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NOTE

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Annex B

EFFECTS OF IONIZING RADIATION ON THE NERVOUS SYSTEM

CONTENTS

I. Introduction

1. Exposure to ionizing radiation brings about effects that involve all systems of the organism. The type and frequency of such effects are strongly dependent on the dose of radiation absorbed and on the conditions of exposure. The purpose of this review is to describe certain aspects of the response of the nervous system to irradiation, to assess this response in terms of hazards to the exposed individual and to explore the possibility of evaluating the expected frequency of particular effects according to dose, that is, of estimating the corresponding risks incurred by man.

2. The effects of radiation on the nervous system were briefly considered by the Committee in its 1962 report to the General Assembly[1] within the general context of somatic effects. Much information has accumulated since that time. As a consequence, the importance of the impairment of the nervous system and of its functions that radiation may occasion is now better appreciated, and it was therefore felt that a more detailed review had now become appropriate. The range of the observations is so vast, however, that no attempt at covering it exhaustively has been made in this review which is largely confined to discussing those topics that are of immediate relevance to the activity of the Committee.

3. The study of the effects of radiation on the nervous system is particularly difficult because of the system's own morphological and functional complexity, the close and intricate relationships between the nervous and other systems of the organism and the multiplicity of end-points whereby changes in the nervous system can be recorded.

4. Direct damage to the nervous system is generally not lethal, except at doses well above those necessary to cause lethal damage to other organs and systems, though radiation may produce serious structural and functional changes. The relationship between these two types of change cannot always be established. In some instances, the response of the nervous system is secondary to damage in other tissues so that doses to the nervous tissue are not the relevant ones for assessing the risks of such particular effects.

5. The functional changes in the nervous system to which radiation exposure may give rise are manifold and often reversible. Whether any particular one should be regarded as damage, and its occurrence as a hazard, is largely a matter of judgement. Thus, a number of functional changes are merely transient physiological responses of certain receptors to a stimulus (ionizing radiation) that the organism does not recognize as different from those that the receptors are designed to detect. While this kind of response can hardly be viewed as damage in normal circumstances, it may involve a hazard in such exceptional situations as might, for instance, occur in space flights, in which the individual required the full command of his reactions to sensory perception.

6. In this review, radiation-induced changes will be primarily considered from the point of view of the resulting prolonged impairment of the functional integrity

of the individual. While this review deals with effects of both high and low doses, it is in the low dose range that results are particularly emphasized, for it is in this range that the population is exposed. As in earlier reports of the Committee, doses of 50 rads and less are considered to be low. The distinction between high and low doses is merely intended to separate by means of an arbitrary cut-off point doses which are likely to produce early clinical (so-called acute) effects from those that do not.

7. Data on the response of the nervous system of man and on the effects of radiation upon it are scanty and come mainly from four sources: (*a*) survivors of the nuclear bombings at Hiroshima and Nagasaki; (*b*) patients irradiated for medical reasons; (*c*) people occupationally exposed; and (*d*) people irradiated accidentally. The reliability of data from each group has limitations. Dosimetry is not always accurately known, and in most cases irradiation has taken place in circumstances that were, for obvious reasons, not well controlled.

8. Survivors of atomic bomb explosions (group *a*) were exposed not only to radiation but also to blast and heat and generally experienced a disaster unprecedented in their lives. The associated trauma may have affected their nervous systems in various ways. When patients receive therapeutic or diagnostic radiation exposure (group *b*), it is often difficult to separate the effects of radiation from the consequences of the condition or disease for which radiation was administered. In medical radiation series, particularly those performed many years ago, the adequacy of dosimetry is often questioned. Finding adequate control groups is often difficult, while the use of inadequate ones may easily lead to biased conclusions, particularly when certain functional effects that are difficult to diagnose objectively are considered. When satisfactory control subjects are available, it is advisable to set up paired statistical controls and to use double blind techniques. For radiation workers (group *c*), it is also difficult to find adequate control groups. Most of the occupational groups receive very low doses, and the relatively few groups who have been exposed to higher dose levels in the past received their exposures when dosimetry monitoring was still far from adequate. In serious accidental situations (group *d*), attempts are usually made to reconstruct the dose distribution within the working space and to determine the occupancy by the the exposed workers when the situation occurred. Since accidents usually involve negligent procedure, only rarely can the dose distribution be accurately established.

9. Because of the paucity of human data, a large part of the evidence on the induction of effects in the nervous system is necessarily derived from animal experiments. Unless this evidence is supported by well controlled observations in human beings, extreme caution should be exercised in extending conclusions to man, since the response of the nervous system to radiation differs from species to species and even between strains within the same species. The need for caution is particularly acute when observations, even negative ones, on the effect of radiation on the behavioural responses of one species are used to infer the possibility of similar effects or lack of them in man.

10. The quantitative assessment of rates of induction of functional or structural changes, and therefore the estimation of the attendant risks, requires a detailed quantitative knowledge of the underlying dose-effect relationship. Such knowledge is largely unavailable for the nervous system. The number of different doses for which effects have been studied in individual experiments is in most cases extremely small, sometimes limited to one dose level only. As there is no reasonable theoretical ground for establishing dose-effect curves, no meaningful extrapolation can be made. On the other hand, a major hindrance to the proper evaluation of the resuls of neuro-radio-biological studies is often the lack of statistical analysis and sometimes of adequate knowledge of the doses involved. All too often data are reported with so little information on such details as rate of delivery, fractionation schedule and quality of radiation as to make assessment and intercomparison of results all but impossible.

11. Most of the experimental results are reported in terms of exposure rather than dose, since it is usually the exposure (in roentgens) that is controlled during the experiment, although the absorbed dose (in rads) is the relevant parameter. With small animals (mice and rats) and the radiation usually employed, however, the assumption that the numerical value of the exposure and that of the dose are the same involves an error that, in the present context, is trivial. Whenever this has proved reasonable, roentgens have therefore been treated as equal to rads in this review. In other cases, the stated units of exposure have been retained, and available details about kilovoltage, filtration, distance, etc. have been included. Unless otherwise indicated, irradiations must be read as single, short-term, whole-body. Dose rates are given only when special significance attaches to them. When the quality of the radiation is not mentioned, it may be assumed to be that of x rays or gamma rays. This is the case with the majority of irradiation experiments involving the nervous system.

II. Effects on the developing nervous system[a]

A. Experimental results

1. *Structural changes*

12. Pre-natal irradiation of experimental animals produces damage in a number of organs and may result in macroscopic or microscopic abnormalities at birth. The cells of the developing nervous system show varying reactions to radiation. Immature cells undergo mitotic delay or become unable to reproduce in large proportions, the proportions being dependent on dose. Particularly in the early stages of development, cell killing may be so extensive as to prevent further development

[a] The main stages in the development of the nervous system are the following:[2, 3]

(a) *Period of cell division.* During this period, the number of neurons reaches almost that found in the adult. This lasts until birth in the rat and until 210 days after conception in man.

(b) *Period of cell growth and differentiation.* In this period, there is an increase in the size of the brain cells and rapid outgrowth of axons and dendrites from the nerve-cell bodies. This occurs during the first ten days after birth in the rat and from 210 days after conception until birth in man.

(c) *Period of rapid myelination.* Electrical activity can now be detected in the brain. Growth of cells is considerably lower than it was previously. This period extends from ten to about twenty days after birth in the rat and from birth to 120 days later in man.

(d) *Period of slower myelination.* It is difficult to determine exactly when this final period begins and ends. In the rat, myelination ends between five and six weeks of age and, in man, between five and ten years of age.

of the embryo. Because different primordia and anlagen of the various parts of the nervous system follow differing patterns of mitotic activity, the ultimate outcome of the irradiation varies not only with dose but also with time of exposure.[4] As differentiation proceeds and less and less cells are dividing, the resistance of the various structures of the nervous system increases. Eventually, mature neurons can usually absorb a dose of at least 1.000 rads without apparent structural damage.

13. The results of pre-natal irradiation have been studied particularly in the mouse and the rat. In both species, malformations of the nervous system can be observed during the subsequent course of development of the animals. Although reports of these malformations are more abundant in the rat than in the mouse, this may merely reflect the fact that the two species have been studied by different investigators with different techniques and for different purposes.

14. In the mouse, the most extensive studies[5] have considered primarily the way in which skeletal defects depend both on dose and on pre-natal age and have indicated that it is mainly in the period of major organogenesis (between six and a half and twelve and a half days after conception) that most malformations are brought about by radiation. These studies have also indicated that, within this period, the interval during which any one type of malformation can be induced by doses of 200 rads is limited to the period from twenty-four to forty-eight hours, though it becomes somewhat wider at higher doses. During the first six days of pre-natal life, irradiation results in high pre-natal mortality and very few malformations. After organogenesis, the ability of radiation to give rise to structural abnormalities is very much reduced, and the yield of malformations becomes progressively lower after the twelfth day of gestation.

15. Other investigators[6-9] have focused particularly on central nervous system malformations in mice irradiated at various times between the seventh and the twelfth day of pregnancy. Exencephalia, myelodysplasia with spina bifida occulta, encephalocele and arrhinencephaly are observed after 200 or 300 rads between the seventh and the ninth day, whereas later irradiation tends to produce hydrocephalus.[9] Microphthalmos, anophthalmos and microcephaly arise after both early and late irradiation at the same doses. There are differences, however, in the temporal sequence between the two strains investigated, one of them, for instance, showing two peak incidences of hydrocephalus, whereas the other presents only one.

16. While most investigators agree that malformations can only be induced during major organogenesis, there have been reports[10, 11] of exencephaly being induced by doses of 15 rads given 0.5 and 1.5 days after conception. The occurrence of exencephaly after irradiation at that early stage, however, appears to be a rare and erratic phenomenon for which no clear dose-effect relationship has been demonstrated so far. Exencephaly has been observed to arise spontaneously in some strains of mice, and there is some indication that its incidence may show seasonal fluctuations.[12] Larger and strictly controlled experiments must be performed before the view can be accepted that irradiation in the pre-implantation period brings about major malformations involving the nervous system.

17. In rats, formation of the nervous system begins on the tenth day after conception. Results of *in utero* irradiation are basically similar in all strains investigated. A dose of 200 rads given on the eighth day kills the embryo, whereas lower doses neither kill the embryo nor produce malformations. With 100 rads on the ninth day, severe malformations of the forebrain and upper head (anencephaly, pseudoencephaly) and eye malformations (anophthalmia) may be observed. Some malformations occur even after 50 rads, but only eye anomalies at 25 rads. The effects are less on the tenth day, though anophthalmia is still observed at 100 rads. Irradiation (200 rad) on the eleventh day gives rise to a high frequency of hydrocephalus with dorsal encephalocele of the third ventricle.[13-17]

18. Between the twelfth and the twentieth day after conception, doses of 200 rads produce a varying degree of reduction of the size of the forebrain accompanied by hypoplasia and disorganization of the cortical neuron layers.[18, 19] Absence or abnormalities of the corpus callosum may occur after irradiation between the twelfth and the eighteenth day, and the presence of aberrant thalamo-cortical fibres is particularly evident in animals irradiated on the sixteenth and seventeenth days. Irradiation from the eighteenth day onwards, and well into the first week after birth, may produce major disturbances in the development of the cerebellum that affect its size and the proportion of its various parts and that disrupt the orderliness of its cellular structures.[20]

19. Detailed histological studies[21] have shown that doses between 20 and 50 rads on the sixteenth day of gestation are followed, in the rat, by disorganization of the cortical structure. Neurons in the outer cortex are smaller and fewer than in controls, less differentiated and with little tendency to vertical arrangements. Certain cortical layers are thinner and less sharply defined, "layer six" in particular showing cellular deficiency and jumbling of neurons. While at maturity the orderliness of the cortex is partly restored, particularly when doses were low, layer six remains deficient and disorganized even after 20 rads. Similar but less striking effects are observed after irradiation on the eighteenth day of pre-natal life. Retardation and alteration of growth of the cortex is clearly evident after a dose of 10 rads on the day after birth, but the damage becomes more and more difficult to detect with time, and no significant structural abnormalities can be detected in mature animals, thus indicating apparent recovery. No data are available on the effects on cortical structure of low doses given before the sixteenth day of intra-uterine life.

20. It is very difficult to predict, on the basis of what has been observed in rodents, the malformations to be expected in man, even allowing for the different time course of development. The relevance of the experimental studies that are reviewed here is mainly in showing the importance of the time of irradiation for the production of malformations of the nervous system in general and of particular anomalies involving this or that structure. The timing of irradiation is so important that, by adjusting it carefully, it is possible to "design and build" abnormal rat brains. Dose is naturally an equally important factor. It is remarkable that, with the exception of exencephalia, whose induction by radiation is still open to question, gross malformations of the nervous system have not been described in the low dose range. Even though a threshold dose for the induction of damage to the developing nervous system has not been established, lasting microscopical changes are clearly observable in the rat cortex

after doses around 20 rads. The available data suggest that the radio-sensitivity of the fœtal nervous system is of the same order as that of the most radio-sensitive tissues of the adult.

21. In certain mammals, at least during the period of organogenesis, structural changes involving the central nervous system have been observed following exposure to a wide range of mutagenic or teratogenic agents. These changes are similar, if not identical, to previously described radiation effects such as micro-ophthalmia, anophthalmia, microcephaly and gross deformities of the spinal cord. The agents implicated and observed to be causative include parts of the vitamin B complex, Prussian blue, certain "pesticides" and certain viruses. The induction of changes appears to be much more directly and precisely related to the particular stage of organogenesis at which exposure occurs than to the "dose" of the mutagen. It is not at present known if the same basic mechanism is involved as in the case of radiation, nor whether there is a threshold effect.

2. *Functional changes*

22. Gross malformations such as those observed after pre-natal doses of 100 rads and higher, if compatible with survival, are naturally accompanied by severe functional impairment. The following paragraphs will review functional changes in animals that do not have overt structural malformations of the nervous system.

23. Adult rabbits exposed to 300 roentgens of whole-body radiation (190-kV x rays, 1 mm Cu, 0.5 mm Al) on the twenty-third day after conception (last third of gestation) show reduction of the amplitude of the encephalogram and of the spike frequency and very poor response to light stimuli.[22] Another investigation has shown electro-encephalographic changes after x-ray exposures ranging from 150 to 400 roentgens.[23] In rabbits irradiated around the fifteenth day of gestation, there was an increase in the proportion of high-frequency waves, whereas, in animals irradiated around the twenty-third day of gestation, there were increments in the amplitude of low-frequency waves and a decrement at higher frequencies.

24. These changes in the wave spectrum may reflect structural disturbances in the different parts of the nervous system during corresponding stages of embryogenesis. In general, low-frequency waves reflect activity of subcortical structures, whereas high-frequency waves reflect activity of cortical structures. Since radiation in the middle of the gestation period has more profound effects on subcortical than on cortical structures, the electro-physiological changes seem to be correlated with the morphological changes.

25. Electro-encephalograms and electro-corticograms have been recorded in rats given 200 rads on the seventeenth, nineteenth or twenty-first day of gestation, or on the third day post-natally.[24] Such pre-natally irradiated animals when at rest exhibit a relatively high frequency of "spiky" waves. This may be attributed to impairment or absence of the outer cortical layers which are usually linked with the thalamus and which inhibit thalamic discharges. Amplitudes, both in the electro-encephalogram and in the electro-corticogram, are somewhat smaller than in normal animals. In the exposed animals, auditory stimulation blocks less readily the large-amplitude slow-wave activity. Animals irradiated post-natally do not differ from controls. On the whole, the changes in electro-cortical activity are less marked than the structural damage. On the other hand, no electro-encephalographic abnormality has been observed two weeks after birth in rats that had received 100 rads nine days after conception.[25]

26. The auditory threshold for sound-stimulated seizures has been shown to be lowered in rats that received x-ray doses of 25 to 100 rads between the fifteenth and the twentieth day of gestation,[26] whereas doses of 5 to 15 rads did not change susceptibility.[27] Studies with electro-convulsive shock have produced results similar to those obtained with auditory stimulation. Rats which have received 100 rads on the fourteenth day of gestation show an earlier response and a lowered threshold for shock-stimulated seizure. The results may be ascribed to impairment of inhibitory elements in subcortical areas.

27. Motor reflexes in rats are also affected by pre-natal x irradiation. In animals irradiated on the tenth day of gestation, 20 rads are ineffective, but 100 rads induce ataxia. In addition, righting reflexes are affected in female animals, while males exhibit myoclonus. Both males and females that have received 185 rads on the fifteenth day of gestation show deficits in righting and hopping reflexes, as well as ataxia, myoclonus, spasticity, seizures and other neurological motor defects.[28] Various locomotor tests have also demonstrated deficits in animals receiving doses of 50 rads or more pre-natally and early post-natally.[29, 30] In general, the deficit is directly related to the dose and, between the fifteenth day of gestation and the first few post-natal days, is less pronounced the later the exposure. Attempts to correlate the motor deficits with cerebellar damage have yielded ambiguous results.[31] Tests of motor performance have involved non-motor nervous activity, thus complicating the problem of finding simple correlations between structure and function. It has also been shown that fractionated daily exposure throughout pregnancy (1 to 2 rad per day) reduces locomotor activity.[32]

28. Different measurement techniques used by a number of investigators have shown that rats receiving from 20 to 200 rads between the thirteenth day of gestation and birth show hyperactivity when placed in novel environments.[23, 33-35] Although the minimal effective dose depends on the measurement technique used, it clearly varies with the age at the time of exposure. When irradiated animals become familiar with the situation, they do not differ from controls. Hyperactivity is part of a general syndrome seen in pre-natally irradiated rats and mice, which may be defined as increased arousal by novel stimuli. It manifests itself in increased, non-directed, locomotor activity and slower specific response to novel stimuli,[34] more rapid conditioning in simple aversive situations,[36, 37] increased heart-rate reactivity,[34] slower adaptation to food-and-water-deprivation schedules[38] and slower adaptation to the environment.[39]

29. While most investigations reveal increased apprehensiveness and restlessness in animals thus irradiated, negative findings have been reported after 150 rads on the thirteenth or fourteenth day of gestation.[33]

30. Behavioural alterations in rats are also apparent from studies of brightness-discrimination learning which has been reported to be reduced at six months of age after some 150 rads on the fourteenth day of gestation and after 300 rads on the eighteenth day.[40] Likewise, olfactory discrimination is drastically

reduced in rats after 200 rads of x rays on the sixteenth day of gestation,[41] and distance discrimination after 100 rads.[42] Performance of visual pattern discriminations, on the other hand, appears to be unaffected by 150 to 200 rads, as tested on the thirteenth, fifteenth, seventeenth or nineteenth day of gestation despite the major cyto-architectural alterations present in the cortex.[4]

31. Alterations of maze performance after pre-natal irradiation have been reported from a number of laboratories. Though most investigations show a deficient response (as measured by learning time and the number of errors in selecting alternative routes) in rats that have received 100 rads or more during the second and third week of gestation,[43, 44] as well as in rats irradiated during the first few days after birth,[45] there have been observations[33] of improved performance after *in utero* exposure, particularly in females.

32. The effects of pre-natal irradiation on learning processes are also shown by studies on the acquisition and consolidation of conditioned reflexes. Most of the investigations used light and sound as stimuli for conditioning rats to perform a mechanical operation, such as opening a gate, necessary to obtain food. While 200 rads on the fifth day after conception failed to produce significant changes in the conditioned performance,[46] irradiation on the twelfth day altered significantly most of the indices by which it was assessed. Thus, the consolidation of a negative conditioned reflex after the positive one had been established was significantly accelerated after 50 rads, but delayed after 100 and 200 rads, as compared with unirradiated controls. In general, the alteration of the conditioned reflex activity became greater with increasing dose.[47]

33. Study of the conditioned reflexes at various ages showed progressive deterioration of the reflexes in animals given 50 and 150 rads on the fourteenth day after conception, the impairment being more pronounced among more highly irradiated animals.[48] Similar observations were made on animals receiving 10 rads per day during the first twenty days after conception.[49]

34. Irradiation on the eighteenth day[35] at doses of 200 rads delayed the occurrence, but particularly the consolidation, of both positive and negative conditioned reflexes. The effect appeared to be larger, with reflexes involving light than with those involving sound as a conditioning stimulus. Differences between controls and animals treated with 50 rads appeared to be smaller and mostly non-significant.

35. Alteration of formation and consolidation of conditioned reflexes has been reported after a total dose of 20 rads fractionated (1 rad per day) over most of pre-natal life.[32] Effects have also been observed after a single dose of 1 rad to the exteriorized uterus on the eighteenth day after conception[50, 51] in the course of a highly complex experiment involving a number of different light and sound stimuli. Differences between irradiated and control rats, as judged by some of the indicators of conditioned reflex activity, such as latent period and intensity and duration of responses, were small but significant. The experiment is the only one showing effects at such a low dose level. Further investigations seem to be required before the functional change due to acute pre-natal exposure to very low doses of radiation can be properly assessed.

36. In summary, even when gross structural malformations are absent, functional and behavioural disturbances, particularly of the learning processes, are consistently seen after birth in animals exposed pre-natally to high doses of radiation at an appropriate time. These observations are not very surprising in view of the histological changes that high doses of radiation consistently produce in the developing brain. However, clear-cut correlations between the various functional disturbances and morphological malformations have not been established. Although there is extensive literature on both structural disturbances and functional changes, few attempts have been made to integrate the two lines of research.

37. Though comparisons are difficult, conditioned responses appear to be generally affected at doses lower than those required to impair maze performance or discrimination learning, although it should be pointed out that not all indicators of conditioned reflex activity always demonstrate deficits. It may also well be[52] that, when the whole nervous system is challenged by a task such as running a maze, the deficit of individual conditioned reflexes is virtually balanced by the intervention of alternative and still undamaged processes and pathways.

38. It is not clear whether the results of the animal experiments can be extended to human situations. All that these experiments show is that certain processes which involve higher nervous activity may be affected by pre-natal irradiation. In higher animals, including man, similar effects may occur, but to what extent and at what doses these may impair the functional integrity of the individual can only be ascertained through observations in the species concerned.

B. Effects in man

1. *Pre-natal irradiation*

39. The literature records several scores of sporadic observations of children with developmental anomalies who had been exposed *in utero*, mostly unintentionally, in the course of therapeutic radiological procedures, including, in a few cases, unsuccessful attempts at terminating pregnancy. Though doses, as well as the size of the populations at risk, are uncertain, useful information on the type of defects produced and on the critical period for irradiation during pre-natal life can be derived from these findings.

40. The various reviews of the literature made in the 1920s and 1930s largely overlapped each other.[53-55] Additional cases were surveyed in a recent review.[56] The most informative analysis of the published cases of pre-natal irradiation[57-59] compared the offspring of women irradiated during pregnancy with the offspring of women irradiated before pregnancy. The latter group comprised 417 live-born among whom three had developmental defects involving the nervous system (one born with exposed brain and two recorded as "microcephalic mongol" and "hydrocephalic mongol", respectively). Among the seventy-five children of women irradiated during pregnancy, eighteen were reported to be microcephalic, four had other forms of severe disturbances of the central nervous system and one had developmental defects, mostly skeletal, involving the head.

41. The proportion of offspring with defects of the central nervous system was therefore far higher after *in utero* than after pre-conception irradiation. While

no microcephalics were observed in the group irradiated before conception, nearly 80 per cent of the malformed children irradiated *in utero* were microcephalics. One of the microcephalic children was reported as "mongoloid" and most of them as "idiots" or "imbeciles". In most cases, microcephaly was associated with eye troubles of various grades of severity, including two cases of amaurosis.[60]

42. Detailed quantitative information is lacking, but fœtal doses are believed to have been high in most of these cases. In many, doses were multiple, and in some they were received over a period of time from intracavitary sources. The reasons for the irradiation were usually unrelated to the pregnancy, which in most instances was, in fact, unrecognized at the time of the exposure. Among the microcephalic children, all but one had been irradiated at least once between the second and sixth month of intra-uterine life, the exception having been irradiated during the first month only.[60]

43. Because of sampling and other uncertainties, these early data have limited value. No quantitative conclusion can be derived from them because doses, although likely to have been high, are inadequately known, but results strongly suggest that microcephaly and mental retardation can be induced by fœtal irradiation. Although the irradiations were carried out on a variety of medical indications, it is not possible entirely to rule out an association between developmental defects and the conditions necessitating the irradiation.

44. The study of children acutely exposed while *in utero* to the explosions of Hiroshima and Nagasaki, however, provides independent information on the effects of pre-natal irradiation in man. This also is not in itself unambiguous, since irradiation was associated with other physical traumas that might also have contributed to the eventual effect.

45. Head size and mental retardation were first recorded at Nagasaki in 1951,[61] subsequently at Hiroshima when the children were nine years old[62] and again at Nagasaki when the children were between thirteen and fifteen years of age.[63, 64] The results of surveys made at seventeen and twenty years of age[65-67] have now become available. They include 1,613 children, or about 16 per cent of all the live-born in both cities that were *in utero* at the time of bombing.

46. The survey carried out at seventeen years of age indicated[65] that, in both cities and in both sexes, mean head circumferences were significantly smaller (by about 1 centimetre or 2 per cent) in the offspring of those that were within 1.5 kilometres of the hypocentre. Dependence of the effect on the age of the fœtus at the time of irradiation was not clearly apparent.

47. The same survey also investigated[66] the prevalence of mental retardation, which was diagnosed only if a subject was unable to perform simple calculations, to make simple conversation, to care for himself or if he was completely unmanageable or had been institutionalized. The results of the survey are shown in tables I and II,[b] indicating a striking relationship between prevalence, on the one hand, and both distance from the hypocentre and the age of the foetus at the time of irradiation, on the other. The tables do not contain data on the offspring of women between 2.0 and 3.0 kilometres from the hypocentre, as these were not included in the survey.

48. It is remarkable that, in both cities, all cases of mental retardation within two kilometres from the hypocentre were born between November 1945 and March 1946, corresponding to exposure between the sixth and the twenty-fourth week of pregnancy, with a peak frequency at thirteen weeks in the proximal group and at fourteen weeks in the distal one, whereas the few cases beyond 3.0 kilometres were randomly distributed with respect to the time of explosions. It must be added that, as indicated in table II, a few (so-called "explained") cases of mental retardation were associated with diseases that might themselves have caused retardation.

49. Comparing (table II) the distal group (1.5 to 2.0 kilometres) with the combined controls (subjects beyond 3.0 kilometres or not in the city at the time of bombing) born during the period November 1945 to March 1946, it appears that the prevalence of mental retardation in the distal group at Hiroshima is about 2 per cent, which is higher than that in the control populations, although the difference is of doubtful statistical significance.[c] No cases of mental retardation were reported in the distal group at Nagasaki.

50. A survey[67] made at Hiroshima twenty years after the bombings includes further details on cases appearing in the surveys above. It contains additional tabulations on the relations between distance, head size, period of gestation and mental retardation (tables III and IV). It is interesting to note that, while the results of the survey largely bear out the observations made ten years earlier, two subjects considered retarded in the survey at ten years of age[62] were not so considered at twenty years, and two that were considered normal at ten years proved to be mentally retarded subsequently.

51. Evidence from the survivors of the bombings does not rule out the possibilities mentioned earlier that the observations might, in part, be the results of trauma due to blast or fire, but the Committee is not aware of other reports concerning mental retardation or microcephaly attributed to these or other calamities. It also seems impracticable to attempt to evaluate the possible role of nutritional deficiencies in this situation.

52. Based on the tabulations in tables I to IV, there seems little reason to doubt that, at some critical period during gestation, doses such as were received in the proximal areas (presumably of the order of 100 rad or more) are associated with an increased incidence of reduced head size and of mental retardation. Based on currently available estimates of air doses in the two cities,[69] rough calculations can be made as to the relationship between incidence and dose at high doses. These calculations suggest that the frequency of mental retardation with reduced head size is of the order of 10 per cent per hundred rads (10^{-3} per rad).

[b] The Nagasaki data in tables I and II differ in two respects from those originally published: (*a*) comparison with other sources indicates that, at Nagasaki, a case of mental retardation that was assigned a distance of 1.7 kilometres actually belonged to the proximal group, as shown in the present tables; (*b*) the original tables were inconsistent with each other with regard to the total number of individuals exposed in the proximal and distal groups at Nagasaki. This inconsistency has been removed in the present tabulation.[68]

[c] When "explained" cases are excluded, the prevalence in the distal group at Hiroshima is about nine times that in the Hiroshima controls born during the same five-month interval (comprising three cases of mental retardation among 171 exposed as against one among 532 controls), but the ratio is reduced to between three and four if controls are broadened to include those in both cities, regardless of month of birth, "explained" cases still being excluded.

53. Similar calculations based on data from the distal groups mentioned in paragraph 49 might indicate a similar magnitude of effect, but no firm conclusions indicating possible effects of low doses can be drawn from this information. In this instance, the observed frequencies are small and therefore exposed to wide sampling fluctuations, and any conclusions are also particularly susceptible to other difficulties common to epidemiological surveys.

54. The prevalences of mental retardation shown by the surveys are not to be read as true rates of induction without further qualifications. They are frequencies observed among conceptuses that have survived intrauterine life and early childhood until they were recorded in surveys. For further enlightenment on this point, the results of surveys of mortality in live-born children who were *in utero* at the time of bombing[67, 70] and early data from Nagasaki[61] giving information on fœtal mortality in relation to distance have been consulted. The evidence available from these sources indicates that ignoring fœtal mortality does not entail an over- or underestimate of the rate of induction by more than 25 per cent in the proximal group and that it induces no bias in the distal group. There is only a suggestion of a higher mortality among retarded children with reduced head size at Hiroshima than among controls, but certainly no more than a minor correction in prevalence rates would seem to be indicated.

55. Recent data[68] have been supplied to the Committee, which take into account actual estimates of doses[d] to the individuals shown in tables I and II. This information is given according to dosage groups, but not according to month of birth, and is presented in table V.

56. From this tabulation, there appears to be no significant difference between the incidences of the control groups and those of the groups receiving low doses, that is, less than 50 rads. As shown in columns A and B of table V, the three groups receiving higher doses show significantly increased incidences with increasing dose (up to 36 per cent in those receiving doses higher than 200 rad). In view of the small numbers of affected individuals in the various groups and of differences in the quality of the radiations received in the two cities, it does not seem reasonable to attempt to estimate the form of the relation between dose and incidence. In so far as the derived percentages indicate significant differences between control and irradiated groups, the relation between dose and frequency is comparable to that derived from cruder data in paragraph 52. It may be noted that three of the four cases in the distal group fell into the lowest dosage category and were so located that they could not have received more than 5 rads.

57. It is of interest to compare these observations with those on leukæmia induction rates during a twelve-year period (1947-1958) among the survivors of post-natal irradiation at all ages in the two cities.[71] These figures are given in table VI. On the other hand, mortality and morbidity surveys at Hiroshima and Nagasaki have failed to show any increased prevalence of leukæmia[72] or neoplasms,[73] even among the groups more heavily irradiated *in utero*, in striking contrast with the rise in mental retardation and reduced head size observed even in lightly exposed groups. Such a discrepancy is unlikely to be accounted for by differences in the resolving power of the various surveys and suggests that, under conditions of single short-term irradiation between the sixth and the twenty-fourth week of pregnancy, the risk of mental retardation is much higher than the risk of leukæmia being induced by radiation at any time during pre-natal life.

58. This conclusion is not disproved by the negative evidence from surveys designed for other purposes,[74, 75] which have not shown any excess of mentally retarded among children exposed *in utero* for medical reasons. Though these surveys have involved sizable samples, only a small fraction of the children were irradiated during the critical time for the induction of mental retardation, most of the cases having been exposed during the last four months of pregnancy. Even if, at the low doses that were presumably received, the rate of induction had been that suggested by the Hiroshima data, the expected excess of retarded children would have been too small for detection. In the present context, therefore, these surveys merely confirm that mental retardation is not induced by radiation during the last stage of gestation.

59. It may be emphasized that theoretical considerations are of little help in suggesting what sort of relationship may exist between dose and incidence of mental retardation, since the mechanism by which it is brought about is almost wholly unknown. It might be supposed that both mental retardation and microcephaly, when due to pre-natal irradiation, reflect destruction and disturbance of the arrangement of large numbers of cells in the cortex, and hence the proportions of affected individuals might not be amenable to the same relatively simple types of formulation that have been used to relate dose and effect in such cases as genetic and cytogenetic damage. Also, since the distributions of head size and intelligence are continuous, the sorting out of individuals into those affected and those unaffected requires choice of an arbitrary cut-off point as the criterion of damage.

60. Since there is doubt about the magnitude of the expected incidence of mental retardation at doses below those received by the proximal group at Hiroshima, it will be important to confirm or disprove, on subjects other than atom bomb survivors, the existence or degree of radiation induction of mental retardation during early pregnancy. Sufficiently large surveys of the offspring of women irradiated at low doses during pregnancy may disclose an excess of *in utero* exposure among certain categories of retarded children. On the other hand, no effort should be spared to secure all the additional information that can be extracted from the survivors of the bombings.

61. Mental retardation is not the only serious effect in the nervous tissue that is associated with pre-natal irradiation. Increased frequency of *in utero* irradiation for medical reasons among children dying of malignancies of the nervous system compared to controls has been observed in two surveys. Both were retrospective, but one[76] relied on the memory of the mothers of the deceased children, whereas the other[77] took advantage of information from hospital records. The observed excess in the latter survey indicates that the incidence of malignancies of the nervous system is about 40 per cent higher among irradiated children than among those that were not irradiated—a relative risk close to that observed for leukæmias in the same survey.

[d] The doses given include estimated contributions from both gamma rays and neutrons. These were added without weighting.

62. As with all medical surveys, the possibility cannot be excluded that the increased radiation risks may be, at least in part, spurious, since there is no way to separate the effect of radiation as such from that of the maternal condition that may have prompted the exposure. Average doses to the fœtuses are unknown but are unlikely to have been higher than 5 rads. Because the surveys are retrospective, rates of induction cannot be given in absolute terms without making assumptions with regard to the prevalence of nervous tissue neoplasms among non-irradiated children. Information is insufficient to ascertain the critical period for the induction of nervous tissue malignancies.

63. No excess of these malignancies has been reported in subjects irradiated *in utero* at Hiroshima and Nagasaki.[70] The number of subjects so exposed was too small, however, for increases of tumours of the nervous system to have been detected in those populations, unless the rates of induction had been much higher than the surveys previously referred to suggest.

2. *Irradiation during childhood*

64. Irradiation of children during the first years of life has been reported to result in a number of functional effects.[78] Thus, deep somnolence lasting for up to fourteen days and arising from six to eight weeks after irradiation of the scalp for epilation purposes (70 kVp x rays, 5 mA, 0.5 mm Al, 26 cm focal distance, 13 min exposure) was observed in thirty among 1,100 children so treated.[79]

65. Investigations[80] of another group of children treated with high cumulative doses (up to several kilorads) for hæmangiomas and for various neoplastic conditions between birth and thirteen years of age showed a high frequency of functional changes that were observed two to seven years after irradiation. Seventy children underwent electro-encephalographic tests which showed local or generalized alterations in fifty cases. These alterations consisted of a general reduction of amplitude of the bio-electric activity of the brain and, in fifteen patients, of rhythm changes in the electro-encephalogram. Locally, those alterations were more pronounced when irradiation had been localized to part of the brain. Bradycardia and hypotension were present in 50 per cent of the children that had received irradiation to the head alone. Similar incidences were reported by other authors.[81, 82]

66. Despite their intrinsic interest, the value of all these investigations is limited by the absence of controls which makes it impossible to separate the effects of irradiation from those of the disease for which the treatment had been applied.

67. Increased incidence of tumours of the nervous system within the radiation field (three neurilemmomas, one neurogenic sarcoma and one tumour of basal ganglion in 36,000 man-years, against one astrocytoma and one brain tumour of unspecified type in 54,000 man-years untreated sibs), has been reported among subjects irradiated in early infancy for thymic enlargement and followed up for an average period of twenty-three years.[83, 84] In this population, the highest excess of malignancies is in respect to carcinomata of the thyroid (nineteen cases against none in controls) as a consequence of the direct exposure of the gland to the x-ray beam and with regard to leukæmias (six among irradiated children and two among controls). The excess of tumours of the nervous system is significant, but the pertinent dosimetry is unknown so that it is not possible to compare even crudely their rate of induction with that of the other types of malignancies. A similar survey of children irradiated between eight and eleven years of age and followed up until the average age of twenty-two years has shown a non-significant excess of brain tumours among them (two in about 17,000 man-years) as compared to their untreated siblings (two in 58,000 man-years).[85]

68. Other evidence for the induction of tumours of the nervous tissue by radiation is provided by a survey of children whose scalps were irradiated for depilatory purposes in the treatment of ringworm infection.[86, 87] Most of the brain was estimated to have received doses within 20 per cent of 140 rads.[88] The age at irradiation was about seven years, and the follow-up time was around fifteen years. A group of children with ringworm, who had been treated at the same time by means other than radiation, served as controls. The two groups appeared to be comparable with regard to sex, race and family income distribution. *Microsporum lanosum*, however, was comparatively more frequent in controls than among irradiated children.

69. Three confirmed brain tumours (two astrocytomas and one malignant glioma) were reported among the irradiated (approximately 30,000 man-years), as against none in the control group (approximately 20,000 man-years). With the doses mentioned in the previous paragraph, this would correspond to a yield over a period of some fifteen years of about ten cases per rad per million exposed, if proportionality of dose and incidence were assumed. Other malignancies also were observed among the irradiated subjects including four cases of leukæmia, or roughly the number expected for adults from the man-years at risk and the mean marrow dose (about 50 rad) that is obtained by averaging over the whole bone marrow the dose received by the bone marrow contained in the skull.

70. The induction of nervous tissue malignancies by irradiation is therefore suggested by three surveys of irradiated children. Data are still too scanty to permit a reliable estimate of the rate of induction per rad for any given radiation exposure, though at least the survey referred to in the previous paragraph suggests that, at a dose between 70 and 175 rads, the rate is likely to be of the same order as that of leukæmia induction in the adult.

71. The same survey also reveals a significant excess of confirmed cases of mental disorders among the irradiated, the over-all incidence being 2.5 times higher than in controls. Mental disorders include personality disorders (eighteen irradiated cases, three controls), psychoneuroses (twenty-five irradiated, six controls) and psychoses (twenty-one irradiated, nine controls), the latter all involving schizophrenia, with a higher relative prevalence of the paranoid type among the irradiated than is observed among controls.

72. These observations are of the highest interest but must be taken with a great amount of caution. The incidence of mental disturbances is notoriously affected by a number of social, environmental and genetic factors that are difficult to allow for. In the survey under review, only race and the income bracket of the subjects have been considered. It would appear that a very close analysis of further variables is required before final judgement on the results with

regard to the induction of mental disorders can be formed. Such an analysis is in progress.[89] The results of a similar, but larger, survey currently under way[90] may also be useful in clarifying the issue.

III. Effects on the adult organism

A. Central nervous system

1. *The central nervous system radiation syndrome*

73. The radiation dose needed to induce dramatic early neurological disturbances in adult animals, with the exception of the burro,[91] is much larger than the dose needed to cause gastro-intestinal or haematopoietic death. The so-called central nervous system radiation syndrome, where death within one to three days is due to irradiation of the head alone or to the whole body, requires, in the mouse for instance, doses of the order of 10 kilorads.[92]

74. In guinea pigs receiving 25 kilorads to the whole body, initial depression of motor activity is followed by enhanced motor activity and by extensor rigidity.[93, 94] In whole-body irradiation of hamsters with 8 kilorads, disturbances of equilibrium develop quickly, but seizures do not occur.[94] In dogs, only lethargy after whole-body exposure to 10 kilorads is seen,[95] whereas burros become aggressive.[96] In rabbits receiving 4 to 9 kilorads to the head only, a two-phase syndrome consists of initial apathy, which is dose-independent in the range studied, followed within hours by ataxia, posture disturbance and epileptiform seizures.[97] The second phase is strongly dose-dependent and has been reported to show a threshold of about 6 kilorads (however, see paragraph 102).

75. In monkeys, severe neurological signs and death in the central nervous syndrome are seen within two days after whole-body doses of about 10 kilorads.[98] Doses between 2.5 and 30 kilorads usually give rise to an early hyperexcitability followed by an early transient incapacitation.[98, 99] Partial recovery, the duration of which is inversely related to dose, follows this early incapacitation. Subsequently and abruptly, a phase of permanent complete incapacitation sets in. No partial recovery is seen after 50 kilorads, and permanent incapacitation within 30 seconds is seen in nearly all animals at 100 kilorads.[99]

76. One case of radiation accident in 1958 has shown, after an estimated head dose of about 10 kilorads of mixed gamma neutron (2:1) radiation, clinical symptoms primarily associated with damage to the central nervous system.[100] The course, from exposure to death, lasted thirty-five hours. The sequence of clinical signs and symptoms fell within the pattern predicted on the basis of animal experiments. The main neuropathological finding in the brain was a severe oedematous condition.[101]

77. Extensive studies[102, 103] were made of the brains of forty-nine Hiroshima and Nagasaki casualties who died between sixteen days and six years after the bombing. Mental and neurological disturbances were noted in several of these patients. No correlation between these disturbances and distance from the hypocentre could be found. All casualties showed signs of acute radiation sickness, and all became severely anaemic. Pathological changes varied from mild to pronounced and consisted predominantly of hæmorrhages and perivascular neuroglial nodules. In some cases, foci of nerve cell destruction of varied size were found in the cerebral and the cerebellar cortex. The changes, in general, were those of a vascular permeability disturbance. They were similar to the changes found in control cases of aplastic anæmia. To what extent brain changes were directly induced by radiation and to what extent they were abscopally determined thus remains problematic.

78. In ten patients surviving accidental gamma and neutron irradiation (average body dose 500 to 600 rad, average head dose 800 to 1,000 rad) cerebral and meningeal signs, as well as changes in the ocular fundus, were seen soon after the irradiation.[104] In another accident involving one person, gamma irradiation of the abdominal and lumbar regions and of the left thigh was massive, doses in the lumbar region of the spinal cord having been estimated at 3 to 5 kilorads.[104, 105] The observed clinical signs of cord damage could be correlated with findings seen at autopsy eighteen days after the accident. There was severe oedema of the lumbar segments of the cord with occlusion of the spinal canal and severe degenerative alterations in neurons of the anterior and posterior horns as wells as in the fibres of the spinal cord.

2. *Structural changes*

(a) *Cellular and subcellular changes*

79. When special methods are used, structural alterations in cellular components of the brain are commonly seen at doses of 100 rads or more. A few general, mainly qualitative, remarks regarding cellular reactions are pertinent here.

80. The *neurons* of the adult are stable amitotic cells, as shown by their inability to incorporate radioactive precursors into their DNA.[106, 107] In general, they have a high intrinsic resistance to radiation. A dose in excess of 250 kilorads is required to destroy the nerve cells of the cerebral cortex of the mouse within thirty days after irradiation by a beam of deuterons 25 micrometres in diameter.[108, 109] A field of this size contains relatively few blood vessels so that the effects may be more directly related to neuronal damage. Alpha-particle irradiation of a large field of the cerebral cortex of the rat in a peak dose of 15 kilorads destroys nerve cells within sixty days.[110] The greater effectiveness of the radiation under the latter conditions is probably due to the supplemental factor of tissue ischæmia brought about by altered blood flow in the transirradiated blood vessels.[111] Species differences in vulnerability exist. Granule cells of the cerebellar cortex become necrotic within a day or two at 5 kilorads in the mouse,[112] but not in monkeys in the same period at a larger dose given to a wider field.[98, 113]

81. Glial cells are, in general, far more radiovulnerable than nerve cells, whether cell death or structural changes are taken as an end-point. *Astrocytes* respond within two days, by glycogen deposition, at a dose as low as 500 to 600 rads.[114-116] This is probably a reflection of reduced aerobic metabolism of the brain tissue.[117] As revealed by metallic staining, astrocytes may become hypertrophic within three weeks or longer after doses of 100 rads or more,[118] this being a reflection of altered vascular permeability to proteins. *Oligodendroglial cells*, associated with the myelination process, undergo acute swelling or hypertrophy also in a wide dose range. In rats and mice, but not in other animals investigated, these cells may selectively

undergo necrosis after an x-ray dose of 150 to 200 rads.[119, 120] *Microglial cells* become activated, and blood-borne lymphoid cells may enter irradiated brain tissue at doses of 100 rads upward.[118] *Subependymal glial cells* become necrotic at doses of 150 to 250 rads in rodents,[119, 120] but not in monkey or man.[111]

82. *Blood vessels* also are relatively radio-vulnerable. Tiny vesicles found in endothelial cells within one hour after x irradiation at doses of 100 rads or more are probably a morphological expression of altered vascular permeability. The response, which can be seen also in pericytes, is reversible at doses up to 500 rads.[121,122] The time period at which altered vascular permeability commences varies with the species. At a given dose of high-energy alpha particles the blood vessels in the brain of the monkey show a much earlier increase in permeability to sodium fluorescein than do the vessels of the rabbit, and the vessels of the rabbit a much earlier increase than do those of the rat.[123] In the rat, it has been shown that vessels suffer first (in the form of circulatory stasis, followed by leakage of trypan blue) and that necrosis occurs in nerve cells afterwards (10-20 krad, >185 MeV protons).[124] Support of the view that nerve-cell damage is vascular-dependent comes also from the observation that diapedetic hæmorrhages in the diencephalon precede nerve cell alterations after x-ray doses of 20 kilorads.[125] The distribution of damaged nerve cells in the irradiated cerebral cortex occasionally assumes a laminar pattern, which has been taken as evidence of inadequacy of the circulation to meet local needs. Such a pattern has been noted in the rat following 50-rad fractions given once a week up to a total of 250 rads.[126]

83. Effects of radiation on neuronal ribonucleic acid (RNA) at low doses[127] and their possible relation to functional alteration are of interest because the formation of RNA in nerve cells may be related to mental activity.[128, 129]

84. Differing radio-vulnerability exists for various subcellular structures. It has been found that, in spinal ganglia, karyosomes suffer first, then the endoplasmic reticulum (20 krad, 185 MeV protons).[130] Labelling techniques have shown that radiation effects on interphasic cells include conspicuous interference with the formation of RNA, a DNA-dependent process.[131, 133] Interphase cell death has also been connected with direct radiation damage of cytoplasmic organelles, in particular of the mitochondrion (the self-replicating organelle involved in cellular energy metabolism) and of the lysosome from which destructive hydrolases may be liberated after membrane damage.[131]

85. The dose-survival relationships in nerve cells are highly complex. This is illustrated, for example, by a study of retinal cells in mice irradiated between four and ninety days of age.[134, 135] As the visual cells undergo maturation, the survival function changes from a simple exponential to highly complex curves with high extrapolation numbers (> 1.000) and wide initial shoulders.

86. Electron microscopic observations have shown that the relative vulnerability of vessels, compared with that of the astrocytes, varies. In one study on the cerebral cortex (hamster), capillary damage was considered the initial event, mainly on the basis that oedematous swelling became apparent in astrocytes before changes could be found in endothelial cells, implying a vasculo-astroglial permeability defect (x-ray dose, 15 krad).[136] In another study on the cerebral cortex (guinea pig), the capillary endothelium was found unaltered although adjacent cells were necrotic (surface dose of alpha particles, 20 krad).[137] In a study of the cerebellar cortex (guinea pig), vessels appeared spared, yet tissue cells were severely damaged (gamma-ray doses, 1-2 krad).[122]

(b) *Histological and related metabolic changes*

87. Depending on radiation quality, dose and field size, structural alterations of the nervous system may appear as acute effects within hours or days after irradiation and may involve varying patterns of exudative phenomena, glial cell hypertrophy and cell and tissue necrosis. Large-field irradiation of the brain can even result in rapid tissue necrosis, as has been observed within a few days following doses of 7 kilorads (23 MeV x rays) or more.[138, 139]

88. When equal doses are absorbed, whole-body irradiation is more effective than head-alone irradiation in bringing about certain changes in the brain, greater depression of RNA labelling in the cytoplasm of nerve cells in the brain (at 500 rad),[140] greater water increase in the brain tissue in certain areas (at 100 rad)[141] and greater reduction in alkaline phosphatase in vessel walls and brain tissue (at 10 krad).[142]

(c) *Late (delayed) effects of irradiation*

89. Experiments with implanted seeds containing radio-nuclides have provided information on the effects of continuous irradiation. For example, after intracerebral application of gold-198 or yttrium-90 in dogs, necrosis developed within the range of the beta radiation after a period of three to six days corresponding to a cumulative dose of 10 to 20 kilorads.[143-145]

90. The evolution of the late reaction in the brain and spinal cord varies widely.[111,143-154] In monkeys, late tissue necrosis has been observed at doses of 624 rads (2 MeV x rays),[118] 800 rads (14 MeV fast neutrons, 55 MeV protons)[111,155] and 1,500 rads (250 kV x rays, 23 MeV x rays).[156-159] In man, the smallest x-ray dose known to have produced late tissue necrosis is 1,250 rads; in this case, exposure was through multiple ports at intervals over a twelve-hour period.[160] The observation in experimental animals, that latency for the development of late necrosis is inversely related to dose and volume irradiated,[161, 162] finds many exceptions in patients given fractionated irradiation. A fractionated dose which, in man, usually causes necrosis within three to twelve months may, in other cases, not result in necrosis until after a lapse of five to eight years.[152, 163, 164]

91. Late necrosis of brain or spinal cord tissue sometimes occurs in human subjects given fractionated radio-therapy for intracranial or extracranial tumours or other conditions. The suggested lowest fractionated x-ray dose (field size, 100 cm^2) that may produce cerebral necrosis in adults has been estimated to be, for example, 3,300 rads given in 10 days and 5,200 rads given in 50 days.[165] Late radio-necrosis of the lower brain stem and upper spinal cord following transirradiation of these parts of the nervous system for tumour in the cervical region may occur, for example, within one year after 5 kilorads given in seventeen days.[166, 167]

92. Since there are many kinds of late radionecrosis, it is likely that pathogenesis varies. Increasing oxi-reductase activity in astrocytes, increasing mitotic activity in vascular endothelial cells and oligodendrocytes and increasing cell population may, it has been contended, contribute in various ways to a progressive metabolic deficiency which may terminate in tissue necrosis.[153] On the other hand, the close spatial relationship of incipient parenchymal lesions to altered vessels has been taken as evidence of a primary role of circulatory and vascular disturbances in tissue breakdown.[168] Long-term electron microscopy observations of the cerebral cortex of rabbits receiving 2,500 roentgens of x or gamma rays have revealed ultrastructural changes in virtually all cellular elements but no tissue necrosis.[169] This suggests that some additional factor is responsible for the necrosis. Circulatory disturbances reaching a certain threshold incompetence may be that factor.

(d) *Repair*

93. Dose-rate studies have given an indication that reparative processes may occur during the period of irradiation. Oligodendrocytes (in rats) are more severely altered when the brain receives x-ray doses of 3 kilorads at 600 rads per minute than at 150 rads per minute.[170] Granule cells of the cerebellum (in mice and rats) become necrotic at a dose of 1 kilorad if given at 1 kilorad per minute but not at 100 rads per minute.[171]

94. That nerve cells can undergo repair shortly after irradiation is inferred from electron-microscopic studies in serially sacrified animals. Nerve cell damage evident in animals sacrificed within a few hours may not be found a day later in other animals. This applies, for example, to cerebral cortical cells (3.5 krad)[172] and hypothalamic cells (5 krad).[173] Biochemical studies also indicate that repair is possible. If damage of nerve cells is limited to the level of biochemical disturbances, the cells have the potential for recovery. In rabbits exposed to 2 to 3 kiloroentgens of x rays, nerve cells removed from the brain stem and studied *in vitro* showed increased cell mass, potassium excess, increased RNA content and succinoxidase activity.[174] By the twenty-fifth day, repair following 3 kiloroentgens was apparently achieved. A tritiated thymidine study of the rat spinal cord showed that the process of repair runs its course in a maximum of about two weeks.[167]

95. The capacity of different kinds of nerve cells to undergo repair varies. Following irradiation, cerebellar Purkinje cells incorporate tritiated leucine in proteins at an accelerated rate in twenty-four hours, while granule cells take up none at all, suggesting that Purkinje cells, as opposed to granule cells, are capable of repairing or compensating the initial molecular damage by stepping up synthesis.[175]

96. Increased synthesis of RNA and protein in neurons and glia may be closely related to regrowth of damaged or interrupted axons and dendrites. In the rat, starting at about two weeks after irradiation of the cortex at doses capable of destroying individual cellular elements, axons grow in great abundance into areas of cell depletion. These axons become myelinated, but the role of oligodendroglial cells in this process has not been established. Moreover, regeneration of myelin occurs in axons demyelinated by large-dose irradiation.[176-178]

97. In human subjects whose spinal cords have been irradiated in the course of radiation therapy for tumours of other organs, the damage that occasionally occurs in the cord following exposure above "tolerance" doses is usually irreversible. That in some instances the pathological process might be reversible is suggested, however, by certain clinical observations.[166, 179] Neurological signs and symptoms consistent with radiation damage of the spinal cord have developed in such cases but have later vanished; the clinical disturbances have appeared after an average latent interval of four months, following radiation doses of 2,600 to 4,200 rads to the cord delivered in forty-six to 100 days. Autopsy in two cases of this kind has revealed no evident histological change.[179]

98. When adult nervous tissue is in a process of reparative cellular proliferation, decreased resistance to radiation should be expected. This has been experimentally verified by studying DNA synthesis in the regenerating hypoglossal nucleus of the rabbit after crushing the hypoglossal nerve.[180] DNA-synthesizing neuroglia and endothelial cells are decreased in number by more than 50 per cent from twenty-four to forty-eight hours after 100 rads of 200 kV x rays, although no changes are observed in the retrograde reaction of nerve cells or in astrocytes.

3. *Functional effects*

99. In this section, only those effects are considered which either occur according to a delayed time schedule or involve a permanent change, suggesting that compensatory or reparatory processes may be involved.

100. In rats, studies of electro-encephalographic patterns after whole-body x irradiation (700 rad) revealed characteristic modifications up to ten days after exposure.[181] At three to twelve hours after irradiation, there was a significant decrease in both "high" (15 to 30 cps) and "low" (1.5 to 7 cps) frequency electrical activity. Within the next two to three days, the recordings were nearly normal. In the subsequent four- to ten-day period, only the low frequency component decreased below the control level. The early change of frequency seems to correspond in time with a period of conditioned reflex depression found in another investigation after head-alone irradiation.[182] The latter decrease similarly coincided in time with the conditioned reflex depression that occurred immediately before and during acute radiation sickness.

101. The electrical activity of the prepyriform cortex of the rat brain was studied after x-ray whole-body doses of 250 and 500 rads. The animals presented an increased amplitude and slightly decreased frequency in the spontaneous electrical activity, as well as shorter latency of evoked potentials. These changes occurred for the duration of the experiment (thirty-five days) at the higher dose but only during the first few days at 250 rads.[183, 105]

102. In rabbits, a slowing of the frequency of the slow-wave component of the electro-encephalogram with a concomitant rise of the amplitude was seen after doses of 100 to 400 rads.[184] A whole-body gamma dose of 400 rads gave rise to trains of slow waves (1 to 4 cps) that appeared to originate from the hippocampus and from there to spread to the whole cortex, occasionally accompanied by spike activity.[209] Epilep-

toid seizures in rabbits were seen in some cases after doses of 400 rads or more.[185]

103. The hippocampus appears to be the brain structure giving the strongest electro-physiological response to whole-body or head-alone irradiation.[186, 187] Spontaneous hippocampal spike activity has been seen for at least a few hours after 100 rads (possibly after 25 rad also) or more in rabbits that did not show spike activity prior to irradiation.[188]

104. In addition to recording the continuous electrical activity of the cerebral cortex, electrical changes evoked by stimulation of sense organs or of some point along the ascending pathways to the cerebral cortex have also been studied. Thus, in rabbits, gamma irradiation (400 or 1.200 R) brought about changes in the electrical activity of the visual nervous system (retina, lateral geniculate body, optic cortex) which seem to be related to dose.[189-191]

105. In monkeys, acute whole-body exposure with 400 to 800 roentgens of 250 kV x rays failed to produce significant changes in electro-encephalographic patterns until near death.[192] Head doses of 4.5 or 6 kilorads, however, resulted in general slowing of wave frequency and increase in amplitude within the first day after exposure, in some cases with patterns of spiking reminiscent of grand mal seizures.[193] At the same time, apathy and asthenia set in, followed by poor co-ordination, loss of the pupillary light reflex and myoclonic twitches and seizures.

106. A detailed analysis of the spontaneous and light-stimulated electrical activity of the brain as recorded by the electro-encephalogram was made in twenty-one medically irradiated individuals.[194] Regardless of whether the whole body, the head or other parts of the body had been irradiated, changes were recorded both immediately after the termination of irradiation and later. Generally, depression of both spontaneous and evoked activity was seen both after the first irradiation and during the course of repeated radio-therapy (150 R twice a week or, in one case, 200 R daily, up to a total of 300 to 2,000 R). Persistence of the alpha waves was accompanied by depression of other electrical activity.

107. Studies of the threshold for the induction of electro-shock seizures in irradiated rats provide further evidence that irradiation gives rise to changes in cortical processes.[196, 197] The threshold for the seizure decreased after x-ray doses of 450 and 950 rads whether delivered to the whole body, to the head alone or to the body alone. This has also been seen after doses of 500 and 10,000 rads of 50 MeV protons to the head. After x-ray exposure, the threshold drop persisted for a period of two to four weeks depending on dose in the group receiving body-alone irradiation, but for six months after irradiation involving either the head alone or the whole body. Within the dose range explored, proton irradiation produced similar drops which lasted until the death of the animals or the end of the experiments (two months in this case). The duration of the clonus was drastically and lastingly reduced after 5 and 10 kilorads of protons, whereas lower doses only produced small and transitory changes.

108. The action of irradiation on already established conditioned reflexes has been the subject of a large number of investigations.[72, 198] Thus, a conditioned avoidance response obtained in the rabbit by using an electric shock as unconditional stimulus and a light flash as conditional stimulus disappeared[199] completely fifteen to twenty minutes after a whole-body exposure of 500 roentgens (180 kV, 0.5 mm Cu + 1.0 mm Al, 70 cm). This was accompanied by the pronounced weakening of the electric activity that usually accompanies the conditioned reflex. The depression of the conditioned reflex lasted from three to seven days, but its recovery was not complete as the responses of the animals remained unpredictable. A similar response was elicited by irradiation of the head alone. In dogs, single and fractionated whole-body exposures of 100 to 190 roentgens caused a temporary reduction of the intensity of the conditioned reflexes.[52, 202-203]

109. At doses much lower than the lethal range for whole-body irradiation, reports are conflicting. The most severe but temporary disturbances are found when complex sequences of interacting conditioned reflexes are used, such as those requiring differentiation between stimuli of different type or different strength.[192] Thus, in dogs, serial conditioned motor reflexes were only slightly depressed for a period of two to four months after whole-body doses of 30 to 40 rads and subsequently returned to normal.[204] On the other hand, in dogs given 10 to 50 rads to the parietal region, the intensity of conditioned salivary reflexes increased at the same time as disturbances of the internal inhibitory processes of the cerebral cortex occurred.[205] In another study,[206] no changes of the conditioned salivary reflexes of dogs receiving for thirty-seven weeks weekly whole-body doses of the order of 20 rads were observed. In this investigation, however, only positive conditioned reflexes were explored, and the authors did not exclude the possibility that a more complicated situation involving discrimination of stimulus patterns and their temporal relationships might have revealed effects not seen in simple conditioning.

110. Contrary to what is seen in conditioning experiments, studies of learning and discrimination carried out with different techniques have, in general, revealed no effect or only small deficits after irradiation of adult experimental animals, except at doses at least close to the lethal range.[207, 208] In some cases, the performance in accomplishing certain simple tasks is even improved in irradiated animals until they are near death.

111. With adult irradiation, as with individuals irradiated antenatally, the response of conditioned reflexes appears to be a more sensitive instrument for exploring the effects of radiation on the nervous system than other behavioural responses, but considerations similar to those made in paragraphs 37 and 38 apply to adult irradiation as well.

112. Alterations in spinal cord reflex activity have been seen in dogs after whole-body irradiation with x rays,[160] and in rabbits after irradiation of the spinal cord only (500 to 1,000 rad).[161] Reflex activity initially increases, then declines, and finally returns to pre-irradiation levels. Suppression of spinal cord reflexes reaches its maximum when radiation sickness signs are severe. In animals that have survived irradiation, normal spinal cord function is gradually restored. Other studies demonstrate that the latent period of the shin-flexor reflex changes after whole-body x irradiation (10 rad) of the rabbit.[162] Initially, the response time is shorter and the reflex shows greater oscillations than normal. Repeated irradiation increases the latent period, sometimes beyond control values.

113. In man, local and whole-body doses (therapeutical or accidental) of hundreds of rads (up to 1,000 rad) may result in changes of unconditioned spinal reflexes which persist for years but eventually disappear. Such changes are found only through special investigations (electro-myography, reflexometry, myotonometry, chronaximetry, etc.). They can be observed for five to ten years after irradiation.[104, 210, 211]

114. Clearly the nervous system does show a variety of changes. From the preceding paragraphs it may be observed that, while changes in spontaneous or evoked electrical activity may be seen after irradiation and are usually of a non-permanent nature, the behavioural and pathological significance of such changes has yet to be appreciated.

B. Peripheral nerves, synapses and receptors

115. The doses required to alter the physiological properties of isolated peripheral nerves are extremely high—at least 10 kilorads of x rays. Such doses are followed by reduced amplitude of action potentials and decreased conduction velocity of nerve impulses.[212-214] Heavy particles in similar doses stop conduction almost immediately in the isolated sciatic nerve of the frog.[215]

116. In rat sciatic nerves receiving *in situ* doses of 3 kilorads of x rays given in three fractions of 1 kilorad each, no electro-physiological changes were detected after three to eleven months, but major morphological alterations were found in this time period in 25 per cent of the animals so treated. The lesions consisted of multifocal necroses of the sciatic nerve associated with degenerative changes of vascularization in it.[216]

117. The mechanisms whereby changes of the bioelectric activity of nerves, and of receptors as well, are produced are not well understood. Various experiments strongly suggest that the effect of radiation involves at least two processes: (*a*) induced increase in passive ion permeability and (*b*) the impairment of the energy-dependent ion-transport mechanism.[217-220]

118. In cats, local x-ray doses of 500 to 600 rads to the lumbo-sacral segments caused an immediate increased amplitude and duration of excitatory synaptic potentials in motor neurons when corresponding afferent nerves were stimulated.[221] During local x irradiation of the spinal cord at a dose rate of 300 rads per minute, a change was observed in the potentials recorded from the anterior roots of the spinal cord when the posterior roots were electrically stimulated.[222] These changes may be related to the increased monosynaptic response variability observed in cats after spinal cord irradiation (100 to 500 rad).[223] In mice, pathological alterations of synaptic structures in the spinal cord were observed as early as one day after a whole-body dose of about 500 rads. Approximately five weeks after irradiation, some of the degenerated synaptic structures seemed to disappear, while others apparently returned to their normal state.[278]

119. Changes in synaptic transmission could be an important factor in the response of the nervous system to irradiation. To cause an inhibition of transmission through an isolated neuro-muscular junction of the frog or rat, doses of about 20 kilorads are required.[224-226] By contrast, much lower doses act on synaptic transmission when irradiation is applied to the whole body or to nervous structures *in situ*. Thus, doses of 800 rads to the upper cervical ganglion of cats facilitates transmission after fifteen to twenty minutes. After an hour or so, inhibition is observed.[227]

120. Cutaneous and visceral receptors respond to high doses of radiation with structural alterations but also with functional changes. Thus, even during the first hour after local irradiation (500 rad) distinct changes can be detected by recording spontaneous bioelectrical potentials in the branches of the cutaneous nerve. These potentials show an increased frequency very soon after irradiation. They exhibit long periods of increased activity even in the absence of tactile stimuli. The reactions of the nerve to such stimuli also become more intense.[200] It has not been determined whether these changes reflect a direct effect on the receptor itself or whether the afferent nerves from the receptor are mainly involved. On the other hand, the increased splanchnic nerve activity that occurs as a result of whole-body or abdominal exposure of cats and rats probably reflects alterations in the function of interoceptors,[228-230] and the isolated Pacinian corpuscle responds to several hundred rads with changes in sensitivity to mechanical stimuli.[231]

121. Observations on dogs irradiated and observed for one year have shown that only when cumulative doses reach 300 rads (150 rad over the year plus 150 rad in a single exposure, or 225 rad over the year plus 75 rad in a single exposure) is there any significant change in the sense of spatial orientation of the body.[204] Experiments on rabbits indicate that such effects depend on the region of the body irradiated and that they change with the progress of time.[232] Permanent damage to the vestibular system has been seen at single local doses to the labyrinth larger than 1,000 rads.

122. It is difficult to determine whether the effects on cutaneous and visceral receptors are the direct result of radiation on them or are secondary to changes in the surrounding tissues.[208, 233] Whether primary or secondary, however, these effects on receptors are likely to play an important role, when the body but not the head is irradiated, in triggering central responses or automatic reflexes responsible for the systemic interactions that will be discussed in section V.

123. In man, reduction of tactile sensitivity and skin sensitivity to vibration has been demonstrated in cases of accidental irradiation in the lethal range of doses[104, 284] and in patients treated locally with high fractionated doses (several kilorads total).[235-238] Inversion of sensations has also been reported[239] after irradiation of the oro-pharyngeal region, salt being "felt" as bitter and bitter as simply cold. Both lowered taste sensitivity, and inversion of taste sensation appeared to be secondary to a central effect rather than a primary consequence of irradiation. Taste changes were, in a number of cases, associated with increased olfactory thresholds, sometimes accompanied by trophic changes in the olfactory mucosa.[240]

IV. Radiation as a stimulus for sensory organs

124. It has been demonstrated that brief bursts of ionizing radiation can stimulate certain receptor systems of many organisms in the same way as does the adequate or normal stimulus for the receptor system involved. The activation of receptors by radiation with small doses appears to be within the normal physiological capacities of receptors and does not seem to

induce any significant injury to the system involved. These events, therefore, should be clearly separated from the effects that are discussed in other sections of this report.

A. Vision

125. The ability of dark-adapted subjects to perceive ionizing radiation as a sensation of light was noted shortly after the discovery of x rays and is now firmly established.[241-243] Perception of x rays depends on the capability of the rod cells[242, 244, 245] which must be dark-adapted for production of the visual radiation sensation. Light sensations have been reported by human subjects after as little as 1 millirad of x rays delivered in less than a second.[245] Peripheral retinal regions where rods are most frequent are more sensitive than the central portion of the retina.[246]

126. Electro-physiological investigations of the eye have shown that the compound series of retinal potentials that arise from light stimulation[248, 249] may also be elicited by radiation of the dark-adapted eye.[242, 244, 245] In humans the "flash" exposure threshold for such response has variously been reported to be 500 millirads[249] and from 1 to 5 millirads.[216]

127. Ionizing radiation may stimulate the retina in a manner related to normal visual processes, although it has been difficult to show whether analogous mechanisms are at work at the rhodopsin level. Absorption of radiation energy by the rods is apparently responsible for the electro-retinographic response as shown by the fact that no response could be elicited in the horned toad, an animal which lacks rod vision.[250] Direct evidence is also gained from the similarity between the adaptation process for x rays and visual rod adaptation.[250]

B. Olfaction

128. It has been demonstrated in rats,[251-254] dogs,[255] cats[255] and monkeys[256] that the olfactory system is very responsive to ionizing radiation at small dose rates (in monkeys, from 8 millirad per second). The evidence suggests that the electro-encephalographic desynchronization and arousal reactions observed immediately after the onset of x-ray exposure may be due to stimulation of the olfactory system, since these reactions are suppressed by destruction of the olfactory bulbs.[251, 252, 257]

129. Microelectrode recordings from single neurons in the olfactory bulb of several species have been used to identify olfactory stimulation by ionizing radiations. Radiation exposure generally results in a prompt increase in the firing rate of these neurons that corresponds to the duration of the exposure[253, 255] However, such responses presumably are not the result of an effect of x rays on the olfactory bulb itself, since the reaction can be abolished by nasal perfusion with saline or alcohol.[253] A peripheral site of action is also indicated by experiments in which ozone in ambient air was shown to mask selectively the response to x rays.[258] It was found subsequently that the responses occur in the olfactory bulb only if the radiation (beta radiation from a strontium-yttrium source) is confined to the olfactory epithelium located in the nasal passages.[259] From these observations, it appears reasonable to infer that olfactory detection of radiation occurs at the receptor level rather than in a more central portion of this system.

C. Sensory systems and behavioural reactions

130. Changes in the electro-encephalogram are seen in rabbits within one second after bursts of radiation of 1 rad or less[187, 259, 260] and persist for only a few minutes. In rats exposed during a quiet period or during sleep, dose rates as low as 0.25 rad per second produce transient electro-encephalographic reactions within seconds.[255] The response increases with dose rate. The electro-encephalographic changes parallel the arousal response which resembles that seen with stimulation of peripheral receptors.[256, 257] The response can be extinguished by repeated exposures, suggesting habituation of a sensory system. Arousal responses can be obtained by irradiating the head only or the body only. Spinal transection (C_2-T_5) prior to exposure abolishes the response in animals in which the body only is irradiated, showing that the arousal resulting from such an exposure is mediated through the spinal cord. Exposure of the head only in such transected animals will still elicit the arousal response.[200, 261, 262]

131. The effect of radiation on sensory systems can lead to changes in the behaviour of animals towards further irradiation and towards cues previously associated with exposure. For example, mice and rats avoid residence in that region of a chamber in which they have previously experienced irradiation,[208, 263] or they exhibit a reduced preference towards distinctively flavoured substances previously consumed during an irradiation.[264, 265] Thus, in rats, the consumption of saccharin-flavoured fluid during a six-hour exposure to cobalt-60 gamma radiation at a dose rate of 5 rads per hour results in a radiation-conditioned aversion to saccharin that persists for about four weeks.[266] When mice are exposed to gamma rays from radium at a dose rate of 20 millirads per minute the threshold dose for the conditioned aversion to saccharin in saline solution is less than 30 rads. The degree of avoidance seems to be a linear function of the accumulated radiation dose.[267] Similar reactions are seen in consumption tests at slightly higher dose rates with cats[268] and monkeys[269] subjected to combinations of radiation and test solutions.

132. The mechanisms leading to radiation-conditioned behaviour are not precisely known. The behaviour depends not only on detection of small doses at low dose rates but also on the induction of a motivational state to avoid a noxious stimulus. Aversive reactions to the same dose are produced more often by abdominal exposure than by head exposure,[270] suggesting that visceral receptors can also be triggered by penetrating radiations. Splanchnectomy or intraperitoneal procaine injection delays or suppresses development of the spatial avoidance response in rats.[271] Conditioned reflexes have also been obtained by abdominal irradiation,[261, 272] suggesting visceral receptor activation.

133. There is as yet no well-confirmed evidence of receptor stimulation by low doses and low dose rates of ionizing radiations in man, with the exception of visual perception in dark-adapted subjects. The evidence for radiation detection and behaviour conditioning in other species has been based on relatively recent findings and will require considerably more development before their implications for human behaviour can be established. In any event, the effects

described do not reflect injury to the nervous system or specific risks to human subjects so exposed.

V. Systemic effects

134. While all systems may show radiation response through interaction with the nervous system, it is mostly with regard to the cardio-vascular and gastro-intestinal systems that information is available, and only these will be discussed here.

A. Effects in animals

135. Hæmodynamic changes occur soon after radiation exposure, particularly at doses in the lethal range. They may be mediated through neuro-regulatory mechanisms that are thought to be operative at several levels of the acute radiation response.

136. As a result of autonomic nervous system involvement, the rabbit is unusual in showing an immediate shock-like hypotensive reaction after x-ray whole-body doses of 600 rads or more.[198, 273] Blood pressure falls within hours after irradiation, and the heart rate increases.[274, 275] Atropinization or vagotomy will reduce the severity of the reaction, and adrenalin injections effectively counteract hypotension.[273] Blood pressure changes may be seen after doses as low as 50 rads.[276]

137. Acute hypotension has also been seen within one to three hours post-irradiation in rats,[277, 278] cats[279, 280] and monkeys[281] after doses in excess of 1,000 rads, but has not been observed in dogs.[276, 282]

138. Rat arterial blood pressure responds differentially to x irradiation (485 rad) during the first twenty-four hours after exposure as peripheral blood pressure falls, whereas the aortic pressure remains unchanged. At 970 rads, the aortic blood pressure also falls and responds weakly to various stimuli during the first few days after whole-body irradiation.[283]

139. The pressor response to electrical stimulation in rabbits is increased the first day after exposure to 800 roentgens (180 kV, 0.5 mm Cu + 1.0 mm Al), despite a simultaneous drop in blood pressure.[284] Changes in the sensitivity of the mechanisms controlling blood pressure have been seen in irradiated cats, where peripheral stimulation of carotid baro-receptors or chemo-receptors elicits weaker than normal pressor responses.[280, 285-290]

140. Systemic interactions in the cardio-vascular system are effective in the local control of motility and permeability of the capillary bed. For example, sectioning the afferent nerve from a skin section on the back of a rabbit locally irradiated (450 rad) reduces such increased permeability.[291] Increased permeability in the rat after 750 to 3,000 rads is seen within twenty-four hours and is at a maximum at three or four days.[292] Anti-histamine drugs prevent increased permeability up to one day post-irradiation, suggesting that the early response is due to histamine mediation. In the rat, the capillary bed of the meso-appendix shows diminished sensitivity to adrenalin for five days after whole-body x-ray doses of 600 rads, but reacts more strongly than normal eight to seventeen days after irradiation. Vasomotor activity shows a similar pattern, and the response has been attributed to circulating vasoactive materials.[293]

141. In most species, after a supra-lethal radiation dose to the head, respiration stops before cardiac failure.[275, 279, 282] With artificial respiration,[282] the pressor response to carotid sinus stimulation disappears in head-exposed dogs while arterial pressure and blood volume remain normal. This suggests that reflex failure after high doses is due to damage of the medullary vasomotor centre, since the pressor response to electrical stimulation of this centre declines in the same manner as the carotid sinus reflex. This interpretation is supported by the results of direct irradiation of medullary centres.[294]

142. It thus seems that the response of the peripheral vascular bed to radiation may involve several levels. Shortly after irradiation, it is possible that changes in local concentration of metabolites or releases of vasoactive chemicals may play a role in such responses. Radiation may also interfere with the autonomic nervous system regulation of vascular activity. At high doses, a direct effect may be operative on medullary and other higher control centres, the function of which may in turn be modified by inputs from a great variety of sensory receptors. Alterations of respiratory reflexes may also be affected indirectly as a result of cardio-vascular changes. However, the actual roles of the central and peripheral nervous systems, as well as of local tissue changes at various times after irradiation, need further clarification.

143. Radiation sickness seen after whole-body doses in the sublethal and lethal ranges is intimately associated with gastro-intestinal disturbances. Central nervous, as well as autonomic, control may be involved in several phases of the gastro-intestinal response.

144. In many species,[295] including primates,[296-298] anorexia is a common and reliable sign of radiation disease in the first week post-irradiation. In rodents, it is accompanied by a longer retention of food in the stomach[299-301] and can be detected six hours after whole-body doses of 20 to 25 rads.[302, 303]

145. In rats, a dose of 1,000 rads to the hind limbs and tail only may also cause gastric retention.[303] This effect is highly unspecific as it can be seen also after toxin injection. Radiation fails to produce retention after adrenalectomy,[301, 304] but large doses of adrenalin or corticoids given to adrenalectomized animals immediately prior to exposure restore the effect.[303] There are strong indications, therefore, that the radiation-induced gastric retention is an indirect effect, being part of the general emergency mechanism.

146. Experiments further indicate that pyloric constriction or spasm is not an essential mechanism in gastric retention.[305] It is more likely that the initial depression in gastric transit is related to a reduction in gastric motility, which may be more subject to sympathetic or humoral control than to direct local injury.

147. Intestinal motility and muscle tone may be promptly altered by x-ray exposure,[306] as shown in preparations in which the intestine is attached to a motility recording device. While no changes of *in vitro* motility of the cat intestine are seen after 10 kilorads[307] or of the guinea pig ileum after 500 rads,[308] the exteriorized rat intestine increases its tonus and motility about one minute after receiving 100 rads.[309] The effect persists longer with increasing dose. Vagotomy in the rat before irradiation has little effect,

showing that pre-ganglionic fibres contribute little to the responses.[309] On the other hand, results of pharmacological ganglion block suggest that the effect of radiation is mediated by intrinsic intestinal ganglia. Rat duodenal segments examined *in vitro* one to three days after whole-body doses of 500 or 1,000 rads show increased motility, with a normal response to acetylcholine. However, the response to serotonin diminishes, suggesting that mucosal damage must play a role in the mechanism of motility changes in the acute radiation syndrome.[310]

148. In many species vomiting is a common response to median lethal doses. In monkeys, irradiation (1.5 to 6 krad) of the head alone does not induce vomiting, while whole-body irradiation will,[193, 311] a difference seen also in dog and cat.[312] This sign does not seem to depend on brain injury but on visceral stimuli, and depends on the feeding schedule prior to exposure,[311, 313, 314] although bilateral destruction of the vomiting centres in the medulla oblongata prevents the immediate response in dogs (800 to 1,200 rad)[315, 316] or monkeys (1.2 krad).[317] Vagotomy also prevents early vomiting in the monkey, suggesting that the response is peripherally initiated.[318, 319] Abdominal exposure may, therefore, be considered essential to the response.

149. It can be concluded that gastro-intestinal reactions to radiation, such as vomiting or changes in motility and retention, mainly involve local neural elements responding to injury of the radio-sensitive intestinal mucosa. The response is mediated by central as well as autonomic pathways.

B. Effects in man

150. The results of animal experiments discussed in the preceding paragraphs clearly indicate the complexity involved in determining whether a given system does or does not play a primary role in the response of another system, even with such high doses of radiation as have been used in most of the experiments. While this review has been confined to interactions between the nervous system and two particularly well studied systems, there are some indications that similar interactions occur with the hæmopoietic and endocrine systems.

151. Observations at high acute doses in man are mostly derived from radiation accidents.[1, 234] The involvement of several systems in the various forms of radiation sickness are easily inferred, but determining the role of each of them in the reactions of the others is complex and deserves further study. Still, an inference as to possible long-term radiation effects on the endocrine system has become available.[320] Five subjects from Oak Ridge (mixed gamma-neutron dose, respective averages 226 and 81 rad; fairly uniform exposure) and one subject from Los Alamos (mixed gamma-neutron dose, about 130 rad; gamma-neutron ratio about 3; exposure geometry not stated) were examined. Daily twenty-four hour urines were obtained for the first two weeks after exposure and, for six hours thereafter, at progressively longer intervals. The samples were bio-assayed for adrenaline and nor-adrenaline, with results showing a modest and temporary increase in adrenaline release, and a marked and prolonged release of nor-adrenaline. The greater output of nor-adrenaline than of adrenaline suggests that, after such exposure, the sympathetic nerves are called into greater play than is the adrenal gland. It seems particularly pertinent that all of these subjects showed a significant release of neurohormone four and six years after exposure. This may represent some prolonged biochemical or physiological aberration of the sympathetic nervous system not heretofore described.

152. Extremely detailed clinical examinations[321] of radiation workers who received less than 5 rads per year for a number of years have failed to show effects of any consequences.[322] However, in workers who were reported to have received doses above current dose limits (that is, from 70 to 100 rad within a period of ten to fifteen years) a number of objective signs involving various systems were described as occurring more frequently than among controls. The estimated doses were based on readings of personal and working area dosimetres, and the exposure may have been highly inhomogeneous.

153. Among the signs observed, moderate hypotension and bradycardia were significantly more frequent than among controls. Hypotension was particularly pronounced in the retinal artery, and plethysmographic investigations revealed slight changes of vascular tonus in the limbs.[323] When these signs were most pronounced, they were sometimes accompanied by electro-encephalographic changes, particularly in response to hyperventilation,[324] and by electro-myographic signs of slight deficiency of tonus and posture control.[325] All these signs progressively disappeared in the course of two or three years after overexposure had ceased.[322] These types of changes appear to be worth studying further under strict control of a number of variables that might distort the magnitude or frequency of objective, but non-specific, signs.

154. From the data available it can be concluded that such changes as have been reported after several years of exposure to levels of radiation about twice as high as current dose limits for radiation workers are mild, reversible and usually well compensated. Subjective complaints that are not uncommon among adults show an increased incidence, but none of the clinical signs that have been reported at those levels of exposure appear to impair the working capacity of the subjects.

VI. Conclusions

155. The sensitivity of the nervous system to radiation varies markedly with the stages of its development. Only during the period from the second to the sixth month of fœtal life does irradiation of the nervous system involve risks higher than those arising from the irradiation of other tissues. Even then, it is not yet established whether such a conclusion is valid at low doses, though this can be suspected on the basis of the limited data available. At other times during development, irradiation of the nervous tissue appears to result mainly in increased incidence of malignancies, the sensitivity of the nervous system being, in this respect, of the same order as that of certain other tissues.

156. When its development is completed, the major effects on the nervous system appear only after radiation doses of the order of kilorads. At doses close to the median lethal dose, the acute radiation syndrome is dominated by symptoms involving the blood-forming and gastro-intestinal systems, although animal experiments indicate that some of these symptoms may be secondary to changes in the nervous system.

157. Such structural changes as may occur following large or massive doses consist of brain- and spinal-tissue breakdown and severe vascular damage. After smaller doses, cellular necrosis or progressive reaction in parenchymal and vascular cells may ensue. Long-term consequences of irradiation of the nervous system at relatively large doses include tissue necrosis and varied cellular reactions of sudden onset months or years after exposure.

158. Functional involvement of the nervous system is apparent even at doses lower than 50 rads, but the effects can be considered as minor. They appear to be transitory and to result in minimal impairments of functional performance. They do not compare in seriousness with the long-term effects in other systems which consist largely of an increased incidence of malignancies. Quantitative relationships between dose and the intensity and frequency of functional changes in the nervous system have not been established in man and should be explored.

159. Radiation can be detected by sensory organs. For example, visual sensation of radiation is known to occur in man at doses lower than 1 rad. There is no evidence that this involves any injury to the retina.

TABLE I. PREVALENCE OF MENTAL RETARDATION AT SEVENTEEN YEARS OF AGE AMONG SUBJECTS WHO WERE *in utero* AT THE TIME OF BOMBINGS[a]

(modified from reference 65)

Distance in metres		*Hiroshima*		*Nagasaki*	
		Male	*Female*	*Male*	*Female*
<1,500	Examined	89	80	18	20
	Retarded	7	6(3)	3(1)	1
	Per cent	7.9	7.5	16.5	5.0
1,500–1,999	Examined	135	131	36	28
	Retarded	2	2(1)	0	0
	Per cent	1.5	1.5	0	0
3,000–4,999	Examined	221	211	71	61
	Retarded	1(1)	1	0	2(2)
	Per cent	0.5	0.5	0	3.3
Not in city	Examined	201	197	60	54
	Retarded	2(1)	1	1	1
	Per cent	1.0	0.5	1.7	1.9
Total	Examined	646	619	185	163
	Retarded	12(2)	10(4)	4(1)	4(2)
	Per cent	1.9	1.6	2.2	2.5

[a] Numbers in parentheses indicate cases with possibly "explained" aetiology.

TABLE II. PREVALENCE OF MENTAL RETARDATION AT SEVENTEEN YEARS OF AGE BY MONTH OF BIRTH[a]

(modified from reference 65)

Distance in metres		*Month of birth*								
		1945 Aug.	*Sept.*	*Oct.*	*Nov.*	*Dec.*	*1946 Jan.*	*Feb.*	*Mar.*	*Apr. May*
						Hiroshima				
<1,500	Examined	15	19	16	15	21	29	30	17	7
	Retarded	0	0	0	1	1	3(1)	7(1)	1(1)	0
	Per cent	0	0	0	6.7	4.8	10.3	23.3	5.9	0
1,500–1,999	Examined	26	21	19	23	29	50	34	35	29
	Retarded	0	0	0	0	1(1)	1	1	1	0
	Per cent	0	0	0	0	3.4	2.0	2.9	2.9	0
Combined controls	Examined	82	80	68	75	91	158	119	89	68
	Retarded	1(1)	1	1	0	1(1)	1	0	0	0
	Per cent	1.2	1.2	1.5	0	1.1	0.6	0	0	0
						Nagasaki				
<1,500	Examined	5	1	4	6	4	2	8	2	5
	Retarded	0	0	0	1	0	1	2(1)	0	0
	Per cent	0	0	0	16.7	0	50.0	25.0	0	0
1,500–1,999	Examined	4	5	9	5	11	6	9	8	8
	Retarded	0	0	0	0	0	0	0	0	0
	Per cent	0	0	0	0	0	0	0	0	0
Combined controls	Examined	14	19	40	22	31	25	30	31	34
	Retarded	0	1(1)	0	0	0	2	0	0	1(1)
	Per cent	0	5.3	0	0	0	8.0	0	0	2.9

[a] Numbers in parentheses indicate cases with possibly "explained" aetiology.

TABLE III. HEAD SIZE BY DISTANCE FROM HYPOCENTRE AT TWENTY YEARS OF AGE IN HIROSHIMA[67]

Distance in metres	*Examined*	*Head size minus 2 SD or more*	*Retarded*
⩽1 200	24	11	11[a]
1 201–1 500	71	12	2
1 501–1 800	68	8	2[b]
1 801–2 200	20	0	0

[a] One child with head size minus one standard deviation (SD).
[b] One child with normal head size had Japanese B encephalitis during infancy.

TABLE IV. HEAD SIZE AT TWENTY YEARS BY GESTATIONAL AGE IN HIROSHIMA[67]

Weeks of gestation	*Examined*	*Head size minus 2 SD or more*	*Retarded*
⩽15	78	25	11
16–25	50	3	4[a b]
26–40	55	4	0

[a] One child with head size minus one standard deviation (SD).
[b] One child with head circumference within 1 SD from the mean had Japanese B encephalitis during infancy.

Note: Of the fifteen retarded children, ten had head circumference at least 3 SD below the mean, three were at least 2 SD below, one was between 1 and 2 SD and one within 1 SD.

TABLE V. PREVALENCE OF MENTAL RETARDATION ACCORDING TO DOSE RECEIVED[68]

The small number of Nagasaki subjects in the group receiving 1 to 10 rads is due to the exclusion of subjects located between 2,000 and 2,500 metres from the sample established in 1958.

A—Includes all cases of mental retardation

B—Excludes cases with possibly "explained" aetiology (shown between parentheses in columns headed "retarded")

	Hiroshima		*Nagasaki*		*Totals*	
Dose in rads	*Retarded*	*Total*	*Retarded*	*Total*	*Per cent retarded*	
					A	B
NIC[a]	3(1)	399	2	114	.98	.78
< 1[b]	2(1)	432	2(2)	137	.78	.18
1–10	3(1)	155	0	6[c]	1.86	1.25
11–49	2(1)	178	0	36	.93	.47
50–99	3(1)	44	0	22	4.55	3.08
100–199	4(1)	29	0	14	9.30	7.13
⩾200	5	14	4(1)	11	36.0	30.0
Unknown[c]	0	14	0	8	—	—

[a] NIC = Not in city at the time of the bombing.
[b] <1 = Persons at 3,000-5,000 metres whose effective dose was zero.
[c] Unknown = Persons whose shielding configuration was such that no dose estimate is available at this time.

TABLE VI. EXCESS INCIDENCE OF MENTAL RETARDATION AMONG OFFSPRING OF WOMEN IRRADIATED DURING PREGNANCY AND OF LEUKAEMIA (1947-1958) AMONG POST-NATALLY IRRADIATED SUBJECTS

Distance in kilometres	*Mental retardation (excess cases per hundred)*	*Leukæmia (excess cases per hundred)*
	Hiroshima	
0–1.5	11.0	0.6
1.5–2.0	2.3	0.04
	Nagasaki	
0–1.5	6.0	0.5
1.5–2.0	0.0	0.03

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