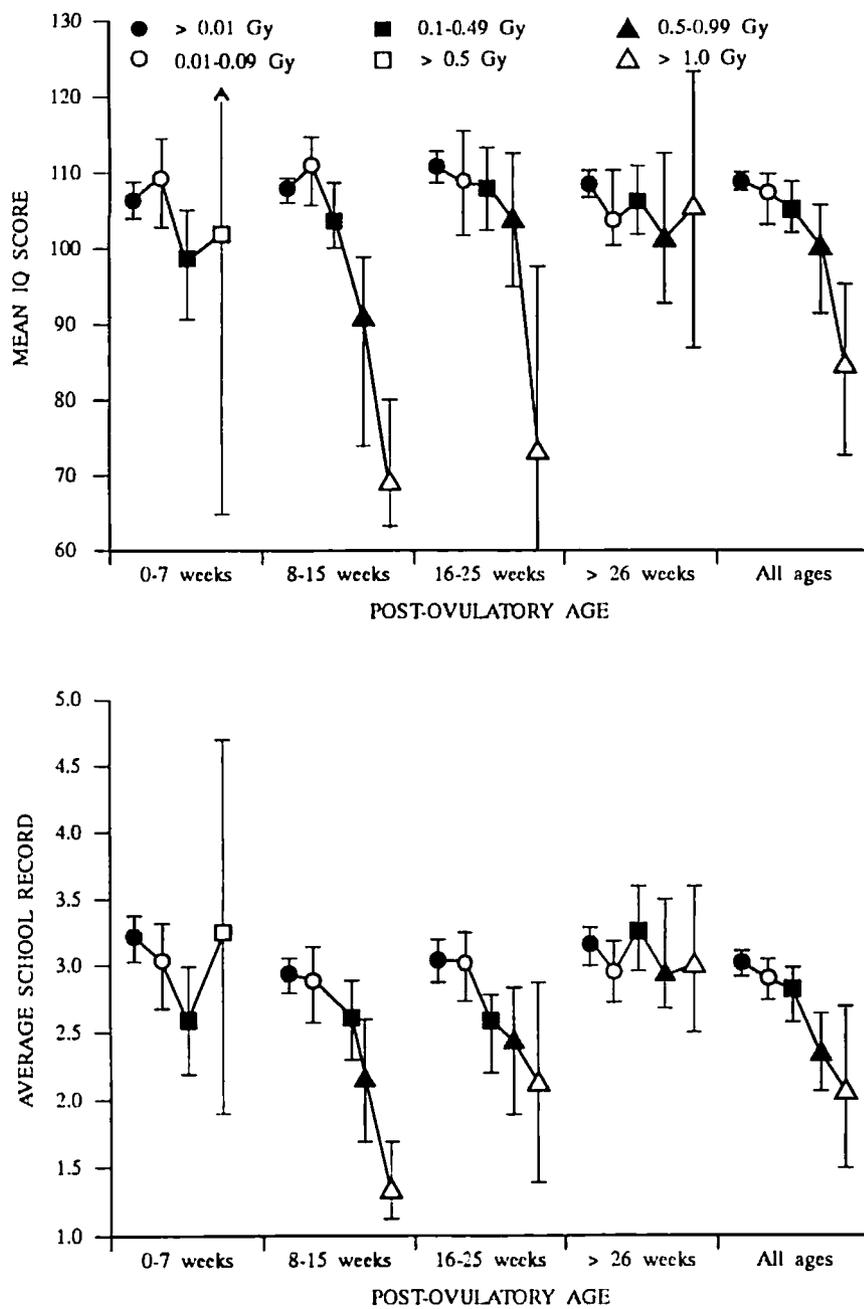Incidence of small head size in individuals exposed *in utero* to the atomic bombings in Japan
[O13]

Figure III.
Change in intelligence scores and school performance
in individuals exposed *in utero* to the atomic bombings in Japan
[O2, S4]

Glossary

abscopal	the effect on non-irradiated tissue of the irradiation of other tissues of an organism
acallosal	in the context used here, implying without a corpus callosum
anencephaly	a congenital anomaly of the brain with the absence of the bones of the cranial vault; usually the cerebral and cerebellar hemispheres are lacking and the brain stem is rudimentary.
anosmia	the inability to smell
apoptosis	a particular form of cell death, apparently programmed, in which death occurs relatively rapidly without conspicuous damage to the cell membrane
arborization, dendritic	development of the tree-like network of nerve processes
astrocyte	a star-shaped neuroglia cell; the final differentiated form of the radial glial cells that provide guidance to the neurons as they migrate from the proliferative zones surrounding the ventricles to the cortex
axon	a nerve fibre that is continuous with the body of a nerve cell and is the essential stimulus conducting portion of the cell. It consists of a series of neurofibrils surrounded by a well-defined sheath, known as the axolemma; the latter is in turn encased in myelin, a mixture of lipids, and a final sheath, the neurolemma.
brain	the mass of nervous matter that lies within the cranium or skull and consists of a number of discrete parts, such as the brain stem, the cerebrum and the cerebellum
brain mantle	the distinctively laminated layering of grey matter covering the cerebral hemispheres
brain stem	the portion of the brain that connects the cerebrum with the spinal column
Broca's area	the region in the left hemisphere involved in language. It lies in the frontal lobe above the lateral sulcus (the Sylvian fissure) between the two anterior limbs of this fissure. It is also known as the parolfactory area or the area subcallosa.
bulb, olfactory	the greyish expanded forward extremity of the olfactory tract, lying on a sieve-like plate above the ethmoid bone and receiving the olfactory nerves
CAM	an abbreviation of the words cell adhesion molecule; a number of surface molecules are known, such as N-CAM, a molecule that allows one neuron to recognize another, or Ng-CAM, that is involved in neuron-glial recognition. N-CAM exists in at least two forms, an embryonic (E-N-CAM) and an adult, which differ in the degree of sialylation.
caudate nucleus	a long horse shoe-shaped mass of grey matter that is closely related to the lateral ventricle throughout its entire length. It consists of a head, a body and a tail.
cerebellum	the posterior portion of the brain, consisting of two hemispheres connected by a narrow mass of tissue known as the vermis
cerebrum	the largest portion of the brain including the cerebral hemispheres. In its earlier stages of development, the cerebrum is characterized by four major layers, namely, the mantle, the outermost margin of the brain; the cortical plate; the intermediate or migratory zone; and the matrix or proliferative zone.
cingulum	a well-marked band of nerve fibres lying immediately above the corpus callosum that relate the cingulate to the hippocampal gyri
cisterna magna	the largest of the cisterns lying in the space between the pia mater and the arachnoid membrane of the brain; it lies between the under surface of the cerebellum and the posterior surface of the medulla oblongata. The term mega cisterna magna implies an abnormal enlargement of this cistern.
coloboma	a mutilation of a structure, generally of the eye. For example, coloboma iridis is a congenital cleft of the iris.
commissure	a bundle of nerve fibres passing from one side to the other of the brain
corpus callosum	the great transverse commissure between the two cerebral hemispheres; it lies beneath the longitudinal fissure and is covered on each side by the cingulate gyrus.

cortex   the outer layers of the cerebral hemispheres and the cerebellum where most of the neurons in the brain are located. The cells of the cortex are arranged in extensive, stacked layers that are distinguishable histologically. Six layers are recognized, namely, the molecular or plexiform layer (Layer I), the outer granule cell layer (II), the outer pyramidal cell layer (III), the inner granule cell layer (IV), the inner pyramidal cell layer (V) and the polymorphous layer (VI). Layer V, the inner pyramidal cell layer, is often further subdivided into two sublayers, known as V_a and V_b. V_a consists of small and medium-sized pyramidal neurons, whereas V_b is made up of large pyramidal neurons. The spheres of projection of these two sublayers are also different.

cortico-cortical cells   the most superficial of the cells of the cortex

cytoarchitectonics   the cytoarchitecture of a structure, particularly the cerebral cortex, where different areas may be mapped according to the manner in which various cells are distributed in the cell layers

dendrite   one of the branching protoplasmic processes of the nerve cell

diencephalon   the part of the brain that includes the thalamus and related structures. It is derived from the posterior part of the prosencephalon.

DS86   the revised system of computing the gamma and neutron doses received by the survivors of the atomic bombing of Hiroshima and Nagasaki; this system was introduced in 1986, hence the acronym DS86 (dosimetry system 1986).

dyslexia (severe)   an uncorrectable inability to read understandably, now attributed to a specific lesion in the language centre of the brain located in the left temporal lobe

ectopia   as used in the present context, the displacement or malpositioning of neuronal cells; synonymous with heterotopia

encephalomeningocele   a protrusion of the brain and its membranes through a bony defect in the skull

enolase, neuron-specific   a form of the glycolytic enzyme enolase, or phosphopyruvate hydratase, which appears to be restricted to neuronal and neuroendocrine tissues and can be a useful marker for neuronal damage

ependymal layer   the layer of cells that line the ventricles; the term subependymal implies the region beneath the ependymal layer.

folia cerebelli   the narrow, leaf-like gyri of the cerebellar cortex

fragile X syndrome   an inherited, X-linked form of mental retardation associated with a characteristic secondary constriction (often called a fragile site) of the X-chromosome. The extent of the mental retardation can vary substantially.

ganglia (ganglion)   a term generally used to describe a knot or knot-like collection of nerve cell bodies outside the central nervous system

gap junction   the cells of a multicellular organism are able to influence the activities of one another through a variety of processes. Collectively, these processes are referred to as inter-cellular communication. Adjacent cells, for example, can transport small molecules back and forth through their cell walls by means of a specific channel, known as the gap junction. Their capacity to do this, however, is influenced or modulated by a number of factors, such as the calcium levels within the cells. Regulation of this communication through gap junctions is presumed to play a role in the occurrence of cancer and in the development of the brain.

gastroschisis   a congenital defect in the abdominal wall, usually with protrusion of the viscera

GFAP   glial fibrillary acid protein, a biochemical marker of glial cells

glomerulus, olfactory   a rounded body in the olfactory bulb formed by the synapses of dendrites of one class of olfactory cells, known as mitral cells, with the axons of the olfactory cells of the nasal mucous membrane

granular neurons   one of the five discrete types of neuronal cells found in the cerebellum; these cells arise in the outer granular layer of the cerebellar cortex and migrate inwards to their sites of function. They make synaptic connections with the spiny processes on the Purkinje cell.

growth cone   the specialized end of a growing axon (or dendrite) that provides the motive force for its elongation

gyrus	one of the prominent rounded elevations of the surface of the hemispheres of the brain; the cingulate gyrus or the callosal gyrus, a synonym, is a long, curved convolution that arches over the corpus callosum.
hemianopsia, homonomous	defective vision or blindness affecting the right halves or the left halves of the visual fields of the two eyes
heterochromia iridis	a difference in coloration of the iris of the two eyes, or different parts of the iris of the same eye
heterotopia	see ectopia
hippocampus	a deeply infolded portion of the cerebral cortex, lying on the floor of the inferior horn of the lateral ventricle. It is a submerged elevation that forms the largest part of the olfactory cortex. It is now thought to be involved in learning and memory since damage to it results in a recognized cognitive defect characterized by severe amnesia and includes deficits in learning mazes.
holoprosencephaly	a failure of the forebrain to divide into hemispheres
horseradish peroxidase	an enzyme derived from horseradish that catalyzes the oxidation of certain compounds by peroxide
hydrocephaly	a condition marked by the excessive accumulation of fluid in the cerebral ventricles, resulting in a thinning of the brain and causing a separation of the cranial bones
hypergonadotrophism	the overproduction or excretion of the gonadotrophic hormones, the hormones of pituitary origin
hypogonadism	inadequate gonadal function, represented either by deficiencies in gametogenesis or the secretion of gonadal hormones
leptomeninges	the combined pia mater and the middle layer of membranes covering the brain and spinal cord known as the arachnoid
LHRH cells (luteinizing hormone releasing hormone cells)	these are specialized ciliated neurons that arise in the olfactory placode and migrate into the cerebrum. Their function is to release the hormone that stimulates the production of the luteinizing hormone, which in turn is involved in the elaboration of the sex hormones.
limbic system	a group of subcortical structures of the brain (the hippocampus, hypothalamus, amygdala) that are concerned with emotions and motivations
macrogyria (also called pachygyria)	a developmental abnormality of the brain in which the gyri are fewer in number than expected and relatively broad, and the sulci are short, shallow and straighter than normal. In its most extreme form, known as argyria or lissencephaly, there may be a total or almost total absence of gyri. Macrogyria is an abnormality in neuronal migration.
mamillary bodies	two protuberances on the under surface of the brain beneath the corpus callosum; they are a part of the brain known as the hypothalamus.
medulla oblongata	the portion of the brain that is continuous above with the pons and below with the spinal cord
mesencephalon (or midbrain)	the part of the central nervous system that arises from the middle portion of the initial divisions of the embryonic neural tube
micrencephaly (microencephaly)	abnormal smallness of the brain
motoneuron (motor neuron)	a neuron that enervates muscle fibres
motor cortex	the region of the cortex lying in front of the central furrow, or sulcus, that divides the cerebral hemispheres into anterior and posterior portions. It is the site of the processing of motor impulses.
myelin	a mixture of lipids arranged around the axons of nerve fibres. Myelination refers to the development or formation of the myelin sheath around a nerve fibre.
neocortex	the laminated, evolutionarily younger portion of the cerebral cortex in humans and higher vertebrates
neurite	see axon

neuroblasts — embryonic cells that develop into neurons

neurofibromatosis, multiple *(von Recklinghausen's disease)* — an inherited neurological disorder characterized generally by the appearance early in childhood of discrete, small, pigmented lesions in the skin, followed by the development of multiple subcutaneous neurofibroma. The latter can develop along almost any nerve trunk. Two different types of this disorder have been identified, each associated with a different genetic locus.

neuroglia (or often just, glia) — the non-nervous cellular components of the nervous system; they provide support to the developing structures of the nervous system and perform important metabolic functions. There are a variety of different glial cells, distinguishable by their morphology and function. One especially important group is the transitory set, known as radial glia cells, that provide guidance to the neurons as they migrate from the proliferative zones to their sites of function.

neuron — a nerve cell, consisting of the cell body and its various processes, the dendrites, axons and ending. Neurons do not normally divide.

neuropil — a collective term describing the network of neuroglia, axons and dendrites and their synapses in the brain

nucleus accumbens septi — an area of the brain immediately beneath the head of the caudate nucleus and medial to the putamen

oligodendroglia — a class of neuroglial cells having few processes that form a sheath around nerve fibres or a capsule around nerve cell bodies

olfactory bulb — a specialized area on the ventral aspect of the cerebral hemispheres, distinguishable about mid-gestation; related to the development of olfaction

omphalocele — congenital protrusion of the abdominal viscera at the umbilicus

optic tectum — the first central station in the visual pathway of many vertebrates. It is located in the midbrain and is analogous in mammals to the superior colliculus, a rounded eminence on the dorsal aspect of the mesencephalon concerned with visual reflexes.

oxycephaly — a condition in which the top of the head is pointed

pachygyria — see macrogyria

paleocortex — the cortex of the primate brain is often divided on the basis of the antiquity of origin of specific segments; the paleocortex is the evolutionarily older part (the neocortex in the younger) and includes the olfactory cortex.

parahippocampal gyrus — a convolution of the interior surface of each cerebral hemisphere, lying between the hippocampal and collateral sulci (or furrows)

PE-86 sample — the sample of prenatally exposed survivors in Hiroshima and Nagasaki. It was constructed, beginning in 1955, based upon birth registrations, ad hoc censuses by the city authorities and the Atomic Bomb Casualty Commission, and interviews of women who were enrolled in the genetics programme in these cities in 1948-1954 and were possibly pregnant at the time of the bombing.

periventricular (or circumventricular) — meaning around the ventricles of the brain

pia mater — the innermost of the three membranes (or meninges) that cover the brain spinal cord. The other two membranes are known as the dura mater, the outermost of the three, and the arachnoid that lies between the pia and dura maters. The arachnoid membrane is separated from the pia mater by the subarachnoid space.

placode, olfactory — a thickening of embryonic cells lying in the bottom of the olfactory pit as the pits are deepened by the growth of the surrounding nasal processes

plasmalemma — the plasma membrane

premotor cortex — the region of the cortex of the brain lying just before the motor cortex, where complex motor movements are organized

prosencephalon (or forebrain) — the most forward part of the three primary division of the neural tube; it gives rise to the diencephalon and telencephalon.

Purkinje cell — a large nerve cell of the cerebellar cortex; these cells are the only ones in the cerebellum that carry nerve impulses out of the cerebellum itself.

pyknosis (also spelled pycnosis)	a degeneration of a cell in which the nucleus shrinks in size and the chromatin condenses into a solid, structureless mass
radial glia	a specialized group of neuroglia cells that assist immature neurons in their migration to the cortical plate; later in the development of the brain these cells will differentiate into astrocytes.
Rathke's pouch	a pouch of embryonic ectoderm that gives rise to the anterior lobe of the pituitary body
rhinencephalon	one of the portions of the telencephalon, specifically that part comprising the structures toward the centre of the furrow separating the forward part of the parahippocampal gyrus from the remainder of the temporal lobe of the brain
rhombencephalon (or hindbrain)	the most posterior of the three initial divisions of the neural tube; it subsequently gives rise to the metencephalon and the mylencephalon.
schizencephaly	an abnormality of the development of the brain in which there are abnormal divisions or clefts of the brain substance
somatosensory cortex	that portion of the cortex of the brain that is involved in the processing of sensory stimuli that arise in the body outside of the brain
subarachnoid	implying beneath the arachnoidea, a delicate membrane interposed between the dura and pia maters; the subarachnoid space lies between the arachnoidea and the pia mater.
subplate neurons	a special group of early arising neurons that appear to be instrumental in the laying down of the first axonal pathways; also known as transient pioneer neurons
sulcus	one of the grooves or furrows on the surface of the brain that bounds or delimits the convolutions, the gyri. The sulcus that separates the corpus callosum from the gyrus cinguli is called the sulcus corporis callosi.
syncytium	a multinucleated protoplasmic mass formed by the secondary union of originally separate cells
synaptogenesis	the process or processes that culminate in the formation of synapses, that is, the places where a nerve impulse is transmitted from one neuron to another
telencephalon	the part of the brain that includes the cerebral hemispheres and is derived from the foremost part of the neural tube
tinea capitis	infection of the skin of the scalp with one or several different genera of fungi
uterine myomatosis	the occurrence of benign neoplasms in the musculature of the uterus
ventricles	as used here, the cavities within the brain derived from the lumen, or open canal, of the primitive neural tube. The term ventricular is used to describe the layer in the brain immediately adjacent to the ventricles.
von Recklinghausen's disease	see neurofibromatosis, multiple

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back
to
first page