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NOTE

Symbols of United Nations documents are composed of capital letters combined with figures. Mention of such a symbol indicates a reference to a United Nations document.

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Chapter I

INTRODUCTION

Constitution and terms of reference of the Committee

1. The United Nations Scientific Committee on the Effects of Atomic Radiation was established by the General Assembly at its tenth session on 3 December 1955, under resolution 913 (X), as a result of debates held in the First Committee from 31 October to 10 November 1955. The terms of reference of the Committee were set out in paragraph 2 of the above-mentioned resolution by which the General Assembly requested the Committee:

"(*a*) To receive and assemble in an appropriate and useful form the following radiological information furnished by States Members of the United Nations or members of the specialized agencies:

"(i) Reports on observed levels of ionizing radiation and radio-activity in the environment;

"(ii) Reports on scientific observations and experiments relevant to the effects of ionizing radiation upon man and his environment already under way or later undertaken by national scientific bodies or by authorities of national Governments;

"(*b*) To recommend uniform standards with respect to procedures for sample collection and instrumentation, and radiation counting procedures to be used in analyses of samples;

"(*c*) To compile and assemble in an integrated manner the various reports, referred to in sub-paragraph (*a*) (i) above, on observed radiological levels;

"(*d*) To review and collate national reports, referred to in sub-paragraph (*a*) (ii) above, evaluating each report to determine its usefulness for the purposes of the Committee;

"(*e*) To make yearly progress reports and to develop by 1 July 1958, or earlier if the assembled facts warrant, a summary of the reports received on radiation levels and radiation effects on man and his environment together with the evaluations provided for in sub-paragraph (*d*) above and indications of research projects which might require further study;

"(*f*) To transmit from time to time, as it deems appropriate, the documents and evaluations referred to above to the Secretary-General for publication and dissemination to States Members of the United Nations or members of the specialized agencies."

2. The Committee consists of Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, France, India, Japan, Mexico, Sweden, the Union of Soviet Socialist Republics, the United Arab Republic, the United Kingdom of Great Britain and Northern Ireland and the United States of America.

Activities of the Committee

3. Since its establishment, the Committee has held nineteen sessions. Its activities during the first sixteen sessions were surveyed in the introductions to the reports that the Committee submitted to the General Assembly in 1958, 1962, 1964 and 1966.[1]

4. The Committee held its seventeenth and eighteenth sessions, respectively, at the United Nations Office at Geneva from 26 August to 6 September 1967, and at Headquarters from 8 to 17 April 1968. Besides considering preliminary material later to be included in the present report, at those sessions the Committee reviewed the information that it required to continue its assessment of world-wide levels of radiation from nuclear tests. Since some of its earlier requests for data had become less relevant than before to the problem of estimating risks to human populations, the Committee outlined its continued requirements in a letter to States Members of the United Nations or members of the specialized agencies or of the International Atomic Energy Agency. The text of the letter, dated 30 April 1968, which was sent to the above-mentioned States by the Secretary of the Committee is attached to this report as annex E.

5. At both sessions the Committee adopted annual progress reports to the General Assembly. These were noted with appreciation by the General Assembly at its twenty-second and twenty-third sessions by resolution 2258 (XXII) of 25 October 1967 and resolution 2382 (XXIII) of 1 November 1968. By the latter resolution, the General Assembly also commended the Scientific Committee for the valuable contributions it had made since its inception to wider knowledge and understanding of the effects and levels of atomic radiation; drew the attention of Member States to the review of information required to continue the Scientific Committee's assessment of world-wide levels of radiation from nuclear tests, as contained in the letter annexed to the report of the Committee; requested the Scientific Committee to complete its current programme of work and to review and formulate plans for its future activities; noted the intention of the Scientific Committee to hold its nineteenth session in May 1969 and to report further to the General Assembly.

6. The nineteenth session of the Committee was held at Headquarters from 5 to 16 May 1969. At that session, the Committee adopted the present report to the General Assembly. The Committee also discussed and formulated plans for its future activities. It decided that it would continue to keep under review and to

[1] *Official Records of the General Assembly, Thirteenth Session, Supplement No. 17* (A/3838); *ibid., Seventeenth Session, Supplement No. 16* (A/5216); *ibid., Nineteenth Session, Supplement No. 14* (A/5814); *ibid., Twenty-first Session, Supplement No. 14* (A/6314). Hereafter these documents will be referred to as the 1958, 1962, 1964 and 1966 reports, respectively.

assess the levels of radiation to which the world population is or may become exposed, including those from radio-active contamination of the environment due to both military and peaceful applications of nuclear energy, those from the increasing industrial and medical uses of radiation and radio-nuclides and those from natural sources present in the environment. The Committee would also continue to provide the General Assembly with assessments of the risks entailed by exposure to radiation and of the mechanisms involved and would evaluate the significance of any new radiation effect that came to its attention. The Committee felt that it might prepare a report on some special aspects of the above-mentioned subjects to the General Assembly at its twenty-seventh session, noted that it would report yearly on its progress and requested that arrangements be made for a session in September 1970 at the United Nations Office at Geneva.

Organization of the work of the Committee

7. As in the past, the Committee met in *ad hoc* groups of specialists who held most of their technical discussions in informal meetings before presenting their conclusions to the full Committee for review.

8. Dr. A. R. Gopal-Ayengar of India and Dr. G. C. Butler of Canada served as Chairman and Vice-Chairman, respectively, during the seventeenth session of the Committee. Dr. G. C. Butler of Canada, Professor B. Lindell of Sweden and Dr. V. Zelený of Czechoslovakia served as Chairman, Vice-Chairman and Rapporteur, respectively, at the eighteenth and nineteenth sessions. At the nineteenth session, Professor B. Lindell of Sweden, Dr. V. Zelený of Czechoslovakia and Professor L. R. Caldas of Brazil were elected Chairman, Vice-Chairman and Rapporteur, respectively, to serve during the twentieth and twenty-first sessions. The names of those scientists who attended the seventeenth, eighteenth and nineteenth sessions of the Committee as members of national delegations are listed in appendix II.

Sources of information

9. The reports received by the Committee from States Members of the United Nations, and members of the specialized agencies and of the International Atomic Energy Agency, as well as from these agencies themselves, between 8 June 1966 and 16 May 1969, are listed in annex D of this report. Reports received before 8 June 1966 were listed in earlier reports of the Committee to the General Assembly. The information received officially by the Committee was supplemented by, and interpreted in the light of, information available in the current scientific literature or obtained from unpublished private communications from individual scientists.

Scientific assistance

10. The Committee was assisted by a small scientific staff and by consultants appointed by the Secretary-General. The scientific staff and consultants were responsible for preliminary review and evaluation of the technical information received by the Committee or published in the scientific literature.

11. Although the Committee itself assumes full responsibility for the report, it wishes to acknowledge the help and advice given by those scientists whose names are listed in appendix II. The Committee owes much to their co-operation and goodwill.

Relations with United Nations agencies and other organizations

12. Representatives of the International Labour Organisation (ILO), the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), and of the International Atomic Energy Agency (IAEA), as well as of the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU), attended sessions of the Committee held during the period under review. The Committee wishes to acknowledge with appreciation their contribution to the discussions.

Scope and purpose of the report

13. The present report is not intended to cover comprehensively the whole field of interest of the Committee. It is limited to a discussion of radio-active contamination of the environment by nuclear tests, radiation-induced chromosome aberrations in human cells and the effects of ionizing radiation on the nervous system. The present report, therefore, being neither comprehensive nor self-contained, must be read in the context of the earlier reviews made by the Committee.

14. The main text of the report is followed by technical annexes in which the Committee has discussed in detail the scientific information on which it rests its conclusions. The Committee wishes to emphasize, as it did in the past, that its conclusions, being based on the scientific evidence now available, cannot be considered as final and will require revision as scientific knowledge progresses.

Chapter II

RADIO-ACTIVE CONTAMINATION OF THE ENVIRONMENT BY NUCLEAR TESTS

1. Debris from atmospheric nuclear tests continues to be the most important man-made radio-active contaminant of the environment. A number of tests have been carried out since the Committee's 1966 report: these have, however, added about 2 per cent to the amounts of long-lived radio-active nuclides still in the environment as a result of tests carried out in the early 1960s, although they have about doubled the current low content of the stratosphere and have thus contributed substantially to the deposition observed since the middle of 1967.

2. Small amounts of radio-active material have leaked from a few underground tests, and the crash of an aeroplane carrying nuclear weapons resulted in a localized contamination by plutonium-239 off the coast of northern Greenland in January 1968. These events have contributed only minutely to the global inventory.

3. Since the 1966 report, levels of long-lived nuclides in food-stuffs and human tissues have continued to decline except in the second half of 1968, when a slight increase in levels of caesium-137 due to recent tests was observed in food-stuffs in some countries of the northern hemisphere.

4. Most of the amount of long-lived nuclides injected into the stratosphere by earlier tests had been deposited by the middle of 1967. However, substantial fractions of the total doses to which the population is committed remain to be received from present body burdens and from the deposit in soil which will continue to be transferred to food-stuffs. This is particularly true in the case of strontium-90 which remains available for absorption by plant roots and is retained for long periods in the human skeleton. Present estimates indicate that roughly one-eighth of the total expected population dose due to strontium-90 had been delivered by the end of 1967, compared with between two-thirds and three-quarters of that due to the total amount of caesium-137 available for deposition in the body. On the other hand, only a small fraction of the expected population dose due to carbon-14, the radio-active half-life of which is much longer, has so far been delivered, and somewhat less than one-tenth of it will have been delivered by the year 2000. By contrast, more than half of the contribution to the dose commitment from external sources has already been delivered.

5. As in its earlier reports, the Committee has evaluated comparative risks of biological damage to the whole world population by means of "dose commitments" derived from the sum of radiation doses received and expected to be received by the world's population as a result of the nuclear explosions which have already taken place. As previously, dose commitments have been estimated for the gonads, for cells lining bone surfaces and for the bone marrow, as these are the tissues whose irradiation may give rise to hereditary effects, to bone tumours and to leukæmias, respectively. The Committee has not made special dose commitment estimates applicable to limited populations, such as those in individual countries, except in a few cases of populations with much higher than average exposures.

6. In the present report, for the purpose of estimating dose commitments, the Committee has used more extensively than heretofore actually measured levels of long-lived radio-nuclides in human tissues. This is particularly so in the case of strontium-90, which poses special problems because of its long retention in soil and bone and because of its complex metabolism in human tissues. By making use of measured levels in tissues, the Committee has been able to avoid some of the assumptions previously needed. Though a large number of other assumptions are still necessary and are common to all methods of calculation, the method now used will enable the Committee to use more efficiently the results of future measurements to verify and, if necessary, modify those assumptions in the future.

7. As far as the world-wide dose commitment is concerned, the major source of uncertainty continues to be the lack of information concerning the levels of any of the radio-active nuclides in the food and tissues of nearly two-thirds of the world population. In its previous reports, the Committee assumed that the numerical constants that describe the transfer of long-lived radio-nuclides were the same as those determined for areas from which measured data had been consistently available.

8. In the present report, the Committee has confined itself to estimating the dose commitment specifically for those populations from which sufficient measurements have been reported. For the rest of the world population, an upper limit to the dose commitment has been estimated.

9. The Committee feels that the uncertainty regarding the estimate applying to a large part of the world population, though unlikely to have caused a serious under-estimate of the global dose commitment, is undesirable, and it recognizes that, because of the very slow turnover of strontium-90 in adult bone, it will be possible, by sampling human bone from those areas of the world from which no data have yet been available, to estimate dose commitments to the population of these areas. The Committee notes with appreciation that the World Health Organization, in response to a recommendation made by the Committee at its eighteenth session, is now undertaking a limited programme of bone sampling, the results of which will be available in the near future.

10. Short-lived radio-nuclides are a source of radiation exposure of the population for a comparatively short time following their release into the environment, and external doses from short-lived nuclides due to tests carried out in 1966, 1967 and 1968 have not

significantly increased the global dose commitment. Measurable iodine-131 levels in milk have been reported mainly from the southern hemisphere following the tests carried out in that area.

11. Since the last report, there has been a continuing interest in the doses received by populations in the subarctic regions where, because of special ecological conditions, there is an enhanced transfer of caesium-137 from deposit to the body, mainly through consumption of reindeer or caribou meat. In these regions, individual doses from internal caesium-137 are of the order of one hundred times greater than the average for the northern hemisphere. There are also indications that, in these regions, levels of strontium-90 in food and tissues may be significantly greater, though not by as much as caesium-137 levels, than the average for the northern hemisphere.

12. There are several other limited regions of the world where levels of caesium-137 in food-stuffs and in humans have been found to exceed by many times the average for the corresponding latitudinal band. This has been attributed to high precipitation and to special soil conditions resulting in increased availability of caesium-137 to plants.

13. The estimated dose commitments are summarized in table I. The table includes estimates for the temperate zones of the northern and southern hemispheres. A third column shows values applicable to the whole world population. Although the Committee has used new and less indirect methods of estimating dose commitments, the present estimates differ little from those given in the previous report.

14. Comparative risks are, as in the 1964 and 1966 reports, expressed as the periods of time during which the natural background would have to be doubled in order to deliver an additional dose equal to the fraction of the dose commitments that will be received by the year 2000. These periods derived from the dose commitment estimates applicable to the whole world population are approximately 11, 26 and 18 months for gonads, cells lining bone surfaces and bone marrow, respectively.

15. The Committee now has increased confidence that its estimates are representative of the doses to which humans have been committed, particularly for those populations in the countries and areas from which measurements are available.

TABLE I. DOSE COMMITMENTS FROM NUCLEAR TESTS CARRIED OUT BEFORE 1968

Tissue	*Source of radiation*			*Dose commitments (mrad)*		
				North temperate zone	*South temperate zone*	*Whole world*
Gonads	External	Short-lived		36	8	23
		^{137}Cs		36	8	23
	Internal	^{137}Cs		21	4	21[a]
		^{14}C[b]		13	13	13
			Total[c]	110	33	80
Cells lining bone surfaces	External	Short-lived		36	8	23
		^{137}Cs		36	8	23
	Internal	^{90}Sr		130	28	130[a]
		^{137}Cs		21	4	21[a]
		^{14}C[b]		16	16	16
		^{89}Sr		<1	<1	<1
			Total[c]	240	66	220
Bone marrow	External	Short-lived		36	8	23
		^{137}Cs		36	8	23
	Internal	^{90}Sr		64	14	64[a]
		^{137}Cs		21	4	21[a]
		^{14}C[b]		13	13	13
		^{89}Sr		<1	<1	<1
			Total[c]	170	51	140

[a] The dose commitments due to internally deposited ^{90}SR and ^{137}Cs given for the north temperate zone are considered to represent upper limits of the corresponding dose commitments to the world population.

[b] As in the 1964 and 1966 reports, only the doses accumulated up to year 2000 are given for ^{14}C; at that time, the doses from the other nuclides will have essentially been delivered in full. The total dose commitment to the gonads and bone marrow due to the ^{14}C from tests up to the end of 1967 is about 180 millirads and that to cell lining bone surface is about 230 millirads.

[c] Totals have been rounded off to two significant figures.

Chapter III

EFFECTS OF IONIZING RADIATION ON THE NERVOUS SYSTEM

1. The nervous system performs various functions in the organism. In the first place, it provides the means for relating the organism to the external environment by means of perception through the sense organs and of control of the skeletal muscles. The nervous system is also the instrument by which immediate or delayed behaviour is expressed, and in man it is responsible for the most complex intellectual functions.

2. With regard to such functions as digestion, respiration, blood circulation and excretion, the nervous system, often in conjunction with the endocrine glands, plays an essential regulatory role by adapting these functions to the changing needs of the organism and thus contributes to maintaining the constancy of the internal environment. This task is largely performed by the autonomic nervous system whose control centres are located in the spinal cord and in certain brain structures.

3. Reflex activity usually involves an orderly progression of events, namely, an initiation of activity at sensory receptors, a relay of impulses to a neural centre and final transmission to a muscle or other effector. While reflex activities are readily analysed, the nervous activity concerned with the highest integrative functions of the organism, such as complex behaviour, are much more difficult to assess.

4. The importance and diversity of these functions emphasize the need for the study of the effects of ionizing radiation on the nervous system. Although ultimately it is the functional effects that may be more important, both structural and functional effects need to be studied. Investigations of functions and structures have been mostly carried out by different researchers, and relatively few attempts at integrating the two approaches have been made. Because the response of the nervous system is so different depending on whether irradiation takes place during its development or afterwards, it is customary and convenient to consider the effects during these two periods in sequence.

Irradiation of the nervous system during its development

5. Observations on experimental animals indicate that pre-natal irradiation can produce severe developmental anomalies. Those of the nervous system are prominent among them. When they are serious enough, further development of the foetus is prevented and death ensues. Anomalies of the nervous system are produced only if irradiation occurs in the period when the nervous system and its various parts are differentiating. Specific anomalies such as microcephaly, encephalocele and hydrocephalus occur in this period only after irradiation at certain so-called critical times.

6. The frequency and severity of anomalies of any given type depend on the radiation dose, but information is insufficient to establish dose-effect relationships for any of the malformations affecting the nervous system. It is likely that the induction of gross malformations of the nervous system requires doses higher than a threshold which, for mice and rats, is probably around 100 rads.

7. Disorganization of the cellular layers of the brain cortex has been observed, however, after an x-ray dose of 20 rads administered to rats on the sixteenth day of pre-natal life and are still apparent when the animals reach maturity. Less pronounced changes also occur in rats after 10 rads given on the first day after birth, but evidence of damage disappears progressively as the animal grows. Such changes have been observed by means of painstaking studies which need to be systematically pursued at various doses and various times of irradiation and observation, and attempts should be made to correlate them with the functional effects that have also been reported after pre-natal irradiation.

8. The functional impairment of animals irradiated pre-natally has been studied by various methods, particularly in rodents. Electro-encephalographic changes seem to reflect disturbances in the inhibitory function of the cortex on lower centres. Visual, olfactory and distance discrimination and other learning processes are also affected. These changes have been observed in adult rats which have received doses of the order of 100 rads or more during the second and third week of their intra-uterine life.

9. Some studies of conditioned reflexes, however, have been reported to reflect changes of learning processes at much lower doses. Slight changes in conditioned reflex performance have been observed in the adult after as little as 1 rad on the eighteenth day of pre-natal life. The assessment of the relevance of these and other behavioural changes for the problem of risk estimation in man requires better knowledge on the comparability of results of studies on animals and on man.

10. That severe damage to the nervous system can be induced in man also is shown by a number of observations of children born of mothers irradiated for medical reasons during pregnancy. Doses are unknown but are believed to have been high. A number of cases of reduction of head size, often accompanied by severe mental retardation, have been reported among these children as a result of irradiation from the second through the sixth month of intra-uterine life. However, contrary to what animal experiments would lead one to expect, major structural changes of the nervous system have seldom been observed, perhaps because these would be incompatible with sufficiently long survival of the human embryo for the damage to be detected at birth.

11. Similar observations have been made among the offspring of women exposed during pregnancy to the

Hiroshima and Nagasaki explosions. Reduced average head size and increased incidence of mental retardation are clearly observed among those exposed within 1.5 kilometres of the hypocentre between the second and the sixth month of intra-uterine life, and the frequency of mental retardation may also be above normal at greater distances, where doses were of the order of a few rads.

12. The value of this latter observation is limited by the fact that the number of cases among the offspring of women irradiated at low doses is extremely small and that the role of other factors cannot be entirely excluded. Where the opportunity exists, any additional investigations on pre-natally irradiated subjects are very desirable in order to establish further the degree of radio-sensitivity of the foetus.

13. Surveys of children whose mothers were irradiated for medical reasons during pregnancy have shown an associated increase (40 per cent) of malignancies, including malignancies of the nervous tissue. The excess was noticeable after doses assumed to be of the order of a few rads, but it cannot be entirely excluded that it may have been associated with the condition in the mother that prompted the irradiation rather than with the irradiation itself. Such an increase has not been reported among survivors of *in utero* exposure to the Hiroshima and Nagasaki bombings, but the expected number of induced cases in that population was very low.

14. An increased incidence of tumours of the nervous tissue has also been observed in a number of surveys of children irradiated for medical reasons in infancy or early childhood. One of these surveys suggests that, at the doses absorbed by the relevant tissues, the incidence of these malignancies is increased by the same order of magnitude as the incidence of leukæmias. The same survey has also shown an increased incidence of serious mental disturbances associated with previous irradiation of the brain around the age of seven years. Most of the brain was estimated to have received doses of approximately 140 rads. However, as the role of a number of variables that may themselves have contributed to that excess cannot at present be assessed, the results of further analysis of these results are required before the relationship between radiation and mental disorders can be considered as proved. Other surveys of brain-irradiated children that are currently in progress should be vigorously pursued.

15. The evidence available induces the Committee to draw attention to the particular hazards that may result from irradiation of the fœtus and of children.

Irradiation of the nervous system in the adult

16. In the adult, the radiation dose required to induce severe structural changes in the nervous system under conditions of whole-body irradiation is higher than the dose needed to cause gross alterations of other systems such as the gastro-intestinal tract and of the hæmopoietic system. Under conditions of short-term irradiation, the median lethal dose for man lies around 400 rads, and death when it occurs is mainly due to the involvement of both of these. Sudden death primarily due to the involvement of the nervous system, on the other hand, occurs after doses of the order of several thousands of rads.

17. Only isolated cases of malignant intracranial tumours of the nervous tissue have been reported after irradiation of adult subjects. It seems, therefore, that the induction of malignancies is unlikely to be a substantial hazard of irradiation of the adult nervous system in man.

18. Functional and behavioural effects are observed in experimental animals after high doses (above 50 rad). These effects include some electro-encephalographic changes and some disturbances of certain conditioned reflexes. The accomplishment of many tasks involving learning and performance is little if at all affected. Such changes as have been induced by radiation disappear with time, but repeated irradiations with the same dose tend to produce greater disturbances. There are both positive and negative reports on the induction of similar, but milder, functional changes by low-dose radiation.

19. It is not clear to what extent such functional effects as have been observed after whole-body doses of 50 rads and above are the primary consequence of damage to the nervous system or whether they result from different stimuli originating in, or from toxic products released by, other damaged tissues and systems such as the cardio-vascular, gastro-intestinal and endocrine systems. Nevertheless, whether primary or secondary, these effects on the nervous system may play a role at the doses at which the acute radiation syndrome may occur.

20. Observations are available on radiation workers exposed in the past for a number of years to average levels of radiation estimated as being higher than current maximum dose levels for radiation protection. Subjective complaints, such as headaches and sleep disturbances accompanied by mild and reversible neurological and cardio-vascular changes, have been reported. No changes of consequence were observed among workers exposed, even for a number of years, within the currently accepted dose limits.

21. Even at very low doses, ionizing radiation may act as a non-specific stimulus. Evidence of this is found in the possibility of using radiation as a conditioning stimulus, the ability of radiation to awaken an animal, the avoidance of a radiation source by an animal, and in the fact that radiation can serve as a visual or olfactory stimulus. Under certain circumstances, ionizing radiation can be perceived by the human retina at doses as low as a few millirads. There is no evidence that these doses induce any injury to the sense organs involved.

22. It seems, in summary, that the most significant fact emerging from a review of the effects of ionizing radiation on the nervous system is the striking dependence of the type and intensity of effects on the age at irradiation. In the adult, except at extremely high doses, the effects that have been observed, whether structural or functional, appear to be of secondary importance compared to those that may arise in other tissues and systems. Functional reactions of the nervous system may also appear at very low doses (10 rad or less). However, they are of a physiological nature, and no damage of the nervous system has been observed. In children, on the other hand, the evidence suggests that, at least with regard to the induction of malignancies, the nervous tissue might be about as susceptible as other tissues such as the thyroid and

blood-forming tissues. It is, however, in the pre-natal period that the vulnerability of the nervous system is highest. There is clear evidence that, from the second to the sixth month of pre-natal life, doses from 50 rads onwards are associated with increases in mental retardation and microcephaly. Evidence on the effects of lower doses during this same period of pre-natal life is still extremely tenuous and does not permit exclusion of the possibility that increased incidence of the same effects may be a result of exposure in this lower range. Available data suggest that even low doses given to the fœtus later in pregnancy may increase the incidence of tumours of the nervous system as well as of other malignancies.

Chapter IV

RADIATION-INDUCED CHROMOSOME ABERRATIONS IN HUMAN CELLS

1. The cells of any given species have a characteristic number of chromosomes, and each chromosome has a characteristic structure and size. Chromosomal changes visible by some form of light microscopy are called chromosome aberrations. These can be separated into aberrations involving changes in structure—the chromosome structural aberrations—and those involving changes in the number of chromosomes. Since chromosomes contain genetic material, the various types of chromosome aberrations may result in genetic effects.

2. In man, as in all other animal and plant species, chromosome aberrations are to be found with low frequencies in both somatic and germ cells of individuals in populations that have not been exposed to radiation over and above natural background levels. Such spontaneous aberrations are changes that may, in some cases, be transmitted to descendant cells. In other cases, the changes are so gross that they result in the death of the cells containing them. Clearly there are differences between the relative importance of such changes in somatic as opposed to germ cells.

3. Chromosome aberrations in human germ cells are associated with and may be responsible for a considerable proportion of spontaneous abortions and, where they are compatible with viability, for a variety of congenital abnormalities. Indeed, as discussed in the 1966 report, it has been estimated that one child out of every 200 live-born has a constitutional chromosome anomaly responsible for a gross physical or mental abnormality. The importance of chromosome aberrations in somatic cells is less clear, although there is evidence that one particular kind of chromosome anomaly may be causally related to the development of human chronic granulocytic leukæmia. On the other hand, in normal healthy individuals peripheral blood lymphocytes may occasionally contain a chromosome aberration (less than one in 2,000 for one specific type of aberration). In itself the presence of such aberrations appears to be of no consequence to the well-being of the individual.

4. Exposure to radiation may result in an increase in the number, but not in the variety, of chromosomal aberrations. These aberrations are clearly of genetic importance and they may, in fact, comprise the major component of the genetic damage resulting from radiation exposure. Thus, a considerable amount of work has been carried out on the mechanisms whereby such aberrations are induced by radiation, on the behaviour of the aberrant chromosomes at cell division and on the genetic consequences of the aberrations.

5. Until relatively recently, most of this work had been carried out on organisms that were particularly well suited for cytological study, because they possessed small numbers of rather large chromosomes. However, in the last decade, and particularly over the last four or five years, a considerable amount of study has been devoted to the induction of aberrations in man. These studies have been made possible through the development of simple and reliable techniques for culturing human cells *in vitro* and through the application and refinement of cytological techniques previously utilized by plant cytogeneticists.

6. As a result of the developments in human cytogenetics, it has become possible to make observations on chromosome aberrations induced in human cells both *in vivo* and *in vitro*. Studies have been carried out on individuals exposed to radiation in the course of their work or for diagnostic or therapeutic purposes, as well as on individuals who had been exposed accidentally or as a consequence of nuclear explosions. In addition, a considerable amount of work has been undertaken on the responses of human chromosomes in cells exposed to radiation *in vitro*. These studies have shown that the human chromosome complement is sensitive to radiation and that it is possible to detect effects following x-ray doses as low as 10 rads delivered to substantial proportions of the body in a short period of time.

In vitro studies

7. The blood leucocyte culture system offers a means of experimenting on freshly obtained human cells which can be easily and painlessly collected in large numbers without any adverse effect on the donor and are amenable to short-term culture, using relatively simple techniques. The obvious advantages offered by this system for studies on the *in vitro* response of human cells to radiation exposure have been exploited by a number of groups of workers, and a considerable amount of data on radiation-induced chromosome aberrations in such cells has been obtained.

8. A variety of studies have been carried out on the influence of various factors, including radiation quality, dose, dose rate and time of sampling, on the yield of radiation-induced chromosome aberrations in human peripheral blood cells. In general, it has been found that, for any given set of factors, there exists a quantitative relationship between the yield of aberrations and dose, as has been observed in all other mammalian and non-mammalian cell systems that have been studied.

9. Although studies in various laboratories on the relationship between aberration yield and dose have shown that separate experiments yield consistent results, significant differences have been observed between laboratories. However, it is now clear that the main factors contributing to the quantitative differences between these results are (*a*) differences in the quality of the radiations employed; (*b*) the use of irradiated cultures as opposed to the irradiation of blood cells *in vitro* prior to culture and (*c*) the use of different durations of culture. When these factors are taken into account, close agreement between different laboratories

is evident. However, further standardization of methods is highly desirable to ensure better comparability.

10. This work has great importance because of the possible use of dose-yield relationships established *in vitro* in attempts to estimate radiation doses absorbed *in vivo* and as an indication of their likely biological importance. In theory, dose estimates can be obtained with this technique through the study of chromosome-aberration yields in the exposed individuals and extrapolation to equivalent yields obtained *in vitro* under defined conditions of exposure. A number of laboratories have had a good measure of success in estimating radiation doses in accidentally exposed individuals by the use of this "chromosome-aberration dosimetry" approach. However, there are a number of important problems, particularly in relation to problems of non-homogeneous exposures of the body. At the present time, it seems clear that the use of chromosome aberrations in biological dosimetry may have considerable potential, but much work remains to be done.

In vivo studies

11. Studies on peripheral blood lymphocytes from patients exposed to diagnostic x rays and from radiation workers receiving long-term irradiation have, in some cases, clearly revealed significant increases in aberration yields after doses of the order of a few rads. The ability to detect such effects at low doses is a consequence of the relatively high sensitivity of the human chromosome complement, of the high quality of cytological preparations from lymphocytes and of the very low frequency of spontaneous chromosome aberrations in such cells.

12. To relate aberration yield to radiation dose *in vivo*, data obtained over a range of exposures, preferably under standardized conditions, are desirable but rarely obtainable. A number of studies, however, have been carried out on individuals irradiated at various dose levels and under various conditions either as a result of accident or for therapeutic purposes. The integral absorbed dose has been estimated from aberration yields in some of the studies on individuals accidentally exposed, sometimes with good agreement with measurements obtained by physical means.

13. Evaluation of the dose under these conditions is fraught with uncertainty since, although the cells (small lymphocytes) that are sampled for studying aberration yields are widely distributed throughout the body, they tend to migrate so that only a small proportion is to be found in the peripheral blood at any one time. Thus, in the case of short-term partial-body exposure by radiation of a given quality, the aberration yield observed in the cells sampled will depend upon a variety of factors, including the volume irradiated, the proportion of small lymphocytes in the exposed volume and, since there is considerable mixing between lymphocytes in different tissues, the time at which blood is sampled after exposure. Similar difficulties arise in cases where limited areas of the body have been exposed to radiation for medical purposes, and blood samples are taken at short defined intervals after exposure.

14. Because at least some of the cells sampled for aberration yields are long-lived, it has recently been possible to obtain dose estimates from blood cells of survivors of Hiroshima who had been exposed to radiation from the nuclear explosion twenty-two years previously. These estimates are in reasonable agreement with indirect estimates of exposures obtained by physical methods.

15. It may be concluded that studies to date indicate that scoring of chromosome aberrations in the lymphocytes of circulating blood is a potentially important biological adjunct to physical dosimetry. Special difficulties, however, arise in the irradiations restricted to parts of the body because of the mixing of lymphocytes from irradiated and unirradiated parts of the body. Thus, this method only reflects an average effect upon lymphocytes irradiated in different parts of the body. Further data are urgently required to improve the validity and broaden the field of application of this method.

Possible biological significance of the aberrations

16. The possible biological significance of chromosome aberrations present in germ cells has been the subject of continued review by the Committee, and the views expressed in the 1966 report are still largely valid. There are no direct observations yet on the genetic consequences of radiation-induced chromosome aberrations in the germ cells of man, although information on the genetic consequences of radiation-induced chromosome anomalies in laboratory mammals is available and was reviewed in detail in the 1966 report. Further study on human meiotic cells is clearly necessary, particularly in order to provide better estimates of the spontaneous frequency of translocations in man and a better understanding of their genetic consequences.

17. At the somatic level, the interest of chromosome anomalies results mainly from their possible role in the causation of malignant changes, with which they are frequently associated. Such a role is, however, still unclear. Only in the case of chronic myeloid leukæmia does the evidence strongly implicate a specific chromosome aberration (the Ph^1 chromosome) as playing a significant role in the initiation of the disease if cells with this aberration are present in the bone marrow. Although it is possible that other specific chromosome abnormalities could be associated with other types of neoplastic change, the evidence is tenuous, whereas the presence of a wide variety of chromosome aberrations in most tumours and their complete absence in some others argues against a simple causal relationship. Chromosome aberrations may well be phenomena that are secondary to, and could be independent of, the neoplastic change, although it is clear that most agents and conditions that produce chromosome aberrations also cause tumours.

18. The incidence of chromosome aberrations and that of tumours both increase with increasing dose, but the relationship between the two effects is complex. Although there is some correlation between radiation-induced chromosome aberrations and malignancies, it is a matter of observation that, of the individuals exposed to low levels of radiation and who have aberrations in many of their cells, very few manifest malignant disease.

19. The considerable interest in the possibility that radiation-induced chromosome aberrations may contribute to life shortening and to immunological deficiency has not so far resulted in any clear conclusions

regarding the relationship between chromosome aberrations and these effects. Although life shortening and acute immunological deficiency may be induced by radiation, the part played by chromosome aberrations, other than by contributing to cell killing in the case of immunological deficiency, is by no means clear.

20. Information on the yields and types of chromosome aberrations in somatic cells does not as yet provide us with a new approach to, or better estimates of, risks except in the one specific case of the Ph[1] chromosome change which correlates with chronic granulocytic leukæmia. Knowledge of an increased frequency of chromosome aberrations in the peripheral blood lymphocytes of an irradiated individual does not enable us to make any quantitative statement regarding the risk of developing neoplastic diseases, immunological defects or other clinical conditions. For the time being, estimates of risk of somatic diseases must, therefore, remain largely based on empirical relationships between doses and observed incidences in groups of irradiated people, as were the estimates earlier obtained by the Committee.

ANNEXES

Annex A

RADIO-ACTIVE CONTAMINATION OF THE ENVIRONMENT BY NUCLEAR TESTS

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I. Introduction

1. Debris from nuclear tests in the atmosphere is still the major radio-active man-made contaminant of the environment. By comparison, the gaseous and liquid wastes presently discharged in limited amounts into the environment from reactors and fuel reprocessing plants and by industrial, medical or research applications of radio-isotopes contribute much less to radio-active contamination and will not be considered in this report.

2. Although several nuclear devices have been tested since the last report of the Committee,[1] these have not added significantly to the global inventory of long-lived radio-active material in the biosphere. Furthermore, since the last report was prepared (June 1966), the rate of deposition of nuclear debris from the atmosphere has decreased substantially, thereby simplifying considerably the problem of predicting the future levels of the long-lived radio-nuclides in the food and tissues of man to be expected from tests carried out so far.

3. Moreover, the results of extensive and comprehensive surveys carried out in a number of countries have contributed considerably to our knowledge of the levels of long-lived radio-nuclides in man and food chains in those countries, as well as to our understanding of the many and complex processes involved in the transfer of radio-activity to the human body.

4. In the present report, the impact of these recent developments on the assessment of the effect of nuclear fall-out on man is reviewed in detail. In particular, the radiation doses to which man has been committed are estimated from the results of the series of measurements now available.

5. Although the estimates of the doses thus obtained do not differ significantly from the previous ones, the Committee now has increased confidence that they are representative of the doses to which humans have been committed, at least for those populations in the countries and areas from which the results of measurements are available.

II. Recent data on environmental contamination

A. Airborne and deposited artificial radio-activity

1. *Atmospheric injections*

6. Six nuclear devices were exploded above ground in central Asia during the years 1966-1968. After each test in 1966 and 1967, increases in surface-air activity were observed in Japan within a few days,[2-7] and in North America[8-11] and Europe[12, 13] within the first two weeks. The debris from the explosion in June 1967, on the other hand, was observed at the surface after some months. Reports describing the behaviour of the debris from the 1968 test are not yet available.

7. Five nuclear devices were exploded above ground at the Tuamotu Islands in the south Pacific during the last half of 1966, three in mid-1967 and five between July and September 1968. Increased surface activities were observed in South America,[14, 15] South Africa,[12, 13, 16] Australia[17-22] and New Zealand[23-25] within a month after each explosion.

8. Temporarily increased surface-air activities have been observed from time to time. The composition of the radio-active material suggests that it has originated from underground explosions.[26-28]

9. In January 1968, an airplane carrying nuclear weapons crashed on the ice in a sparsely populated area near Thule off the coast of northern Greenland. Most of the radio-active material, mainly consisting of plutonium-239, was spread over an area of approximately 12,000 m^2. There was no nuclear explosion and no evidence was found that radio-activity had spread from the immediate vicinity of the place of accident.[29]

2. *Inventories*

(a) *Strontium-90 and caesium-137*

10. No significant amounts of nuclear debris were injected into the atmosphere between 1963 and mid-1967, and the stratospheric content of long-lived nuclides has consequently decreased steadily. Thus, in the period 1963-1966, the total content of strontium-90 in the atmosphere decreased at an approximately constant rate with an apparent half-life of about one year.[30, 31] The same half-life was found for the manganese-54 presumably produced in the 1961 and 1962 test series presumably produced in the 1961 and 1962 altitudes in 1962 showed a somewhat smaller rate of removal with a half-life of about 17.5 months. It is estimated that the explosions in 1967 added 170 kilocuries and 0.6 kilocuries of strontium-90 to the stratosphere of the northern and southern hemispheres, respectively, while those in 1968 added a further 160 kilocuries and 240 kilocuries[32, 33] (figure 1). Because of the small amount of debris from earlier tests still remaining in the stratosphere in 1968, these recent additions have increased the stratospheric inventory by about 50 per cent. However, they have only added an amount equal to about 4 per cent of the global inventory (deposited plus stratospheric) due to the earlier tests.

11. The $^{137}Cs/^{90}Sr$ ratio in nuclear debris may vary to some extent, depending not only upon the particular processes taking place in the nuclear devices but also upon fractionation phenomena. However, observations on the $^{137}Cs/^{90}Sr$ ratio in atmosphere and deposit in the years 1966-1968 have not revealed any systematic trend, and, for the purposes of estimating global inventories, it can be assumed that its value is 1.6.[12, 13, 34-36]

(b) *Carbon-14*

12. The content of artificially produced carbon-14 in the stratosphere decreased from (36 ± 8) 10^{27} atoms at the beginning of 1963 to (17 ± 4) 10^{27} atoms at the beginning of 1965.[37] No recent data on the stratospheric content in the southern hemisphere are available, but the indications are that the decrease has been small since 1965. The tropospheric content of carbon-14 in the northern hemisphere has gradually decreased since the years 1963-1964, when maximum concentrations of about 100 per cent of the natural level were observed, to about 65 per cent in 1967.[38] In the southern hemisphere, the concentration has gradually increased as a consequence of interhemispheric mixing so that the tropospheric concentrations were about the same in both hemispheres in 1967.[38] No observations on the effect of the explosions in 1967 and 1968 on the carbon-14 levels have been reported.

(c) *Plutonium-238*

13. The burn-up of the radio-isotope power source SNAP-9A in the upper atmosphere in April 1964 released 17 kilocuries of plutonium-238.[39, 40] Because of the high altitude of injection and the small particle size of the debris, the rate of depletion of the upper stratosphere was small during the first years, the apparent half-life being about ten years.[41] The rate of

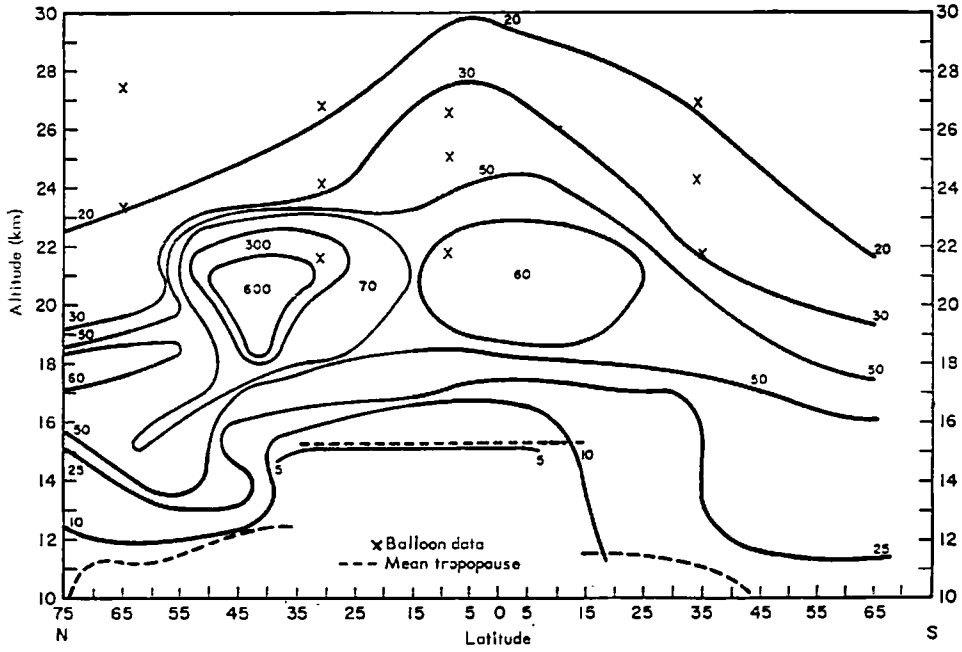


Figure 1. ^{90}Sr concentration contours, August 1967[32] (pCi (100 scm)$^{-1}$, where 1 scm = 1.226 kg air)

depletion has gradually increased, and the apparent half-life in the stratosphere after 1966 has been estimated to be between two and three years.[42, 43] Measured upper-air concentrations accounted for about 3 kilocuries in the northern hemisphere and 8 kilocuries in the southern hemisphere in mid-1967,[42] and the cumulative deposit to the end of 1967 was estimated to be 2.2 kilocuries and 4.7 kilocuries in the northern hemispheres, respectively.[43]

3. *Deposition*

(a) *General*

14. In the period 1965-1967, the annual deposition of strontium-90 decreased by about 50 per cent per year in the northern hemisphere and by a somewhat smaller amount in the southern hemisphere.[13, 44] The latitudinal variation was, in general, the same as earlier, with the highest deposition in the middle latitudes of each hemisphere (figure 2). In the northern hemisphere, a pronounced seasonal variation with maxima in spring was observed throughout the period (figures 3 and 4). A similar but less pronounced variation was also observed in the southern hemisphere.

15. Most of the strontium-90 and caesium-137 deposited up to the middle of 1967 was due to explosions occurring before 1963. In the second half of 1967, steadily increasing $^{144}Ce/^{137}Cs$ ratios in the northern hemisphere indicated that a larger part of the long-lived nuclides came from recent explosions.[13] It has been estimated that about half of the long-lived nuclides deposited in the northern hemisphere in 1968 came from recent explosions.[13]

16. The nuclear atmospheric explosions occurring between 1966 and 1968 have all resulted in deposition of short-lived fission products. A study by Hardy[45] on $^{89}Sr/^{90}Sr$ ratios in deposition indicates that most of the deposition occurring within the first half-year after an explosion is deposited in the hemisphere where the explosion took place. However, small amounts of fresh debris from explosions in the southern hemisphere have occasionally been observed in the northern hemisphere and vice versa.[13, 45, 46]

17. Fresh nuclear debris consists of a mixture of a large number of beta- and gamma-emitting nuclides. The composition changes with time and may also be affected by fractionation of the debris. The total beta activity or the amount of any single nuclide will, for that reason, not give a quantitative measure of the deposit occurring soon after an explosion. However, the content of barium-140 in ground-level air or precipitation can be used as a convenient indicator of the amount of fresh deposit, as it can easily be measured by gamma-spectrometric methods and also because it has a half-life of the same order of magnitude as iodine-131, which is the nuclide of main concern as regards doses from fresh deposit. Debris from the explosions in central Asia has normally been observed at ground level in the northern hemisphere during the first month after explosion.[13, 45] The levels have been moderate, peak values of barium-140 observed in the United Kingdom between 1966 and 1968 ranging from 0.01 to 0.1 pCi kg^{-1} in ground-level air. The ground-level activities in the southern hemisphere due to the explosions in the south Pacific have shown barium-140 peak values of about 1 pCi kg^{-1} in South Africa,[13] Australia[19] and Argentina.[15] Occasional high total beta activities in ground-level air have been observed in Japan[5-7] and North America.[9]

18. The global annual deposition of strontium-90 has been estimated from the results of two worldwide networks operated by the United Kingdom Atomic Energy Research Establishment (AERE) and the United States Atomic Energy Commission Health and Safety Laboratory (HASL). Statistical analysis of deposition data indicated that the latter network had underestimated the deposition by as much as 20 per cent,[47] and this has now been confirmed.[48, 49] The cumulative global deposition at the end of 1966 was, from the AERE network, 12.5 megacuries[48] and, after allowing for the collection efficiency of the samplers, 12.6 megacuries[48] from the other network.

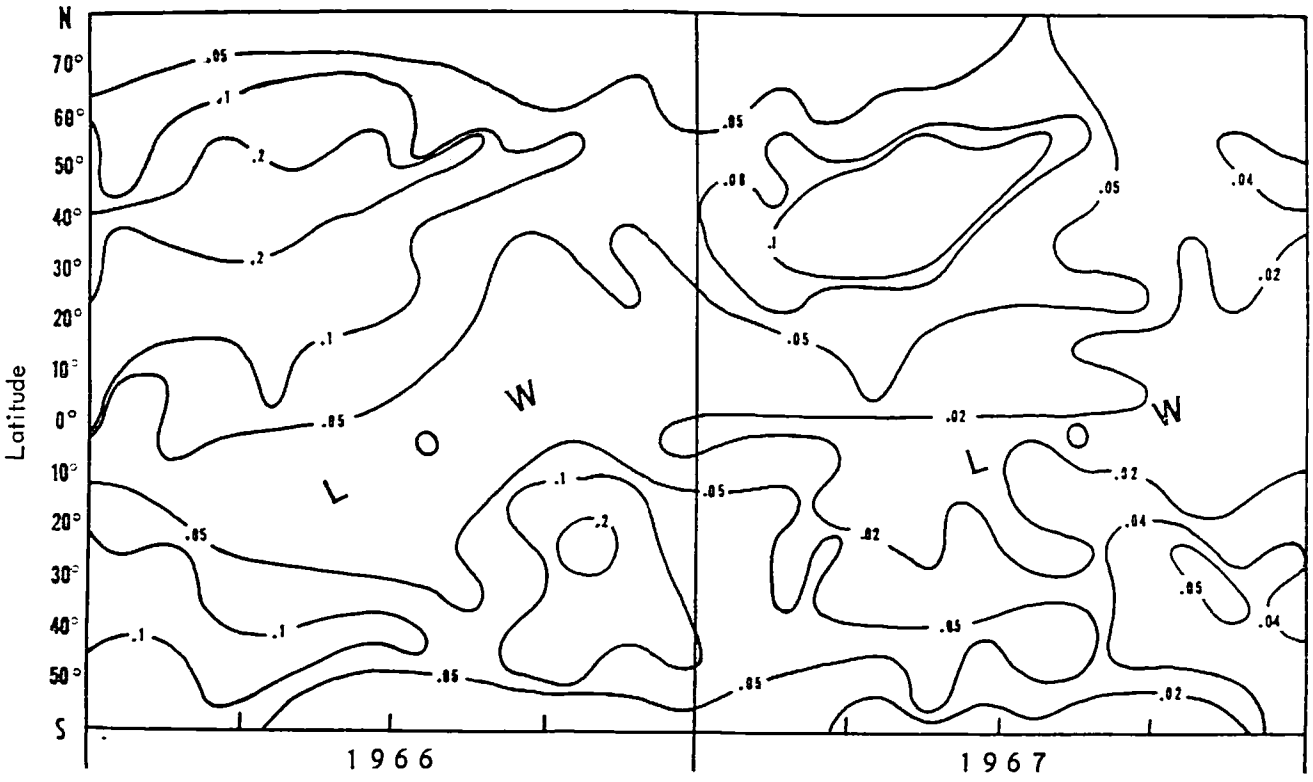


Figure 2. Monthly zonal average deposition of ^{90}Sr by latitude and time, 1966-1967[44] (mCi km^{-2} per month)

19. The cumulative deposit has been independently estimated from the results of a world-wide sampling programme of strontium-90 contents of soils[50] to be 13 megacuries. The cumulative deposits from 1958 to 1967 are given in figures 5 and 6 and table I. Table II summarizes the strontium-90 inventory from 1963 to 1967, as derived from upper-air and deposition data.

20. No comprehensive information on global caesium-137 deposition comparable to that on strontium-90 is available. For most practical purposes, it is sufficient to assume a constant $^{137}Cs/^{90}Sr$ ratio and so calculate the caesium-137 deposition from the deposition of strontium-90. The value of the ratio to be used for estimating global inventories of caesium-137 was discussed in paragraph 11.

(b) *Relative deposition on land and ocean*

21. Deposition in the oceans was discussed in detail in the Committee's 1966 report.[51] The main concern in this connexion was that large differences in deposition rates between oceans and land could, if unrecognized, give rise to significant errors in the estimates of the global inventory. Although this did not directly affect estimates of the dose commitments to the world's

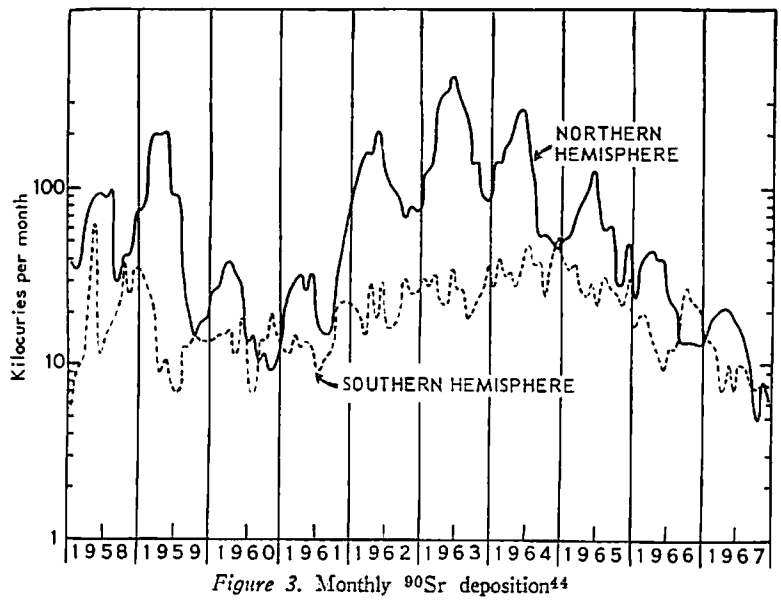


Figure 3. Monthly ^{90}Sr deposition[44]

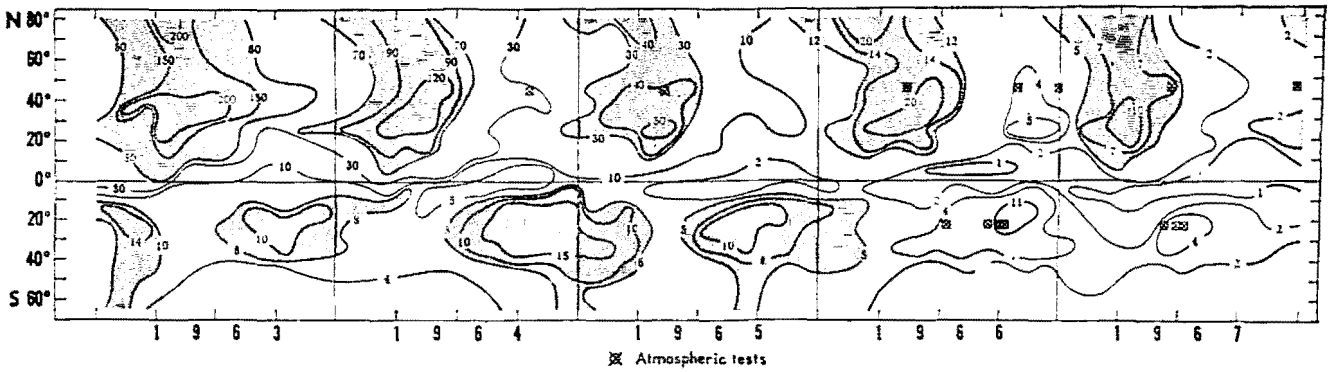


Figure 4. ^{90}Sr concentrations in surface air based on observations made between 35°W and 155°W[115] (dpm per 1,000 scm, where 1 scm = 1.226 kg air)

population, it was felt that the possibility of large systematic errors in assessing the inventory needed to be studied closely. The experimental data on this subject are still somewhat contradictory.

22. The evidence for excess strontium-90 fall-out in the oceans comes primarily from the sea-water measurements themselves which, when integrated over the entire volume of the oceans, result in an estimate of the inventory substantially larger than that extrapolated from land measurements. Systematic observations of strontium-90 concentrations in surface water of the north Atlantic have also suggested that the rate of deposition there is higher than over land.[52, 53]

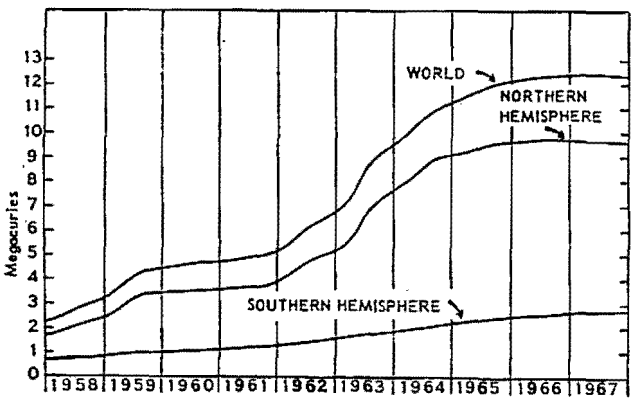


Figure 5. Cumulative ^{90}Sr deposits[44]

23. However, the possibility of large differences between land and ocean deposition is unlikely because of other considerations. The most compelling is that the estimates of the global strontium-90 inventory,[54] when corrected for radio-active decay, have been virtually constant during the period 1963-1967 (table II). As the estimates of the deposit were based on measurements made at land stations, a considerably higher deposition onto the oceans should have resulted in systematically decreasing estimates of the total inventory.

24. Studies of the cumulative deposit of strontium-90 onto ocean shores in Norway and Iceland[55] also fail to show any significant difference between the deposit close to the sea and some kilometres inland. In addition, an experiment carried out at Crater Lake, Oregon, United States, showed that there was no measurable difference in strontium-90 deposition onto a fresh-water surface of about 60 km^2 compared to that onto adjacent land.[56] These results suggest that, if there is enhanced deposition of strontium-90 onto the oceans, this may not be due to different conditions of strontium-90

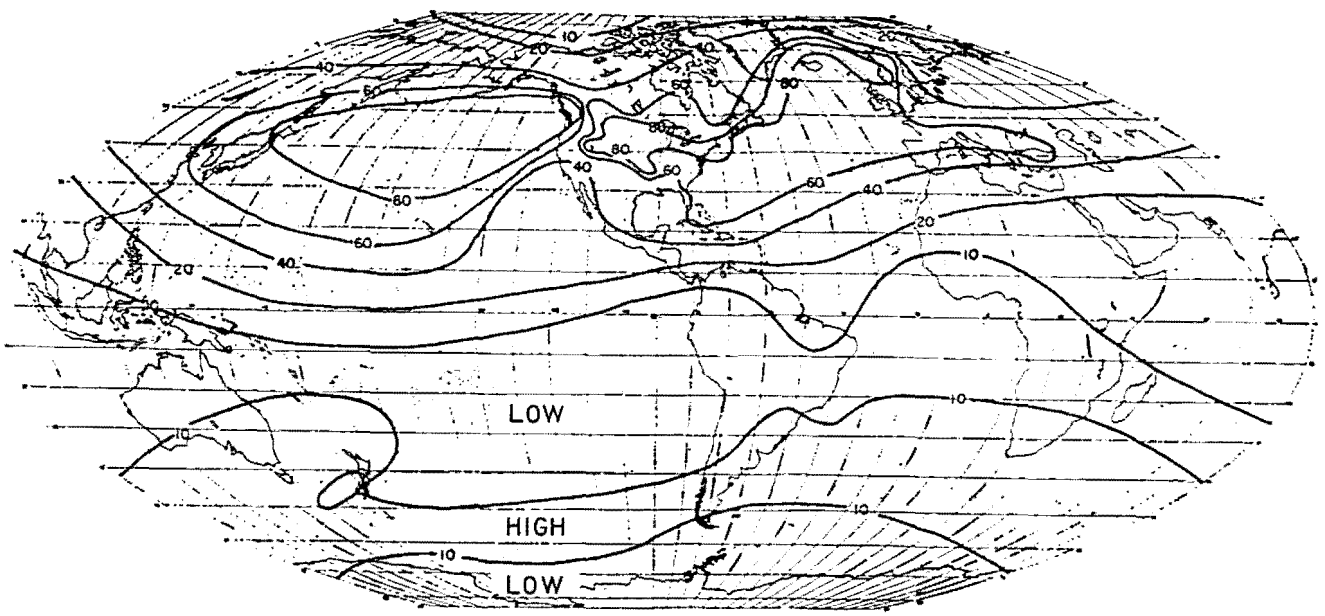


Figure 6. Isolines of cumulative ^{90}Sr deposits based on analyses of soils collected 1965-1967[50] (mCi km^{-2})

removal from the lower troposphere over the oceans from those over land.

25. Karol[57] studied the deposition of radio-active aerosols from the troposphere onto the land and sea surfaces, using a quantitative meteorological model and data on surface-air concentrations. His computations from the model indicate that, within a zonal belt, the average rate of deposition on land and on the sea should be the same.

26. In view of the above considerations, the fall-out over the ocean per unit area in each latitude band is assumed, as in previous reports and for the purposes of the Committee, to be equal to that over the land.

B. Artificial radio-activity in food and tissues

1. *Strontium-90*

27. The levels of strontium-90 in milk and whole diet in the period 1966-1968 are shown in tables III and IV, respectively. In the northern hemisphere, levels have been declining steadily from the peaks of 1963. Based on annual averages, the over-all decline up to 1968 has been by a factor of between three and four. In the southern hemisphere, maximum contamination levels were reached somewhat later, and the subsequent decline has been less marked. Levels are still generally higher in the northern hemisphere than they are in the southern hemisphere, though the difference had narrowed considerably by 1968. In some areas, particularly the Faroe Islands and Iceland, levels of strontium-90 in milk and diet are significantly higher than the average values typical for most of the northern temperate zone. As already indicated in earlier reports, these elevated levels are mainly due to high rainfall and poor soil conditions, particularly low calcium content.

28. The decline in strontium-90 levels reflects the decrease in the annual rate of deposition, which by 1968 was very small, so that levels of strontium-90 in food-stuffs during that year were largely due to absorption from the accumulated deposit in soil. It is to be expected that the further decline in contamination levels will, from now on, be much slower, as they will follow the processes of decay and leaching of strontium-90 in soil.

29. Strontium-90 levels in human bone (table V) are also declining. As expected, the highest rate of decline has been observed in bone from the younger age groups (figure 7), but measurements on adult vertebrae from the northern hemisphere have also indicated declining levels from the peaks experienced in 1965 and 1966. In the case of Denmark, for example, $^{90}Sr/Ca$ ratios in adult vertebrae in 1968 were about 25 per cent lower than the peak levels observed in 1965. Measurements of the levels in other bones, particularly in the slower metabolizing long-bone shafts, are less plentiful, but there is an indication that the 1968 levels may be slightly lower than those in 1967 (figure 7).

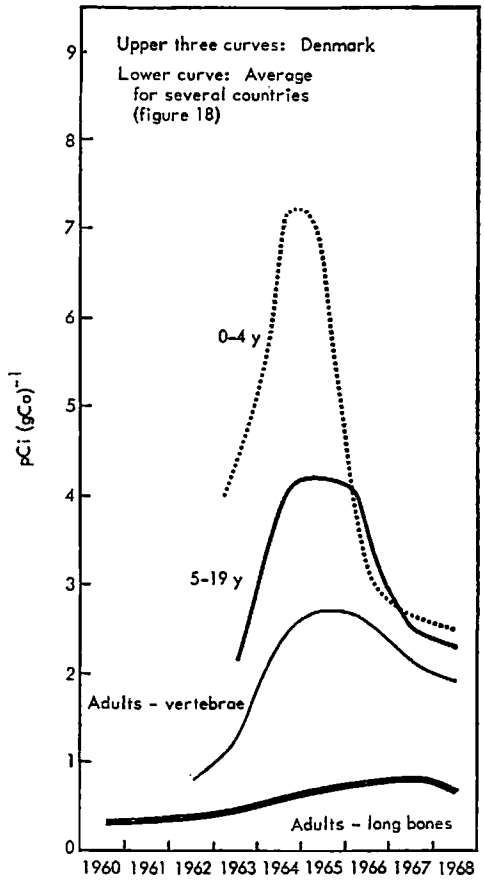


Figure 7. Time variation of $^{90}Sr/Ca$ ratios in human bone for various age groups

2. *Caesium-137*

30. The annual mean levels of caesium-137 in milk declined steadily in the northern hemisphere from 1965 to 1967 (table III). The levels in 1967 were of the order of 10-20 per cent of the 1964 peak values. In the southern hemisphere, the decrease has been smaller. The available 1968 data indicate that the levels in milk in some countries of the northern hemisphere have increased since the middle of the year as a result of deposition from recent nuclear explosions.[57, 58] The observations of the caesium-137 content of whole diets, summarized in table IV, indicate that levels have varied in the same way as they have in milk. In some regions of the world (for example, in some parts of Florida (United States),[59] New Zealand,[23-25] Norway,[61] the Ukrainian Soviet Socialist Republic[60] and and the United Kingdom,[7] and in the Faroe Islands[62] and Jamaica[63]), levels of caesium-137 in milk, and in several areas (for example, Florida[59] and the Ukrainian SSR), levels in meat, are substantially higher than the corresponding latitudinal averages. These higher levels are possibly due, as in the case of strontium-90, to a combination of high rainfall and specific soil conditions.

31. Changes in dietary contamination have been reflected in changes of caesium-137 levels in man (table VI). The mean body burdens in 1967 have usually been about 30 per cent of the 1964 values. The smaller decrease of body burdens compared with that in milk levels, is mainly due to the fact that part of the diet is produced the year before consumption. The exceptionally high body burdens observed in subarctic regions persist, and it seems that the relative rate of decrease is smaller than that in temperature regions as a whole.

3. *Iodine-131*

32. The atmospheric tests carried out in the southern hemisphere during the years 1966-1968 resulted in measurable iodine-131 levels in milk in South America,

Africa and the south Pacific region (table VII). The highest integrated level reported from one explosion series was 27 nCi d l^{-1} in the Buenos Aires area in the second half of 1966.

33. In the northern hemisphere, detectable levels of iodine-131 were observed in Japan after atmospheric explosions in 1966 and 1967[5, 7] and in the United Kingdom in January 1967.[65]

4. *Carbon-14*

34. The concentration of carbon-14 in the human body has been steadily approaching tropospheric levels. Since 1966, the body content has been approximately in equilibrium with the now slowly decreasing tropospheric levels arising from injections before 1963 (figure 8).[66]

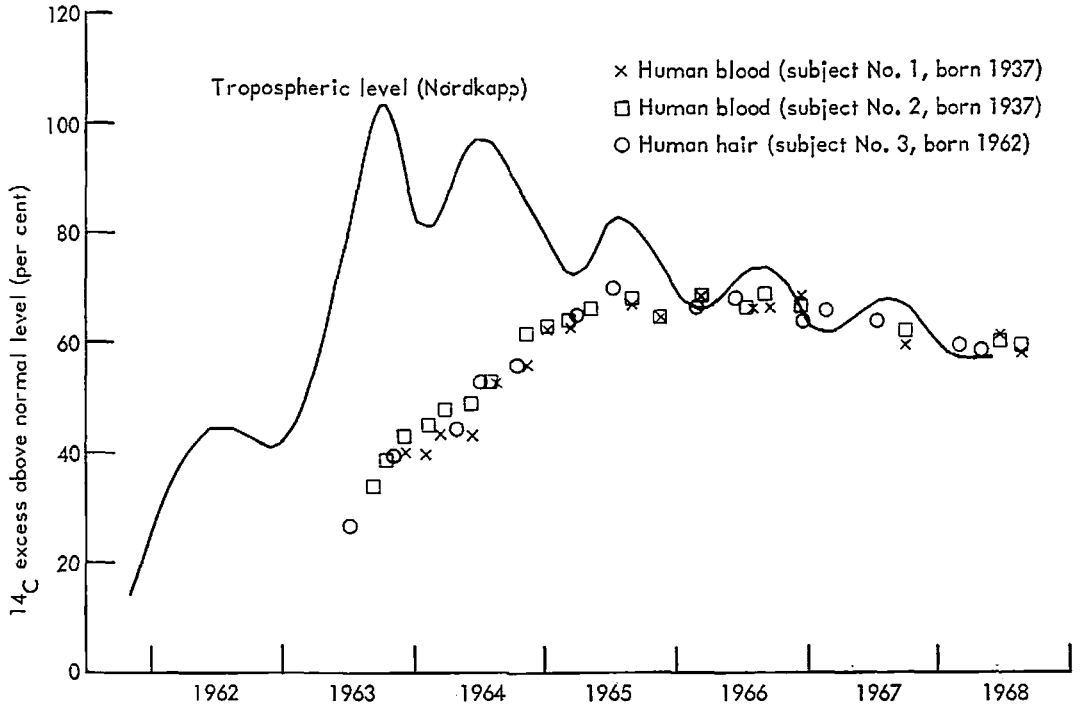


Figure 8. ^{14}C concentration trends in the troposphere and in human blood and hair in Scandinavia[66]

III. Assessment of radiation doses from environmental contamination

A. General

1. *Concept of the dose commitment*

35. When a group of persons is exposed to radiation, it is often desirable to estimate the expected frequency of the injurious effects that may follow. If dose and effect are linearly related and there is no threshold, neither the individual doses nor the time distribution of the dose need be known, and the frequency is obtained from the product of the average radiation dose received and the rate of induction of the biological effect of interest per unit of dose. It is called the absolute risk and represents the probability that the average individual will show the effect after receiving a given dose.

36. However, since the rate of induction of certain effects may vary with dose and dose rate, the actual rates of induction at the levels of radiation to which human populations are exposed cannot necessarily be specified, and thus absolute risks cannot be estimated.

37. For doses of a similar order of magnitude, however, and as long as linearity may be assumed, an approximate comparison of the risks from two sources can be made by considering the ratio of the radiation doses delivered to the same tissue by each source during the same time interval. The dose rate from natural radiation is a convenient reference for this purpose.

38. If, however, a source gives rise to radiation at a varying rate, it is convenient to integrate the mean per capita dose rate over an infinite period of time. As long as the dose thus calculated is finite, some indication of the relative risk can be obtained from the ratio of the dose to that delivered over a finite time interval (for example, one year) by a reference source such as natural background.

39. As a measure of the mean integrated doses, the Committee in its 1962 report[67] adopted the concept of the dose commitment proposed by Lindell.[68]

2. *Definition of the dose commitment*

40. The dose commitment was defined by the Committee in the annexes of the 1964[69] and 1966[70] reports. In the latter, it was defined as follows: "...the dose commitment to a given tissue is...the integral over infinite time of the average dose rates delivered to the world's population as a result of a specific practice, e.g. a given series of nuclear explosions. The actual exposures may occur over many years after the explosions have taken place and may be received by individuals not yet born at the time of the explosions...".

41. When a population is exposed to ionizing radiation, the tissues of individual members receive radiation doses, the magnitudes of which depend on complex

physical and biological factors. If $R_i(t)$ is the dose rate to the tissue under consideration received at time t by an individual i born at time t_i, the dose received up to time t is

$$D_i(t) = \int_{t_i}^{t} R_i(\tau)d\tau, \qquad (1)$$

where $R_i(\tau)$ can assume values other than zero only during the individual's lifetime.

42. If, at time τ, the population consists of $N(\tau)$ individuals, then the average dose rate at that time is, summing over all is,

$$R(\tau) = \frac{1}{N(\tau)}\Sigma R_i(\tau). \qquad (2)$$

and the average dose received up to time t by the population is

$$D_p(t) = \int_{-\infty}^{t} R(\tau)d\tau. \qquad (3)$$

The use of $-\infty$ as the lower integration limit in equation (3) conveniently avoids the need to define the time scale relative to the exposure.

43. The average dose received by the population, accumulated over infinite time, is

$$D_p(\infty) = \int_{-\infty}^{\infty} R(\tau)d\tau. \qquad (4)$$

and is called the dose commitment.

3. *General problems of estimating dose commitments*

44. The age structure of a population is defined by three functions of time:

$N(t)$ = the total number of people in the population at time t;

$\nu(t)$ = the birth-rate at time t;

$f(t,\theta)$ = the probability that a person born at time θ is alive at time t.

For the purposes of the present discussion, these three functions will be regarded formally as being continuous.

45. The size of a cohort born in a small time interval $d\theta$ around time θ is then

$$N(\theta)\nu(\theta)d\theta, \qquad (5)$$

and the size at some later time t will be

$$f(t,\theta)N(\theta)\nu(\theta)d\theta. \qquad (6)$$

46. If the mean dose rate at time τ to the living members of the cohort is $R(\tau,\theta)$, the mean dose accumulated up to time t will be

$$D(t\theta) = \int_{\theta}^{t} R(\tau,\theta)f(\tau,\theta)d\tau. \qquad (7)$$

At time t, each cohort θ contributes a fraction

$$\frac{f(t,\theta)N(\theta)\nu(\theta)\,d\theta}{N(t)} \qquad (8)$$

to the total population, and the mean population dose rate will therefore be

$$R(t) = \int_{-\infty}^{t} \frac{R(t,\theta)f(t,\theta)N(\theta)\nu(\theta)d\theta}{N(t)} \qquad (9)$$

from which the dose commitment as defined in paragraph 43 is obtained.

47. Equation (9) simplifies considerably in the special case of a stationary population in which birth-rate ν and average life span u_m are constant and related by

$$\nu = \frac{1}{u_m} \qquad (10)$$

so that

$$D_p(\infty) = \frac{1}{u_m}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} R(t,\theta)f(t,\theta)d\theta dt = \frac{1}{u_m}E_c(\infty). \qquad (11)$$

where

$$E_c(\infty) = \int_{-\infty}^{\infty} D(\infty,\theta)d\theta \qquad (12)$$

is the mean infinite dose integral over all cohorts. In the case of a single individual, $D_i(\infty) = E_i(\infty)$.

48. The numerical values of $E_c(\infty)/u_m$ and $D_p(\infty)$ in real populations are practically the same for all nuclides of interest in the present connexion, with the exception of strontium-90, where the difference is, at most, 20 per cent. $E_c(\infty)/u_m$ can therefore be used as an approximation for the dose commitment, as this has some advantages. Firstly, its value is easier to estimate than that of the dose commitment itself, and, secondly, the numerical estimates obtained are less sensitive to assumptions concerning the demographic characteristics of the population.

49. The dose commitment to specific tissues may require special treatment. For example, the dose to the gonads is associated with the genetic risk only to the end of the reproductive period. The genetic dose commitment is obtained therefore by replacing the survival function $f(u)$ with a corresponding fertility function $f_g(u)$. If all births are assumed to occur at the mean reproductive age u_g of the parents, then

$$\begin{aligned} f_g(u) &= 1, \quad \text{when } u \leqslant u_g; \\ f_g(u) &= 0, \quad \text{when } u > u_g. \end{aligned} \qquad (13)$$

50. In many cases, there is an appreciable lag between the receipt of a dose and the overt manifestation of biological damage. The effect of this lag ∂ can be roughly taken care of by replacing the mean life span u_m by $u_m - \partial$. In practice, however, the distribution of lag times, particularly at low dose rates, is not well enough known to make it possible to allow for this effect in the calculation, and it is therefore usually neglected.

51. The radiation doses received by fœtuses are not normally included in the dose commitment. Not only is the contribution extremely small, but the type of damage suffered, as well as the relative tissue sensitivities, may not be the same at this stage as they may be later in life. It may be useful therefore to define a separate dose commitment for the fœtal subpopulation. Thus,

$$D_f(\infty) = \int_{-\infty}^{\infty} R_f(\tau)d\tau, \qquad (14)$$

where $R_f(\infty)$ is the mean dose rate delivered to the fœtus during an age interval Δu in which the fœtus is susceptible to a particular type of damage; otherwise, $R_f(\tau) = 0$. The size of the subpopulation is $\nu N \Delta u$. Fœtal rates from external sources and from internal sources that are reasonably uniformly distributed will be about the same as those received by the mother so that, for these sources, $D_f(\infty) \approx D_g(\infty)$. To estimate the dose rates to the foetus from particular radio-nuclides, the distribution of these radio-active sources in the mother and in the foetus must be known.

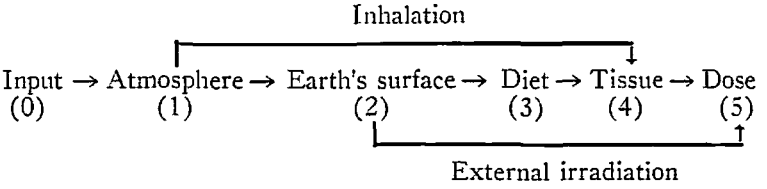
52. Although the dose commitment has mainly been applied to the case of exposure of the world population to radiation from nuclear tests, the concept is, in principle, applicable to other cases. For estimating the value of the dose commitment, however, it may be necessary to take into account various specific properties affecting the distribution of dose among members of the population. The dose commitment is then obtained as the average of the dose commitments to the relevant subpopulations, appropriately weighted by subpopulation size.

B. General transfer functions

1. *Introduction*

53. Doses due to environmental contamination from nuclear tests are delivered to tissues from sources inside and outside the body. In the latter case, the dose commitment can, in principle, be estimated straightforwardly, following the general procedures discussed in the previous section. In the case of doses resulting from radio-nuclides deposited within the body, the calculations are complicated because there is no practical way of measuring tissue doses directly from such sources. The primary measurement therefore is the burden of the nuclide in the body or tissue rather than the dose rate, and the latter must be calculated from physical principles and the distribution of the source within the body.

54. Calculating the dose commitment then becomes mainly a problem of predicting changes in the amounts and distribution in the body of the relevant radio-nuclides. In practice, this may involve not only considerations of the metabolism of the nuclides in various organs and tissues but also in food-stuffs. The chain of events leading from the primary injection of radio-active material into the atmosphere to irradiation of tissues can be represented schematically as follows:



Some of the possible simultaneous pathways are shown in the diagram, indicating the possibility that several steps may be bypassed.

55. Since the dose commitment from a given source is the integral over infinite time of the mean per capita dose rate resulting from that input, steps in the sequence from input to the final dose commitment can be conveniently described in terms of the ratios of the infinite integrals of appropriate quantities in step j of the sequence to the infinite integral of the appropriate quantity in the preceding step i. These ratios define the transfer coefficients P_{ij} that appear as links in the pathway from input of radio-activity into the atmosphere to the subsequent radiation dose to man.

56. The tissue dose from a given source, acting through a given sequence or chain of events, is the product of the input from that source and of all the relevant transfer coefficients. The total dose rate to the tissue is then the sum of the doses contributed by each sequence. For instance,

$$Dose = Input\ [(P_{01}P_{12}P_{23}P_{34}P_{45}) + (P_{01}P_{14}P_{45}) + (P_{01}P_{12}P_{25})] \qquad (15)$$

57. Reference will sometimes be made to the value of the coefficient obtained when numerator and denominator have been integrated to some finite time. In this case, the general symbol t or a specific year will be given in parentheses immediately following the symbol P. In some sequences, intermediate steps may not be involved, and this will be indicated by the numeric suffixes attached to the symbol P. For example, the case of external radiation in which diet and tissue steps are not involved will be referred to as P_{25}. On the other hand, cases will arise in which an intermediate step, although involved, may not in practice be treated separately in the calculations. This will be indicated by the use of a single symbol P with a suffix showing the numbers of all the steps implicitly included. For example, P_{234} indicates the ratio of the infinite-time integral of the levels in tissue to the infinite-time integral of the fall-out deposit.

58. The units in which the values of the P coefficients will be expressed vary with the specific nuclide and with the nature of the quantities being linked.

2. *Specific transfer functions*

(a) *Transfer from primary source to atmosphere (P_{01})*

59. A source of radio-active environmental pollution, such as a nuclear explosion, is characterized by the production rate U of the nuclide considered. Depending on conditions, variable amounts of the radio-active materials are released into the environment. If the rate of release into the atmosphere is W, the transfer coefficient P_{01} is defined by

$$P_{01} = \frac{\int_{-\infty}^{\infty} W dt}{\int_{-\infty}^{\infty} U dt} = \frac{IW}{IU} . \qquad (16)$$

(Subsequently, I will be used as a shorthand notation for integration over time from $-\infty$ to $+\infty$).

60. In the case of nuclear explosions, information on P_{01} is often lacking, and in practice the dose commitment is estimated from IW, i.e., the total amount of radio-active material injected into the atmosphere.

(b) *Transfer from atmosphere to earth's surface (P_{12})*

61. The subsequent atmospheric inventory depends on the rate of removal by deposition onto the earth's surface and on radio-active decay. The transfer coefficient P_{12} is defined by

$$P_{12} = \frac{IF_r}{IW} , \qquad (17)$$

where F_r is the rate of deposition in units of radio-activity per unit time, and IF_r is thus the total integrated deposit.

62. The numerical value of P_{12} depends on the time lag between injection and deposition. If this time lag is small compared to the radio-active half-life of the nuclide considered, P_{12} is close to one. As the mean residence time of debris injected into the stratosphere is, at most, a few years and the residence time in the troposphere is a few weeks, P_{12} for long-lived nuclides, such as strontium-90 and caesium-137, can for practical purposes be taken to be unity. For short-lived nuclides, explosion yield, height of injection, particle-size of the debris, etc. have a considerable influence on the numerical value of P_{12}. For nuclides, such as carbon-14, that appear in gaseous form, no meaningful P_{12} can be defined.

63. The integrated deposit up to time t is defined by

$$F(t) = \int_{-\infty}^{t} F_r(\tau) d\tau \qquad (18)$$

and the cumulative deposit by

$$F_d(t) = \int_{-\infty}^{t} F_r(\tau) e^{-(t-\tau)/T_p} d\tau, \qquad (19)$$

where T_p is the radio-active mean life.

64. Deposition and population density vary widely over the earth's surface, and, for that reason, weighting factors must be applied when relating mean deposition to dose commitment. If $\bar{F}_A$ is the mean deposition in some area A consisting of a number of regions i with deposition F_i and population N_i, a population factor is defined as

$$Z_A = \frac{\Sigma F_i N_i}{\bar{F}_A \Sigma N_i} \qquad (20)$$

which, if the area is the whole globe, can be used to estimate the dose commitment from the mean global deposit. The ratio $G_i = F_i/\bar{F}_A$ is called the geographical factor and can be used to describe local variations in deposit.

(c) *Transfer from deposit to diet (P_{23})*

65. The levels and time distribution of radio-activity in food-stuffs are determined by a number of complex processes occurring in the biosphere. The over-all effect of these processes is summarized by the transfer coefficient P_{23} defined by

$$P_{23} = \frac{IC}{IF_r}, \qquad (21)$$

where C is the mean dietary content of the nuclide considered and IC, consequently, the total integrated dietary content. Often a direct estimate of P_{23} cannot be made, and it is then necessary to consider more closely the processes involved. For this purpose, it is convenient to use a transfer function.

66. If $dC(t,)$ is that part of the radio-active concentration in the diet at time t that is attributable to the amount of radio-activity $F_r(\tau)d\tau$ deposited during the interval $d\tau$ at time τ, the transfer function is defined as

$$K(t,\tau) = \frac{1}{F_r(\tau)} \frac{\partial C(t,\tau)}{\partial \tau}, \qquad (22)$$

where $K(t,\tau)$ is subject only to the assumption that the transfer processes are unaffected by the consequent radiation doses received in the biosphere. The level of activity in the diet at time t, being the sum of the remaining portions of all previous deposits, is therefore

$$C(t) = \int_{-\infty}^{t} K(t,\tau) F_r(\tau) d\tau. \qquad (23)$$

67. Many important processes affecting transfer through the biosphere have a pronounced yearly cycle. The effects of this periodicity can be largely smoothed out by taking yearly averages of $C(t)$ and $F_r(t)$. When $K(t,\tau)$ is derived from such yearly averages, it is generally assumed that the value of $K(t,\tau)$ is determined by the time lapse $t-\tau = u$. The integrated dietary level is then obtained by summing over all times the annual mean amounts in the diet, or

$$IC = \int_{-\infty}^{\infty} C(t) dt = \int_{0}^{\infty} K(u) du \int_{-\infty}^{\infty} F_r(t) dt$$

$$= IF_r \int_{0}^{\infty} K(u) du. \qquad (24)$$

68. If yearly average are used and it is desired to derive an explicit form for the function $K(u)$ from the

levels measured in individual food-stuffs and the annual deposit, the periods selected for averaging should be chosen with care. For example, when a calendar year is selected, it may become necessary to introduce additional terms to allow for the fact that the fodder used in one year may have been produced during a preceding year. Similar problems can also arise in the southern hemisphere because the time of harvest there is spread over two calendar years. Such additional terms are necessary to obtain reliable predictions of future national contamination levels, but, for estimating transfer functions applicable to larger areas from which no measurements are available, results averaged over periods much longer than a year are greatly to be preferred.

69. When deposition occurs in a time period shorter than a year, the consequent level in diet may depend on the time of year when deposition occurs as well as on the elapsed time. In this case,

$$K(t,\tau) \approx K(t_1,t-\tau) \approx K(t_1,u), \qquad (25)$$

where t_1 is the middle of the deposition period. The integrated dietary level is then

$$IC = IF_r \int_0^\infty K(\tau_1,u)du. \qquad (26)$$

70. The transfer coefficient $K(t,\tau)$ has been defined for total diet. In practice, diets are composed of various types of food-stuffs to which different transfer functions may apply. Analogous functions can be derived for each dietary component. If these are denoted by $K_i(u)$, then

$$K(u) = \Sigma\, a_i K_i(u) \qquad (27)$$

and

$$IC = IF_r \Sigma a_i \int_0^\infty K_i(u)du, \qquad (28)$$

where a_i is the fraction that component i contributes to the total diet and the summations are over-all components.

71. The levels of a radio-active nuclide in diet may be expressed in any convenient units, such as activity per unit mass, activity taken in per day or activity per unit mass of some stable element.

72. Very little is known quantitatively about the form of the transfer function $K(u)$, particularly for u longer than a few years, which may be much shorter than the period of interest. In its previous reports, the Committee assumed that

$$K(u) = p_r + p_d\, e^{-\lambda u} \quad 0 < u < 1 \text{ year} \qquad (29)$$

$$= p_d\, e^{-\lambda u} \quad u > 1 \text{ year} \qquad (30)$$

and

$$P_{23} = p_r + p_d\, T_m, \qquad (31)$$

where p_r and p_d are constant factors of proportionality referring to the transfer into food-stuffs from the current deposition and the accumulated deposit in soil, respectively, and where λ is the rate constant of the assumed exponential process by which the nuclide is removed from soil so that T_m is the mean residence time equal to λ^{-1}.

73. The methods available for determining the values of p_r and p_d, as well as the limitations of applying an over-simplified model, were discussed in the Committee's 1962 and subsequent reports. It was shown that, in general, the contributions so far have been largely determined by current deposition. This means that the values of p_d and T_m could not be estimated reliably.

74. Since the Committee's last report, the annual amounts of fall-out have declined sufficiently to make the short-term effects negligible, and estimating a numerical value of P_{23} is now easier. Thus,

$$\int_{-\infty}^{\infty} C(t)dt = \int_{-\infty}^{t'} C(t)dt + \int_{t'}^{\infty} C(t)dt, \qquad (32)$$

and if t' is selected so that $F_r(t') \approx 0$, then, following the Committee's previous assumptions,

$$C(t') = p_d\, F_d(t'), \qquad (33)$$

and the dietary levels at some later time τ are then

$$C(\tau) = p_d\, F_d(t')\, e^{-\lambda(\tau - t')} \qquad (34)$$

so that

$$\int_{t'}^{\infty} C(\tau)d\tau = p_d\, F_d(t')\, \lambda^{-1} \quad = C(t')\, T_m \qquad (35)$$

and

$$IC = \int_{-\infty}^{\infty} C(t)dt = \int_{-\infty}^{t'} C(t)dt + C(t')\, T_m. \qquad (36)$$

The first term on the right is obtained by summing the measured dietary levels up to time t'.[71]

75. The present formulation has the important advantages that (*a*) the estimate of IC thus obtained is less sensitive to errors introduced by the assumptions and becomes increasingly independent of the assumptions as t' increases and (*b*) the integral on the right side of the equation can be considered a lower limit of the estimate of IC, while, if T_m in the second term on the right is taken to be the radio-active mean life, then the sum of the two terms is the maximum value that IC could attain. It is therefore possible to apply limits to the numerical estimate of P_{23} since

$$\int_{-\infty}^{t'} C(t)dt/F(t') < P_{23}$$

$$< \left[\int_{-\infty}^{t'} C(t)dt + C(t')\, T_m \right] /F(t'). \qquad (37)$$

(d) *Transfer from diet to tissue (P_{34})*

76. The transfer coefficient P_{34} is defined by

$$P_{34} = \frac{IQ}{IC}, \tag{38}$$

where Q is the population mean level of radio-activity in a given organ or tissue. The level of radio-activity may be expressed in different ways, such as total amount of radio-activity, activity per unit mass of organ or activity per unit mass of some stable nuclide in the organ.

77. When a given amount of a radio-nuclide enters the body, a varying amount becomes deposited in the different organs and tissues. Subsequently, through both radio-active decay and biological elimination, the levels in the different parts of the body decline. If $dQ(t,\tau)$ is that fraction of the radio-activity in a given organ or tissue at time t following the intake of an amount $C(\tau)d\tau$ during the interval $d\tau$ at time τ, we can define a general transfer function, $m_i(t,\tau)$ as

$$m_i(t,\tau) = \frac{1}{C(\tau)} \frac{\partial Q(t,\tau)}{\partial \tau} . \tag{39}$$

78. The level of activity in the organ or tissue at time t is obtained by summing the contributions from all earlier intakes, that is,

$$Q_i(t) = \int_{-\infty}^{t} C(\tau) m_i(t,\tau) d\tau. \tag{40}$$

Since it can be assumed that, at the low levels of activity in the body resulting from nuclear weapons tests, the various metabolic processes are unaffected by the radiation doses received, equation (40) is generally valid.

79. An average function $m(t,\tau,\theta)$ can similarly be defined for the members of a cohort θ so that

$$Q(t,\theta) = \int_{\theta}^{t} C(\tau) m(t,\tau,\theta) d\tau, \tag{41}$$

where $Q(t,\theta)$ is the mean level of the nuclide at time t in members of the cohort.

80. The mean level weighted by population at time t is, in analogy to the mean population dose rate as defined in equation (9),

$$Q(t) = \int_{-\infty}^{t} \frac{Q(t,\theta) f(t,\theta) N(\theta) \nu(\theta) d\theta}{N(t)} . \tag{42}$$

(e) *Transfer from tissue to dose P_{45}*

81. If an integrated radio-activity level IQ results in a dose commitment $D_p(\infty)$, the transfer coefficient P_{45} is

$$P_{45} = \frac{D_p(\infty)}{IQ} . \tag{43}$$

In this case, the corresponding transfer function is the dose-rate function g.

82. If $Q_i(t)$ is the level of a radio-nuclide in a given organ or tissue of an individual at time t and $R_i(t)$ is the dose rate received by the organ or tissue of interest, the dose-rate function is defined by

$$g_i(t) = \frac{R_i(t)}{Q_i(t)} . \tag{44}$$

The organ or tissue of interest need not necessarily be the same as that containing the nuclide. The dose-rate function is only valid for a given distribution of the nuclide in the body. If different parts of the body have varying metabolic properties resulting in time-dependent changes in the distribution of the nuclide, the dose-rate function will also change with time. An example of this type of behaviour will be discussed later in connexion with strontium-90 in the skeleton.

83. The average dose-rate function for a cohort is similarly defined as

$$g(t,\theta) = \frac{R(t,\theta)}{Q(t,\theta)}, \tag{45}$$

where $Q(t,\theta)$ and $R(t,\theta)$ are, respectively, the level of the nuclide in the organ or tissue of interest and the dose rate at time t averaged over the living members of the cohort θ.

84. In most cases, $g(t,\theta)$ can for practical purposes be regarded as a constant g so that

$$P_{45} = g . \tag{46}$$

When $g(t,\theta)$ varies considerably with age, it is usually more convenient to calculate P_{345} directly.

85. The mean cohort dose rate is, from equation (45), given by

$$R(t,\theta) = Q(t,\theta) g(t,\theta), \tag{47}$$

and thus, according to equation (41),

$$R(t,\theta) = g(t,\theta) \int_{\theta}^{t} C(\tau) m(t,\tau,\theta) d\tau \tag{48}$$

and equation (7)

$$D(t,\theta) = \int_{\theta}^{t} f(t'\theta) g(t',\theta) \left[\int_{\theta}^{t'} C(\tau) m(t',\tau,\theta) d\tau \right] dt' \tag{49}$$

in which it is convenient to change the order of integration to obtain the equivalent expression

$$D(t,\theta) = \int_{\theta}^{t} C(t') \left[\int_{t'}^{t} f(\tau,\theta) g(\tau,\theta) m(\tau,t',\theta) d\tau \right] dt'. \tag{50}$$

86. Adding together the mean doses for all the cohorts in a population gives

$$E_c(t) = \int_{-\infty}^{t} D(t,\theta) d\theta =$$

$$\int_{-\infty}^{t} \int_{\theta}^{t} C(t') \left[\int_{t'}^{t} f(\tau,\theta) g(\tau,\theta) m(\tau,t',\theta) d\tau \right] dt' d\theta. \tag{51}$$

When the fractional survival of the members of a cohort depends only upon age and is therefore inde-

pendent of θ, then $f(\tau,\theta) = f(\tau-\theta) = f(u)$ where u is the age of the cohort at time t. Similarly, when physiological processes and dietary habits are also constant in time and depend only upon the age of the cohort,

$$g(\tau,\theta) = g(\tau - \theta) = g(u) \qquad (52)$$

and

$$m(\tau,t'\theta) = m(\tau - \theta,t' - \theta) = m(u,u'), \qquad (53)$$

where u' is the cohort age at time t'. Equation (51) can then, after integrating to infinity over all cohorts, be written

$$E_c(\infty) = \int_{-\infty}^{\infty} C(t)dt \int_{0}^{\infty}\int_{u'}^{\infty} f(u)g(u)m(u,u')dudu', \qquad (54)$$

in which the double integral is constant in time so that

$$E_c(\infty) = A_1 \int_{-\infty}^{\infty} C(t)dt \qquad (55)$$

with

$$A_1 = \int_{0}^{\infty}\int_{u'}^{\infty} g(u)f(u)m(u,u')dudu'. \qquad (56)$$

87. Thus, in principle, the value of $E_c(\infty)$ can be estimated if the value of the constant A_1 and the accumulated levels of the nuclide in the diet are known and if the physiological and demographic properties of the population considered in deriving equation (54) are generally valid. Combining equations (11) and (55) and bearing in mind the considerations in paragraph 48, it follows that

$$P_{s45} = \frac{D_p(\infty)}{IC} \approx \frac{E_c(\infty)}{u_m IC} = \frac{A_1}{u_m}. \qquad (57)$$

The practical problems of evaluating the constant A_1 and applying equation (57) to real populations vary markedly according to the different radio-nuclides involved and will be left to later sections.

(f) *Dose from external radiation (P_{25})*

88. If a deposit IF_r results in a dose commitment due to external radiation of $D_{pext}(\infty)$, the transfer coefficient P_{25} is

$$P_{25} = \frac{D_{pext}(\infty)}{IF_r}. \qquad (58)$$

89. The corresponding transfer function is defined as

$$h(t,\tau) = \frac{1}{F_r(\tau)} \frac{\partial R(t,\tau)}{\partial \tau} \qquad (59)$$

in analogy with transfer functions discussed earlier. In practice, $h(t,\tau)$ is normally approximated by

$$h(t,\tau) = h_{oi} e^{-\lambda_i(t-\tau)}, \qquad (60)$$

where h_{oi} is a dose-rate conversion factor, accounting for the average effects of weathering, shielding by buildings, etc., on which the properties of $h(t,\tau)$ depend in a complicated manner.

C. Transfer of specific nuclides

1. *Strontium-90*

(a) *Metabolism in man*

90. In previous reports, the time integral of the strontium-90 body burden was estimated from the time integral of the levels of the nuclide in diet using a theoretical model of uptake and elimination of calcium in bone together with a proportionality factor (observed ratio) allowing for the differential transfer of calcium and strontium from diet to bone. By contrast, in the present report, the time integral of the body burden is estimated from the levels of strontium-90 measured in human skeletons. This method depends more critically on knowing how strontium-90 is distributed and retained in the skeleton. The experimental foundation for the values of the parameters to be used in the new method of estimation are reviewed in the following paragraphs. It will be shown later that the estimates of the diet to bone transfer coefficient P_{s4} obtained by the two methods agree well with one another. To make for easier comparison of the relative merits of the two methods, a brief summary of the use and limitations of the concept of the observed ratio and other aspects of the relative transfer of calcium and strontium through food chains are also reviewed in the following sections.

(i) *Distribution of strontium-90 in the body*

91. More than 99 per cent of the calcium, stable strontium and strontium-90 in the body is found in the skeleton.[71] The small amount of experimental information available suggests that stable strontium is distributed uniformly throughout the various bones of the skeleton.[72] Similarly, strontium-90 in the skeletons of children and adolescents appears to be uniformly distributed, although no systematic studies have been carried out on a large scale. In contrast, the distribution of strontium-90 in the adult skeleton is not uniform, the highest $^{90}Sr/Ca$ ratios being found in those bones, such as vertebral bodies and ribs, which are predominantly trabecular, and the lowest in those, such as femoral shafts, that consist predominantly of compact bone.

92. To compare measured $^{90}Sr/Ca$ ratios in adult bones from countries in which different types of bone have been collected, normalization factors are required. The normalization factor for a given bone is the ratio of the $^{90}Sr/Ca$ ratio in that bone to the $^{90}Sr/Ca$ ratio either in another bone, selected as standard, or in the whole skeleton. Several investigators have measured normalization factors, and their results are compared in table VIII and figure 9.

93. The number of samples in some cases is small, intraskeletal relationships have not always been measured on the same individuals and there have been differences in methods of computation used by different workers so that these observations are difficult to interpret.

94. There are wide variations between individuals as shown, for example, by a recent study in Czechoslovakia[73] in which $^{90}Sr/Ca$ ratios in vertebrae and femoral shafts of the same individual were compared. In the fifty-four individuals examined, the correlation between the $^{90}Sr/Ca$ ratios in the two bones was only 0.3, which, though significant at the 95 per cent probability level, does indicate that normalization factors

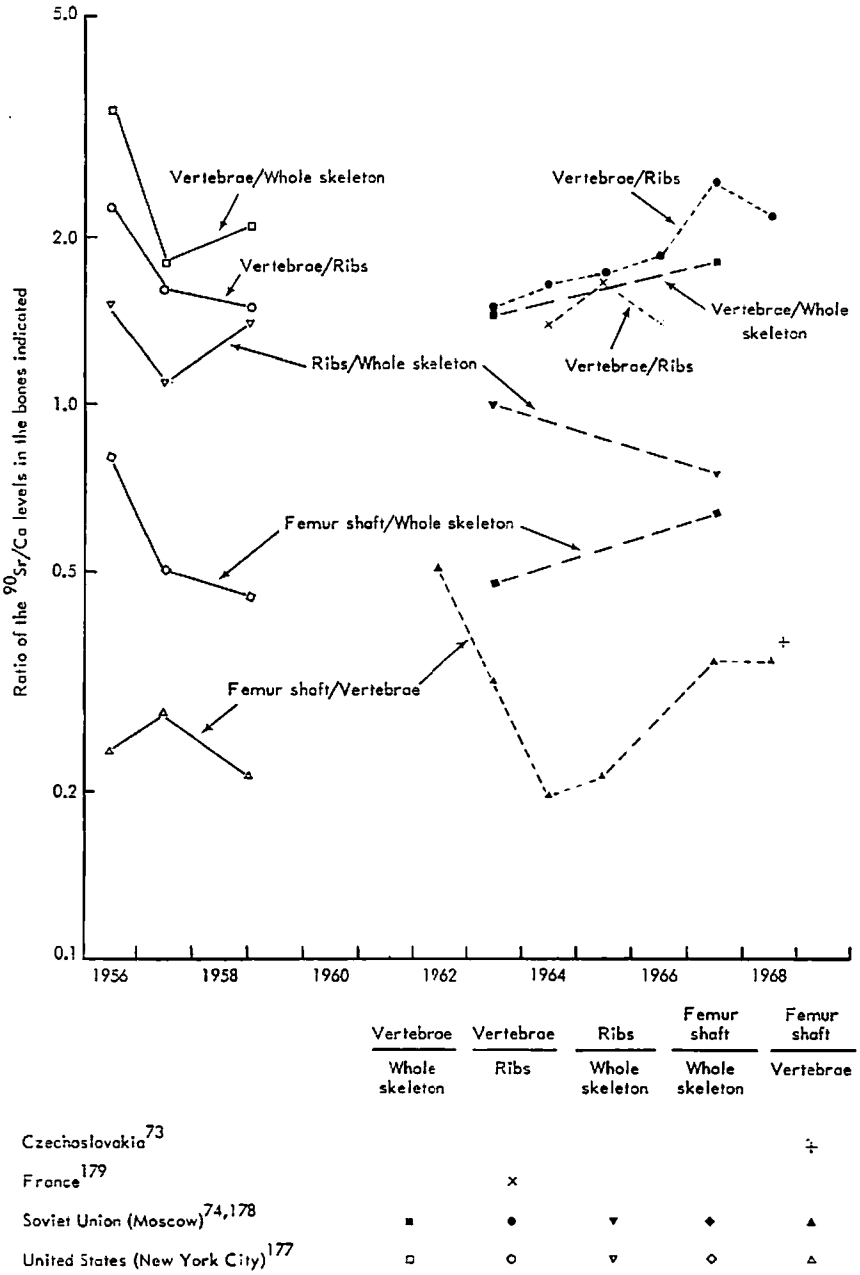


Figure 9. Variability of normalization factors as reported by different workers[a]

[a] Lines connect comparable measurements for ease of reading and are not meant to imply any systematic variation in time.

measured on and applied to a small number of samples may be misleading.

(ii) *Strontium retention functions*

95. *Adults.* Experiments on human subjects in which strontium retention has been measured directly by whole-body counting of strontium-85 or inferred from total excretion, together with measurements made on subjects accidentally contaminated with strontium-90, show that strontium retention can be described by a sum of exponentials such as

$$R(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t} . \quad (61)$$

96. The first two time constants correspond to half-lives of two or three days and ten to twenty days, respectively, the third one to a half-life of at least several hundred days. However, the physical half-life of strontium-85 is sixty-five days, and retention can only be followed experimentally for periods up to about 500 days.

97. Longer-term retentions have been followed by Müller *et al.*[75, 76] and by Wenger and Soucas[77] using a group of luminous dial painters accidentally contaminated with strontium-90. Wenger and Soucas found one subject who, just after intake ceased, was excreting strontium-90 with a half-life of about 300 days, while another subject, studied 940 days after intake ceased, showed a half-life of about 2,500 days. Müller studied a group of fifty-two persons for about 2,500 days (just over six years) and found that the excretion curve could be separated into a fraction with a half-life of about 700 days and one with a half-

life of about 6,000 days. Rundo[78] described measurements made on a man with a twenty-year history of exposure to radio-active materials. When his estimated strontium-90 content was plotted semi-logarithmically against time from 1957 to 1967, a good straight line was obtained, corresponding to an effective half-life of 4.2 years and indicating a biological half-life of 5.1 years (1,870 days).

98. Although this spread in the estimates is due in part to individual variation, there are probably also differences in the computational methods used by different investigators as well as differences in the history of contamination between subjects.

99. Alternatively, the results of retention experiments can be fitted to a function of the form

$$R(t) = Ae^{-\lambda t} + Bt^{-C} \qquad (62)$$

where $R(t)$ is the retention t days after intake, B is the fraction of the intake that is retained at one day and released as a power function of time and C is a constant less than unity. So far as the dose commitment is concerned, the exponential term is of no consequence, since λ corresponds to a half-life of a few days only. The power function alone gives a good fit to the strontium-85 retention for periods from twenty or thirty days after the uptake to about 500 days. Müller reports that it still fits after 2,500 days.

100. Since B varies, depending on whether the nuclide is injected directly or is taken by mouth, the power function retention should be represented by

$$R(t) = f'_a Bt^{-C} \qquad (63)$$

where f'_a is the fraction absorbed from the gastro-intestinal tract into the blood. Experimental values for the parameters f'_a, B and C vary from person to person as reported by the same investigator and also between investigators.

101. Several workers[70, 80] have studied small groups of subjects and obtained estimates of B, f'_a and/or the product f'_aB. The considerable variation found among the results of different workers is probably due not only to the small samples studied but also, in cases of ingestion, to differences between experimental conditions. Typical values of the parameters are $f'_a = 0.2$, $B = 0.5$, $C = 0.2$.

102. Measurements of stable strontium in adults[72] suggest that metabolic equilibrium is established, and this is incompatible with a power-law function. Marshall[81] postulated that there is a transition from a power-law to a mono-exponential function occurring t_y years after a single intake and that the time constant of the exponential λ is related to the constant C in the power function by the relation $\lambda = C/t_y$. He estimated that, for humans, t_y is about 3,000 days which, combined with a value of $C = 0.2$, gives $\lambda = 0.025$ y^{-1}.

103. Bryant and Loutit[82] and Rivera and Harley[83] estimated that the fractional replacement rates of stable strontium in adult vertebral bodies and femur shafts are 0.08 y^{-1} and 0.02 y^{-1}. If the body is in strontium balance, these values must be equal to the rates of excretion of the element from these bones, implying that the final mono-exponential function following a single intake has a biological time constant of 0.02 y^{-1} which is in close agreement with Marshall's estimate. During a period of chronic intake of strontium-90, however, the long-term excretion will have components corresponding to the 0.08 y^{-1} elimination rate constant for vertebral-body-like bone and to the 0.02 y^{-1} rate constant for femur-shaft-like bone. However, in a recent study,[84] a model slightly different from that used for estimating the 0.08 y^{-1} and 0.02 y^{-1} replacement rates has been introduced, which yields replacement rates lying between 0.03 and 0.04 y^{-1} for vertebrae and between 0.02 and 0.03 for ribs.

104. If the strontium-90 levels in bone are integrated over decades as is usual when calculating the dose commitment, the contributions from terms having time constants corresponding to half-lives less than a year or so are small and can be neglected. On the other hand, evaluating the long-term excretion rate constant from an analysis of year-to-year variations in the annual mean levels in bone of strontium-90 due to weapons testing is difficult because of the fast initial excretion.

105. *Juveniles.* What has so far been said applies to adults, and it is not known whether and to what extent these considerations apply to children and adolescents (age < 20). Attempts have been made to estimate strontium-90 excretion rates for children from the relatively small amount of data available on levels in bone and in diet.[83, 85, 86] The results obtained are shown in figure 10. In these studies it is implicitly

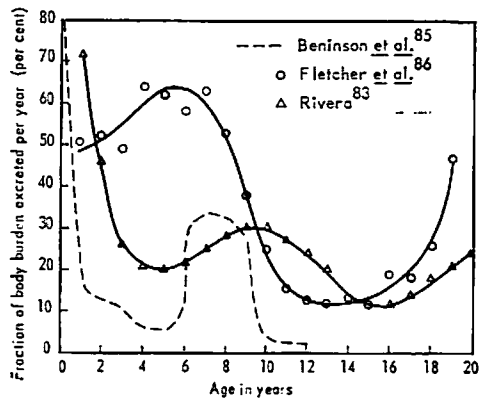


Figure 10. Fraction of body burden excreted per year as a function of age

assumed that annual excretion rates are a function of age only and that, at any given age, strontium-90 is eliminated at the same rate regardless of the time at which the strontium-90 was originally laid down. These assumptions would be strictly correct with a simple exponential excretion function but might be a poor approximation if excretion followed a power law.

(iii) *Observed ratio*

106. The observed ratio between bone and diet is the proportionality factor expressing the relationship at a steady-state between the ^{90}Sr/Ca ratio in bone and the ratio in which the two elements are available from the diet from which the bone is derived. The observed ratio is, within a limited range, independent of the calcium concentration.

107. Interest in the observed ratio rests mainly in the possibility that, through its use, the levels of ^{90}Sr/Ca in bone may be estimated from known levels in diet. The observed ratio can be measured only in systems at a steady-state or where the strontium and

calcium being introduced cannot be confused with that already present. Two methods have been used to estimate the observed ratio for adults:[87] (*a*) measuring the ratio of stable strontium to calcium in the diet and in bone; (*b*) administering simultaneously radio-isotopes of both strontium and calcium. In these methods, it is assumed that the person has consumed a diet with a constant stable strontium to calcium ratio and that the system is at equilibrium.

108. The observed ratio obtained from double-tracer experiments (simultaneous administration of radio-active calcium and strontium isotopes) is not critically dependent upon the interval between intake and measurement, provided sufficient time is allowed for removal of the fractions associated with soft tissues rather than with bone.

109. Values of the observed ratio estimated from stable strontium to calcium ratios in bone and diet for a number of countries are shown in table IX. The range is from 0.15 to 0.33 with an average of 0.22.

110. Values of the observed ratios as a function of age in juveniles have been estimated from strontium-90 to calcium relationships, and the results obtained are shown in figure 11. However these estimates have been derived from the estimates of annual excretion rates referred to in paragraph 105, and therefore the validity of the results thus obtained depends on ex-

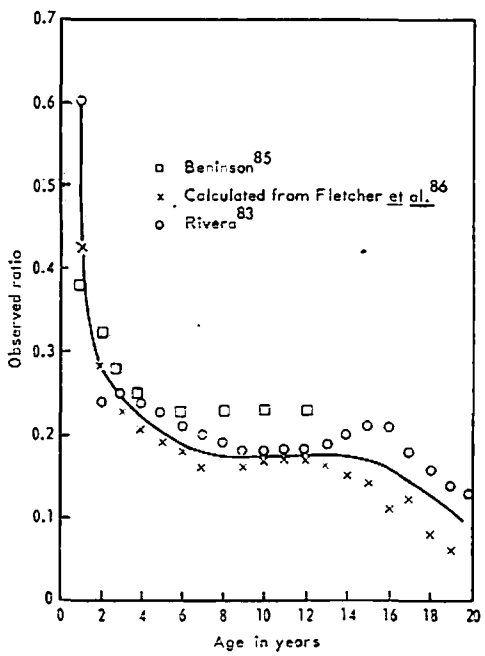


Figure 11. Value of the observed ratio for juveniles

cretion being a mono-exponential rather than a power function of time.

111. *Effect of diet composition on observed ratios.* A number of factors associated with diet composition that may alter the value of the observed ratio have been studied experimentally with laboratory animals.[67] Attempts to demonstrate similar effects in man, however, have generally led to inconclusive results. When measurements are made on levels of strontium-90 from fall-out, the experimental conditions can rarely be defined properly, and the results are difficult to interpret.

112. Knizhnikov and Marei[88] have measured observed ratios for both stable strontium and strontium-90 between bone of still-born and maternal diet in the Soviet Union, finding a value of 0.08 for the former compared with 0.05 for the latter. They suggest that the difference is due to the difference in availability between strontium absorbed from soil and that deposited on the surface of cereal grain. A different interpretation is, however, possible if it is assumed[84] that only a fraction of the strontium and calcium deposited in the fœtus comes from the maternal diet, the rest being derived from the maternal skeleton.

113. Carr *et al.*[89] measured $^{90}Sr/^{85}Sr$ ratios in urine of subjects fed for four weeks on a diet containing whole-grain bread baked from wheat grown on soil contaminated with high levels of strontium-90 and milk from a cow injected with strontium-85 prior to milking. Close agreement between the urinary and dietary isotopic ratios suggests that strontium availability is not affected by the composition of the diet. This experimental result does not conflict with the suggestion of Knizhnikov and Marei, because the strontium-90 in the cereal grain was derived from soil rather than directly deposited.

114. The $^{90}Sr/Ca$ ratios in diets for Moscow and New York City are plotted in figure 12. The average

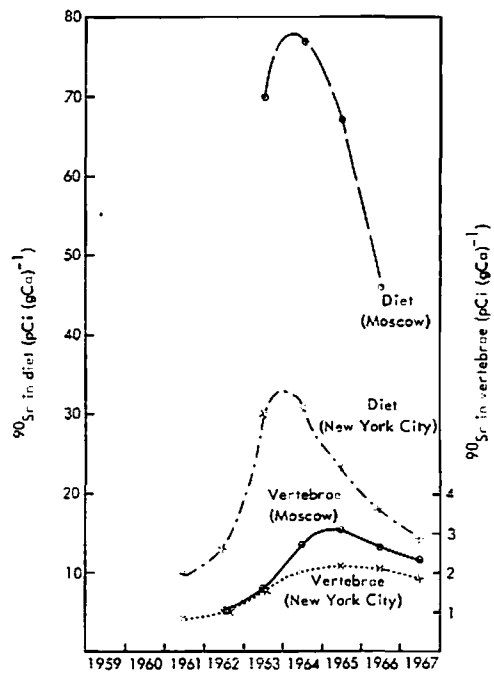


Figure 12. $^{90}Sr/Ca$ ratios in whole diet and adult human vertebrae in Moscow[74, 180] and New York City[181]

diet levels for the two cities during the years 1963-1966 are in the ratio 2.5, but the average levels in adult vertebrae during the same period (also shown in figure 12) are in the ratio of only 1.3, implying that in Moscow the observed ratio for strontium-90 is nearly half that in New York City. On the other hand, the observed ratios for stable strontium are very nearly equal for the two cities (table IX).

115. Knizhnikov and Marei[88] have also suggested that fluorine in drinking water may reduce the value of the observed ratio. Their measurements show stable strontium observed ratios declining from 0.18, when

the fluorine content is low, to half this value when the fluorine concentration is about 1.5 parts per million. Conflicting results have been obtained by other workers,[90] however, and a proper assessment is not yet possible.

(b) *Food-chain mechanisms*

116. Because of the diversity of food-stuffs entering human diets and the many ways in which they are produced, prepared and combined in different areas of the world, a comprehensive quantitative description of the transfer of strontium-90 through food chains would be complex. Further limitations are imposed in practice by the lack of detailed information concerning the calcium intake of a large fraction of the world population, the levels of strontium-90 in the different food-stuffs and the effect of local climatic and agricultural practices on transfer processes.

117. To overcome these problems, the Committee in its 1962 report classified food-stuffs into four broad types—milk, cereals, starchy roots and vegetables—for each of which a representative value of the transfer coefficient was derived from data then available. Likewise, total diets were classified into three main types depending on the proportions contributed to them by the different food-stuff classes. Weighted mean transfer coefficients were thus obtained for each diet-type. When further weighted by the size of the population consuming them and the level of the strontium-90 deposit for the latitude where the food-stuffs were produced, these coefficients could be combined to give a weighted global mean transfer coefficient.

118. In the 1962 and subsequent reports, the global transfer coefficient thus obtained was used to estimate the $^{90}Sr/Ca$ ratio in new bone from the world-wide mean deposit and the observed ratio between bone and diet. The limitations of this approach were discussed in the 1962 report (annex F, paragraphs 12 and 18), and the inherent uncertainties were pointed out.

119. In its 1962 report, the Committee also emphasized that the transfer coefficients would be reliable only when applied over large areas. This conversely implied that transfer coefficients could only be reliably estimated from results averaged over wide areas. For this purpose, means weighted by production or population must be used, as simple arithmetic means of survey results obtained over wide areas where there exist different climatic and agricultural methods may be misleading.

120. In the case of food-stuffs obtained from plants, difficulties arise because of the variability in the reported results of measurements of the calcium as well as of the strontium-90 content, and recent experience has shown that contamination levels expressed in activity per unit mass of calcium are often more variable than when expressed as activity per unit mass of the commodity. A number of factors undoubtedly contribute to the variability, including, particularly, errors of sampling, for the calcium contents of plants vary according to variety, local soil conditions, cultivation methods and local climate.

121. In the tropics and subtropics, soils deficient in calcium are common.[91] Though of low fertility, these soils are used for food production. From such soils, $^{90}Sr/Ca$ ratios in vegetable produce may be significantly higher than would be predicted by empirical relationships established in temperate zones. Nevertheless, this effect is probably offset by the appreciably lower accumulated deposit of strontium-90 in the tropical zone, and, for the purposes of this report, it will be assumed that the integrated diet levels will not exceed those estimated for the populations living in the northern temperate zones where the average strontium-90 deposits are maximal.

(c) *Transfer functions*

(i) *Transfer coefficient—deposit to diet*

122. When the $^{90}Sr/Ca$ ratios in individual food-stuffs are known, values of P_{23} can be estimated by the method described in paragraph 74.

123. *Milk.* The $^{90}Sr/Ca$ ratios in milk from areas or countries in the northern temperate latitudes are shown in table X. There is some scatter among the individual results, reflecting the changing patterns of deposition rates and weather from year to year and from place to place. Nevertheless, over a reasonably long averaging time, the effects of these variations are largely smoothed out.

124. The value of P_{23} (milk) has been calculated from the average annual levels shown in the last column of table X and from the average integrated deposit for the latitudinal band, 65 mCi km^{-2} (figure 13). The average milk level integrated to 1967 is 137 pCi y (gCa)$^{-1}$. Taking the observed level in 1967—9 pCi (gCa)$^{-1}$—and assuming a mean life of strontium-90 in soil of twenty-one years, the integrated level in milk subsequent to 1967 will be 189 pCi y (gCa)$^{-1}$.

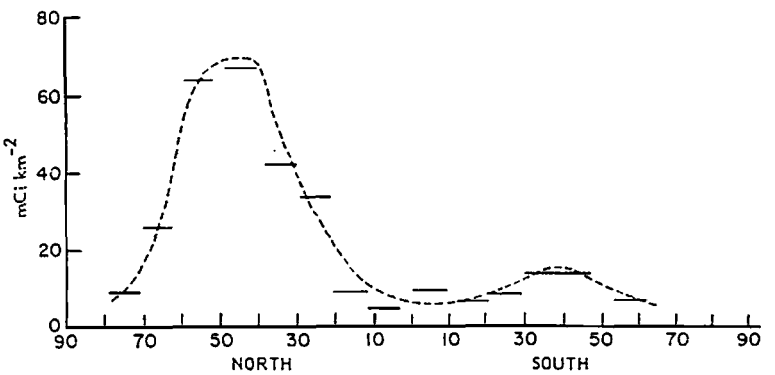


Figure 13. Average latitudinal distribution of deposited ^{90}Sr from analyses of soils collected 1965-1967[50]

Consequently, the integrated level in milk over all time due to tests carried out prior to 1963 will be 137 + 189 = 326 pCi y $(gCa)^{-1}$, corresponding to P_{23} (milk) = 5 pCi y $(gCa)^{-1}$ per mCi km^{-2}.

125. The above calculation is based on data from relatively large but well-defined milk sheds or, in the case of the larger countries, on mean levels weighted either by production or by population. Other cases, where mean levels have not been weighted, have been omitted since the results are not necessarily indicative of the milk consumed by the general population. Also omitted from the calculations are the $^{90}Sr/Ca$ levels in Japanese milk which, because of the use of special cattle feed, are not typical of the latitudinal band as a whole.

126. The countries represented in the calculation contribute about 58 per cent of the total European production and 46 per cent of the total production in the northern hemisphere. If the $^{90}Sr/Ca$ ratios observed in the milk of Moscow and the Ukrainian Soviet Socialist Republic could be taken as representative of milk produced in the Soviet Union, the estimate of P_{23} (milk) would represent about 70 per cent of the total milk production of the northern hemisphere, most of which is produced in the latitudinal band 40-60°N.

127. Similar calculations for the southern hemisphere are not as useful at present because the annual deposition there in 1967 was still significant compared with the accumulated soil deposit. Only about 10 per cent of the world milk production comes from the southern hemisphere, and of this about half is produced in the band of maximum deposition (30-50°S) which includes, principally, Argentina, New Zealand and the more densely populated region of Australia. Cumulative levels (unweighted means) in milk relative to the cumulative deposit in these countries are comparable with the corresponding levels in the middle latitudes of the northern hemisphere, suggesting that the values of P_{23} (milk) in the south are also comparable with those obtained for the north.

128. *Other food-stuffs.* Other food-stuffs, mainly of vegetable origin, include cereals, vegetables and starchy roots. Since starchy roots are of minor importance, they will not be considered further. Rice is the staple food of about half of the world population, and nearly 1,000 million people rely on it for almost all of their caloric requirements. The only systematic study on rice contamination, however, is that reported from Japan[95] where production amounts to about 7 per cent of the world total. Rice is particularly difficult to sample reliably because, being predominantly a subsistence food crop, more than half of the world harvest and as much as three-quarters of the harvest in individual countries never enter markets but are consumed on the farms where the crops are grown.

129. The results obtained in Japan may not be typical of the Far East in general. Most of the rice consumed in the world is of the long-grained *indica* variety, whereas in Japan it is the round or short-grained *japonica* variety that is grown, and Japanese methods of cultivation are unique. The levels of contamination vary widely. In 1961, when deposition rates were low, individual measurements in Japan varied by a factor of two when expressed on a per unit mass basis and by a factor of 4.5 when expressed relative to calcium content. In 1963 and 1964, the range varied by a factor of seven for levels expressed on a per unit mass basis, but no data on calcium contents were given. Rice is milled and polished, and these processes remove some of the minerals and, particularly, much of the strontium-90 content. The Japanese results indicate that 90 per cent may be removed this way.

130. Japan is the only country where the levels of strontium-90 contamination in wheat and rice can be compared. The results show that, on a per unit mass basis, polished rice contains between one-thirtieth and one-fortieth of the amount of strontium-90 of whole-grain wheat, while, on a per gramme of calcium basis, the relative contents vary between one-fifth and one-tenth.

131. The reported strontium-90 contents of whole-grain wheat from countries in the northern temperate zone are shown in figure 14. The levels observed in

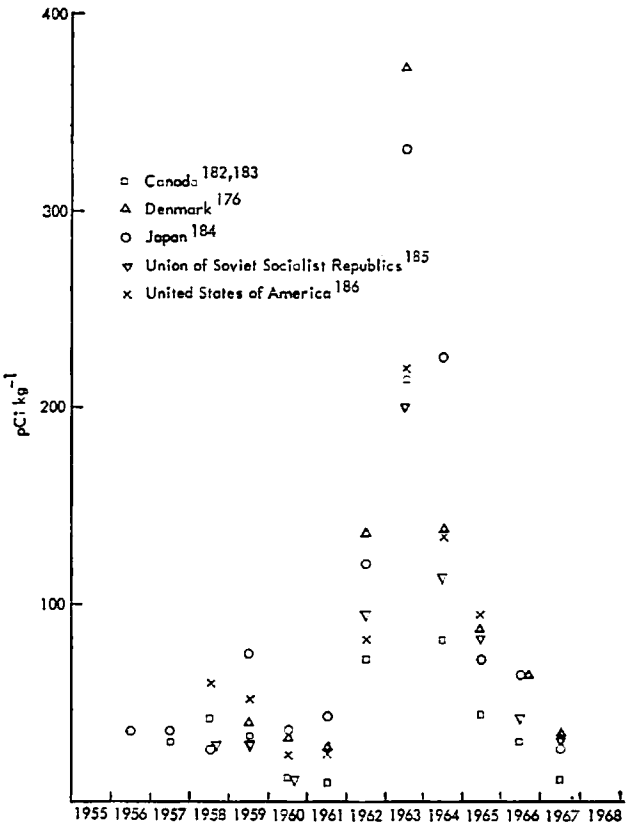


Figure 14. ^{90}Sr content of whole wheat grain in the north temperate zone

North America are generally lower by a factor of two than those of Europe. Few sets of data on levels in wheat and the corresponding deposition cover a sufficient period to allow a meaningful integration. Since using the high levels from Denmark would lead to a conservative estimate of P_{23} (wheat), and since that country has furnished fairly complete results, the estimate of P_{23} (wheat) has been based on these data. If a value of 40 pCi kg^{-1} is taken for each of the years 1955-1958, the cumulative levels up to 1967 are 1,050 pCi y kg^{-1}. The level in 1967 was 34 pCi kg^{-1} which, with a mean life of twenty-one years for strontium-90 in soil, implies future levels integrated to infinite time of about 700 pCi y kg^{-1}. Thus, the total expected contamination in wheat is 1,750 pCi y kg^{-1}, and this, combined with an average deposition of 65 mCi km^{-2} for the latitudinal band, gives a value of P_{23} (wheat)

$= 27$ pCi y kg^{-1} per mCi km^{-2}. An average value of 0.33 gCa kg^{-1} in wheat then gives P_{23} (wheat) $= 81$ pCi y (gCa)$^{-1}$ per mCi km^{-2}.

132. A comprehensive study of contamination in other cereals—rye, oats and barley—is also available from Denmark. The results imply that the value of P_{23} is the same for the four grains when contamination is on a per unit mass basis, whereas for oats it is about half that for wheat, rye and barley when expressed in terms of ^{90}Sr/Ca ratios.

133. While milling removes about 80 per cent of the strontium-90 contamination acquired by direct deposition and about 50 per cent of the calcium, only about two-thirds of the stable strontium are removed by milling,[96-99] implying that the resulting decontamination will be less when most of the strontium-90 comes from soil. Since milling removes two-thirds of the stable strontium, the integrated future level in white flour, assuming 70 per cent extraction, is

$$700\ \frac{1/3}{0.7} = 333 \text{ pCi y kg}^{-1}.$$

Similarly, since milling removes about four-fifths of the strontium-90, the corresponding integrated level up to 1967 is

$$1{,}050\ \frac{1/5}{0.7} = 300 \text{ pCi y kg}^{-1}.$$

Thus, combining the two contributions and dividing by the mean integrated deposition for the north temperate zone (65 mCi km^{-2}) gives a value of P_{23} (white flour) of approximately 10 pCi y kg^{-1} per mCi km^{-2}, corresponding to 50 pCi y (gCa)$^{-1}$ per mCi km^{-2} if the calcium content of white flour is taken to be 0.2 g kg^{-1}. Similar values of P_{23} are implied by results of strontium-90 measurements in Argentina and Australia; the quantitative assessment is, however, difficult because of the relatively high rates of deposition in the southern hemisphere during the year of observations (1967).

134. The levels of strontium-90 contamination of green vegetables have been measured in a few countries in Europe, Australia, Japan and the Soviet Union (figure 15). However, some surveys were discontinued before deposition rates became negligible. Most were started in the early sixties, thus missing some contributions from the earlier years, and all were confined to relatively few types of vegetables. The results from Japan and the Soviet Union are only available on a per unit mass basis. Representative sampling is very difficult because of the large number of varieties grown, the different sizes of crops grown and harvested at various times of the year in different countries and the variable calcium contents of different types of vegetables.

135. Also shown in figure 15 are the levels of strontium-90 in white flour observed in Denmark and the Netherlands. These suggest that, when deposition is high, green vegetables will contain much less strontium-90 per unit mass than white flour, although the reverse appears to be the case when contamination is mainly derived from the soil. It is to be expected therefore that, in the future, levels of contamination per unit mass will be higher in vegetables than in flour. However, differences by a factor of three or four are to be found between individual types of vegetable, and the exact relationship will consequently vary with the composition of the mixture of vegetables. If it is

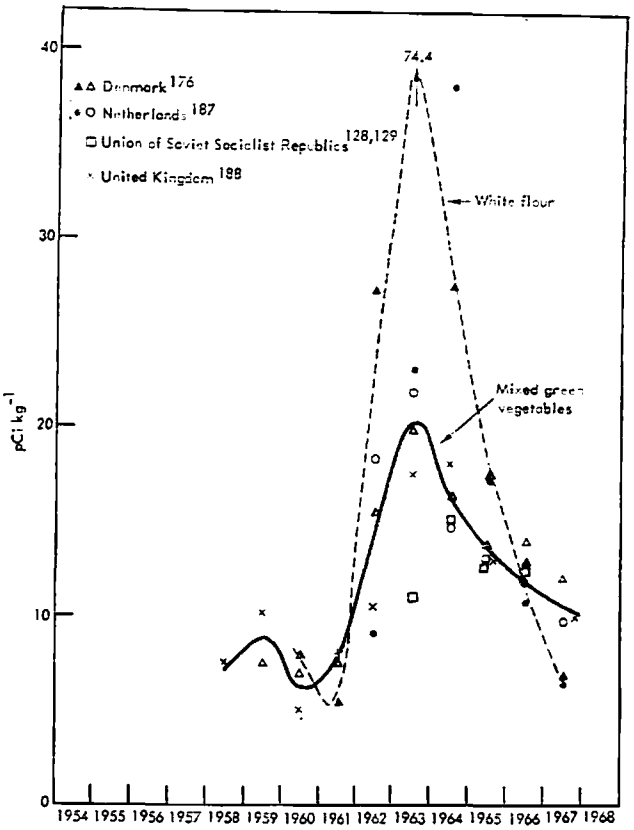


Figure 15. ^{90}Sr content of green vegetables and white flour in the north temperate zone

assumed that contamination levels increased linearly from zero at the beginning of 1954 to the earliest recorded measurements, the data given in figure 15, when treated by the method given in paragraph 74, can be shown to correspond to a value of P_{23} (vegetables) equal to about 5 pCi y kg^{-1} per mCi km^{-2}. The calcium contents of green vegetables are variable, but for present purposes a value of 0.33 gCa kg^{-1} is reasonable so that P_{23} (vegetables) is equal to about 15 pCi y (gCa)$^{-1}$ per mCi km^{-2}.

136. The values mentioned in paragraph 135, however, cannot be used in other areas where types of plants consumed, soils, climate, number of crops and harvest times are different.

137. *Whole diet.* The assumptions underlying the calculations above imply that the relative amounts of strontium-90 in the different types of food observed in 1967 will henceforth remain constant. The ratio of ^{90}Sr/Ca in diet to that in milk in several countries in 1967 varied between one and 1.5 (table XI). With the above-mentioned assumptions, P_{23} (diet) could be estimated to lie between P_{23} (milk) and a value one and a half times higher, namely, between 5 and 7.5 pCi y (gCa)$^{-1}$ per mCi km^{-2}.

138. The transfer coefficient P_{23} for total diet can also be estimated from the P_{23} factors for individual food-stuffs and the corresponding contributions from each food-stuff to the total calcium intake. In a typical high-milk-type diet, these contributions are roughly 80 per cent for milk, 5 per cent for white flour and 15 per cent for vegetables. The value of P_{23} (diet) can therefore be estimated, from equation (28) and the estimates of P_{23} for the three types of food-stuffs, to be

9 pCi y $(gCa)^{-1}$ per mCi km^{-2}, in acceptable agreement with the estimates presented in paragraph 137.

139. Estimates of P_{23} (whole diet) for the high-milk-type diet are insensitive to errors in the estimates of P_{23} for cereals and vegetables. Obviously, for diets in which milk is a less prominent component, the estimates would be more sensitive. Similarly, errors introduced by using the simplifying assumption that strontium-90 is depleted from the soil reservoir by an exponential process having a mean rate constant of 4.5 per cent removal per annum cannot exceed a factor of about two. Thus, in the case of milk, for example, the strontium-90 levels already observed would lead to a value of P_{23} equal to 2.1 pCi y $(gCa)^{-1}$ per mCi km^{-2} (paragraph 124) even if no further uptake of the nuclide from the soil occurred. On the other hand, if radio-active decay (about 2.5 per cent per annum) were the sole removal process, the value of P_{23} could not exceed 8 pCi y $(gCa)^{-1}$ per mCi km^{-2}. The margin of error is even smaller with other food-stuffs because the fraction of the time-integrated levels obtained by extrapolation is smaller.

140. For the purpose of this report, the value of the transfer coefficient P_{23} (whole diet) for the high-milk-type diet is taken to be 9 pCi y $(gCa)^{-1}$ per mCi km^{-2}.

(ii) *Transfer coefficient—diet to tissue*

141. To estimate the transfer coefficient P_{34}, Lindell[68] introduced five basic assumptions:

(*a*) strontium is incorporated into bone at a rate directly proportional to the rate of calcium incorporation;

(*b*) the $^{90}Sr/Ca$ ratio in new bone is proportional to the $^{90}Sr/Ca$ ratio in the diet from which it is derived. The proportionality factor is independent of age and, for the purposes of calculation, is taken to be equal to the observed ratio (OR) in adults under steady-state conditions;

(*c*) strontium-90 is eliminated exponentially with a time constant independent of age;

(*d*) all members of the population have the same mean life span u_m so that

$$f(u) = 1 \qquad 0 < u < u_m$$
$$f(u) = 0 \qquad u \geqslant u_m;$$

(*e*) the dose-rate function γ is constant.

142. If strontium-90 levels in diet and bone are expressed in $^{90}Sr/Ca$ ratios, it follows from the first three assumptions that

$$m(u,u') = OR\,\frac{a(u')}{B(u)}\,e^{-k_1(u-u')}, \qquad (64)$$

where u' is the age at time of uptake; u the age at some later time; $B(u)$ the mass of calcium in the skeleton at age u; $k_1 = k_{sr} + \lambda$ the rate of strontium-90 loss; and a the rate of calcium incorporation given by

$$a(u') = k_0 B_a \qquad u' > 20$$
$$a(u') = \phi(u')(1 + k_0 u') \qquad 0 < u' \leqslant 20$$

in which k_0 is a constant, $\phi(u')$ is a growth function and B_a is the mass of calcium in the adult skeleton. The constant A_1, defined by equation (56) as

$$A_1 = \int_0^\infty \int_{u'}^\infty f(u)g(u)m(u,u')\,du\,du',$$

can then, after introducing assumptions (*d*) and (*e*), be written

$$A_1 = \int_0^{u_m} \int_{u'}^{u_m} m(u,u')\,du\,du' = \gamma \int_0^{u_m} F_m(u')\,du', \qquad (65)$$

where

$$F_m(u') = \int_{u'}^{u_m} m(u,u')\,du, \qquad (66)$$

and is called the dose-increment factor.

143. Lindell defined an average dose-increment factor as

$$\bar{F}_m = \frac{1}{u_m}\int_0^{u_m} F_m(u')\,du' \qquad (67)$$

so that

$$\bar{F}_m = \frac{A_1}{\gamma u_m OR} \qquad (68)$$

Since, according to equation (57), $P_{34}P_{45} = A_1/u_m$ and since $\gamma = P_{45}$, then $P_{34} = \bar{F}_m\,OR$. In its previous reports, the Committee adopted values of 0.6 and 0.25 for $\bar{F}_m$ and OR, respectively, corresponding to $P_{34} = 0.15$. Lindell[68] showed that $\bar{F}_m$ is not critically sensitive to the value of the mean life span nor to the numerical values assigned to k_0 and k_{sr} as long as they are about the same order of magnitude.

144. Alternatively, if measurements of $^{90}Sr/Ca$ ratios in human bone are available for all age groups in the population, P_{34} can be estimated directly, and Lindell's first two assumptions can be avoided. The strontium-90 level integrated up to some time t is

$$G_t = \frac{1}{u_m}\int_{-\infty}^{t} \int_0^{u_m} S(t',u)\,du\,dt'. \qquad (69)$$

The strontium-90 in the bone at time t will further contribute to the exposure so that, if it is assumed that the nuclide is eliminated exponentially, the integrated future levels due to the amounts ingested up to time t will be

$$H_t = \frac{1}{u_m}\int_0^{u_m} \int_{u''}^{u_m} S(t,u'')\,\frac{B(u'')}{B(u)}\,e^{-k_1(u-u'')}\,du\,du'', \qquad (70)$$

where u'' is the age at time t and u is the age at some later time.

145. It follows then that the integrated strontium-90 level in bone due to the amounts ingested through diet up to time t is $G_t + H_t$. Hence,

$$P_{34} = \frac{G_t + H_t}{C_t}, \qquad (71)$$

where

$$C_t = \int_{-\infty}^{t} C(t')dt'. \qquad (72)$$

Equation (70) can be written

$$H_t = \frac{1}{u_m} \int_{0}^{u_m} S(t,u'')W(u'')du'', \qquad (73)$$

where

$$W(u'') = \int_{u''}^{u_m} \frac{B(u'')}{B(u)}\, e^{-k_1(u-u'')}\, du \qquad (74)$$

and is called the integral weighting factor. It has been evaluated for several values of k_1 in adults combined with various excretion functions in children. The results are shown in figure 16.

146. The integral weighting factors are strontium-90 bone burdens integrated over the balance of life for an initial strontium-90 burden of 1 pCi $(gCa)^{-1}$ at age u''. The value of H_t can therefore be obtained for any year by multiplying the appropriate integral weighting factors by the corresponding $^{90}Sr/Ca$ ratios observed in bone in each age group, summing the products over the whole population and dividing the sum by u_m as in equation (73).

147. In practice, the number of samples of bone available in each yearly age group is too small, and therefore average integral weighting factors are calculated for groups of ages. Thus, all samples from persons twenty years of age and over are combined to obtain a single average value for adults, and samples from children and adolescents in the age range five to nineteen years are similarly combined. For ages between zero and four years, it is preferable to have results of bone analyses for each individual year of age, and these are available from a number of countries.

148. Values of H_t have been estimated for adult vertebrae assuming $k_{sr} = 0.1\ y^{-1}$ for this type of bone. The reasons for choosing vertebrae rather than whole skeleton are discussed in paragraph 159. The same value of k_{sr} was assumed for children. Although there is no experimental evidence to support this assumption, the value of H_t obtained does not depend critically on it, both because the effect of calcium accretion during growth is large and because the integrated levels up to twenty years of age contribute less than 25 per cent to the integrated levels of the whole population.

149. The values of P_{34} for each of the years in which data are available have been calculated for Australian vertebrae and are tabulated, together with the values of G_t, H_t and C_t, in table XII. From this it can be seen that, except for the first year or two, P_{34} is, as expected, reasonably constant, the mean value from 1961 to 1967 being 0.21. Apart from possible

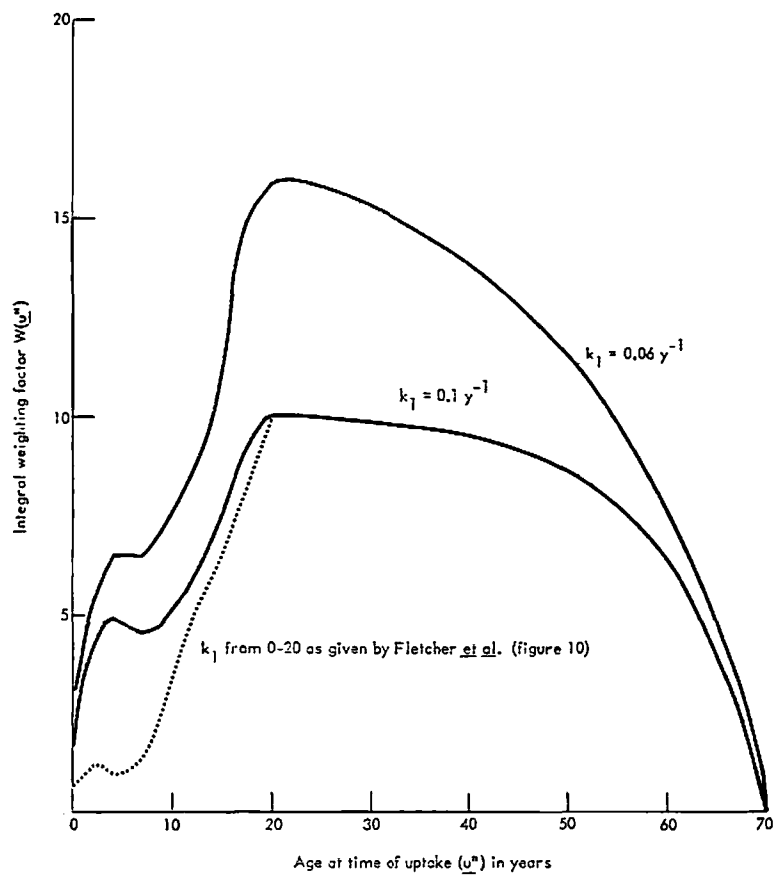


Figure 16. Variation of integral weighting factor $W(u'')$ in bone with age of uptake u'' and ^{90}Sr excretion rate constant

errors (mostly due to sampling) in the original data, the greatest source of uncertainty is the value of the excretion rate for strontium-90. In the absence of further large-scale tests, it will soon become evident whether the value of 0.1 y^{-1} is reasonable or not, for, if the true value is greater or less than this, then the values of P_{34} obtained in future years will either decrease or increase systematically.

150. A value of P_{34} was also calculated for those countries in the north temperate latitudes in which milk contributes a large fraction of the total dietary intake of calcium. For this purpose, the reported $^{90}Sr/Ca$ ratios for each age group were averaged over all the countries from which sufficient data were available (figure 17), and the integrated diet levels were obtained from the average levels in milk of the countries in the same geographical area (table X) multiplied by the average diet-to-milk ratio for this diet type (table XI). The results are shown in table XIII.

151. The mean value of P_{34} equal to 0.2 thus obtained agrees with that previously calculated from the Australian data. The $^{90}Sr/Ca$ ratios measured in vertebrae from Poland and the Soviet Union, also shown in figure 17, lie within the limits of variability of those from countries in which milk is a relatively more important dietary constituent. Despite differences in the levels of dietary contamination in these two countries, the corresponding levels of strontium-90 in bone weighted by population and integrated to 1967 are also about the same, though the corresponding value

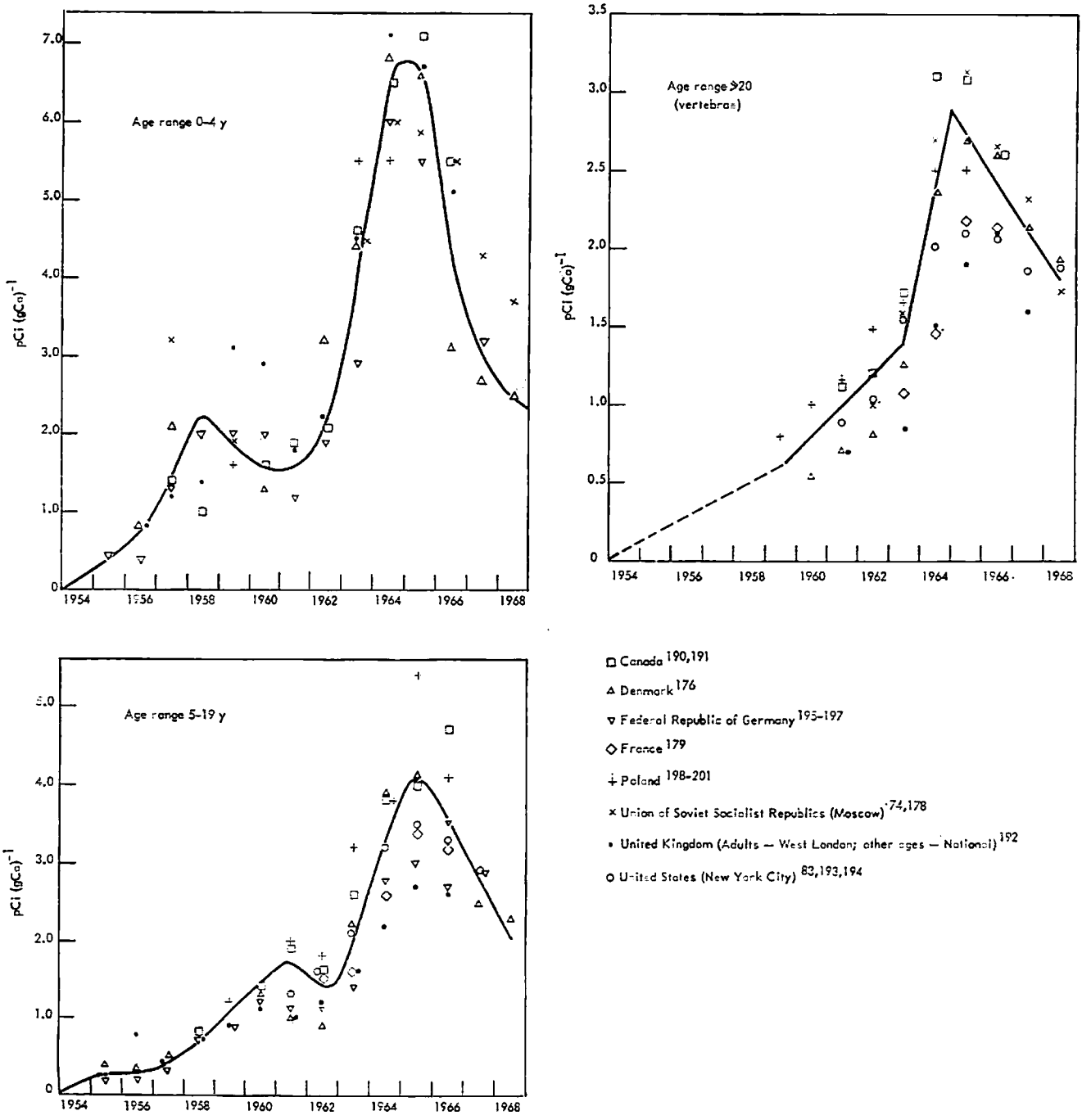


Figure 17. $^{90}Sr/Ca$ ratios in human bone samples in the north temperate zone

of P_{s4} would be about a factor of three lower. The relative strontium-90 levels in adult skeletons for countries in which bones other than vertebrae have been sampled can be estimated from the data in figures 18 and 19. Thus, levels in tibia from Finland are very

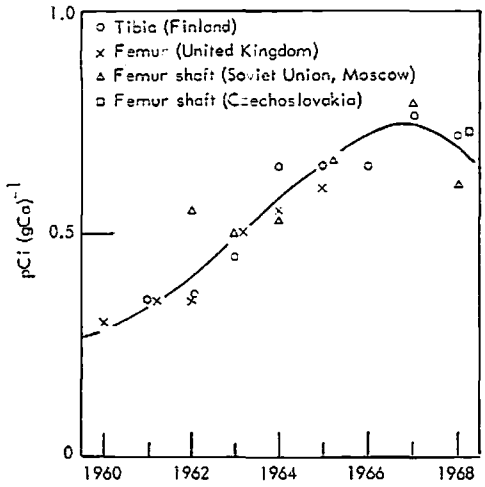


Figure 18. $^{90}Sr/Ca$ ratios in long bones

similar to those measured in femur from the United Kingdom and the Soviet Union (figure 18). On the other hand, when levels of strontium-90 in ribs from

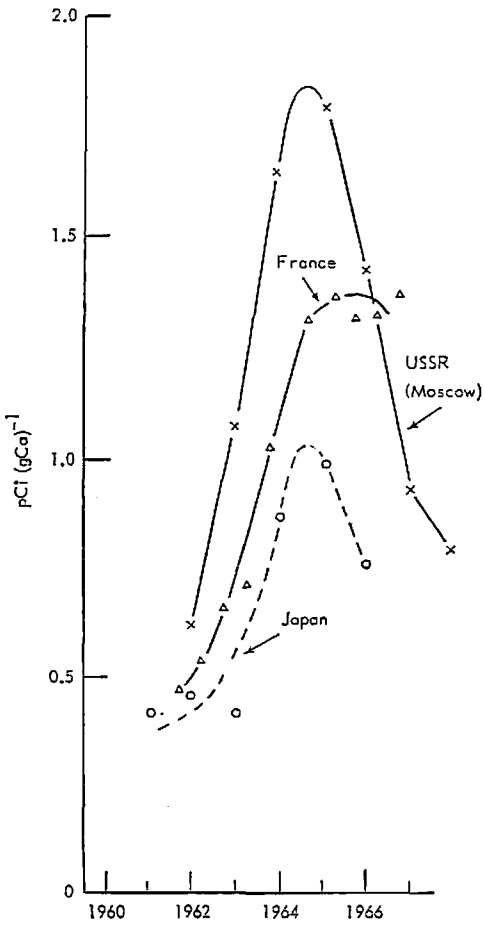


Figure 19. $^{90}Sr/Ca$ ratios in adult ribs

Japan are compared with those from France and the Soviet Union (figure 19), it can be inferred that strontium-90 levels in skeletons from Japan tend to be somewhat lower than the average for the latitudinal band as a whole.

(iii) *Dose-rate factor*

152. *Adults.* The mean dose rates to active bone marrow and endosteal tissue applicable in the case of uniform contamination of the skeleton with strontium-90 have been calculated by Spiers.[317] However, in what has so far been experienced, skeletal contamination in adults has been manifestly non-uniform, $^{90}Sr/Ca$ ratios in typical trabecular bone (vertebral bodies) being more than three times higher than those found in typical compact bone (femur diaphyses). Since the dose rates to bone marrow and endosteal cells are largely due to the strontium-90 contained in trabecular bone, averaging the strontium-90 body burden throughout the whole skeleton underestimates the $^{90}Sr/Ca$ ratio and, hence, the dose.

153. The magnitude of the error introduced when the skeleton is non-uniformly labelled can readily be ascertained by separating the dose contributions from strontium-90 in trabecular and cortical bone and then weighting according to the $^{90}Sr/Ca$ ratios in the two bone types.

154. The results of the calculations are given in tables XIV and XV for bone marrow and endosteal tissues, respectively. From table XIV it is seen that the bone-marrow dose rates arise from two separate sources, that is, from the strontium-90 in the two bone types, trabecular and compact, as follows:

0.369 mrad y^{-1} per pCi $(gCa)^{-1}$ in trabecular bone
0.180 mrad y^{-1} per pCi $(gCa)^{-1}$ in compact bone.

Similarly, from table XV it is seen that the dose rates to endosteal cells are

0.678 mrad y^{-1} per pCi $(gCa)^{-1}$ in trabecular bone
0.206 mrad y^{-1} per pCi $(gCa)^{-1}$ in compact bone.

If the skeleton is uniformly labelled at 1 pCi $(gCa)^{-1}$, then the bone-marrow and endosteal-cell dose rates are, respectively, 0.369+0.180 or 0.55 mrad y^{-1} per pCi $(gCa)^{-1}$, and 0.678+0.206 or 0.88 mrad y^{-1} per pCi $(gCa)^{-1}$. To the latter figure Spiers added a contribution (0.25 mrad y^{-1} per pCi $(gCa)^{-1}$) due to the dose delivered to the endosteal tissues in shafts of long bones. Since this correction was not based on direct experimental data, it must be regarded as an arbitrary safety factor leading to an over-estimate of the dose-rate factor.

155. For the non-uniformly labelled skeleton, it is assumed that the $^{90}Sr/Ca$ ratio found in vertebral bodies is representative of the levels in trabecular bone throughout the skeleton, whereas that in femoral diaphyses is representative of compact bone. From the empirically observed normalization factors in 1967 (table VIII), the levels in vertebral bodies and femoral diaphyses are, to one significant figure, 2 and 0.6 pCi $(gCa)^{-1}$, respectively, when the average $^{90}Sr/Ca$ ratio in whole skeleton is 1 pCi $(gCa)^{-1}$.

156. The weighted mean dose-rate constant to the whole active bone marrow, when the average $^{90}Sr/Ca$ ratio in whole skeleton is 1 pCi $(gCa)^{-1}$, is then calculated as follows:

Trabecular bone contribution=2.0 $0.369 = 0.74$ mrad y^{-1}

Compact bone contribution=0.6 $0.180 = 0.11$ mrad y^{-1}

Total= 0.85 mrad y^{-1}

so that, with a concentration of 1 pCi $(gCa)^{-1}$ in vertebral bodies, the dose rate to the whole active marrow is 0.43 mrad y^{-1}.

157. Similar arguments apply to the dose to the whole endosteal tissue (except the long-bone-shaft endosteum), the weighted mean tissue dose rate to which is calculated as follows:

Trabecular bone contribution=2.0 $0.678 = 1.36$ mrad y^{-1}

Compact bone contribution=0.6 $0.206 = 0.12$ mrad y^{-1}

Total= 1.48 mrad y^{-1}

so that, with a concentration of 1 pCi $(gCa)^{-1}$ in vertebral bodies, the dose rate to endosteal cells is 0.74 mrad y^{-1}. If the long-bone-shaft endosteum contribution is added, the mean dose-rate factor can be shown to be 163 mrad y^{-1} per pCi $(gCa)^{-1}$ averaged over the whole skeleton, or 0.82 mrad y^{-1} per pCi $(gCa)^{-1}$ in vertebral bodies.

158. The dose rates for the whole of the skeleton and the whole of the bone marrow are then

	Bone marrow	*Endosteal tissue*
(a) *Non-uniform*	0.43 mrad y^{-1} per pCi $(gCa)^{-1}$ in vertebral bodies	0.82 mrad y^{-1} per pCi $(gCa)^{-1}$ in vertebral bodies
(b) *Uniform*[a]	0.55 mrad y^{-1} per pCi $(gCa)^{-1}$ in any bone	1.13 mrad y^{-1} per pCi $(gCa)^{-1}$ in any bone,

[a] The dose-rate factors for uniform distribution of strontium-90 given here are the same as given in *Table 6* of publication 11 of the International Commission on Radiological Protection.

where the non-uniform factors apply during at least some part of the lives of those in the population who were adults or late teenagers during the periods of maximum fall-out levels and where the uniform factors apply to those who were children or yet unborn at that time. For present purposes, however, the dose-rate factors for uniform distribution can be applied without serious error throughout the period for which the dose commitment is calculated.

159. There are, however, several advantages to using strontium-90 levels in vertebral bodies for calculating the dose commitment. Vertebral bodies are a convenient source of autoptic bone material and have been widely used in a number of countries. As discussed earlier, there is uncertainty about the values of normalization factors and, particularly, about their future time course. Applying dose-rate factors for vertebral bodies makes it possible to use most of the data directly without multiplying the results by factors that tend to be arbitrary, that may vary with time and that require further assumptions. According to data given by Spiers, vertebral bodies contain more than 40 per cent of the active bone marrow in adults and nearly the same fraction of endosteal cells. Thus, vertebral bodies contain a larger fraction of the critical tissues than any other group of bones, although the largest fractional dose-rate contribution comes from the flat bones—pelvis, clavicles and scapulae—which, however, have not been used in bone surveys. The dose-rate contribution of vertebrae is only slightly less, and these two types of bone together contribute 60 per cent of the total dose rates to bone marrow and endosteum.

160. Strontium-90 is assumed to be uniformly distributed in the skeletons of children and adolescents so that, in the past, normalization factors have been applied only to measurements obtained from bones of persons more than twenty years of age. This has meant that average $^{90}Sr/Ca$ ratios for whole skeletons have shown a sharp discontinuity at age twenty which is not plausible on physiological grounds. The use of $^{90}Sr/Ca$ ratios in adult vertebral bodies largely removes the discontinuity in a rational way.

161. *Children.* Spiers has applied methods similar to those used for adults to calculate dose-rate factors for children. However, the experimental material available to him was very much smaller, consisting only of a vertebra and a femur from a five-year-old child.

162. The dose-rate factor calculated by Spiers for bone marrow in a five-year-old child is 0.82 mrad y^{-1} per pCi $(gCa)^{-1}$, or about 1.5 times the corresponding value for adults with uniformly labelled skeleton. It is not known how this value changes for other ages between birth and twenty years of age. No corresponding estimate of the dose-rate factor for endosteal cells in children is given. However, when estimating the dose commitment of the whole population, the value of the dose-rate functions for adults can, with little error, be taken to be constant with age.

2. *Caesium-137*

163. The dose commitment from ingested caesium-137 is easier to estimate than is that from strontium-90, because caesium-137 can, for dosimetric purposes, be considered to be distributed uniformly in the body and because it is excreted rapidly. In contrast to strontium-90, the long-term uptake of caesium-137 into diet from soil in temperate regions is generally less important than direct deposition on vegetation. The total dietary intake of caesium-137 can be estimated more reliably therefore from directly measured levels, since only a relatively small allowance for long-term uptake is necessary.

164. Caesium-137 and strontium-90 produced by nuclear explosions in the atmosphere are transported to the earth's surface without fractionation, as shown by the relative uniformity of the observed $^{137}Cs/^{90}Sr$ ratios in air and deposit.[12, 13, 34-36, 101]

(a) *Caesium-137 in food chains*

165. The main dietary sources of caesium-137 are milk, meat, vegetables and cereals.[64] In some regions, fish from inland lakes is locally important.[102, 316] In general, however, levels tend to be highest in meat and cereals and lowest in vegetables.[103] Direct comparison of intakes between different regions thus requires observations on representative diets (table IV).

166. Within areas with reasonably uniform deposition and with similar soil types, levels in different food-stuffs are fairly closely correlated.[60, 104] Measurements on a single item can therefore be used to detect regions where large deviations from normal may occur. Milk is convenient for this purpose, as representative samples can be obtained easily and analysis

is simple. A large number of milk analyses from different regions have been reported (table III).

167. When allowance is made for differences in deposition, levels of caesium-137 in diet and milk as a rule vary by relatively small amounts between those regions from which data have been available. Observations from regions with non-western diets are, however, scarce, and no definite conclusions can be drawn about average levels in these areas.

168. Exceptionally high values have been observed in reindeer and caribou meat in subarctic regions. The special conditions in these regions are discussed separately in paragraphs 191 and 192. High milk concentrations have also been observed in other areas (paragraph 30) where the higher uptake seems mainly to be due to predominance of soils low in micaceous clay and exchangeable potassium so that pastures are poor and/or high in organic matter. In addition, high precipitation may in some cases (for example, in mountainous areas) result in enhanced caesium-137 deposition and uptake. Tracer experiments indicate that uptake of caesium-137 from red, lateritic and alluvial soils common in the tropics and subtropics is considerably higher than uptake from the clay soils of temperate regions, but no measurements in local food products or people in the tropics are available.[64, 105]

(b) *Transfer from deposit to diet*

169. The transfer of caesium-137 to diet is normally characterized by high uptake during the first years after deposition and by a relatively small uptake subsequently.[64] No quantitative description of the transfer from deposit to whole diet has so far been attempted. However, in its 1964 report, the Committee accepted that the transfer to milk could be described by the following equation originally applied to British data by Bartlett and Mercer:[106]

$$C(t) = p'_r F_r(t) + p'_{2c} [F_r(t-1) + F_r(t-2)], \quad (75)$$

where $C(t)$ denotes the caesium-137 concentration in milk, $F_r(t)$ the mean deposition rate in year t, and p'_r and p'_{2c} are constants determined empirically from observed levels. Equation (75) gives a transfer coefficient $P_{2s}=p'_r+2p'_{2c}$ and corresponds to a transfer function (paragraph 66) with $K(0) = p'_r$, $K(1) = K(2) = p'_{2c}$ and $K(u) > 2 = 0$. The uptake after more than two years is thus formally neglected.

170. More elaborate models have been used to describe the relationship between levels in deposition and in milk by Bartlett and Russell[107, 108] and by others.[104] In these models, the long-term component has explicitly been taken into account by assuming $K(u) \geqslant 2 = p_a e^{-u/T_m}$, where p_a is a constant derived from tracer experiments.

171. Milk levels show a pronounced yearly cycle depending on deposition rates and agricultural practice, but the yearly mean level is representative of the dietary intake in that year. Meat and grain products, which provide about half of the caesium-137 intake in western-type diet, are often stored and may thus be representative of an earlier fall-out situation. The relative contributions of different types of food-stuffs consumed therefore vary with deposition rates, even though at production level they remain unchanged in any given year. If the dietary levels are integrated over a number of years, the effect of such variations cancel out, but there may remain a long-term change in the proportions by which different types of food contribute to diet, if there is a real difference in the soil uptake between plants.

172. If observations on dietary levels are available for most of the deposition period, P_{2s} can be estimated directly by means of the relation

$$P_{2s} = \frac{\int_{-\infty}^{t} C(\tau)d\tau}{F(t)} + \frac{\int_{t}^{\infty} C'(\tau)d\tau}{F(t)}, \quad (76)$$

where C' is the part of the dietary level due to deposition before time t. The first term to the right will be called $P_{2s}(t)$. Observations on total diet are nowhere available for the whole period of interest, but they can be inferred from observations on body content, as the integrated body content over a reasonably long time is directly proportional to the dietary intake (paragraph 182). For example, Gustafsson and Miller[109, 316] give the integrated dietary intake of caesium-137 for the years 1961-1967 in the Chicago area as 180 pCi y $(gK)^{-1}$. The total uptake can then be estimated by multiplying this value by the ratio between the integrated body levels in the years 1953-1967 and the levels in the period 1961-1967, giving 275 pCi y $(gK)^{-1}$. The total mean deposition of caesium-137 in Chicago up to 1967 was about 85 mCi km^{-2}, and thus $P_{2s}(1967) = 3.25$ pCi y $(gK)^{-1}$ per mCi km^{-2}.

173. To estimate the second term to the right of equation (76), some assumptions regarding the long-term uptake must be made. It is generally assumed that the dietary level caused by a given deposit decreases with time at least at a rate corresponding to the radio-active decay. An upper limit to the value is thus obtained by multiplying C(67) by the radio-active mean life T_m which, with the Chicago data, gives a value of 4.4 for the second term so that $P_{2s} = 7.65$ pCi $(gK)^{-1}$ per mCi km^{-2}.

174. Since a considerable part of the 1967 dietary levels was due to uptake from caesium-137 deposited in the years 1965-1967, this method over-estimates the second term. In the following paragraphs, an estimate of the proportion of the dietary level in 1967 resulting from deposition in 1965 and earlier will be made, taking into account the special deposition pattern during the years 1964-1967. The integrated dietary level due to deposition before 1965 can then be obtained by extrapolating this proportion. As the cumulative deposit increased very little during the period 1965-1967, this extrapolated term can be used as an estimate of

$$\int_{1968}^{\infty} C'(\tau)d\tau.$$

175. The ratio between the dietary levels in 1966 and 1967 can be written

$$\frac{C(66)}{C(67)} = \frac{L(66) + K(2)\,F_r(64) + K(1)\,F_r(65) + K(0)\,F_r(66)}{L(67) + K(2)\,F_r(65) + K(1)\,F_r(66) + K(0)\,F_r(67)}. \quad (77)$$

where $L(66)$ is the uptake in 1966 due to deposition in 1963 and earlier and $L(67)$ the uptake in 1967 from deposition in 1964 and earlier. It will be assumed that these terms are directly proportional to the cumulative deposit in 1963 and 1964, respectively. The annual deposit in the northern hemisphere decreased by about 50 per cent per year[110] from 1964 to 1967. The fact that

$$\frac{F_r(64)}{F_r(65)} \approx \frac{F_r(65)}{F_r(66)} \approx \frac{F_r(66)}{F_r(67)} \qquad (78)$$

implies that

$$\frac{C(66)}{C(67)} \approx \frac{F_d(63) + k[F_r(64) + F_r(65) + F_r(66)]}{F_d(64) + k[F_r(65) + F_r(66) + F_r(67)]}, \qquad (79)$$

where k is a constant reflecting the rate of uptake from comparatively fresh deposit. In order to avoid the lag effects discussed in paragraph 171, milk rather than total diet was chosen to estimate k.

176. When the pertinent deposition and milk data for the United States are inserted in equation (79), it is found that $k = 33$, implying that somewhat less than 20 per cent of the milk level in 1967 was due to deposition before 1965. The future dietary content due to deposition before 1965 can thus be estimated as $0.2\ C(67)\ T'_m$, where T'_m is the effective mean residence time in soil. The sum of this term and the observed integrated dietary content up to 1967 gives an over-estimate of the total integrated dietary content due to deposition before 1965, as the effect on diet during the years 1965-1967 from deposition in this period is included. As the integrated deposit increased very little between 1965 and 1967, this over-estimate is small, however. P_{23} is obtained by dividing the total integrated dietary content thus obtained by the integrated deposit at the end of 1964. The pessimistic assumption that T'_m is equal to the radio-active mean life (forty-four years) gives an estimate of $P_{23} = 4.1$ pCi y $(gK)^{-1}$ per mCi km^{-2}.

177. A fairly large number of observations on the body content of caesium-137 are available, and the dose commitment can then be estimated, without knowledge of P_{23}, from the ratio $P_{23}/P_{23}(t)$ (paragraphs 172 and 186). Since

$$\frac{P_{23}}{P_{23}(t)} = \frac{\int_{-\infty}^{\infty} C'(\tau)d\tau}{\int_{-\infty}^{t} C(\tau)d\tau}, \qquad (80)$$

this ratio can be estimated for different regions in the northern hemisphere, using, for example, milk data and the method indicated in paragraphs 172 to 174. This method has the advantage that information on local deposition is not required.

(c) *Metabolism of caesium-137 in the body*

178. Caesium-137 ingested by man is rapidly distributed in the body, about 80 per cent being deposited in muscle and 8 per cent in bone.[100] About 10 per cent is rapidly excreted, and the remainder is excreted at a slower constant rate. The observed half-life in adults varies between less than fifty and more than 200 days and seems to depend on body weight, sex and dietary habits.[111, 112] Even within a relatively homogeneous group, the variability in half-life is considerable.[113] The half-life in children is shorter than in adults and is of the order of ten days for new-born infants.[100] Based on published data, McCraw[114] gave the empirical equation $T_{\frac{1}{2}} = 12.8\ (u^{\frac{1}{2}} + e^{-u})$ days, where u is age in years. There has been some indication that a small part of caesium might be fixed in bone with long residence time,[109] but no quantitative observations have been reported.

179. The average body content of caesium-137 in a population at a given time varies with individual values of the biological half-life and with dietary habits. The observed caesium-137 levels (in pCi $(gK)^{-1}$ are 20-30 per cent lower in women than in men.[115-119] Levels in children are, as a rule, lower than in adults.[109, 116, 117] For estimating the dose commitment, it will be assumed that the caesium-137 level (in pCi $(gK)^{-1}$) in children is the same as in adults, an assumption which probably results in a small over-estimate of the population average.

180. Although the most accurate determinations of caesium-137 body burdens are by whole-body counting, this method has limitations, as most body counters are immobile. For that reason, measurements on human blood, urine, etc. may serve as a useful supplement to whole-body counting in regions where representative whole-body measurements are not feasible. Such methods also make it possible to use pooled samples from a large number of individuals, and this may be important in regions where there is reason to suspect large variations due to unknown ecological factors.

181. The relation between caesium-137 concentration in blood and body burden has been studied by Yamagata[120] who has also made an extensive survey of body burdens using blood samples.[121, 122] Recently a study by Jaakkola *et al.*[123] has shown a very good correlation between body burden expressed in nCi $(gK)^{-1}$ and blood concentration and a much poorer correlation with caesium-137 concentrations in twenty-four-hour urine samples. The results indicate, however, that pooled urine samples from at least twenty individuals give a reasonable estimate of the average body burden. These results are confirmed by similar investigations made by Ramzaev *et al.*[125] The caesium-137 concentration in human hair has also been found to be well correlated with body content.[126, 318]

(d) *Transfer from diet to body*

182. The short residence time of caesium in the human body (T''_m) implies that the ratio between integrated body content and total dietary intake over some extended period of time (more than, say, two years) will be a good estimate of the transfer coefficient P_{24}, that is,

$$P_{24} = \frac{\int_{-\infty}^{\infty} Q(\tau)d\tau}{\int_{-\infty}^{\infty} C(\tau)d\tau} \approx \frac{\int_{t_1}^{t_1+\Delta t} Q(\tau)d\tau}{\int_{t_1}^{t_1+\Delta t} C(\tau)d\tau}, \qquad (81)$$

when $\Delta t \geqslant 2$ y.

183. The coefficient P_{34} can be estimated directly, using data from the United States[103, 109] and Denmark.[124] Expressed in picocuries of caesium-137 per gramme of potassium, the integrated body content of adults in the United States during the years 1961-1967 was 500 pCi y $(gK)^{-1}$ and the corresponding dietary intake 180 pCi y $(gK)^{-1}$ so that $P_{34} = 2.8$. For Denmark, the integrated body content during the years 1963-1967 was 533 pCi y $(gK)^{-1}$ and the dietary intake 184 pCi y $(gK)^{-1}$, giving $P_{34} = 2.9$. In this case, P_{34} can be regarded as dimensionless.

184. Alternatively, body contents and dietary intakes can be expressed in terms of total activity. Because the integrated body content, when so expressed, is equal to the total dietary intake multiplied by the fractional intake f_1 and by the caesium-137 mean life in the body T''_m,

$$P_{34} = f_1 T''_m \qquad (82)$$

and is thus expressed in units of time. Since fractional intake is close to one,[71] P_{34} is close to the mean residence time in the body. Taking the total content of potassium in the body as 140 grammes and a yearly intake of 1,400 grammes, and using the same data as in the previous paragraph, the values of P_{34} then become 0.27 and 0.31 year for the United States and Denmark, respectively, corresponding to a mean biological residence time of about 100 days. The value of the transfer coefficient thus obtained differs from that obtained in the previous paragraph by the ratio of the potassium body content to the potassium yearly intake or by approximately 0.1 y^{-1}.

185. When observations on total deposit and integrated body burdens are available, numerical estimates of the factors P_{23} and P_{34} are not necessary if the body can be assumed to be in equilibrium with the diet, as in that case the dietary step can be bypassed and the deposit linked to body burden by means of a transfer coefficient P_{234}. In the Committee's 1964 and 1966 reports, P_{234} was estimated from the following equation relating body burden and deposit:

$$Q(t) = P_r F_r(t) + P_{2c}\,(F_r(t-1) + F_r(t-2)). \qquad (83)$$

where P_r and P_{2c} were empirical constants. This equation is analogous to equation (75) and

$$P_{234} = P_r + 2P_{2c}. \qquad (84)$$

186. A more direct estimate of P_{234} can be obtained from

$$P_{234} = \frac{\int_{-\infty}^{\infty} Q(\tau)d\tau}{F(\infty)} = \frac{P_{23}}{P_{23}(t)} \frac{\int_{-\infty}^{t} Q(\tau)d\tau}{F(t)}. \qquad (85)$$

187. The United States data discussed in paragraphs 172 to 175 give, as a conservative estimate,

$$P_{234} = \frac{4.1}{3.25} \frac{744}{85} = 11 \text{ pCi y } (gK)^{-1} \text{ per mCi km}^{-2}, \qquad (86)$$

which is consistent with the value obtained by multiplying P_{23}, as given in paragraph 176 by P_{34} as obtained in paragraph 183.

188. A study of the variation of P_{234} in different parts of the northern hemisphere can be made by comparing integrated body burdens. As, in the northern hemisphere, the deposition rates have varied fairly uniformly with time and as body burdens up to 1967 have mainly been due to short-term uptake, the ratios between body burdens in different parts of the hemisphere in the same time periods should be directly proportional to $F(67)\,P_{234}(67)$.

189. Body burdens in different regions and ratios relative to Gustafsson's and Miller's values are given in table VI from which it is seen that, with the exception of the regions discussed in paragraph 168, the ratios in the northern hemisphere lie between one and two with most values around 1.5, the only exception being Japan with a value of 0.6. It is notable that the ratios in northern Europe tend to increase at the end of the period, indicating that the long-term contribution is somewhat higher than in the United States. This increase is modest, however, and it seems reasonable to assume that the long-term contribution after 1967 is of the order of 25 per cent of the total, as in the United States. Studies of the dietary intake in the different parts of the Soviet Union[127, 128] indicate that the levels in the Moscow and Leningrad areas, from which body burdens have been reported, are reasonably well representative of the entire Soviet Union.

(e) *Dose-rate factor*

190. According to Spiers,[100] a caesium-137 body content of 1 pCi $(gK)^{-1}$ gives a dose rate of 18 μrad y^{-1} for a man weighing 70 kilogrammes and 15 μrad y^{-1} for a child weighing 8 kilogrammes. If the caesium-137 body content is expressed as pCi $(gK)^{-1}$, the dose-rate function $g(u)$ is thus approximately independent of age, and it will be assumed that

$$P_{45} = 18 \text{ } \mu\text{rad y}^{-1} \text{ per pCi } (gK)^{-1} \qquad (87)$$

which, combined with the estimate of P_{234} from the United States data, gives

$$P_{2345} = P_{234}P_{45} = 0.20 \text{ mrad per mCi km}^{-2}. \qquad (88)$$

(f) *Subarctic regions*

191. Caesium-137 levels in the food-stuffs produced in subarctic regions are generally higher than those expected from the amounts of the nuclide deposited per unit area and are especially high in reindeer and caribou meat, as well as in fish from lakes with water low in mineral content.[129] The body burdens of caesium-137 in individuals eating large quantities of reindeer or caribou meat are more than ten times higher than the local population average,[130-132] as shown in table VI.

192. Levels of caesium-137 in reindeer and caribou are high because the lichens, which are an important food for these animals during winter, effectively entrap and retain a substantial proportion of the deposit falling onto them. The apparent half-life of caesium-137 in lichens due to grazing and leaching varies from 2.5 to fifteen years[133-135] so that estimates of the dose commitment for these regions are uncertain. Miettinen and Rahola[131] have calculated average integrated body burdens of about 30 nCi y $(gK)^{-1}$ for Finnish Lapps (reindeer breeders) during the years 1961-1968. Assuming an apparent half-life of between 2.5 and fifteen years, the long-term contribution after 1968 is from 12 to 75 nCi y $(gK)^{-1}$. Thus, the total integrated body

burden should be from 40 to 100 nCi y $(gK)^{-1}$, or about 100 times the average for the northern hemisphere.

3. *External radiation*

193. The exposure from gamma-emitting nuclides deposited on the ground was discussed extensively in the Committee's 1962 and 1966 reports, and the methods used earlier for estimating the corresponding dose commitment are still valid.

194. Theoretical and experimental studies on the transmission of gamma radiation from radio-active deposits make it possible to calculate the resulting air dose, provided the properties of the ground and the distribution of radio-activity in the top layer are known.[136-139] However, as this information is largely unavailable, estimated air doses are only approximate. No new data regarding shielding by buildings and screening by the human body warrant any change in the Committee's earlier estimate[140] of a combined shielding and screening factor of 0.2.

195. The effect of the radio-activity distribution in the top layer on the dose-rate conversion factor has been assessed for the case in which the activity decreases exponentially with depth.[137-139] When the relaxation length l (which corresponds to the depth at which the activity has decreased by a factor of e) increases from zero (i.e., plane source) the dose-rate factor initially decreases rapidly but subsequently rather slowly. When l increases from 1 to 3 centimetres, the dose-rate factor for caesium-137 decreases from 60 to 40 per cent of the plane-source value.[137] From such calculations and studies of the actual distribution,[141, 142] it can be deduced that ground roughness and weathering result in a reduction factor of from one to 0.3 as compared to a plane source.

196. As the short-lived nuclides deliver most of their dose contribution within a relatively short period of time, no reduction factor for soil penetration is required. As regards caesium-137, the main dose contribution occurs after the nuclide has penetrated into the soil. In order to take account of this, a soil shielding factor is applied for caesium-137. The value of this factor is taken to be 0.5. The dose-rate factors given by Beck[138] are used (table XVI). The largest contribution to the dose commitment from external radiation comes from caesium-137. As the $^{137}Cs/^{90}Sr$ ratios in deposit are fairly constant, the caesium-137 external dose commitment can be estimated from either caesium-137 or strontium-90 deposition data.

197. Measurements of air doses due to deposit from nuclear explosions have been reported from Japan,[143, 144] the United Kingdom[145] and Sweden.[146] The yearly mean exposures, ranging from 4 to 12 milliroentgens in Japan, from 4 to 6 milliroentgens in the United Kingdom and from 6 to 9 milliroentgens in Sweden, have not varied appreciably between 1965 and 1967. In Japan, comparatively high exposures were observed during the period December 1966-January 1967, presumably due to fresh debris from tests in central Asia.

198. Estimates of external doses based on deposit measurements have been reported from Argentina[15] and Australia.[17-19] In Argentina, doses to gonads and bone marrow from short-lived nuclides deposited after the 1966, 1967 and 1968 tests in the south Pacific were estimated to have been 4.9, 0.9 and 1.3 millirads, respectively. In Australia, the corresponding doses were well below 1 millirad.

199. While deposition of shorter-lived nuclides during the years 1965-1967 was all due to tests carried out in that period, that of the longer-lived nuclides included a contribution from earlier tests which cannot easily be isolated and which have already been included in the estimate of the external dose commitment given in the 1966 report. The Committee estimates that the external global dose commitment due to short-lived nuclides from tests between 1965 and 1967 is, at most, 2 per cent of the external dose commitment from tests up to 1964.

4. *Carbon-14*

200. Because carbon-14 circulates in nature and its radio-active half-life is long compared with that of the other long-lived nuclides, strontium-90 and caesium-137, the dose from carbon-14 will be received over a very much longer period of time. It is therefore convenient to consider the dose commitment due to carbon-14 in two ways, namely, the total dose commitment itself and that fraction of it which will be delivered up to the year 2000, when most of the dose commitment from the other long-lived nuclides will have been delivered. It is the numerical value of the latter fraction which is usually added to the dose commitments due to the other nuclides to obtain the over-all dose commitment from weapons tests so far carried out, but it must be remembered that there will be a further, and larger, contribution from carbon-14 which will be delivered after the year 2000.

201. Most of the carbon-14 produced by nuclear explosions has been injected into the stratosphere where naturally produced carbon-14 also originates. Transport processes are thus essentially identical for natural and artificially produced carbon-14. If it is assumed that present levels of natural carbon-14 on earth reflect a steady-state condition and that the carbon balance will not change appreciably in the future, it is possible to estimate the dose commitment without any specific assumptions regarding transport processes, population structure, etc. by means of the expression

$$D_p(\infty) = \gamma_0 \frac{W}{B} \cdot \qquad (89)$$

where γ_0 is the dose rate due to natural carbon-14, B is the production rate of natural carbon-14 and W is the amount of artificially produced carbon-14.[67]

202. The exchange processes determining the biospheric levels are characterized by a rapid exchange with time constants of the order of a few years at most between different parts of the atmosphere, biosphere and ocean-surface layer. The transfer into deep ocean and humus is a slower process with time constants of the order of tens of years, and the back-transfer to the atmosphere is still slower with time constants of many hundreds of years.[147, 148] After a few years, the atmospheric and biospheric levels due to an atmospheric injection will thus decrease at a rate mainly determined by the transfer to deep ocean and humus, and the effect of a back-transport will be quite small, at least during the first fifty years. This is the situation obtaining now, since no significant additions to the artificial carbon-14 inventory have been made since 1962.

203. Quantitative studies of the transfer processes usually rely on compartment models with first-order kinetics. Complicated models have been applied,[149-151] but, for the purpose of estimating the dose commitment up to the year 2000, a model with four compartments

is sufficient: (*a*) stratosphere: (*b*) troposphere and biosphere; (*c*) ocean-surface layer; and (*d*) deep ocean and humus.[152] The errors introduced by using this simplified model are small compared to the errors due to uncertainties in estimates of the exchange coefficients.

204. The exchange of artificially produced carbon-14 between different parts of atmosphere and the oceans has recently been studied by Nydal,[149] who estimated the stratosphere-troposphere exchange coefficient to be 0.5 y^{-1}, in agreement with earlier estimates.[152] He further found a mean residence time of four years in the troposphere, a value also obtained by Young and Fairhall.[150] From estimates of the net production rate of carbon in land plants,[153] it can be concluded that the largest part of the carbon dioxide in the atmosphere is taken up by the oceans.

205. Estimates of the rate of uptake by deep ocean and humus are, at present, mainly based on observations of the natural carbon-14 balance.[147,148] The exchange coefficients thus derived refer to well mixed compartments, and it cannot be assumed that they are quantitatively applicable in the present connexion.

206. When the exchange coefficients discussed in paragraphs 203 to 205 are applied to the four-compartment model, it follows that an injection of 10^{27} atoms of carbon-14 in the stratosphere leads to a concentration in the troposphere (expressed in per cent of the natural level) of

$$l(t) = 0.16\, e^{-0.00012t} + 1.96\, e^{-0.029t} + 2.84\, e^{-0.35t} - 4.96\, e^{-0.68t}, \qquad (90)$$

where t is the time after injection in years. The first term allows for radio-active decay. The time constants in the last two terms of this expression are mainly determined by the rapid exchange processes in atmosphere, biosphere and ocean-surface layer, whereas the time constant in the second term to the right is determined by the slower processes discussed in paragraph 205.

207. By the end of 1967, no major atmospheric injections of carbon-14 had occurred in four years. It is found from equation (90) that the second term to the right represents about 80 per cent of $l(t)$ when t is between four and forty years, and the approximate integrated tropospheric level for the years 1968-2000 is, therefore, obtained by assuming that $C(t)$ decays with a time constant 0.029 y^{-1} in this period. Thus,

$$\int_{1968}^{2000} l(t)dt \approx C(1967) \int_{0}^{32} e^{-0.029t}\, dt = 21\, l(1967) \qquad (91)$$

208. As was pointed out in paragraph 205, the exchange coefficients determining the time constant 0.029 are tentative. The integrated tropospheric level is, however, not very sensitive to the value of the time constant. If its true value is in the range 0.01-0.06, it is found that

$$\int_{1968}^{2000} l(t)dt = (20 \pm 7)\, C(1967). \qquad (92)$$

209. The integrated tropospheric concentrations up to 1967, inclusive, can be estimated from data summarized in the Committee's 1964 report[152] and by Nydal[149] (figure 20) to be 510 and 390 per cent year of natural carbon-14 in the northern and southern hemispheres, respectively. In both hemispheres, the concentrations in 1967 were about 65 per cent of the natural level. Thus, the integrated level up to the year 2000 is estimated to be about $510 + 21 \times 65 = 1{,}875$ in the northern hemisphere and 1,750 in the southern hemisphere, or about 1,800 per cent year of carbon-14 globally.

210. As the exchange between tropospheric air, food-producing plants and land animals is rapid, human body levels have followed tropospheric levels with a delay of one to two years.[154, 155] Measurements on human blood and hair indicate that equilibrium has been virtually established since 1965[156] (figure 8), and it can thus be assumed that the integrated body burden up to the year 2000 is the same as the integrated tropospheric content. The dose commitment up to the year 2000 is thus obtained from equation (92) by multiplying by the dose-rate constant γ_0.

211. The dose rate due to the natural carbon-14 produced per year is 0.7 mrad y^{-1} in bone marrow and soft tissue and 0.9 mrad y^{-1} in cells lining bone surfaces.[100]

5. *Iodine-131*

212. Iodine-131 has a short radio-active half-life so that its presence in the biosphere is important only during the first few months immediately following a nuclear explosion. This means that appreciable mixing does not occur before deposition and that the actual fall-out pattern depends very much on the weather during the first week or so following the explosion. Because deposition patterns are so variable and unpredictable, doses can only be calculated if the levels of the nuclide in food are measured directly or if the local transfer coefficients and deposit are known. Since these are often not available from large areas of the world, it is not possible to estimate dose commitments on the global scale but only those to local groups of persons whose food supplies have been adequately monitored.

213. If dose commitments are required, it is essential to have ready a monitoring system whereby representative dietary samples can be obtained and analyzed rapidly. In those areas where milk is a major dietary component, it has been found that, within a specified region, there is usually a strong correlation between the concentration of barium-140 in ground-level air and iodine-131 concentration in milk. Since it is comparatively simple to obtain air samples, such a measurement can be used to trigger full milk sampling systems.

(a) *Iodine-131 in food chains*

214. Where it is a major dietary component, milk dominates as a source of iodine-131 ingestion. In areas where little milk is consumed, the main source of iodine-131 intake is probably vegetables.[64, 213] Once deposited on grass, iodine is removed by various processes such as cropping, leaching and volatilization. Several studies have indicated an effective half-life of three to six days.[157] The efficiency of transfer from grass to milk depends on many factors associated with local farm practices. During winter, transfer will obviously be negligible in areas where cows eat stored feed. Breed of herd, season, density of herbage and milk yield may affect the transfer appreciably.[64, 158, 159]

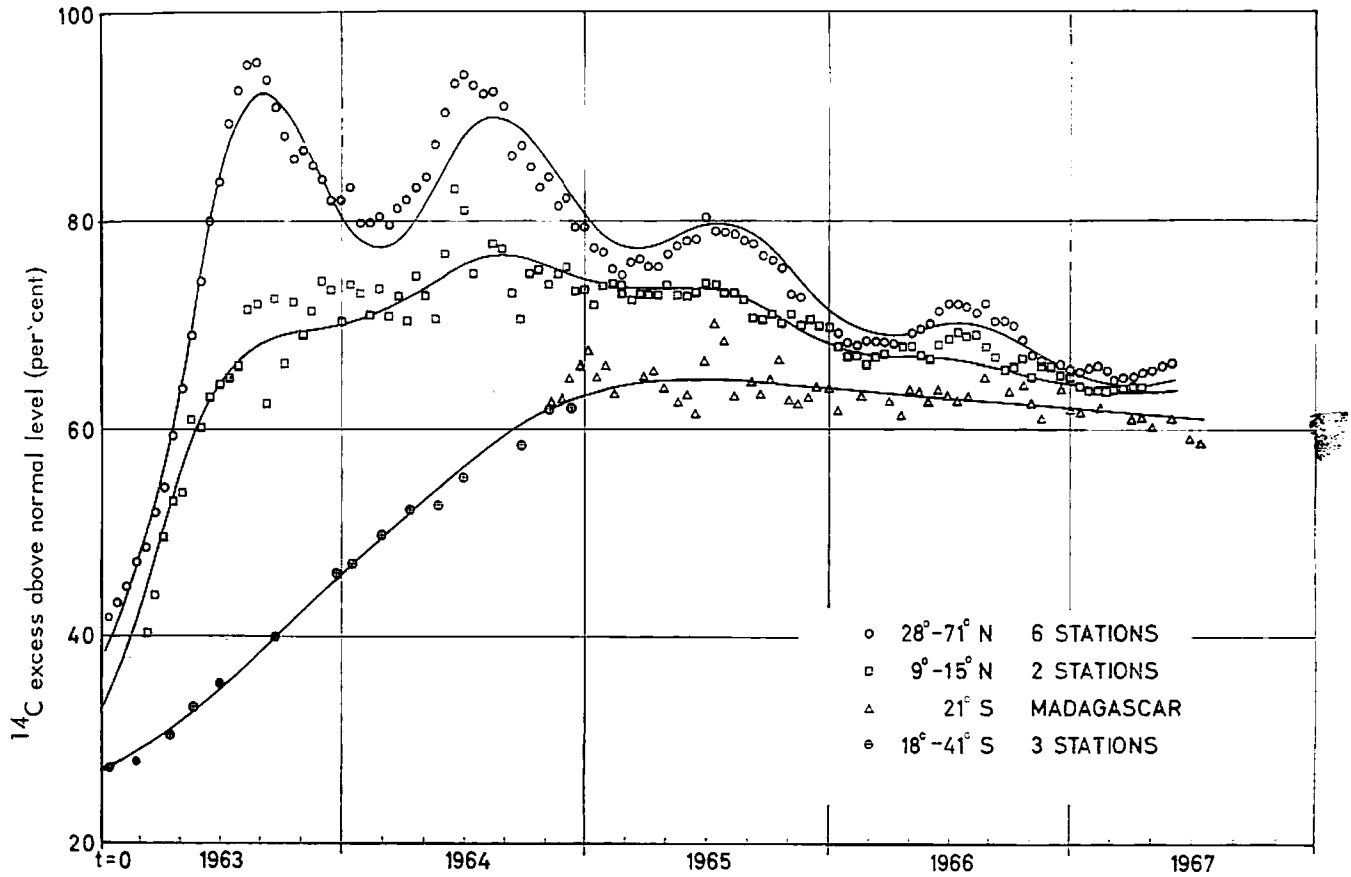


Figure 20. ^{14}C variation in the troposphere[149]

(b) *Metabolism of iodine-131 in the body*

215. Iodine-131 is concentrated in the human thyroid which receives a dose many orders of magnitude greater than any other organ.[100] For a given dietary intake, the resulting dose to the thyroid is at least ten times higher in six-month-old infants than in adults, although the total iodine-131 content of the thyroid is about the same.[160-162]

(c) *Dose-rate factor*

216. In the Committee's 1964 report,[163] it was estimated that an integrated milk level of nCi d l^{-1} results in a thyroid dose of 11.5 millirads to children one to two years of age, in close agreement with later estimates. Corresponding mean doses for individuals in age groups zero to ten, ten to twenty and twenty to seventy years of age are, according to Neill's and Robinson's data,[162] 6.1, 2.5 and 0.7 millirads, respectively.

6. *Other nuclides*

217. Relatively large amounts of iron-55 were produced in the nuclear test series during 1961 and 1962. As iron is readily transferred in the biosphere and taken up by man, relatively high activity levels have been observed in the subsequent years. A number of investigations on iron-55 in food chains and in man have been reported.[164-170] Although the body burdens are comparable to those of caesium-137, the resulting dose rates are far smaller since the dose-rate factor for iron-55 is quite small.[165]

218. Studies on other nuclides produced by nuclear explosions, such as sodium-22, manganese-54, krypton-85, plutonium-239, and tritium, indicate that the internal dose commitments due to these nuclides are of minor importance.[171-174]

D. Dose commitments from external and internal contamination

1. *Introduction*

219. For the purpose of estimating dose commitments, particularly from internally deposited caesium-137 and strontium-90, the world population is divided into three groups:

I(*a*). *Populations living in regions from which a relatively large amount of data on contamination by these long-lived nuclides is available and where transfer processes are sufficiently well understood to make possible reasonably reliable predictions of future levels.* The regions included are those in which the principal source of caesium-137 and strontium-90 in the diet is dairy produce, such as western Europe and North America in the north temperate zone and Argentina, Australia and New Zealand in the temperate zone of the southern hemisphere.

I(*b*). *Populations living in regions in the northern temperate zone from which a relatively large amount of environmental data is also available but where some transfer processes are different from those in* I(*a*). These regions include parts of the Soviet Union and other areas of eastern Europe in which the principal source of caesium-137 and strontium-90 in diet are whole wheat and rye. This group also includes the

population of Japan which differs from the eastern European populations insofar as rice and vegetables are the principal sources of strontium-90 and caesium-137.

II. *Populations in the remaining regions of the world from which almost no environmental data are available and little is known about transfer processes through food chains.* For these regions, it is thus necessary not only to predict future levels but also to estimate past levels. These regions include, in particular, the tropical and subtropical belt.

220. In addition to these broad population groups, there are substantial groups of individuals for whom the dose rates may be much higher than typical values for the temperate zone because of special climatic and dietary factors. An important example is that of the arctic and subarctic regions where people include reindeer and caribou meat and fresh-water fish in their diets. As they are a relatively small fraction of the world's population, the enhanced doses that they receive do not contribute significantly to the world-wide dose commitment.

221. The dose commitment due to carbon-14, on the other hand, does not depend significantly on dietary and social habits, and, since the deposit of carbon-14 is more or less uniform over the globe, it will be equal for all populations.

222. Dose commitments for the population belonging to group I(*a*) will be calculated first, using equation (16) and the values of the transfer coefficients relevant to each case, as estimated in the preceding paragraphs. The special problems arising in the case of populations belonging to groups I(*b*) and II will then be considered separately.

2. *Distribution of world-wide deposit of long-lived radio-nuclides*

223. The distribution of deposit over the surface of the earth is shown in table XVII. The average integrated deposit of strontium-90 in the north temperate latitudes to the end of 1967 is about 65 mCi km^{-2}, whereas that of caesium-137, obtained by multiplying the value for strontium-90 by 1.6 (paragraph 20), is 104 mCi km^{-2}. The corresponding values in the south temperate latitudes are 14 mCi km^{-2} and 22 mCi km^{-2} for strontium-90 and caesium-137, respectively.

3. *Dose commitments to group I(a) population*

(a) *Internal dose commitments*

(i) *Strontium-90*

224. The following values of the transfer coefficients are used

(*a*) P_{23} = 9 pCi y (gCa)$^{-1}$ per mCi km^{-2} (paragraph 140)

(*b*) P_{34} (vertebrae) = 0.2 pCi y (gCa)$^{-1}$ per pCi y (gCa)$^{-1}$ (paragraph 151)

(*c*) P_{45} (bone marrow) = 0.55 mrad y^{-1} per pCi (gCa)$^{-1}$ (paragraph 158)
P_{45} (endosteal cells) = 1.1 mrad y^{-1} per pCi (gCa)$^{-1}$ (paragraph 158)

Thus we obtain

$D_p(\infty)$ (bone marrow) = 64 mrad in the northern hemisphere
= 14 mrad in the southern hemisphere

$D_p(\infty)$ (endosteal cells) = 128 mrad in the northern hemisphere
= 28 mrad in the southern hemisphere

(ii) *Caesium-137*

225. Since P_{234} P_{45} = 0.2 mrad per mCi km^{-2} (paragraph 190),

$D_p(\infty)$ = 21 mrad in the northern hemisphere
= 4 mrad in the southern hemisphere

(iii) *Carbon-14*

226. The total dose commitment from carbon-14 is estimated from equation (89). The rate of production of natural carbon-14 is 2.6 10^{26} atoms per year, and the amount of carbon-14 injected by tests carried out up to 1967 is 650 10^{26} atoms so that

$$D_p(\infty) = \gamma_0 \frac{650}{2.6} \cdot \qquad (93)$$

Since γ_0 equals 0.7 mrad y^{-1} in bone marrow and soft tissues and 0.9 mrad y^{-1} in cells lining bone surfaces (paragraph 211), the corresponding dose commitments are 180 and 230 millirads, respectively.

227. The fraction of the dose commitments to be received by the year 2000 are obtained from equation (92) and the appropriate values of γ_0, giving 13 millirads to bone marrow and soft tissues and 16 millirads to cells lining bone surfaces.

(iv) *Strontium-89*

228. Internal doses due to strontium-89 are insignificant compared with those from other sources of radiation.

(b) *External dose commitments*

(i) *Caesium-137*

229. From table XVI, the air-dose-rate conversion factor for caesium-137 is 0.04 mrad y^{-1} per mCi km^{-2} so that, taking a mean life of caesium-137 of forty-four years and, as in the 1966 report, a shielding factor equal to 0.2, the dose-rate factor is 0.35 mrad per mCi km^{-2} to gonads, bone marrow and cells lining bone surfaces. The corresponding dose commitments are 36 and 5 millirads in the northern and southern temperate zones, respectively.

(ii) *Short-lived nuclides*

230. The external dose commitment from short-lived nuclides is taken to be equal to that from caesium-137 as found in the 1966 report. The Committee recognizes that this is an approximation that may over-estimate the dose commitment from this source.

4. *Dose commitments to populations of group I(b) and group II*

231. Although, during the period up to 1968, levels of strontium-90 and caesium-137 in diets of eastern Europe (as represented by the Soviet Union and

Poland) have consistently been higher by a factor of between two and three than those in western European diets, the corresponding levels in human tissues have only differed fractionally.

232. Because the difference that this observation implies between the values of the diet-to-tissue transfer coefficients of the two populations is not well understood, there is some doubt concerning predictions of the future time course of the body burdens, if the present disparity between the dietary levels of the two groups continues. However, since future levels must continue to decline, the levels integrated over future time in group I(*b*) populations cannot greatly exceed those predicted for group I(*a*), because the rate of decline of levels in the future cannot be less than that determined by the rate of radio-active decay. The uncertainty is larger for strontium-90 since, for caesium-137, a smaller proportion of the total expected dose is yet to be delivered.

233. In the case of Japan, measured levels of both long-lived nuclides in human tissues have been somewhat lower than those found in the corresponding tissues of populations belonging to group I(*a*) in the northern hemisphere. Thus, the dose commitments for strontium-90 and caesium-137 calculated for group I(*a*) populations living in the northern temperate zone somewhat over-estimate those applicable to Japan. Until better information is available, therefore, the Committee is satisfied that the dose commitments calculated for the northern temperate zone are also applicable without serious error to populations belonging to group I(*b*).

234. It is only possible to speculate about the values of dose commitments to populations belonging to group II. In its previous reports, the Committee had assumed that levels of caesium-137 in human tissues would be proportional to the levels of deposit, though there was no evidence to support this. Body burdens of strontium-90 were assumed to be proportional to levels of contamination in food-stuffs, the latter being estimated from the levels of the deposit using deposit-to-food-stuff transfer coefficients estimated in the temperate latitudes and allowing for the different proportions each foodstuff contributed to the diet. The deposit-to-diet transfer coefficients for both caesium-137 and strontium-90 may be greater in tropical and subtropical areas than in the temperate zones because of differences in climate, soil and agricultural practices. However, in regions belonging to group II, the cumulative deposit is smaller by a factor of between two and ten than it is in the north temperate zone. Thus, even though the deposit-to-diet transfer coefficients for individual foodstuffs may be several times greater than the corresponding values in the temperate zones, it seems unlikely that the levels of contamination in group II dietary components will significantly exceed those observed in group I(*a*). When allowance is made for the different dietary composition, the most pessimistic assumption is that the levels in whole diet will, at most, be as high as those observed in eastern European populations. The Committee believes therefore that the dose commitments estimated for internally deposited strontium-90 and caesium-137 in the northern temperate zone may be taken as reasonably reliable upper limits for the group II population.

235. Estimates of dose per unit deposition due to external sources are based on measurements and parameters appropriate to the north temperate zone and may, because of the effect of different living habits on shielding, be too low for populations living in other areas. However, the maximum error due to this effect cannot exceed a factor of two, and, since accurate data are not available, it will be assumed for present purposes, as in previous reports, that the dose commitment due to external sources is proportional to the integrated deposit.

236. The world-wide average dose commitment from external sources is therefore calculated in the following way. The distribution of the world population and fall-out by latitude is given in table XVII, from which it has been estimated that the mean deposit over the world surface is 26 mCi km^{-2}. Since the population-weighting factor Z is 1.56 (table XVIII), the average deposit of strontium-90 weighted by population is 40 mCi km^{-2} and that of caesium-137, after applying the ratio 1.6 (paragraph 10), 64 mCi km^{-2}. Using the same factors as given in paragraph 227, this corresponds to a dose commitment from external caesium-137 of 23 millirads. The corresponding dose commitment due to short-lived radio-nuclides is also taken to be 23 millirads (paragraph 230).

237. The dose commitments due to internally deposited carbon-14, strontium-90 and caesium-137 to the world population are taken to be the same as those estimated for the north temperate zone (paragraphs 222-228). As noted in paragraph 234, the doses obtained for strontium-90 and caesium-137 are considered to represent upper limits of the dose commitments for those populations that live outside the north temperate zone.

238. Dose commitments estimated for the north and south temperate zones, as well as the average for the world weighted by population are summarized in table XIX.

TABLE I. ANNUAL AND CUMULATIVE WORLD-WIDE ^{90}Sr DEPOSITION[44]

(values in megacuries)

	Annual deposition			*Cumulative deposit*		
	Northern hemisphere	*Southern hemisphere*	*Total*	*Northern hemisphere*	*Southern hemisphere*	*Total*
Pre-1958				1.7	0.6	2.3
1958	0.74	0.31	1.05	2.39	0.83	3.22
1959	1.10	0.19	1.29	3.41	0.99	4.40
1960	0.26	0.17	0.43	3.59	1.14	4.73
1961	0.35	0.19	0.54	3.84	1.28	5.12
1962	1.45	0.31	1.76	5.16	1.55	6.71
1963	2.62	0.33	2.95	7.62	1.84	9.46
1964	1.66	0.44	2.10	9.06	2.21	11.27
1965	0.78	0.36	1.14	9.61	2.51	12.12
1966	0.33	0.21	0.54	9.70	2.65	12.35
1967	0.17	0.11	0.28	9.62	2.69	12.31

TABLE II. ^{90}Sr INVENTORY[54]

(values in megacuries)

	1963			*1964*			*1965*			*1966*			*1967*			
	Mar.	*July*	*Nov.*	*Mar.*	*July*	*Nov.*	*Mar.*	*July*	*Nov.*	*Mar.*	*July*	*Oct.*	*Jan.*	*Apr.*	*July*	*Oct.*
Stratosphere	6.5	5.1	3.8	3.0	2.1	1.7	1.3	0.9	0.8	0.6	0.5	0.4	0.3	0.3	0.3	0.4
Troposphere	0.5	0.2	0.2	0.4	0.3	0.1	0.2	0.1	0.1	0.1	0.1	0	0	0	0	0
Local fall-out	2.4	2.4	2.4	2.3	2.3	2.3	2.3	2.2	2.2	2.2	2.2	2.2	2.1	2.1	2.1	2.1
Global fall-out	7.2	8.7	9.4	9.9	10.9	11.2	11.5	11.9	12.1	12.2	12.3	12.3	12.3	12.4	12.4	12.4
TOTAL	16.6	16.4	15.8	15.6	15.6	15.3	15.3	15.1	15.2	15.1	15.1	14.9	14.7	14.8	14.9	14.9
Corrected for decay to March 1963	16.6	16.5	16.1	16.0	16.1	15.9	16.1	16.0	16.3	16.3	16.4	16.3	16.2	16.3	16.6	16.7

TABLE III. ^{90}Sr AND ^{137}Cs IN MILK

Region or country	^{90}Sr to calcium ratio (pCi g^{-1})				^{137}Cs concentration (pCi l^{-1})				References
	1965	1966	1967	1968	1965	1966	1967	1968	
Argentina	6.5	5.2	5.2	3.8	20	21	11	10	15
Australia	9.2	7	5.3		47	28	20	15	247-250
Austria	31	23			138	70			212,236
Belgium	19	13			73	36			214
Canada	19	13	10	8	108	51	33	25	215-219
Czechoslovakia	18	16							220
Denmark	17	12	8		56	26	14		124,221,222
Faroe Islands	115	73	51		1 100	800	586		202-204
Finland	18	13	10	9	190	143	106	78	208,209
France	28	21	17	14	115	58	29		225,226
	30		15	12	130		34	24	227
Germany—Federal Republic of	24	16	12		107	61			223,224
Greenland	Dried milk imported from Denmark								205-207
Hawaii	7	4.3	3		50	25	9		240
Iceland	80				750				210
India	11	11			24				246,251
Israel	3.3	2.3	2.0		25	14	11		228,229
Italy	19	13			140	80			230
Jamaica	11	9			270	200	184		240
Japan	15	11				56			231,232
Mexico	1.5				55				245
Netherlands	17	15	9		107	43	37		233
New Zealand	12	7.9	6.4	5.2	60	40	31	23	25
Norway	40	28	16	11	360	234	181	146	211
Panama	4.9	4			37	21	22		240
Puerto Rico	8	6	4		42	21	14		240
Sweden		18	13	10	117	71	46	40	234,235
Switzerland	39	28	15		69	28	15		236
Ukrainian Soviet Socialist Republic	10	8							237
Union of Soviet Socialist Republics	16	12	8		78	56			127,239
	20	16	13		215	90	51		185
United Arab Republic	15	13		6					242-244
United Kingdom	19	12	9		98	46	20		65,238
United States	14	11	9		57	29	16		240
Alaska	14	12	6		57	34	20		186
Chicago	12	9	8						240
New York City	19	12	10	9					241
San Francisco	9								240
Venezuela	4.3	4			20	14	9		240

TABLE IV. ^{90}Sr AND ^{137}Cs IN TOTAL DIET

Region, area or country	^{90}Sr to calcium ratio ($pCi\ g^{-1}$)				^{137}Cs daily intake ($pCi\ d^{-1}$)				References
	1965	1966	1967	1968	1965	1966	1967	1968	
Northern hemisphere									
Austria	40	23			231	135			212,236
Denmark	23	14	10		193	79	44		124,221,222
Faroe Islands	56	33	22		880	500	480		202-204
Federal Republic of Germany	36	29	25		132	84			223,224
Finland	34	21			340	260			28
France									
Paris	30	22	19	17					227
Southeast	34	27	22	18					227,252
Greenland	27	15	9		194	89	297		205-207
India (Tarapur)	24				35				251
Israel	22				92				253
Japan (urban)	25	24	18		34	18	14		257
Netherlands	29	21	12		160	87	47		233
Norway	54	38			660	420			28
Sweden	32	22			221	132			28
Ukrainian Soviet Socialist Republic	57	42			221				127
Union of Soviet Socialist Republics	63	40	28		236	147			127,128
United Arab Republic		45		13					242,244
United Kingdom	18	Survey discontinued			106				256
United States	22	16	12		105	55	30		240
Alaska	29	29	16		140				240
Chicago	19	15	12		130				254,255
Hawaii	21	10	6		65	65	35		240
New York City	24	18	17	14	170				241
San Francisco	11	6	5.5	4.3	108				241
Southern hemisphere									
Argentina	9	7	7	5			24	18	15
Australia	11	7	6						249

TABLE V. $^{90}Sr/Ca$ RATIOS IN HUMAN BONE

(number of samples in parentheses)

Region or country	*Year*	*New-born and/ or still-born*	*0-1 year*	*1 year*	*2 years*	*3 years*	*4 years*	*5-19 years*	*19 years*	*Bone type (adults)*	*References*
					Northern hemisphere						
Canada	1965	2.9 (10)	7.4 (77)	8.6 (16)	10.0 (17)	7.5 (23)	6.3 (16)	4.0 (103)	3.1 (71)	V[a]	260
	1966	3.2 (20)	5.7 (151)	6.4 (32)	7.1 (28)	7.0 (17)	5.5 (18)	4.7 (125)	2.6 (15)	V	272
	1967	2.8 (9)	4.0 (141)	5.4 (44)	5.2 (35)	6.2 (20)	5.0 (15)	3.8 (138)	2.6 (59)	V	272
Czechoslovakia	1965	4.0 (37)	5.0 (51)	6.9 (10)	3.5 (5)	4.2 (8)	5.5 (3)	4.8 (56)	2.2 (141)	V	220
	1968								1.7 (54)	V	73
Denmark	1965	2.9 (14)				6.6 (25)		4.1 (31)	2.7 (23)	V	221
	1966	1.9 (19)	2.9 (34)	2.6 (2)	3.3 (3)	4.6 (2)	4.4 (2)	3.5 (35)	2.6 (32)	V	222
	1967	1.8 (22)				2.7 (32)		2.5 (31)	2.1 (42)	V	124
	1968	1.2 (10)				2.5 (51)		2.3 (19)	1.9 (34)	V	58
Finland	1965	4.8 (1)				5.1 (19)		2.9 (41)	0.65 (47)	T[b]	258
	1966	2.1 (2)				4.1 (22)		2.4 (46)	0.65 (78)	T	258
	1968	1.7 (10)				2.1 (14)		2.4 (23)	0.72 (131)	T	258
Federal Republic of Germany	1965	2.5 (92)	6.2 (10)			5.5 (9)		2.7 (13)	1.1 (43)	T	261
	1966	2.1 (76)	5.5 (4)			5.1 (9)		2.7 (14)	1.0 (47)	T	261
	1967	1.5 (116)	2.9 (15)			3.6 (9)		2.9 (36)	0.9 (62)	T	261
France	1965	2.92 (32)	6.8 (47)			7.6 (13)		3.3 (35)	2.2 (69)	V	179
	1966	2.21 (21)	4.8 (46)			5.3 (13)		3.2 (56)	2.1 (56)	V	179
Japan	1965	2.2 (12)				5.1 (13)		2.5 (27)	1.0 (20)	R[c]	262
	1966	1.9 (8)				3.3 (35)		2.1 (27)	0.8 (23)	R	262
Norway	1965	5.4 (20)	11.4 (11)			11.8 (3)		7.4 (9)			259

	1966	3.0 (22)	6.3 (10)			10.0 (9)			5.6 (9)	3.1 (4)	V	259
	1967	2.8 (17)	4.4 (14)			6.5 (10)			5.7 (8)	4.3 (10)	V	259
	1968	2.9 (34)	4.2 (9)			6.2 (5)			5.0 (9)	3.7 (10)	V	259
Poland	1965		6.8 (4)	4.0 (3)				3.5 (3)	5.4 (4)	2.5 (23)	V	263
	1966		5.0 (6)	6.1 (2)					4.1 (3)	2.9 (67)	V	263
United Kingdom	1965	2.5 (101)	7.1 (86)	9.1 (11)	6.1 (8)		6.8 (8)	4.5 (5)	2.7 (58)	0.9 (23)	F[d]	264
	1965	3.0 (2)				6.8 (20)			3.2 (5)	1.9 (48)	V	264
	1966	2.2 (90)	4.9 (74)	6.5 (8)	5.6 (6)		4.8 (9)	4.8 (7)	2.6 (74)	2.2 (53)	V	264
	1967	2.2 (87)	3.3 (60)	4.8 (12)	4.1 (7)		2.3 (1)	3.2 (6)	2.1 (74)	1.6 (108)	V	266
Union of Soviet Socialist Republics	1965	3.5 (99)	5.0 (39)			5.8 (16)			3.7 (1 559)	1.6 (546)	Normalized to whole skeleton[e]	178
	1966	2.5 (132)	4.1 (81)			5.5 (48)			4.0 (1 389)	1.6 (1 032)		178
	1967	2.0 (94)	3.0 (51)			4.3 (45)			2.5 (416)	1.6 (266)		178
	1968	1.7 (37)	2.6 (7)			3.7 (16)			2.10 (871)	1.0 (165)		178
United States												
New York City, N. Y.	1965	2.8 (6)	5.0 (5)	7.0 (3)	7.2 (2)		6.7 (6)	4.1 (2)	3.5 (39)	2.1 (16)	V	268
	1966		4.3 (80)	7.0 (2)	6.2 (3)			5.0 (1)	3.3 (19)	2.1 (22)	V	269
	1967		4.1 (9)	3.2 (5)	3.2 (5)		3.2 (3)	4.0 (4)	2.9 (31)	1.9 (54)	V	270
	1968		3.3 (8)	3.6 (4)					3.1 (42)	1.9 (33)	V	243
San Francisco, Cal.	1965	1.6 (13)	3.3 (13)	3.8 (6)	3.1 (1)		3.0 (3)	1.8 (5)	1.7 (19)	1.2 (30)	V	268
	1966	1.2 (18)	2.3 (14)	3.1 (4)	3.8 (2)		2.9 (4)	2.7 (3)	1.6 (16)	1.2 (9)	V	269
	1967	0.9 (27)	1.6 (19)	1.7 (3)			1.5 (2)	1.9 (2)	1.4 (11)		V	270
	1968	0.7 (20)	1.8 (1)	1.7 (5)					1.4 (14)	1.2 (23)	V	243
All regions	1965		3.9 (22)	4.1 (12)	4.8 (18)		4.3 (15)	3.0 (14)	2.6 (155)	1.8 (60)	V	186
	1966		3.9 (6)	4.1 (14)	4.1 (15)		4.3 (16)	3.2 (16)	2.6 (193)	2.1 (61)	V	186
	1967		1.3 (5)	3.3 (9)	4.6 (7)		3.6 (12)	4.5 (2)	2.7 (93)	1.7 (40)	V	186

TABLE V. $^{90}Sr/Ca$ RATIOS IN HUMAN BONE (*continued*)

(*number of samples in parentheses*)

Region or country	*Year*	*New-born and/ or still-born*	*0-1 year*	*1 year*	*2 years*	*3 years*	*4 years*	*5-19 years*	*19 years*	*Bone type (adults)*	*References*
					Southern hemisphere						
Argentina (littoral area)	1965	1.6	2.0	2.3	2.0	——— 1.7 ———		1.5			15
		(12)	(39)	(8)	(5)	(4)		(12)			
	1966	1.4		2.0	2.2	——— 2.0 ———		1.5	1.6		15
		(26)		(10)	(13)	(12)		(16)	(10)		
	1967	1.5	2.1	2.0	2.7	——— 1.6 ———		1.7			15
		(21)	(30)	(16)	(13)	(15)		(37)			
	1968	1.4	1.5	1.8	2.1	——— 1.9 ———		1.8			15
		(48)	(49)	(15)	(10)	(15)		(42)			
Australia	1965	1.4	2.8	3.4	2.8	2.3	2.5	1.5	0.95	V	247
		(53)	(121)	(23)	(13)	(11)	(9)	(102)	(460)		
	1966	1.5	2.0	2.5	2.7	2.5	2.3	1.5	1.0	V	248
			(171)	(14)	(16)	(7)	(10)	(78)	(381)		
	1967	1.0	1.3	1.7	2.2	1.8	1.7	1.5	1.0	V	249
		(65)	(120)	(18)	(8)	(8)	(9)	(65)	(276)		

[a] V—Vertebrae
[b] T—Tibiae
[c] R—Ribs
[d] F—Femora
[e] Adult vertebrae (Moscow) for years 1965-1968 were 3.1, 2.7, 2.3 and 1.8 pCi $(gCa)^{-1}$, respectively.

TABLE VI. ^{137}Cs BODY BURDENS
$(pCi\ (gK)^{-1})$

A—Body burden

B—Ratio between United States and local values (adjusted, when appropriate, to adult average, assuming the average ratio between male and female values to be 1.3)

Region, area or country	*Latitude*	*Sex*		*1956*	*1957*	*1958*	*1959*	*1960*	*1961*	*1962*	*1963*	*1964*	*1965*	*1966*	*1967*	*1968*	*References*
								Northern hemisphere									
United States average[a]	30–50°N	MF	A	31.5	36.5	47.0	57.0	48.0	32.5	43.0	79.5	140.0	111.5	69.0	41.0		109
Belgium	~50°N	MF	A					50	33	38	95	158	135	87	50	29	273
			B					1.04	1.02	0.91	1.20	1.13	1.21	1.26	1.22		
Canada (Ottawa)	~45°N	MF	A										170				274
			B										1.52				
Denmark	55–60°N	MF	A									185	168	107	74	46	127
			B									1.32	1.51	1.54	1.81		
Federal Republic of Germany	47–55°N																
Karlsruhe		MF	A							28	75	151	114	83	49		117
			B							0.65	0.94	1.08	1.08	1.20	1.20		
Nordrhein-Westfalen		M	A									249	186	128	76		117
			B									1.55	1.45	1.62	1.64		
Finland	~60°N	MF	A								152	211	188	150			275–277
			B								1.91	1.51	1.69	2.18			
France	~50°N	MF	A								118	227	194				278
			B								1.48	1.62	1.74				
Israel	~35°N	M	A													48	279
Italy	40°N	MF	A								107						280
			B								1.35						
Japan	30–45°N	MF	A									93	77	54			281–282
			B									0.58	0.60	0.68			
Norway	~60°N	MF	A										430	290			28
			B										3.85	4.20			
Poland	50–55°N	MF	A								157	164	185		71		263,283
			B								1.98	1.17	1.66		1.73		
Sweden	~60°N	MF	A				74	68	54	45	111	205	187	139	107	74	284,285
			B				1.30	1.42	1.66	1.05	1.40	1.46	1.68	2.02	2.61		
Switzerland	~50°N	MF	A									185	161	92	50		116
			B									1.32	1.44	1.33	1.22		
Union of Soviet Socialist Republics																	
Moscow	~55°N	M	A								181	258					286
			B								2.28	1.84					
Leningrad		MF	A								145	174	142	92	68		115,287
			B								1.83	1.24	1.27	1.33	1.66		
United Arab Republic	~30°N		A												23.5	14.5	288

TABLE VI. ^{137}Cs BODY BURDENS (*continued*)

Region, area or country	*Latitude*	*Sex*		*1956*	*1957*	*1958*	*1959*	*1960*	*1961*	*1962*	*1963*	*1964*	*1965*	*1966*	*1967*	*1968*	*References*
United Kingdom ...	50–60°N	MF	A	32	37	48	58	49	36	35	81	155	150	77	38		289,290
			B	1.02	1.01	1.02	1.02	1.02	1.11	0.81	1.02	1.11	1.35	1.11	0.93		
United Kingdom ...	50–60°N	F	A			55	57	50	33	44	92	149	109	60	33		118
			B			1.32	1.13	1.17	1.15	1.15	1.31	1.21	1.10	0.99	0.92		
United Kingdom ...	56–60°N	M	A										148	89	45		118
			B										1.16	1.12	0.96		
Subarctic regions[b]																	
Alaska (Anaktuvuk Pass)	65–70°N	M	A							3 000	4 500	9 100	6 600	4 900	4 300		291,292
Canada	60–70°N																
(Eastern Arctic Eskimos)		M	A											5 800			293
(Central Arctic Eskimos)		M	A												11 000		293
Finland	65–70°N																
Reindeer breeders, Lapland		M	A							3 600	4 600	8 900	10 300	8 900	6 300	5 900	131
Union of Soviet Socialist Republics	65–70°N																
(Reindeer breeders, Nenets district)		M	A										11 000				132
Southern hemisphere																	
Argentina	30–40°S		A											31	20	16	15
Australia	30–40°S		A										65	42	37	18	294

[a] Average body burdens for the years 1953, 1954 and 1955 were 2.0, 7.0 and 14.5 pCi $(gK)^{-1}$.
[b] Average spring to summer values for groups largely subsisting on reindeer or caribou meat.

TABLE VII. ^{131}I IN MILK AND THYROID DOSES

Region, area or country	Time integral of ^{131}I concentration in milk (pCi d l^{-1})			Integrated thyroid doses to infants (mrad)			References
	1966	1967	1968	1966	1967	1968	
Argentina							
Bariloche	7 602	1 392		88	16		15
Buenos Aires	26 995	4 346	2 477	312	50	29	15
Salta	15 028	1 800		174	21		15
Australia							
Malanda (Highest)	11 000	10 360	4 540	127	120	55	22
Hobart-Launceston (Lowest)	1 500	380	790	17	4	9	22
Chile (Santiago)	4 000			46	9	< 10	14,295
Colombia (Bogota)	400			5	5	< 10	14,295
Ecuador (Quito)	2 500			29		< 10	14,295
Fiji (Suva)	12 600–15 000			146–174			23
Madagascar (Diego Suarez)	13 000		6 500	150	22	80	14,295
New Zealand	1 000			12			23
Peru							
Lima	6 000		4 000	70	23	50	14,295
Tacna						120	
Society Islands (Papeete, Tahiti I.)					55		295
Western Samoa (Apia)	> 7 300			> 84			23

TABLE VIII. RELATIVE DISTRIBUTION OF ^{90}Sr IN ADULT SKELETON

A — samples not necessarily taken from same individuals

Date	Vertebrae / Whole skeleton	Ribs / Whole skeleton	Femur diaphyses / Whole skeleton	Vertebrae / Ribs	Vertebrae / Femur diaphyses	Number of samples	References
1956	3.4	1.5	0.8	2.3	4.3	2	177
1957	1.8	1.1	0.5	1.6	3.6	9	177
1958/1959	2.1	1.4	0.45	1.5	4.7	59	177
1959	—	—	—	2.1	5.6	11	296
1961	—	—	—	1.6	3.1	4	296
1963	—	—	—	1.4	—	A	179
1963	1.5	1.0	0.5	1.5	3.1	A	74
1964	—	—	—	1.4	—	A	179
1965	—	—	—	1.7	—	A	179
1965	—	—	—	1.7	4.7	A	74
1966	—	—	—	1.4	—	A	179
1967	1.9	0.75	0.6	2.5	2.9	40	74
1968	—	—	—	—	2.7	54	73

TABLE IX. BONE/DIET OBSERVED RATIOS

Region or country	Observed ratio	References
Australia	0.33	[a]
Canada	0.24–0.26	305
Denmark	0.33	[b]
Japan	0.13–0.16	306,307
Union of Soviet Socialist Republics (Moscow)	0.20	88
United Kingdom	0.23–0.25	308,309
United States	0.18	310
	0.16–0.20	311
Chicago	0.15	312
New York City	0.17	312
San Francisco	0.22	312

[a] Calculated from data published in references 247-249, 297-303.

[b] Stable strontium in diet from reference 176 and in bone from reference 304.

TABLE X. ANNUAL AVERAGE $^{90}Sr/Ca$ RATIOS IN MILK BY COUNTRY OR AREA IN THE NORTH TEMPERATE ZONE

pCi $(gCa)^{-1}$

Year	Country or area										United States of America				
	Canada[218]	Czechoslovakia[220]	Denmark[176]	Federal Republic of Germany[117]	Finland[200]	France[211]	Netherlands[167]	Ukrainian SSR[237]	USSR Moscow[36]	United Kingdom[185]	Whole Country[186]	Chicago[318]	New York City[313]	Salt Lake City[186]	Mean
1955	—	—	—	3	—	—	—	—	—	4	—	—	—	—	3.5
1956	—	—	—	4	—	—	—	—	—	6	—	—	—	—	5.0
1957	—	—	—	6	—	—	—	—	—	6	—	—	5	4	5.3
1958	—	—	—	5	—	—	—	—	—	7	—	7	8	4	6.2
1959	—	—	9	9	—	—	—	—	8	10	—	7	11	6	8.5
1960	—	—	4	7	7	—	—	—	6	6	—	8	8	6	6.5
1961	—	—	4	6	6	—	—	—	4	6	7	6	7	4	5.6
1962	—	—	12	11	13	—	9	—	13	12	11	9	12	8	11.0
1963	26	21	24	26	22	—	25	27	23	26	19	17	26	19	23.2
1964	28	20	25	27	23	—	22	20	18	28	19	16	23	23	22.5
1965	19	18	17	24	18	24	17	11	14	19	14	12	19	17	17.4
1966	13	12	12	16	13	19	15	9	15	12	11	9	12	10	12.7
1967	10	—	9	12	10	14	9	—	8	9	9	8	10	5	9.4
1968	8	—	—	—	9	12	—	—	—	—	—	—	—	—	—
												Total 1955-1967			137

TABLE XI. RATIO OF $^{90}Sr/Ca$ RATIOS IN WHOLE DIET AND IN MILK[236]

Country	1963	1964	1965	1966	1967	Mean for 1963-1967
Argentina	1.8	1.5	1.3	1.3	1.3	1.4
Australia	1.1	1.0	0.9	0.9	1.2	1.0
Denmark	1.3	1.7	1.3	1.2	1.2	1.4
Federal Republic of Germany	1.3	1.6	1.7	1.8	—	1.6
Finland	—	—	1.8	1.6	—	1.7
France	—	—	—	1.0	1.3	1.2
Norway	—	—	1.3	1.3	—	1.3
Sweden	—	—	1.4	1.5	—	1.5
United Kingdom	0.9	0.9	1.0	—	—	0.9
United States	1.2	1.4	1.4	1.4	1.5	1.4
Hawaii	1.6	2.2	3.5	2.1	2.0	2.3
India	—	—	—	3.6	—	3.6
Japan	2.1	2.2	2.3	2.3	—	2.2
Union of Soviet Socialist Republics	2.3	3.1	3.7	3.0	—	3.0

TABLE XII. ESTIMATION OF P_{51} FROM BONE MEASUREMENTS IN AUSTRALIA[a]

Year (t)	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967
Population average $^{90}Sr/Ca$ ratio	.26	.28	.19	.30	.32	.63	.66	.76	.84	1.21	1.26	
Levels integrated to year $t-1$: G_{t-1}		.26	.54	.73	1.03	1.35	1.98	2.64	3.40	4.24	5.45	6.71
Levels integrated from t to ∞: H_t	1.63	1.92	1.22	1.91	2.14	4.45	4.64	5.30	5.83	8.40	8.87	8.31
$G_{t-1} + H_t$	1.63	2.18	1.76	2.64	3.17	5.80	6.62	7.94	9.23	12.64	14.32	15.02
Dietary level integrated to t	4.5	8.3	12.4	17.2	21.6	26.3	32.1	38.5	47.6	58.3	65.5	71.5
P_{51}	.36	.26	.14	.15	.15	.22	.21	.21	.19	.22	.22	.21

[a] From data given in references 247-249, 297-303.

TABLE XIII. ESTIMATION OF P_{34} FROM BONE MEASUREMENTS IN NORTH TEMPERATE LATITUDES[a]

Year (t)	*1954*	*1955*	*1956*	*1957*	*1958*	*1959*	*1960*	*1961*	*1962*	*1963*	*1964*	*1965*	*1966*	*1967*	*1968*
Population average $^{90}Sr/Ca$ ratio	0	0.17	0.28	0.44	0.65	0.70	1.01	1.21	1.32	1.73	2.88	3.33	2.78	2.32	1.92
Levels integrated to year $t-1$: G_{t1}	0	0	0.17	0.45	0.89	1.54	2.33	3.34	4.55	5.87	7.60	10.48	13.81	16.59	18.91
Levels integrated from t to ∞: H_t	0	1.14	1.89	3.00	4.23	5.46	7.10	8.60	9.42	11.95	19.57	23.06	19.91	16.73	13.92
$G_t1 + H_{-t}$	0	1.14	2.06	3.45	5.12	7.00	9.43	11.94	13.97	17.82	27.17	33.54	33.72	33.32	32.83
Levels in diet[b] integrated to t	—	4.90	11.90	19.30	28.00	40.00	49.00	57.00	72.50	104.50	135.30	158.50	175.90	188.10	200.00
P_{34}	—	0.23	0.17	0.18	0.19	0.18	0.19	0.21	0.19	0.17	0.20	0.21	0.19	0.18	0.16

[a] From data given in figure 17.

[b] Dietary levels obtained from milk levels (table X) multiplied by 1.4.

TABLE XIV. VALUES OF $\overline{D}_m/D_0$[a] FOR CORTICAL AND TRABECULAR BONE IN ADULT SKELETON[317]

			Trabecular bone				*Cortical bone*			
Groups of bones	*Basis of calculation*	*Fraction of bone involved*	*Trabecular contribution*	*Mean* $\overline{D}_m/D_0$	*Marrow fraction,* f_m	$f_m\overline{D}_m/D_0$	*Cortical Contribution*	*Mean* $\overline{D}_m/D_0$	*Marrow fraction,* f_m	$f_m\overline{D}_m/D_0$
Hip bone	Hip bone	0.6	0.189	0.1134	0.287	0.0326	0.051	0.0306	0.287	0.0088
Scapulae Clavicles		0.4	0.114	0.0456		0.0131	0.072	0.0288		0.0083
Cranium	Cranium	1.0	0.120	0.1200	0.119	0.0143	0.272	0.2720	0.119	0.0324
Ribs Mandible Sternum	Ribs	1.0	0.138	0.1380	0.114	0.0157	0.136	0.1360	0.114	0.0155
Humeri	Femur	0.53	0.161	0.0853	0.057	0.0049	0	0	0.057	
Femora		0.47	0.134	0.0630		0.0036	0.060	0.0282		0.0016
Vertebrae	Lumbar vertebra	1.0	0.124	0.124	0.423	0.0525	0	0	0.423	0
Sacrum										
						TOTAL 0.1367				TOTAL 0.0666

[a] D_0 is the dose rate to a very small tissue-filled cavity. It is usually taken to be 2.7 mrads y^{-1} per pCi $(gCa)^{-1}$. D_m is the mean dose rate to the bone marrow. Therefore, the bone marrow dose rate factor due to strontium-90 in trabecular bone is $0.1367\ 2.7 = 0.37$ mrads y^{-1} per pCi $(gCa)^{-1}$ and that from strontium-90 in cortical bone is 0.0666 $2.7 = 0.18$ mrad y^{-1} per pCi $(gCa)^{-1}$.

TABLE XV. VALUES OF $\overline{D}_s/D_0$[a] FOR CORTICAL AND TRABECULAR BONE IN ADULT SKELETON[317]

Groups of bones	Basis of calculation	Fraction of bone involved	Trabecular bone: Trabecular contribution	Trabecular bone: Mean $\overline{D}_s/D_0$	Trabecular bone: Endosteal fraction, f_s	Trabecular bone: $f_s\overline{D}_s/D_0$	Cortical bone: Cortical contribution	Cortical bone: Mean $\overline{D}_s/D_0$	Cortical bone: Endosteal fraction, f_s	Cortical bone: $f_s\overline{D}_s/D_0$
Hip bone		0.6	0.299	0.179		0.0545	0.051	0.0306		0.0093
Scapulae	Hip bone				0.304				0.304	
Clavicles		0.4	0.238	0.095		0.0288	0.072	0.0288		0.0088
Cranium	Cranium	1.0	0.200	0.200	0.140	0.0280	0.272	0.272	0.140	0.0381
Ribs										
Mandible	Ribs	1.0	0.229	0.229	0.134	0.0307	0.136	0.136	0.134	0.0182
Sternum										
Humeri		0.53	0.284	0.150		0.0090	0	0		0
	Femur				0.060				0.060	
Femora		0.47	0.256	0.120		0.0072	0.060	0.0282		0.0017
Vertebrae										
	Lumbar vertebra	1.0	0.258	0.258	0.362	0.0934	0	0	0.362	0
Sacrum										
						TOTAL 0.2516				TOTAL 0.0761

[a] D_0 is the dose rate to a very small tissue-filled cavity. It is usually taken to be 2.7 mrads y^{-1} per pCi $(gCa)^{-1}$.D_s is the mean dose rate to the endosteal tissues on the surface of the trabeculae. Therefore, the dose-rate factor to cells lining bone surfaces due to strontium-90 in trabecular bone is 0.2516 2.7 = 0.68 mrads y^{-1} per pCi $(gCa)^{-1}$ and that from strontium-90 in cortical bone is 0.0761 2.7 = 0.21 mrads y^{-1} per pCi $(gCa)^{-1}$.

TABLE XVI. AIR-DOSE CONVERSION FACTORS FOR A PLANE SOURCE[138]

	^{137}Cs	^{134}Cs	^{106}Ru	^{125}Sb	^{54}Mn	^{95}Zr	^{140}Ba	^{141}Ce	^{103}Ru
Dose-rate conversion factor $K_j B_j$[a] mrad y^{-1} *per mCi* km^{-2}	0.079	0.006	0.032	0.063	0.109	0.358	0.349	0.009	0.073
Mean life T_{mj} years	44.0	1.13	1.44	3.90	1.24	0.257	0.051	0.129	0.157
$K_j B_j T_{mj}$	3.48	0.007	0.05	0.25	0.14	0.09	0.02	0.001	0.011

[a] The conversion factors include dose contributions from daughter nuclides.

TABLE XVII. LATITUDINAL POPULATION AND FALL-OUT DISTRIBUTION[50, 315]

Latitude	Area (Mm^2)	Population (per cent)	Total ^{90}Sr deposition 1964-1967 (mCi km^{-2})	Cumulative ^{90}Sr deposition to 1967 (mCi km^{-2})	Total ^{90}Sr deposition 1966-mid-1968 (mCi km^{-2})
70–80°N	11.6				1.7
60–70°N	18.9	0.4	8.8	26.1	3.5
50–60°N	25.6	11.9	18.9	63.8	4.9
40–50°N	31.5	17.7	20.1	66.6	10.5
30–40°N	36.4	23.4	14.6	42.4	9.2
20–30°N	40.2	25.2	11.1	34.0	7.6
10–20°N	42.8	8.4	8.9	9.1	4.2
0–10°N	44.1	4.0	5.7	4.7	5.6
0–10°S	44.1	4.2	3.5	9.4	3.8
10–20°S	42.8	1.7	2.9	6.4	14.1
20–30°S	40.2	1.5	5.1	8.1	30.7
30–40°S	36.4	1.4	6.2	13.6	19.7
40–50°S	31.5	0.1	7.6	13.6	11.9
50–60°S	25.6				1.8

TABLE XVIII. ESTIMATES OF FACTOR Z

		^{90}Sr 1964-1967	^{90}Sr cumulative to 1967	^{89}Sr 1966-mid-1968
	Mean deposition, $\overline{F}$ (mCi km^{-2})	11.5	42.0	6.3
Northern hemisphere	$\Sigma N_i F_i / \Sigma N_i$	14.3	42.8	7.8
	Z	1.24	1.02	1.24
	Mean deposition, $\overline{F}$ (mCi km^{-2})	4.4	9.0	12.3
Southern hemisphere	$\Sigma N_i F_i / \Sigma N_i$	4.2	9.3	12.9
	Z	0.95	1.04	1.04
	Mean deposition, $\overline{F}$ (mCi km^{-2})	7.9	25.5	9.3
Global	$\Sigma N_i F_i / \Sigma N_i$	13.4	39.8	8.3
	Z	1.69	1.56	0.89

TABLE XIX. DOSE COMMITMENTS FROM NUCLEAR TESTS CARRIED OUT BEFORE 1968

				Dose commitments (mrad)			
				Present estimates			1966 Estimates
Tissue	Source of radiation			North temperate zone	South temperate zone	Whole world	Whole world
Gonads	External	Short-lived		36	8	23	23
		^{137}Cs		36	8	23	25
	Internal	^{137}Cs		21	4	21[a]	15
		^{14}C[b]		13	13	13	13
			TOTAL[c]	110	33	80	76
Cells lining bone surfaces	External	Short-lived		36	8	23	23
		^{137}Cs		36	8	23	25
	Internal	^{90}Sr		130	28	130[a]	156
		^{137}Cs		21	4	21[a]	15
		^{14}C[b]		16	16	16	20
		^{89}Sr		<1	<1	<1	0.3
			TOTAL[c]	240	66	220	240
Bone marrow	External	Short-lived		36	8	23	23
		^{137}Cs		36	8	23	25
	Internal	^{90}Sr		64	14	64[a]	78
		^{137}Cs		21	4	21[a]	15
		^{14}C[b]		13	13	13	13
		^{89}Sr		<1	<1	<1	0.15
			TOTAL[c]	170	51	140	150

[a] The dose commitments to internally deposited ^{90}Sr and ^{137}Cs given for the north temperate zone are considered to represent upper limits of the corresponding dose commitments to the world population.

[b] As in the 1964 and 1966 reports, only the doses accumulated up to year 2000 are given for ^{14}C; at that time, the doses from the other nuclides will have essentially been delivered in full. The total dose commitment to the gonads and bone marrow due to the ^{14}C from tests up to the end of 1967 is about 180 mrads, and that to cells lining bone surfaces is about 230 mrads.

[c] Totals have been rounded off to two significant figures.

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Annex B

EFFECTS OF IONIZING RADIATION ON THE NERVOUS SYSTEM

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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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Annex C

RADIATION-INDUCED CHROMOSOME ABERRATIONS IN HUMAN CELLS

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I. Introduction

1. It has been known for a long time that aberrations of chromosome structure (chromosome aberrations or chromosome structural changes) and alterations in chromosome number arise spontaneously at a low rate in somatic and germ cells of plants and animals and that the frequency of such aberrations increases following exposure to ionizing radiations. These aberrations may, in fact, comprise the major component of the genetic damage resulting from radiation exposure, but in many instances the genetic consequences of certain kinds of aberrations are so disastrous as to result in the early death of the cells containing them.

2. Although a considerable fraction of induced chromosome aberrations may behave as dominant lethal events, all aberrations that do not result in an "immediate" loss of viability are mutational changes which may be transmitted to descendant cells and to the offspring of the irradiated individual. Chromosome aberrations are clearly, therefore, of great genetic importance, and a considerable amount of work has been devoted to studying the mechanisms of their induction by radiation, their behaviour at mitosis and meiosis and their genetic consequence.

3. Up until relatively recently, most of this work had been carried out on species particularly well suited to the demands of cytological study (that is, species having a relatively small number of rather large chromosomes) and on organisms amenable to use in breeding experiments (1958, 1962 and 1966 reports[1-3] of the Committee). This work has provided, and will continue to provide, fundamental knowledge on the actions of radiations on chromosomes and also information on the genetic hazards of radiation exposure in the particular species chosen for study. However, extrapolation from these species to man is beset with difficulties, particularly in the absence of any comparable information on the radio-sensitivity of human chromosomes that could serve as a reference point. Quantitative estimates of the radiation hazard to man's chromosomes have, therefore, been fraught with uncertainties.

4. In the late 1950s, routine cytogenetic studies on mammalian chromosomes became possible as a consequence of the development of simple and reliable methods of culturing mammalian cells *in vitro* and of techniques similar to those previously used in plant cytogenetics. Refinements of these techniques[4-7] opened the way for cytological studies on the response of mammalian chromosomes to radiation exposure.

5. In the original work carried out by Bender[8] and by various other authors[9-11] in the United States, studies were made on the effects of x radiation on chromosomes in human epitheloid and fibroblast cell populations cultured *in vitro*, and comparisons were later made between the responses of human cells and of cultured cells obtained from spider monkeys and Chinese hamsters.[12] At about the same time, Fliedner *et al.*[13] reported that chromosome aberrations could be detected in cells from bone-marrow samples taken from a number of persons accidentally exposed to a mixed neutron-gamma-ray beam.

6. Prior to all these observations, a large number of earlier reports had shown that the chromosome aberrations induced by the irradiation of mammalian cells were similar to the aberrations induced in other animal and plant cells.

7. At the same time that these developments in mammalian radiation cytogenetics were occurring, the general field of human cytogenetics was rapidly emerging. The initial work in this field soon confirmed that the kinds of chromosome aberrations already well known to occur in plants and animals also arose spontaneously in man, and demonstrated that, in man, these aberrations were responsible for a number of very important harmful traits (1962 and 1966 reports[2, 3] of the Committee). These advances in human cytogenetics were given further impetus by the development[14] in 1960 of a simple and reliable technique for obtaining preparations of mitotic cells from cultured peripheral blood leucocytes. As a result of these developments, information on the spontaneous frequency and on the general consequences of chromosome aberrations in man has been continually accruing.

8. The advent of the peripheral blood culture technique afforded an opportunity to examine, by means of a simple and painless procedure, the response of human chromosomes in individuals exposed to ionizing radiations. Moreover, since large numbers of mitotic cells could be obtained from only a few millilitres of blood, frequent cell samples could be taken from an individual at various time intervals after exposure. The first studies of this kind were carried out by the Edinburgh group[15] in the United Kingdom, and in the last nine years a great deal of information has been obtained on chromosome damage and the potential hazards of radiation to man's genetic materials.

9. Observations have been made on chromosome aberrations induced *in vivo* in persons x-rayed for diagnostic reasons, in personnel subjected to low-dose occupational exposure (either externally or internally, or to a mixture of both external and internal radiation), in patients exposed to therapeutic radiation and in individuals accidentally exposed to radiation. In addition to this, information is also available on members of the surviving populations at Hiroshima and Nagasaki. Much of the information on patients given therapeutic doses has come from partial-body irradiation studies, and here the data are somewhat difficult to interpret since accurate physical dosimetry, particularly in relation to the cells sampled, is difficult to obtain. More recently, a little information has been gathered from a few patients exposed to low doses of whole-body radiation.[16]

10. Although in terms of application of our knowledge we are clearly most interested in results obtained from *in vivo* studies, a great deal of information can be and is being obtained from *in vitro* studies. Here, cultured cells can be exposed to accurately measured radiation doses, and accurate information on dose-response kinetics, etc. can be obtained. Such knowledge forms an important background to the *in vivo* work, and it has been generally thought it may well prove possible to extrapolate directly from the *in vitro* state to the *in vivo* state, provided certain requirements are met.

11. In view of the developments in this field over the past few years, the Committee decided that an appraisal of the progress made in this area was necessary. The time seemed particularly opportune for two reasons. First, a number of laboratories have made use of chromosome aberration yields as a method of estimating absorbed dose in individuals accidentally exposed to radiations, and a considerable amount of information on the relation between dose and aberration yield from both *in vivo* and *in vitro* exposure has been accumulating. Second, as a consequence of the developments in human cytogenetics, there has been an increasing amount of information on the importance of certain aberrations as causal factors in human congenital abnormalities and also on the possible association between certain kinds of chromosome aberrations in somatic cells and the development of neoplastic disease.

12. As the Committee is primarily concerned with evaluating risks and with reviewing pertinent scientific data, information on the genetic consequences of chromosome aberrations in man and on the possibility of using the levels of chromosome-aberration yield following radiation exposure as a measure of dose is particularly relevant. In the present report, therefore, emphasis has been placed on somatic cell damage, and attention has been centered on methodology, the possible application of aberration yields in dosimetry, their biological significance and their possible use in the assessment of risk.

II. The types of aberrations produced, their structure and behaviour

A. The general pattern of response

13. The types of chromosome aberrations induced in human cells are identical in structure and behaviour with the aberrations induced in other animal and plant cells having similarly organized monocentric chromosomes. These aberrations are usually considered to be of two basic types—the simple deletion, which may be the result of a single break in the chromosome thread, and the exchange, which involves at least two breaks and an exchange of parts either between different chromosomes (interchange) or between different parts of the same chromosome (intrachange).

14. The detailed mechanisms of formation of the aberrations are not fully understood, and two hypotheses are currently in vogue (see reference 17). The more generally accepted classical theory, which was developed principally by Sax[18-20] and later by Lea and

Catcheside (see reference 21), proposes that x-ray induced simple deletions are a consequence of single breaks in the chromosome produced through the action of a single electron track, whereas exchange events are a consequence of the aberrant rejoining of breaks produced through the action of one or more (usually two) separate electron tracks.

15. On this classical theory, the evidence obtained from dose, dose-rate and dose-fractionation studies is interpreted to indicate that broken chromosome ends remain available for rejoining with themselves (thus restituting the original chromosome structure) or with other broken ends (thus giving rise to an exchange aberration) for only a limited time period (rejoining time) of around thirty minutes.[18, 21] This timing, however, is very dependent upon conditions.[23] Since the exchange aberrations can only be produced if the two breaks involved are closely associated spatially[21, 22] and are produced close together in time, it follows that, on this theory, the yield of simple deletions should increase linearly with increasing x-ray dose, and two-break exchanges should increase as approximately the square of the dose, when exposure times are short relative to the rejoining time (see references 17 and 21).

16. On the exchange hypothesis of Revell,[24] all aberrations, including the so-called simple chromatid deletions, are believed to be a consequence of exchange. On this hypothesis a proportion of the simple deletions could result from the interaction of the effects of two separate electron tracks. The deletions are believed to be the consequence of an incomplete exchange between two regions within a chromosome so that the deletion is associated with an inversion or duplication of a short length of the chromosome at the point of "failed union". Thus, on this hypothesis, simple deletions can show either a negligible or a significant "dose-squared" component in their rate of increase with increasing x-ray dose.[25] On both hypotheses, with high LET radiations all aberration types increase linearly with increase in dose.[17, 23]

17. In general, although there are certain exceptions, proliferating somatic cells spend by far the majority of their lifetimes in an interphase state and pass relatively rapidly through the division process of mitosis. The duration of interphase may range from the life span of the individual in a non-dividing differentiated cell, to a number of years in a mitotically quiescent cell or to a period of less than one day in the case of an actively proliferating cell. In all cases, however, the duration of the mitotic phase is usually, at most, an hour or two and is, therefore, short in relation to interphase. Thus, although the chromosome aberrations produced in irradiated cells are only observed when the chromosomes appear at mitosis (or at meiosis in the gonads), on the average almost all the aberrations produced are a consequence of damage sustained in an interphase state.

18. The aberrations observed in dividing cells are thus visible manifestations of radiation damage sustained at an earlier point in time. A number of cellular (enzymic) processes may, therefore, intervene between the initial radiation exposure and the final development of an aberration. Thus, for a given cell type, radiation dose, quality, etc., the final yield of aberrations may be modified by physiological as well as physical factors. The influence of such modifying factors was considered in some detail in the Committee's 1962 and 1966 reports.[2, 3]

19. The types of aberrations induced following radiation exposure fall into three groups according to the unit of breakage or exchange that is involved. Aberrations which involve both chromatids of a chromosome at identical loci are generally referred to as *chromosome-type* aberrations, whereas those in which the unit of aberration formation is the half-chromosome or chromatid are termed *chromatid-type* aberrations. The third category of aberrations known as *subchromatid-type* aberrations appear to involve breakage and exchange of subunits of a chromatid.

20. Which of the three basic types of chromosome aberrations are observed at mitosis (or at meiosis) depends upon the stage of development of the cell at the time of irradiation. In a mitotically proliferating cell, the interphase period of the cell cycle can be partitioned into three phases:[26] the pre-DNA synthesis or G_1 phase of early interphase; the DNA synthesis or S phase; and the post-DNA synthesis or G_2 phase of late interphase. With few exceptions, cells not actively proceeding through a mitotic cycle usually rest in the G_1 phase (for example, the peripheral blood small lymphocyte in normal healthy individuals), and such cells are sometimes referred to as being in a G_0 state.[27] However, there are exceptions to this general rule, and certain types of mitotically inactive cells (for example, certain epidermal cells in the mouse ear)[28] may rest in a G_2 phase.

21. Irradiation of all resting cells and of the majority of proliferating cells in a G_1 phase results in the production of chromosome-type aberrations. At the very end of the G_1 phase[29, 30] there is a transition from the chromosome-type aberration to the chromatid-type, and this transitional phase extends from late G_1 into early S (figure 1). Thus, most of the cells irradiated while in S and all the cells exposed while in G_2 yield chromatid-type aberrations. Subchromatid-type aberrations are only produced in cells irradiated in the early prophase of mitosis (or mid-prophase of meiosis), and cells exposed to radiation at the metaphase or later stages of mitosis yield chromosome-type aberrations at their next mitosis (see figure 1 and reference 17).

22. In addition to aberrations involving changes in chromosome structure, certain kinds of damage may also result in alterations in chromosome number and yield aneuploid or polyploid cells (paragraphs 77-89). Such changes in chromosome number are the result of errors (non-disjunction) in chromosome or chromatid segregation at meiosis or mitosis, and these errors are often, although not invariably, a consequence of the presence of chromosome structural changes.

23. It should be emphasized here that all of the varieties of chromosome structural changes and of changes in chromosome number that are to be observed in irradiated cells are also to be found in cells exposed only to natural background irradiation. The frequency of such spontaneous aberrations in unirradiated cells from normal healthy individuals is, of course, extremely low (table I), but the kinds of changes found are precisely the same as those induced as a consequence of radiation exposure.

B. Chromosome-type aberrations

24. Chromosome-type aberrations, in which both chromatids of a chromosome are broken or exchanged at the same locus and in an identical fashion, are the aberrations that have been most frequently studied in human cells. This is because most of the work on man

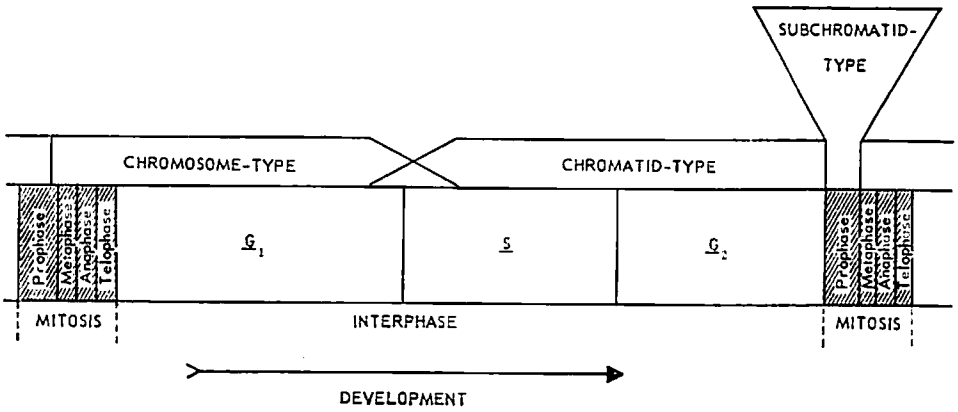

Figure 1. Relation between type of aberration induced by radiation and stage in cell cycle at time of irradiation

has been carried out on peripheral blood leucocytes that were irradiated while in a resting G_1 phase and examined at a mitotic metaphase following the stimulation of development of these cells in culture.

25. Studies on metaphase somatic cells reveal that seven kinds of chromosome-type aberrations can be distinguished cytologically (figure 2). Aberration types (i) to (v) are produced within single chromosomes

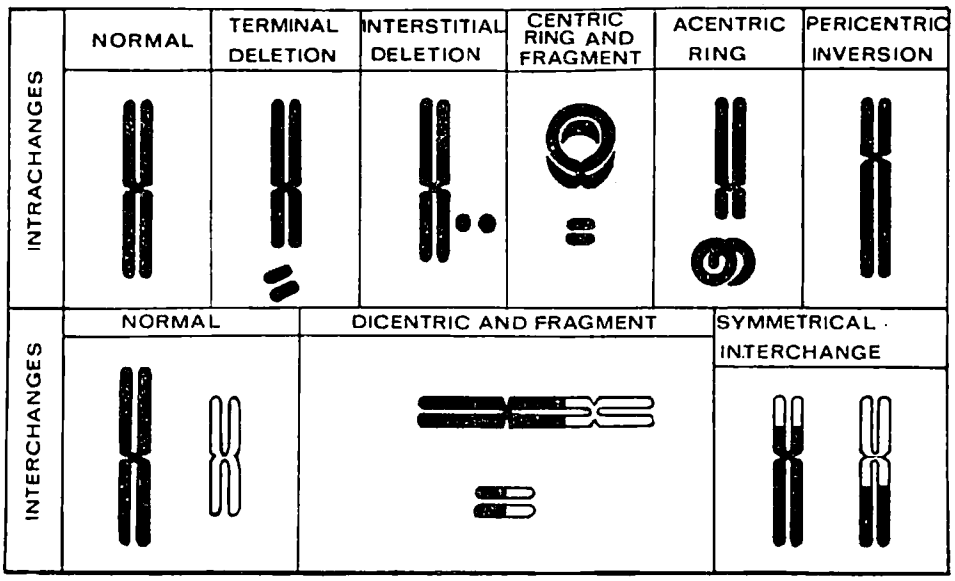

Figure 2. Chromosome-type aberrations that can be distinguished cytologically at mitosis

and are referred to as *intrachanges,* whereas types (vi) and (vii) involve an exchange of parts between different chromosomes and are, therefore, *interchanges.*

26. (i) *Terminal deletions* are paired acentric fragments which have the appearance of resulting from a simple break across the chromosome and are not associated with an exchange aberration such as a ring or interchange (paragraphs 28, 33-34). Some authors refer to terminal deletions simply as free acentric fragments.

27. (ii) *Minutes (interstitial, isodiametric or dot deletions)* are pairs of acentric fragments, smaller in size than terminal deletions, characteristically appearing as paired spheres of chromatin, hence the terms, dot or isodiametric deletions. These deletions are usually not terminal but intercalary and are the consequence of two closely juxtaposed transverse breaks across the chromosome.

28. (iii) *Acentric rings* are the result of two transverse breaks and an exchange within the chromosome. The linear separation between the two breaks is greater than in the case of minutes so that the excised paired fragments are larger and are ring-shaped. The distinction between minutes and rings is often arbitrary, since it is based purely on the size of the interstitial region of the chromosome that is deleted.

29. (iv) *Centric rings* are ring-shaped chromosomes resulting from an exchange between two breaks occurring on either side of the centromere. The centric-ring aberration is clearly distinguished from its acentric counterpart and is accompanied by one (rarely two) acentric fragments.

30. (v) *Pericentric inversions* result from two breaks, one on each side of the centromere, followed by the inversion of the centromeric segment and its reincorporation into the chromosome. If the two breaks (or points of exchange) are not equidistant from the centromere, then the pericentric inversion is clearly characterized by the altered location of the centromere within the chromosome. However, if, as is probably most often the case, the exchange points are approximately equidistant from the centromere, then the in-

version cannot be detected in mitotic cells but could be detected in meiotic cells following chromosome pairing.

31. Paracentric inversions, where both points of exchange lie on the same side of the centromere, cannot be cytologically detected in mitotic cells but could be identified at meiosis.

32. In types (ii) to (v), the exchange event may, in a small proportion of cases, be incomplete, only two of the four free ends involved in the exchange actually undergoing rejoining. Thus, an incomplete paracentric inversion will be scored as a terminal deletion, and a ring chromosome may be accompanied by two, rather than one, acentric fragments.

33. (vi) *Symmetrical interchanges (reciprocal translocations)* are exchange aberrations resulting from a breakage in each of two chromosomes followed by aberrant rejoining such that the distal regions of the two chromosomes are transferred (translocated) from one to the other. The aberrations are described as being symmetrical since they do not result in the formation of a dicentric structure (paragraph 34). Occasionally, if the exchange is incomplete, an acentric fragment may result. If the exchange is equal, that is, if an equal length of chromatin is translocated from one chromosome to the other, then the exchange could be detected at meiosis. Such an exchange could not be detected in somatic cells, however, except when incomplete, in which case it would appear as a simple terminal deletion. Symmetrical interchanges between acrocentric chromosomes are sometimes referred to as centric fusions. They result from the translocation of entire chromosome arms, the exchange occurring in the region of the centromeres of the chromosomes involved.

34. (vii) *Asymmetrical interchanges (dicentric aberrations or more complex polycentrics)* are exchange aberrations due to a breakage in each of two or more chromosomes followed by aberrant rejoining such that the proximal regions of the chromosomes become united, thus forming a dicentric or polycentric structure and an associated acentric fragment (rarely two fragments, when the exchange is incomplete and the two distal regions do not unite).

35. As mentioned above, incomplete rejoining in exchange results in an increased frequency of free fragments associated with an aberration. It should be stressed, however, that the fragment associated with an exchange aberration, such as a dicentric or centric ring, is part of the exchange aberration and is not scored as a separate fragment, that is, as a terminal deletion. The presence of a dicentric- or centric-ring structure with no accompanying fragment is an almost certain indication that the aberrant cell has proceeded through at least one mitotic division after irradiation and prior to observation.

36. Mention has been made of the difficulties in detecting certain forms of pericentric inversions (inter-arm intrachanges) and of symmetrical interchanges in somatic cells so that not all seven chromosome-type aberrations considered can be scored with equal efficiency. It is to be expected that pericentric inversions that do not result in a change in the relative arm lengths of a chromosome must comprise a significant proportion of the total of such aberration types. This is so because, as a result of the V-shaped arrangement of the chromosomes following anaphase separation and of the restrictions on chromosome movements in interphase,[17, 31] there must be a much higher probability of exchange between points equidistant from the centromere than between points at different distances. Similarly, in the case of symmetrical interchange aberrations, exchanges between points equidistant from the centromeres of the two chromosomes involved will be very frequent. Thus, if the chromosome complement contains a number of chromosomes having arms of equal or similar lengths, as is the case in the human complement, then a symmetrical exchange often will not result in an altered morphology of the exchanged chromosome(s), and the aberration will pass undetected.

37. The inefficiency of scoring symmetrical and equal inter- and intrachange chromosome-type aberrations is not encountered in the comparable chromatid-type aberrations. At the chromatid-type level, because of the close pairing between sister chromatids, asymmetrical and symmetrical aberrations can all be scored with equal efficiency. Studies on chromatid-type aberrations in plants and animals have shown that the symmetrical and asymmetrical variants of any given aberration type occur at approximately equal frequencies,[17, 21] and it has generally been assumed that this approximate equality must also obtain at the chromosome-type level. This assumption has recently been confirmed in studies on the morphologically well-marked large chromosomes of the plant *Vicia faba*, where the frequency of involvement of these chromosomes in symmetrical (reciprocal translocation) and asymmetrical (dicentric) chromosome interchange was shown to be equal.[32]

38. Since it is to be expected that asymmetrical and symmetrical interchange events occur with equal frequency in irradiated human cells, it is possible to estimate from published data[16, 33-35] that the efficiency of scoring symmetrical events in man's chromosomes is not more than 20 per cent. This follows from the fact that the frequency of dicentric- plus centric-ring aberrations should equal the frequency of reciprocal translocations plus pericentric inversions, whereas, in the data available, dicentric and ring chromosomes are approximately five times as frequent as abnormal monocentric chromosomes. Similarly, the frequency of acentric-ring plus minute aberrations should correspond to the frequency of paracentric inversions. As noted earlier, paracentric inversions cannot be detected in mitotic cells.

39. In addition to the general difficulties in detecting symmetrical aberrations, it should be noted that the efficiency of their detection varies between different observers. However, these problems do not arise in the case of the asymmetrical aberrations. It is for these reasons that it has long been the practice of radiation cytogeneticists working on plant and animal cells to classify chromosome-type aberrations into terminal deletions, minutes, acentric rings, centric rings and dicentrics (polycentrics) and to use data on these aberrations, but not data on pericentric inversions and symmetrical interchanges, for quantitative studies.

40. It should be stressed that the aberrations described under the above five headings form the bulk of the structural alterations that can be observed. They can be scored efficiently and there is little variation due to subjective differences between different observers. In the case of the possible use of chromosome aberration yields as indicators of absorbed dose in man, there is little doubt that the classification of the

aberrations into these categories is essential. However, it is important to note that the aberrations that are simplest and least ambiguous to score include many of those that may result in cell death.

41. For instance, at the anaphase stage of mitosis, a proportion of the dicentric aberrations form chromatin bridges linking the two anaphase groups and interfering with the mechanical separation of the two daughter cells. Such an interference frequently results in the death of the cells. In addition, chromosome fragments lacking centromeres may be excluded from the daughter nuclei produced as a result of mitosis, and, depending upon the gene content and amount of material lost, such genetically deficient nuclei may be inviable. In general, therefore, a considerable proportion of the asymmetrical aberrations constitute a short-term hazard in the sense that the cells that carry them have a very much reduced potential for survival. However, those cells that can survive will still be mutant and constitute a long-term hazard both to the individual and, if present in the germ line, to his offspring.

42. On the other hand, symmetrical aberrations, which are simply a consequence of the rearrangement of chromosome material either within or between the chromosomes in the complement, will not result in any chromatin deficiency when induced in somatic cells. Cells carrying such aberrations will encounter no mechanical difficulties in proceeding through the mitotic process and may be perfectly viable. However, if such changes are present in the germ line, then, as a consequence of chromosome pairing and segregation at meiosis, they may result in sterility and in the production of unbalanced gametes. For example, a number of spontaneous translocations are known to exist in man[3] and these are, in certain cases, responsible for a reduced fertility and, in others, for the production of viable offspring with harmful traits, for example, Down's syndrome.

43. It should, therefore, be re-emphasized here that the criteria for scoring aberrations are not based on their particular biological importance. Thus, although the symmetrical aberrations which result in little or no change in chromosome morphology are difficult to score objectively, they nevertheless may constitute a very important long-term hazard, since they result in transpositions and rearrangements of chromatin between non-homologous chromosomes and in duplications and inversions of the genetic materials. Moreover, these aberrations are equally as frequent as their asymmetrical counterparts. At present, the scoring of such symmetrical aberrations in somatic cells is both tedious and extremely inefficient, but their detection might well be improved with the advent of mechanization and computer techniques in cytogenetics.[36-42]

44. The method of classification of the aberrations that has been outlined is that generally in use by radiation cytogeneticists and is based on the structure of the aberrations. This method of scoring does not involve any assumptions as to the precise mechanism of formation of any particular aberration and does not group together aberrations that are structurally different but which may have similar mechanical consequences at mitosis.

45. An alternative system, which does involve assumptions as to the mechanism of formation of aberrations, was originally proposed by Darlington and Upcott[43] in their early work on chromosome aberrations in plant cells. This system, however, was superseded by the descriptive classification. In more recent years, an additional and more general classification has been introduced.[44, 45] This classification places emphasis on the cells carrying the aberrations, cell types being defined, as indicated in the subsequent paragraphs, on the basis of the kinds of aberrations that they contain.

46. *Type A Cells* have no apparent evidence of a structural chromosome abnormality. They may be divided into "modal A cells" that are apparently normal diploid cells and "non-modal A cells" that are aneuploid, that is, that contain fewer or more chromosomes than the normal diploid number.

47. *Type B cells*, as originally defined,[44] included two sorts of cells, those containing chromatid gaps or isochromatid gaps (non-staining regions of the chromosome either affecting one or both chromatids), which are not discontinuities and do not result in the formation of acentric fragments, and cells containing simple chromatid breaks (chromatid terminal deletions) but not isochromatid aberrations nor presumably chromatid minutes. In other words, type B cells, as originally defined, contain either non-staining gaps or one of the many possible types of chromatid-type aberrations. Fortunately, however, the phrase, "type B cells", has come to be used to describe cells containing chromatid-type aberrations of any kind (see reference 33) as opposed to cells carrying chromosome-type aberrations (type C cells).

48. *Type C cells* contain chromosome-type aberrations. Type C cells were originally put into three categories, C_1, C_2, C_3,[44] but later[45] they were reclassified into two categories, C_u and C_s. C_u cells contain asymmetrical aberrations or incomplete symmetrical aberrations, that is, dicentrics (polycentrics), ring chromosomes or fragments. The suffix, u, in C_u denotes the fact that the cell contains an "unstable" aberration which will either result in mechanical difficulties at mitosis or result in a loss of chromosome material in the form of an acentric fragment. C_s cells contain "stable" aberrations, that is, complete symmetrical aberrations (symmetrical interchanges or pericentric inversions), which can only be detected if the exchange events result in a change in the position of the centromere or in the lengths of the chromosomes involved in a rearrangement (paragraph 36).

49. It has already been stressed that the C_s cells can only be detected with very low efficiency. It should also be pointed out that certain types of C_u cells (for example, those containing small terminal or intercalary deletions) may be unambiguously scored as clear C_u cells at the first mitosis after irradiation, but that, if viable, their descendants could well be scored at the second or subsequent mitosis following irradiation as either normal A cells or as C_s cells.

50. The use of the C_s and C_u form of classification may be useful as a short-hand system, particularly when considering the fate of cells carrying aberrations over very long periods of time after irradiation; this is precisely where this general scoring system has been largely employed. Nevertheless, there can be no question that the maximum information can only be obtained when aberrations are categorized on the basis of their detailed structure. The Committee, therefore, strongly recommends that the detailed system of scoring be employed, particularly in those cases where attempts are made to obtain information on dose-response relationships.

C. Chromatid-type aberrations

51. Chromatid-type aberrations occur if damage is sustained either at the time of, or following, chromosome splitting and replication in late G_1 and S of the cell cycle[17, 29, 30] (paragraphs 19-21). In the case of unsplit G_1 chromosomes, any radiation damage sustained is itself replicated when the cell proceeds into S so that the whole chromosome (both chromatids) is involved in a chromosome-type aberration, both sister chromatids being affected in exactly the same way and at identical loci. Chromatid-type aberrations are thus distinguished by the fact that the unit of breakage or exchange is the single chromatid.

52. Chromatid-type aberrations are, therefore, induced in cells irradiated while in the DNA synthesis (S) and post-DNA synthesis (G_2) stages of interphase. Such aberrations also arise spontaneously, presumably as a consequence of replicating errors. They can be readily induced by exposure of cells *in vivo* and *in vitro* to a wide variety of chemical agents and have been found in peripheral blood leucocytes taken from individuals suffering from certain virus infections and in cultured fibroblasts exposed to viral and other infectious agents.

53. A large proportion of the chemical agents that produce mutations in micro-organisms, insects and plants induce chromatid-type aberrations in plant[46-48] and mammalian[47, 49] cells exposed *in vivo* or while in continuous culture *in vitro*. A number of these agents, particularly those known to interact with DNA or to interfere with DNA synthesis (including carcinogenic hydrocarbons such as dibenzanthracene),[50] have now been tested in human cells and shown to produce chromatid-type aberrations in peripheral blood leucocytes and in fibroblasts exposed *in vitro*.[51-70] Similar aberrations are also to be found in leucocytes taken from patients treated for certain clinical conditions with potent mutagens, for example, nitrogen mustard.[71-75]

54. Considerable interest has recently been aroused in the possibility that the hallucinatory drug, lysergic acid diethylamide (LSD-25), might act as a mutagenic agent in man. Cohen *et al.*[76] originally presented evidence indicating that exposure of peripheral blood leucocytes in culture to LSD resulted in the production of chromosome aberrations; in addition, a low, but significantly increased, aberration yield was found in cultured peripheral blood cells taken from a patient extensively treated with this drug over a period of four years.

55. More recent studies on LSD users (which frequently include individuals taking other drugs in addition to LSD) have yielded conflicting results. Some authors[77-79] have reported small, but significantly increased over normal, aberration yields in cultured leucocytes of LSD users, whereas others have found no evidence of a change in aberration yield in LSD users[80, 81] or in patients treated with LSD.[81, 82] Studies on the mouse[83] have yielded suggestive evidence of a slight effect on high doses of LSD on meiotic chromosomes, whereas mutation studies in *Drosophila* have either shown no effects[84] at does levels comparable to those used in the mouse work or significant increases in the yield of recessive lethals when massive, highly toxic, doses were used.[85]

56. The demonstration by a number of workers[86-108] that viral infections may produce chromatid-type aberrations in human and in other mammalian cells and the possible implications of virus infection in relation to carcinogenesis (paragraphs 286-288) has prompted a variety of studies on this aspect of aberration production. A wide variety of both DNA and RNA viruses has been reported as being responsible for the production of chromatid aberrations in human peripheral blood leucocytes and in human and other mammalian fibroblast cells maintained in continuous culture. The viruses that have been claimed to induce aberrations include Sendai virus,[86] chicken pox virus,[87] measles virus,[99, 100, 102] yellow fever,[93] vaccinia,[109] poliomyelitis,[88] the Schmidt-Ruppin strain of the Rous sarcoma virus,[94, 99, 103] herpes simplex,[104, 107] cytomegalovirus,[105] infectious hepatitis virus[87, 88, 95, 96] and various human and simian adenoviruses.[106]

57. Studies on human embryo cells exposed to avian pseudo-plague virus have shown that infection with viable virus results in the formation of chromosome structural changes but that no such changes are produced following exposure of the cells to heat-inactivated virus.[110] In addition, chromatid aberrations have been reported in cultured human fibroblasts infected with *Mycoplasma*[111, 112] and similar aberrations reported[113] in *Drosophila* exposed to Rous sarcoma virus and in other arthropods infected with a "Rickettsia-like" organism.[114]

58. Although there are conflicting reports on the presence or absence of aberrations in cultures of peripheral blood leucocytes from patients suffering from various virus infections,[91, 93, 108] there is no doubt that, under certain conditions, viral and other infectious agents can induce chromatid-type aberrations in human cells. The general conclusion arrived at by many workers in this field is that the effects of these agents on chromosomes are very similar to the effects of chemical mutagens that interfere with DNA synthesis. This conclusion is supported by the observations of Nichols *et al.*[68] of a synergistic action of the Schmidt-Ruppin strain of the Rous sarcoma virus and of cytidine triphosphate (a nucleoside triphosphate that induces chromatid-type aberrations in human cells) in producing chromatid aberrations in human leucocytes treated *in vitro*. Moreover, the aberrations induced by nucleosides and by viral agents are both localized to particular chromosomes and chromosome regions[67, 68] and thus differ from radiation-induced aberrations which are more randomly distributed.

59. It is important to note that Stich and Yohn[106] have recently obtained evidence that, at least in the case of certain types of adenovirus, aberrations are only produced by viruses which initiate but do not complete a full replication cycle. Moreover, it should be pointed out here that chromatid aberrations observed in peripheral blood leucocytes of patients suffering from virus infection are actually produced when the cells are in culture. (Chromatid-type aberrations produced *in vivo* would appear, if the cells were viable, in the first mitosis observed in culture as "derived" chromosome-type changes.) Indeed, it has been suggested[115] that the conflicting reports from different individuals and laboratories may be simply due to positive results being obtained more often when cells are allowed to proceed through more than one cell cycle in culture prior to observation.

60. It should be strongly emphasized that, in the case of the viruses, of the alkylating agents and of the majority of the other chemical mutagens that have been studied, *only* chromatid-type structural changes

have been seen at the *first mitosis* following treatment. The aberrations produced by these agents presumably arise as a consequence of misreplication,[116, 117] so that aberrations are not directly produced in cells exposed while in the G_1 phase of interphase. On the other hand, exposure of such G_1 cells to ionizing radiations results in the formation of typical chromosome-type aberrations.

61. The kinds of chromatid-type aberrations produced by ionizing radiations in S and G_2 cells and by a variety of mutagens, including ultra-violet and the chemical and infectious agents referred to above, are all basically similar and are similar to those that arise spontaneously in culture. However, because the unit of aberration formation is the chromatid, and because sister chromatids remain closely paired at mitosis, these aberrations exhibit a greater variety and are more efficiently detected at mitosis than their chromosome-type counterparts.

62. The variety of possible chromatid-type aberrations has been discussed in detail by a number of authors,[17, 118] and a detailed description and illustration of these aberrations will not be given here. In brief, the aberrations include terminal deletions, intercalary deletions (chromatid minutes), acentric rings, isochromatid deletions, duplications, inversions, interarm asymmetrical intrachanges (centric rings), interarm symmetrical intrachanges (equivalent to pericentric inversions) and symmetrical (reciprocal translocations) and asymmetrical (chromatid dicentrics) interchanges.

63. In addition to these chromatid-type structural changes, cells irradiated in the S or G_2 phases of interphase, or subjected to infectious agents or to certain chemical mutagens, may also contain achromatic lesions that are usually referred to as gaps or erosion zones. These gaps do not represent transverse breaks across the chromatid thread but are simply unstained regions similar in appearance to normal secondary constrictions or nucleolar organizing regions.[24, 119] There is evidence from studies on plant chromosomes that these gaps are reparable lesions that do not result in a permanent structural change in the chromosome.[120, 121].

64. Information on the spontaneous yield of chromatid-type aberrations in human cells has been obtained from studies on peripheral blood leucocytes. Although a number of reports (paragraphs 65-66) have indicated that the frequency of spontaneous chromatid aberrations (more particularly chromatid deletions) in these cells may be somewhat variable (averaging around 0.05 per cell), there is no doubt that much of this variability is due to cells being allowed to proceed through more than one cell cycle in culture before sampling. The aberrations are, therefore, produced in culture (probably as a consequence of misreplication). Culture conditions are extremely important in this connexion, particularly since the cells and cell products themselves contribute to changing conditions.

65. Mouriquand *et al.*[122] in a study of 1,000 leucocytes taken from ninety individuals and cultured for seventy-two hours prior to observation, reported a chromatid-deletion frequency of 0.057 per cell and a chromatid-gap frequency of 0.077 per cell. In a somewhat larger study carried out by Court Brown *et al.*,[123] the frequency of chromatid aberrations, including gaps, in 12,000 leucocytes cultured for seventy-two hours was around 1 per cent. More recently, in a survey[124] in which care was taken to sample cells at their first mitosis in culture, 1,200 leucocytes from 400 individuals were examined, and it was found that the frequency of chromatid-type aberrations in these cells was very low (0.033 aberrations per cell) and did not vary with the age of the donor. Moreover, in this latter survey, it was clearly shown that the frequency of these aberrations increased with increasing duration of the period of leucocyte culture.

66. A number of workers have noted the presence of chromatid-type aberrations in peripheral blood leucocytes irradiated *in vitro* during the G_1 phase and in cells obtained from individuals exposed to ionizing radiations. The frequency of these aberration types in irradiated individuals is very low (for example, around 0.02 aberrations per cell)[125] and is usually similar to the frequency of these aberrations in blood cells of unirradiated personnel. Indeed, studies on patients following radio-therapy treatment,[16,126,127] accidental or occupational radiation exposure[125,127-132] and exposure to radiation following a nuclear explosion[133-135] have revealed no significant differences in yields of chromatid-type aberrations between irradiated and control personnel.

67. On the other hand, there have been some suggestions of a slightly increased chromatid-type aberration yield in irradiated personnel.[136] and, in two instances, reports of much higher yields in cells irradiated *in vitro* and sampled seventy-two to ninety-six hours after exposure.[137,138]

68. Since chromatid-type aberrations cannot be directly induced by the irradiation of unstimulated leucocytes, their presence in such cells is generally agreed to be almost certainly due in part to a possible secondary effect giving rise to these aberrations in culture (and this is particularly true in *in vitro* radiation experiments) and largely to effects occurring in culture that may have no connexion whatsoever with a radiation exposure. It should also be pointed out that, when relatively high yields of "spontaneous" chromatid aberrations are observed, very few exchange aberrations are noted, virtually all the aberrations being simple deletions (see reference 139). This very low frequency of exchange suggests that some of the chromatid breaks that are observed may well be consequences of the mechanical forces operating when the cells are being dried during cytological processing.

69. Chromatid-type aberrations can, of course, be induced by radiation *in vitro* if the radiation is delivered during late interphase.[11, 140-146] Moreover, such aberrations are induced if the cells are exposed to radio-activity labelled DNA precursors.[147, 148] Similarly, these aberration types will be produced *in vivo* in those cells that are actively engaged in proliferation at the time of radiation exposure. However, these chromatid-type aberrations will be lost before cells develop into circulating lymphocytes, or, if the aberrations are symmetrical and therefore do not result in mechanical difficulties in the separation of chromatids at anaphase, they will pass into the daughter cells, proceed through a replication phase and reappear as "derived" chromosome-type changes at the following mitosis (paragraph 74 and figure 3).

70. Since chromatid-type aberrations can only be induced in cells irradiated while in the S or G_2 phases

of the cell cycle, they are clearly quite useless as indicators of dose in cells, such as the peripheral blood leucocytes of man, exposed to radiation while in the G_1 phase. However, these aberrations can be used as dose indicators in normally proliferating cell populations, although it should be noted that the yield of chromatid-type aberrations at any given dose level is very much dependent upon the exact stage of development of the cell at the time of exposure (see reference 149).

71. Detailed studies on cells of the plant *Vicia faba*[121] have shown that the chromatid-type aberration yield induced by x rays in mid-G_2 cells may be three or four times higher than the yield induced in early G_2 cells. Moreover, G_2 cells are more sensitive than S cells, and variations also occur within the S phase. Similar variations have also been observed in mammalian cells irradiated either *in vivo* or *in vitro*. For instance, the yield of chromatid-type aberrations in Chinese hamster fibroblasts receiving doses of 250 rads from cobalt-60 gamma rays *in vitro* was found to be three times higher in cells exposed while in G_2 than in cells exposed while in S.[150] Similarly, data on bone-marrow cells taken from Chinese hamsters that had received 100 rads from x rays[151] (240 kV, 15mA, HVL = 2mm of Cu) or 100 rads from cobalt-60 gamma rays[151] *in vivo* also show that cells in G_2 are much more sensitive than cells irradiated in earlier phases of the cycle.

72. The limited number of studies that have been carried out with human cells on change in aberration yield with change in cell phase all accord with the earlier observations made on plant and other animal cells in showing that changes in response occur with changes in development phase. Most of the studies on radiation-induced chromatid-type aberrations in human cells have either been made on samples observed at only one fixation time after x irradiation[141, 143, 144] or many hours after exposure,[8] or on samples fixed at unspecified times after irradiation. The four studies on peripheral blood leucocytes[142, 144, 146] and on "fibroblast-type" cells in culture,[11] where samples were fixed at various times after irradiation, indicate that, for a given x-ray exposure, the yield of chromatid-type aberrations is higher in G_2 than in S cells. This change in response both within and between cell phases at the chromatid-type level underlines one of the difficulties inherent in the use of these particular aberration types as indicators of dose.

73. The intraphase variation in sensitivity that has been observed for chromatid-type aberrations is not apparent with the chromosome-type aberrations. Studies on plant cells[18, 22, 153, 154] and human peripheral blood leucocytes[34, 115, 155-157] (paragraphs 124-137) indicate that the yield of chromosome-type aberrations is constant throughout the G_1 phase. In the plant and animal studies referred to above, it has generally been found that, at a given dose level, the yield of chromosome-type aberrations is less than the yield of chromatid-type aberrations. The limited comparisons that have been made between the frequencies of those two kinds of aberrations in human peripheral blood leucocytes suggest that a similar pattern exists, the maximum sensitivity occurring in cells irradiated while in G_2.[141, 142, 144]

74. It should be emphasized here that symmetrical chromatid intrachanges (including duplication, deficiencies and pericentric inversions) and symmetrical interchanges will all result in an abnormal monocentric chromosome in one (or in both in the case of interchange) of the daughter cells produced as a result of mitosis. The replication of these abnormal chromosomes will result in the appearance of "derived" symmetrical chromosome-type aberrations at the second mitosis following their induction. Similarly, if asymmetrical chromatid interchanges and chromatid fragments are included in the daughter nuclei, then these also will result in "derived" chromosome-type aberrations appearing at the second mitosis. Such asymmetrical chromatid aberrations (for example, dicentric chromatids) have a finite probability (up to P = 0.5) of being transferred intact to one of the daughter nuclei so that up to one-half of them will inevitably result in "derived" chromosome-type aberrations (figure 3).

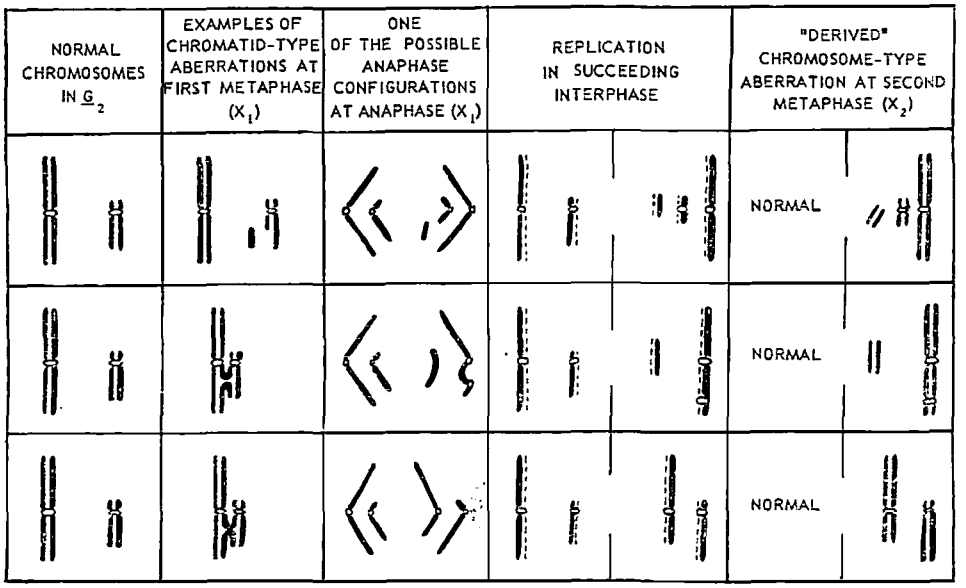

Figure 3. Examples of "derived" chromosome-type aberrations at the second (X_2) mitosis after irradiation[a]

[a] These aberrations have been derived from aberrations that were of the chromatid-type at the first mitosis after irradiation. Note that only a limited number of the possible anaphase configurations are shown and that in many instances an acentric fragment will be lost and may not, for example, be found in association with the chromosome(s) from which it is derived.

D. Subchromatid-type aberrations

75. Subchromatid-type aberrations are exchanges within or between chromosomes which appear to involve a subunit of the chromatid.[17] These aberrations arise spontaneously in meiotic prophase cells of a wide variety of plant and animal species[14] but have not so far been recorded in man. They can be induced by chemical agents, ultra-violet light and ionizing radiations,[17, 46, 48] but they are produced only in cells exposed while in early prophase of mitosis or meiosis.

76. Because subchromatid-type aberrations are relatively infrequent and because they cannot be induced by irradiation of unstimulated peripheral blood leucocytes (these cells being in early G_1), no information on their frequency in irradiated human cells is available. They will, therefore, not be considered further in this review.

E. Aneuploidy

77. In cytological preparations of cells from normal diploid individuals, a small percentage of the cells appears to be deficient for one or more chromosomes (i.e., are hypodiploid) and an even smaller percentage may contain one or possibly more extra chromosomes (i.e., are hyperdiploid). The frequency of such aneuploid cells may vary between individuals as well as between samples taken concurrently from the same individual. A certain proportion of the aneuploid cells is certainly an artefact resulting from cell breakage during cytological processing. However, there is reason to believe that aneuploidy is a natural phenomenon in peripheral blood leucocytes of standard diploid individuals and that its frequency may be related to age and sex of the individual.

78. Cytogenetic surveys on human populations[122, 124, 158-164] have shown that aneuploidy is slightly more frequent in peripheral blood leucocytes of females than of males. In females, this aneuploidy is largely a consequence of the loss of a chromosome in groups 6 to 12 (possibly an X chromosome, presumably the inactive X), whereas, in males, it is largely a consequence of the loss of the Y chromosome. Aneuploidy in blood leucocytes of the new-born may be less than 3 per cent but may reach a value as high as about 13 per cent in adult females and 7 per cent in males. In males, this increase with age is not clearly apparent until around age sixty-five, but, in females, it is apparent a decade earlier. Kerkis *et al.*[162] have suggested that this increase of aneuploidy with age may be a consequence of differences in the response of cells to hypotonic treatment in culture.

79. It has been shown[122] that the incidence of aneuploidy in any given cell culture increases with increasing culture time as a consequence of cells undergoing more than one mitotic division in culture. Reference has already been made to the fact that the presence of chromosome structural changes in cells will frequently lead to chromosome loss, and this is to be expected particularly with aberrations that may result in bridges at anaphase. Thus, the presence of even a low frequency of spontaneous or radiation-induced aberrations at the first division of the cells in culture will lead to an increase in hypodiploidy in the daughter cells observed at the second and subsequent mitoses.

80. In addition to the increasing frequency of hypodiploidy with increasing age, it should be mentioned that, in rare instances, certain individuals may contain two or more cell lines differing in chromosome number as a result of chromosome loss or gain occurring in the early stages of development of the individual. These particular instances of chromosome mosaicism are not entirely relevant here, since the majority of such cases are to be found in individuals having a cell line possessing one or more chromosome additional to the normal diploid chromosome number or, in abnormal females, containing a proportion of cells lacking an X chromosome.

81. A number of workers have reported an increased incidence of aneuploidy (hypodiploidy) in peripheral blood leucocyte cells obtained from individuals exposed to radiation,[44, 128, 129, 165-168] and similar increases have been reported in *in vitro* studies.[136, 138, 169-172] Thus, two groups of workers[136,138] suggest, on the basis of their *in vitro* data, that the incidence of aneuploidy increases linearly with increasing x-ray exposure, at least up to a certain dose. It should be pointed out, however, that in all these studies, the cells sampled had been allowed to grow in culture for seventy-two hours or more so that in many cases cells in their second and third division in culture were being sampled (paragraphs 124-137).

82. In some of the earlier[12, 173, 174] and in most of the more recent studies,[16, 127, 132, 133, 135] no differences have been found in the incidence of aneuploidy in blood leucocytes from irradiated individuals or in cells irradiated *in vitro* as compared with controls. Buckton *et al.*[16] quote a mean value of 3.8 per cent aneuploidy for fifty-three patients treated with x rays for ankylosing spondylitis and a value of 3.7 per cent in unirradiated control patients. Similar values of 3 per cent were noted by Ishihara and Kumatori[175] in their Thorotrast patients and in controls, although rather higher values of around 10 per cent in both control and irradiated personnel were found by Visfeldt.[127]

83. There seems little question that many of the hypodiploid cells that have been noted in radiation studies were either cells that were carrying chromosome structural changes, such as dicentrics, or were more probably cells that had contained aberrations but had proceeded through more than one mitosis in culture and had lost aberrant chromosomes (for example, dicentrics or centric rings) at their first division. The incidence of aneuploidy cannot, therefore, be simply correlated with a previous radiation history and cannot be used in a quantitative manner as an indicator of radiation absorbed dose.

84. In genetic terms, the loss of a normally genetically active chromosome from the complement is serious, and, if it does not result in the death of the cell, clearly constitutes a mutation. The presence of aneuploid cells in the germ line would lead to the formation of inviable zygotes, except in the case of the loss of one sex chromosome (as discussed in the 1966 report[3] of the Committee) or in very rare instances of the loss of a chromosome in group G.[176-178]

F. Polyploidy

85. Many workers have noted that irradiation *in vivo*[15, 44, 126, 179, 180] or *in vitro*[136, 140, 173] may result in an increased incidence of polyploidy in peripheral blood leucocytes. Thus, Kelly and Brown[136] reported that, with x-ray doses of up to 400 rads *in vitro*, the incidence of polyploidy increased in proportion to the square of the x-ray dose; these authors used culture times of

seventy-two to ninety-six hours. Other authors, for example, Fischer *et al.*[179] in their work with Thorotrast patients, although noting an increase in polyploidy in blood cells of irradiated patients, have found no quantitative relationship between the frequency of polyploidy and radiation dose. On the other hand, in some of the other early work, both *in vivo*[128, 129] and *in vitro*.[125] there appeared to be no association whatsoever between radiation exposure and an increase in polyploidy.

86. More recent work has shown that few or, quite often, no polyploid cells are observed following *in vivo*[45, 181, 182] or *in vitro*[115, 183] irradiation, provided the leucocytes are cultured for no more than forty-eight to fifty-four hours. However, if cells are cultured for longer periods of time, then polyploid cells appear (even in unirradiated samples), and their incidence increases with increasing culture time up to sixty-eight hours.[115]

87. It has been noted[45, 182, 183] that a very high proportion of polyploid cells contain aberrations, particularly chromosome dicentrics and centric rings, in pairs (i.e., the aberrations have been duplicated). In the studies of Ishihara and Kumatori[182] on the incidence of polyploidy in leucocyte cultures irradiated *in vitro* and sampled seventy-two hours or ninety-six hours later (that is, cells in their second, third or fourth mitosis after irradiation—paragraphs 124-137), it was found that the tetraploid and octoploid cells consistently contained a higher frequency of chromosome aberrations than the diploid cells in the cultures: that is, the number of pairs of identical aberrations in the polyploid cells was greater than the number of single aberrations found in an equivalent number of diploid cells.

88. In leucocyte cultures sampled ninety-six hours after an exposure to 350 roentgens of gamma rays, the same authors found that all the polyploid cells contained pairs of aberrations (mainly dicentrics, tricentrics, and rings), whereas only one-third of the diploid cells contained aberrations of any sort. This kind of observation suggests that polyploidy in these cases is largely a consequence of the presence of chromosome aberrations. Asymmetrical aberrations will interfere with the separation of sister chromatids at mitosis, and interlocked chromosomes and chromosome bridges will prevent a clean separation of the anaphase groups. Thus, the nucleus may not be allowed to complete its division but passes into interphase in its doubled state and re-emerges as a polyploid nucleus at the next division.

89. It is clear from these considerations that the bulk of the observed polyploidy is probably a consequence of the mechanical difficulties arising from the presence of asymmetrical aberrations in cells that are allowed to proceed through a number of divisions in culture. Polyploidy is, therefore, a secondary phenomenon, and, since its incidence will vary not only with dose but also with the number of mitotic cycles completed *in vitro*, it cannot be used as a reliable indicator of absorbed radiation dose. It is probable that polyploidy in somatic cells may be of little significance in terms of somatic hazards (for instance, polyploidy exists as a natural phenomenon in a proportion of normal adult liver cells), although there is no direct information on this point. Polyploidy in primitive germ cells (meiocytes) will, however, result in the formation of unbalanced gametes.

G. Endoreduplication

90. The presence of cells containing endoreduplicated chromosomes has, on occasion, been noted in peripheral blood leucocyte cultures exposed to x irradiation.[140, 146, 184, 185] As in the case of polyploidy, cells showing endoreduplication are sometimes found in untreated leucocyte cultures, and the process of endoreduplication can be facilitated by exposure of the cells to certain spindle inhibitors, such as colcemid.

91. No relationship has been found between radiation dose and the frequency of endoreduplication.[140, 146, 184, 185] Moreover, it is clear that endoreduplication necessitates two or more cycles of chromosome replication in culture and is, therefore, rarely observed in leucocytes cultured for forty-eight hours, whereas it increases in frequency with increasing culture time.[140, 186] The incidence of endoreduplication has no real merit as an indicator of absorbed radiation dose.

H. Conclusions

92. The aberrations that have been described must now be considered from the two viewpoints of their importance in relation to genetic hazards, particularly in somatic cells, and of their use in providing a measure of absorbed dose. These aspects will, of course, be considered in detail in the later sections, but there are a number of both general and specific points that can best be made at this time.

93. It is clear from the description of the aberrations that all result in some kind of genetic change and that the majority result in genetic deficiencies. If the deficiencies are small, they may be tolerated. The amount of loss that can be tolerated will depend both upon the nature of the genetic information lost and upon the normal destined role of the cell in the body. Genetic deficiencies in stem cells will, in general, be of far greater importance than similar deficiencies in cells that were undergoing differentiation.

94. Many of the asymmetrical aberrations will be cell-lethal so that their consequences are more or less immediate. Cell death may follow, either as a direct consequence of the loss of genetic information in the form of acentric fragments or even whole chromosomes, etc., or as a result of the mechanical difficulties that occur at mitosis. Aberrations in resting cells may play no role until the cells are stimulated to undergo mitosis. Only in those tissues that normally contain proliferating cells, therefore, will chromosome aberrations be a significant contributory cause of the cell depletion that occurs very shortly after radiation exposure. However, only a proportion of the aberrations will result in early cell death, since the presence of certain structural changes, such as the symmetrical aberrations described, does not result in a rapid lowering of cell viability. If symmetrical aberrations are produced in germ-cell precursors, they may result in genetic imbalance in the gametes, leading either to dominant lethality in the embryo or to drastic effects in the resultant offspring. It is clear, therefore, that the aberrations that will contribute to long-term hazards in both somatic cells and germ cells are essentially the small deficiencies and symmetrical changes (duplications, inversions and reciprocal translocations) that are difficult to score efficiently and are not cell-lethal.

95. In considering the various kinds of chromosome aberrations produced by ionizing radiations (and by other agents), it has already been indicated that certain types of aberrations may offer a more useful index than others in the context of their possible application as biological indicators of absorbed dose. Aneuploid and polyploid cells produced following radiation exposure have been shown to arise largely as a secondary consequence of the presence of chromosome structural changes. Moreover, the presence of these abnormal cell types depends upon the fact that cell division must intervene between the time of radiation exposure and the time of observation. These particular anomalies are, therefore, not only less frequent than the chromosome structural changes that give rise to them, but also highly variable in their frequency, and must be considered as very inferior biological endpoints relative to the chromosome structural changes.

96. A vast amount of information exists on the relationship between radiation dose and the yield of the two kinds of chromosome structural changes (i.e., chromosome-type and chromatid-type aberrations) in a variety of plant and animal cells. This has shown[17, 22] that, for a given quality of radiation, there exists a strict relationship between aberration yield and absorbed dose and that, for certain aberration types, the yield is markedly dependent upon the dose rate and the stage in development of the cell at the time of irradiation. Detailed studies, particularly with plant materials, have shown that, for a given cell type and known sampling time after irradiation, the variation between individuals is small and that different observers score similar aberration yields when materials are exposed under similar conditions. Indeed, trained observers using materials such as *Tradescantia* microspores and *Vicia faba* root-tip cells can, through determining aberration yield, estimate doses to within a few per cent.

97. The experience and information obtained on chromosome damage in species other than man suggest that a similar strict relationship between radiation dose and chromosome aberration yield should also apply to human cells, and *in vitro* radiation studies strongly indicate that such a relationship, in fact, exists. Moreover, there is every prospect that, in man, the variation in response at the chromosome level between different individuals will be of the same order as the small variation observed between individual plants, and preliminary studies indicate that this is, in fact, the case.

98. It has been stressed earlier that chromatid-type aberrations are only induced by radiation when cells are exposed while in the S or G_2 phases of interphase. These aberrations are, therefore, of little use as dose indicators in the case of peripheral blood leucocyte cells existing in a normal G_1 state, but they can be used in normally proliferating cells. However, it should be emphasized that great care must be exercised in using such aberrations, since, even within the confines of the G_2 (or S) period, the yield of chromatid-type changes is very markedly influenced by the degree of development of a cell *within* a given interphase stage. No such dependence has been noted in relation to chromosome-type aberrations induced in G_1 cells.

99. In addition to the constant sensitivity of G_1 cells to chromosome-type aberration induction by radiation, these particular aberration types have an added advantage as possible indicators of radiation-absorbed dose since their spontaneous frequency is extremely low. A number of cytogenetic surveys on human populations, in which chromosome analysis has been carried out on peripheral blood leucocytes taken from hundreds of individuals, have shown that the presence of an asymmetrical chromosome-type aberration is an extremely rare event. For instance, an analysis of some of the available data (table I) indicates that a dicentric aberration occurs, at most, about once in a sample of about 2,000 cells, and possibly its frequency may be even less than one in 8,000 cells.

100. It is evident from the foregoing considerations that, on general cytological grounds, chromosome-type aberrations are superior to other forms of chromosome aberrations in terms assessing absorbed dose. It should also be noted that the simplest and most convenient source of human material for studying aberration yield following *in vivo* exposure are the peripheral blood leucocytes and that the aberrations that are induced in these cells by ionizing radiations are chromosome-type aberrations.

101. It has already been concluded that the frequency of chromatid-type aberrations in cultured peripheral blood leucocytes may bear no relationship to the radiation exposure of an individual, and it has been pointed out that these aberrations may arise spontaneously in culture or be produced in culture following virus attack or exposure to certain chemical agents. It should be added here that the aberrations that may be induced by virus attack will not influence the yield of chromosome-type aberrations, provided that only cells in their first division in culture are sampled. One can feel fairly sure on this point, since the frequency of chromosome-type aberrations in blood cells of individuals previously exposed to a virus infection is no higher than in unexposed individuals.

102. The fact that (paragraph 74) chromatid-type aberrations seen at the first mitosis following irradiation can result in "derived" chromosome-type changes at the second division will be of importance if cells are allowed to proceed through more than one division in culture. The relative importance of such "derived" changes will depend markedly on dose and will be small when the yield of true chromosome-type aberrations is high but will be very important when the yield of true chromosome-type changes is low.

103. Although the possible complications introduced by chromatid-type aberrations and their "derived" chromosome-type counterparts is obviated if only cells in their first mitosis after irradiation are sampled (paragraphs 124-137), we should note that the exposure of individuals (as opposed to cells *in vitro*) to certain chemical agents[187] may well result in increased frequency of chromosome-type aberrations in their peripheral blood leucocytes. It is important, however, to recall that leucocytes (small lymphocytes) carrying chromosome-type aberrations may survive in the body for long periods (up to many years). This complication of *in vivo* effects of chemical mutagens may only be important in relation to individuals that have been treated for certain clinical conditions with potent chemical mutagenic agents,[71, 75] for example, nitrogen mustard.

104. Finally, it should be stressed that, when attempts are made to obtain information on absorbed dose through scoring chromosome-type aberration yields, it would be valuable if the aberrations were

classified in detail in the form described in paragraphs 25 to 34.

III. Materials and methods of study

A. Introduction

105. Any tissues containing cells that are normally involved in proliferation or cells that can be made to proliferate by various means can be utilized for chromosome analysis. Chromosome studies on mammalian cells have been carried out on a variety of proliferating tissues, including skin, intestinal epithelium, corneal epithelium, bone marrow, various lymph nodes, spleen, thymus and gonads (particularly testis). In addition, certain cells from tissues that do not normally proliferate in the adult animal can be made to undergo mitosis; this has been done mainly with liver tissue and blood. Mitotic divisions occur in liver cells when the liver regenerates following partial hepatectomy, and blood leucocytes can be stimulated by various means to proceed into a mitotic phase in short-term *in vitro* cultures.

106. All the above cells or tissues have been used by various workers in studies on radiation-induced chromosome aberrations. In laboratory mammals, bone marrow, lymphatic tissues, corneal epithelium, liver cells, peripheral blood leucocytes and gonads have been the principal tissues used. In man, the great majority of the work has been carried out with peripheral blood leucocytes, and some information has been obtained using bone marrow and skin.

107. Chromosome preparations can be made from cells that are proliferating *in vivo* without the necessity for *in vitro* culture, and direct preparations made in this way exclude the possibility of adverse effects arising during *in vitro* culture. However, in the case of man, the only tissue from which a sufficient number of dividing cells can be directly obtained without recourse to surgery is the bone marrow. Mitotic cells can, of course, be obtained from skin, but to obtain sufficient cells of good cytological quality from small samples of skin requires *in vitro* culture.

108. Excellent techniques[188, 189] exist for obtaining direct chromosome preparations for human bone-marrow cells, but, to obtain good quality spreads, the cells must in all cases be exposed to certain pre-fixation treatments, including treatment with colchicine and hypotonic saline so that some handling of the living cells *in vitro* is required. In the case of human skin, the standard technique (see reference 190) involves setting up primary cultures and making cytological preparations from outgrowing fibroblasts some days after culture initiation.

109. One major disadvantage of the use of bone marrow and skin cells in terms of their possible use in "aberration dosimetry" is the fact that these tissues consist of populations of asynchronously developing cells. Thus, when an individual is exposed to radiation, bone marrow and skin cells in all stages of development in the mitotic cycle will be irradiated. This means that both the type and yield of chromosome aberrations will change quite rapidly with time even in the first few hours after exposure.

110. Information on the sensitivity of man's proliferating cells (both somatic and gonadal) to radiation-induced chromosome damage is of the utmost importance in relation to assessing hazards. However, it is clear that, except under very exceptional circumstances, for example, where serial-marrow aspirates can be taken shortly after irradiation and when the time of exposure is accurately known, the idea of using chromosome damage in these particular cell systems as a general means of estimating absorbed dose cannot be entertained.

111. Because of the change in radiation response with cell-development phase, cells that are exposed to radiation while in a resting phase and are then stimulated under controlled conditions to proceed into mitosis offer the best possible system for radiation dosimetry from the cytological viewpoint. Although regenerating liver cells fall into this category, clearly their use in man must be ruled out. However, the development of a technique (paragraphs 113-123) for culturing peripheral blood leucocytes and stimulating them to undergo mitosis in short-term culture has provided a most suitable cytological system. The peripheral blood leucocyte culture technique is simple and reliable. By using this technique, large quantities of mitotically active cells can be obtained quickly and painlessly and, if required, large numbers of samples can be taken from any one individual without causing bodily injury or suffering.

112. Peripheral blood leucocytes from normal healthy individuals do not usually undergo mitosis in peripheral blood vessels, and exposure of these cells to tritium-labelled thymidine[191-193] reveals that less than one cell in 1,000 undergoes DNA synthesis. It has been established [193-195] that these leucocytes rest in an early interphase or G_1 state so that, following radiation exposure, they contain chromosome-type aberrations if and when they appear at mitosis. Moreover, since these cells are all in the same stage of development, the variation in response between cells should be minimal. Since most of the work on radiation damage in man's chromosomes has been carried out with these cells, and because some differences between results obtained in different laboratories have emerged, some of the details and various modifications of the techniques used will now be briefly considered.

B. The peripheral blood culture techniques

113. A number of recent articles[196, 197] have detailed the basic principles of the leucocyte culture technique and have described the earlier developments by Osgood and his colleagues[198, 199] and by Nowell[200, 201] that culminated in the successful use of this system for human cytogenetics.[14, 202] In this brief account, therefore, we shall be concerned only with the general principles and with certain specific variations in methodology that have been used in the studies on radiation-induced chromosome damage to be considered in the succeeding sections.

114. The culture of peripheral blood leucocytes involves the introduction of leucocytes, either following their separation from the other blood elements or simply in whole heparinized blood, into a tissue-culture medium containing a mitotic stimulant. The tissue-culture media used contain a standard, defined, synthetic medium (such as TC medium 199) with antibiotics plus serum (or plasma), the serum making up from 10 to 40 per cent of the total volume (usually about 6-10 ml). The serum used may be autologous or homologous (usually AB) human serum, or fœtal or adult bovine serum.

115. The mitotic stimulating agent (or mitogen) normally employed is the plant mucoprotein phytohemagglutinin (PHA), and it is clear that the cells that are stimulated to transform into blast cell types under the action of PHA and then to proceed into mitosis are the small lymphocytes.[192, 203, 204] Although PHA is the mitogen that has been used in almost all radiation work, another plant extract from the pokeweed (*Phytolacca americana*) is also effective.[205]

116. The fact that PHA stimulation appeared to be restricted to the immunologically competent cell was partly responsible for the work that led to the finding that small lymphocytes from donors sensitive to a particular antigen may be stimulated to transform into blast cells and divide in the presence of this antigen.[206-208] In fact, this conversion to blast cells also occurs when lymphocytes from different donors are mixed in culture in the absence of any plant mitogen.[208, 209]

117. The amount of heparinized blood used for a single culture may be as little as a fraction of a millilitre ($\sim$ ¼ ml) if whole blood is inoculated into a culture vessel containing around 5 millilitres of culture medium, giving a so-called microculture; or, leucocytes may be separated from samples of around 5 to 10 millilitres of whole blood and approximately 107 cells inoculated into a culture bottle containing 5 to 10 millilitres of culture medium.

118. In cultures containing PHA and incubated at 37°C, the small lymphocytes are stimulated to undergo RNA and protein synthesis, enlarge in size and proceed through a DNA-synthesis phase and thence pass into mitosis. The first cells to reach mitosis do so after thirty-six to forty hours in culture. At forty-eight hours, a considerable number of cells are in their first division in culture (paragraphs 124-137). We should note, however, that temperature is, of course, a very important factor in influencing the rate of cell development and that fluctuations of as little as 1°C have marked effects. Moreover, there may be other, as yet undefined, factors that may influence the cell development rate.

119. The cells that are stimulated to pass into mitosis may go through a series of cell cycles so that the maximum number of cells in division in the culture are usually to be found approximately seventy-two hours after culture initiation. The cultures, however, are strictly short-term and cannot be maintained indefinitely, since there is a continued decline in the number of viable mitotic cells after the first few days. In a large proportion of the laboratories that carry out human cytogenetic studies, peripheral blood leucocytes are cultured for seventy-two hours so as to obtain the maximum number of divisions. This practice has also, unfortunately, been the custom in much of the work in radiation cytogenetics.

120. Up to four hours (or more in certain cases) prior to termination of a culture, a small amount of colchicine or diacetylmethylcolchicine ("Colcemid" —around 0.05 μg ml^{-1} of medium) is added to accumulate cells at the metaphase stage of mitosis. After an appropriate time, the culture medium is removed, following centrifugation (5 or 10 minutes) at about 25 to 100 G, and the cells resuspended in a hypotonic solution such as 1 per cent sodium citrate[3] or a 0.75 molar solution of KCl for a few minutes before they are fixed in acetic alcohol.[210] Suspensions of the cells in acetic alcohol are dispensed as drops onto clean microscope slides and allowed to dry, the cells flattening out during the drying process. Most laboratories have their own variations on the general cytological technique outlined here, but the end result is the production of a number of slides containing scores of well spread metaphase cells from each culture. These cells are usually stained with acetic orcein or Giemsa, etc., according to individual preferences.

121. Although first class preparations are required for accurate scoring, the variations between laboratories in their detailed cytological procedure after fixation may not be of great importance in the context of influencing the frequency of the chromosome aberrations that are eventually scored in metaphase cells. However, it has been suggested [211, 212] that variations in the techniques of culture (for example, the question of type of serum used and the use of whole blood or leucocytes separated by sedimentation or by centrifugation) may be important, since different aberration yields have been obtained in *in vitro* studies carried out by laboratories using slightly different techniques (paragraphs 154-170).

122. In most of the work on chromosome aberrations induced following *in vivo* radiation exposures, leucocytes have been separated from blood samples either in buffy coat, namely, following fairly high speed centrifugation ($\sim$ 3,000 rpm in a clinical bench centrifuge, or around 1,800 G), or by low-speed centrifugation ($<$500 rpm or about 25 G) and/or gravity sedimentation with or without the presence of an agglutinating agent. Separated leucocytes have also been used in many of the *in vitro* studies, whereas in other *in vitro* work small samples ($\sim$ 0.3 ml) of whole blood have been used to set up microcultures.[213]

123. It is not yet known whether there is any selective loss of cells suffering from radiation damage when high speed centrifugation is used. At equivalent dose levels, however, aberration yields are significantly higher in laboratories using the microculture technique following *in vitro* irradiation of whole blood than in laboratories using cells obtained following buffy coat separation (paragraphs 154-183). Recent comparisons[214, 215] have indicated that there is no difference in aberration yield between leucocytes separated by gravity sedimentation and leucocytes cultured as part of a whole blood inoculum. Direct comparisons between each of these techniques carried out within the different laboratories are certainly required.

C. Culture sampling time

124. It has already been indicated that chromosome-type aberrations in peripheral blood leucocyte cells offer the best cytological combination, if aberrations are to be used for biological dosimetry. Consideration should, therefore, now be given to the influence of culture sampling time on the yield of these aberrations, since in recent years it has been clearly shown that the yield of chromosome-type aberrations declines, as is, of course, to be expected, with increasing leucocyte culture time.

125. Most of the published data on chromosome-type aberration frequencies in human leucocytes cultured *in vitro* have been obtained from cells that were allowed to grow in culture for seventy-two hours before fixation and slide preparation. As has already been mentioned, however, it has been known for some

time that a number of cells enter into mitosis as early as thirty-six hours after culture initiation and that a high proportion of the cells can be seen in division at forty-eight hours. The presence of mitotic cells in culture at forty-eight hours after culture initiation was noted in some of the early studies by Nowell[201] and also by Bender and Prescott.[195] More recent work has now made it quite clear that, at seventy-two hours after initiation, a majority of the mitotic cells may be in their second or third division in culture. It is, in fact, now evident that the cell-cycle time between successive mitotic divisions in culture is about twenty to twenty-four hours. [62, 115, 216, 217]

126. It was established by Buckton and Pike[45, 181] from their studies on patients exposed to x rays for treatment for ankylosing spondylitis that the frequency of chromosome-type aberrations in the blood cells of these patients varied according to the duration for which the cells were allowed to grow in culture. Cells observed after seventy-two hours were found to contain fewer aberrations than cells from the same blood sample that were allowed to grow in culture for only forty-eight hours. In cultures fixed after seventy-two hours, tetraploid cells were present, and these cells contained duplicated aberrations. Such duplicated aberrations were not observed at the earlier times, tetraploid cells being rare or absent in cultures that were allowed to grow for only forty-eight hours.

127. Observations similar to those of Buckton and Pike were reported by Ishihara and Kumatori[175] from their studies on blood cells obtained from Thorotrast patients and from *in vitro* studies on x-irradiated blood samples obtained from normal individuals. These latter authors observed that the yields of aberrations in both *in vivo* and *in vitro* studies were twice as high in cells harvested after forty-eight hours as they were after seventy-two hours in culture and roughly four times as high as the aberration yields in the same cell populations after ninety-six hours in culture. Moreover, their later studies[182] on the incidence of polyploidy are also in accord with the observations of Buckton and Pike. Similar observations of a decline in aberration yield with increasing culture time were made by Nowell,[218] although in his studies the longer culture times of seventy-two and 120 hours were used.

128. In summary, the work at Edinburgh in the United Kingdom and at Chiba in Japan showed (*a*) a reduction in the yield of chromosome-type aberrations with increasing period of culture from forty-eight to seventy-two hours; (*b*) the virtual absence of polyploid cells at forty-eight hours but their presence in high frequency at seventy-two and ninety-six hours; and (*c*) the presence of duplicated aberrations in many of the polyploid cells. These observations led inescapably to the conclusion that a considerable proportion of the cells observed in samples cultured for seventy-two hours and ninety-six hours were cells in their second (X_2) or later (X_3, X_4, etc.) divisions in culture. This conclusion was later confirmed by workers in the Soviet Union[217] who showed that many of the cells observed at metaphase after seventy-two hours in culture at 37°C were in their third mitosis.

129. The reduction in the frequency of chromosome-type aberrations with increasing culture time follows from the fact that the aberrant chromosome structure may be lost at anaphase of mitosis and that a proportion of the cells carrying aberrations will, therefore, be unable to participate in any further mitotic activity. For instance, acentric fragments tend to be excluded from anaphase groups at mitosis so that both daughter cells, if viable, may be difficult to distinguish from normal cells when they divide at the second division in culture, particularly if the fragments are very small.

130. In the case of dicentric- and centric-ring aberrations, a proportion of these structural changes will result in anaphase bridges so that the aberrations and, in most instances, the cells carrying them, will be lost from the dividing population. Recent studies by Norman and his colleagues[34, 218] on aberration yields in cells cultured for fifty hours and seventy-two hours indicate that the probability of loss of a dicentric is 0.5 per division. Although aberrations and cells carrying aberrations may be lost, undamaged cells will proliferate normally and will, therefore, comprise an ever-increasing proportion of the cell population as culture time increases.

131. Attention was earlier drawn to the fact that by far the majority of workers have used seventy-two-hour culture periods in their *in vivo* and *in vitro* studies and that most of these quote the autoradiographic data of Bender and Prescott[194] as demonstrating that cells observed at mitosis after seventy-two-hours in culture are cells in their first mitosis in culture. In fact, Bender and Prescott stated that "the cells are in their first post-labelling division at seventy-two hours" when the cells were exposed to tritium-labelled thymidine for thirty minutes after forty-eight hours in culture. In their experiment, it was clearly pointed out that "numerous mitoses accumulated (by colchicine) between forty-two and forty-eight hours in culture", and the authors refer to "the first wave of mitoses" occurring at this time. From the recent extensive data of Sasaki and Norman[216] and of Heddle, Evans and Scott,[115] it would appear that the first post-labelled mitoses seen at seventy-two hours may well have been cells in their second mitosis in culture, the majority of the cells being exposed to label in the interphase period following the first mitosis in culture.

132. In studies of Sasaki and Norman,[216] cultures of separated leucocytes were exposed to tritium-labelled thymidine after various times during culture and then sampled at various fixation times to determine the frequency of labelled mitotic figures and the patterns of label over the chromosomes. In addition, cells were also x irradiated, and the frequencies of polyploid cells and of cells containing doubled sets of acentric fragments were studied after culturing for either fifty hours or seventy-two hours. The results obtained with these four different parameters showed that, at seventy-two hours, 70-80 per cent of the cells were in their second mitosis in culture, whereas there were no indications of second division cells being present after fifty hours in culture.

133. In the work of Heddle *et al.*,[115] the mitotic index, the incidence of polyploidy and the yield of chromosome-type aberrations were studied using a whole blood microculture technique. These three parameters were scored in a series of cultures grown for periods of from thirty-six to 100 hours. The cultures were terminated at successive four-hour intervals throughout this period, and the cells were subjected to a four-hour colchicine treatment prior to fixation. This technique made possible an effectively continuous sampling of all cells from the time of first appearance of mitosis in culture up to sixty-four hours later. The results showed that first division cells were observed

up to fifty-two hours and that a small proportion of second divisions appeared at around sixty hours. At approximately sixty-four hours, a significant proportion of the cells were in their second division, and, at seventy-two to seventy-six hours, by far the majority of cells were in their second or even third divisions with only a few first division cells present.

134. The data of Heddle *et al.*[115] show that, in cultures irradiated *in vitro* with x rays (150 rad) and sampled at seventy-two hours, the yield of dicentric and ring aberrations was approximately half the yield found in similar cultures grown for up to fifty-six hours. Furthermore, it was shown that this culture time of seventy-two hours was at a transition point between a peak of mitotic activity (due to second divisions) occurring at sixty to sixty-four hours and a later peak (due to third divisions) occurring at seventy-six hours.

135. One of the reasons contributing to the use of seventy-two hours as a standard culture time was the possibility that irradiated cells were delayed in their progression through the cell cycle. It is well known that irradiation can result in mitotic delay in proliferating cells but that the amount of delay depends, amongst other things, on the stage of development of the cells at the time of irradiation. For instance, it has been reported[219] that x irradiation of human fibroblast-type cells in tissue culture results in virtually no delay at the first post-irradiation mitosis of cells irradiated in early G_1 but in a considerable delay in the development of cells irradiated while in late G_1, S or G_2. The recent data of Sasaki and Norman[216] on blood cells given a dose *in vitro* of 500 rads from x rays and of Heddle *et al.*[115] on microcultures given a dose *in vitro* of 150 or 300 rads from x rays have indicated that little or no mitotic delay occurs at these dose levels.

136. The data of Evans[155, 156] show that the response of the peripheral blood leucocytes to x-ray-induced chromosome damage does not change with development of the cells through the G_1 phase in culture. But these data, obtained from cells sampled at one fixation time, do not preclude the possibility that more than one cell population with differing radiosensitivities may be present in culture. There is not a great deal of information available on this point, but the data of Norman[34] and of Heddle *et al.*[115] show that there is no difference in aberration yield between cells that undergo an early, as opposed to a late, transformation to blast cell types. The available observations, therefore, suggest that, if there is a variation in the average rate of development of blood cells in culture between different individuals, and if there is some indication that certain blood donors may be "slow growers",[115] then this may be of little consequence provided that only first division cells are sampled for aberration yield.

137. This point of cell cycle times has been considered at some length, since, for comparing quantitative data on aberration yield, it is clearly of the utmost importance to ensure that aberration frequencies are determined using only first division cells. On the information that is at present available, this would necessitate the use of cultures grown for around forty-eight hours at 37°C. We should note, however, that at least one laboratory[45] has reported the presence of a proportion of cells in their second mitosis in cultures exposed to colcemid in their final three hours and terminated at forty-four to fifty-two and a half hours. This has led other workers[216, 219, 221] to expose fifty-hour cultures to colcemid for twenty-four hours prior to fixation in order to prevent cells from proceeding into a second mitosis in culture. The duration of colcemid or colchicine prefixation treatment may, therefore, be an additional factor to consider in conjunction with duration and other conditions of culture.

D. Conclusions

138. Chromosome analysis in man can be carried out quite readily on cells from three sources, namely, skin, bone marrow and peripheral blood. For qualitative work, cells from each of these three sources can be used, and a number of studies have, in fact, been made on the persistence and proliferation of cells containing symmetrical aberrations in bone marrow and in blood. In these studies, the presence of clones of cells derived from an original single cell containing a radiation-induced symmetrical aberration have been noted in individuals studied many years after exposure to ionizing radiations.[134, 222-224] The possible importance of such persistent symmetrical aberrations as long-term somatic hazards is considered later.

139. At the quantitative level, where the question of using the aberrations produced in proliferating cells to estimate absorbed dose is concerned, various physical and general biological problems arise. These problems will be considered later, whereas this section has been confined to the relative cytological merits of the various proliferating cell systems. From this discussion, it is clear that, from the cytological viewpoint, as well as because of the ease and simplicity of obtaining single or repeated cell samples, the peripheral blood lymphocytes are far superior to bone-marrow or skin cells for quantitative work.

140. These peripheral blood lymphocytes exist in a uniform stage of development in G_1 so that only chromosome-type aberrations are produced in them following radiation exposure. The more complex chromatid and subchromatid-type aberrations that will be induced in a proportion of the skin and bone-marrow cells are, therefore, normally absent. However, some chromatid-type aberrations are observed in irradiated lymphocytes, but these have been shown to arise during cell development in culture, and their relatively low frequency does not raise complications in the scoring of the chromosome-type changes if only cells in their first post-irradiation mitosis are scored.

141. Despite the apparent simplicity of the peripheral blood leucocyte system, certain differences in *in vitro* response have been observed between different laboratories (paragraphs 154-183). Some of these differences are a consequence of the use of radiations of differing qualities (paragraphs 154-177) but, from the discussion of the methods of leucocyte culture used in various laboratories, it is evident that there are at least two other factors of importance.

142. First, it is clear that different aberration frequencies are observed if cultures are allowed to grow for various periods of time in excess of fifty-four hours and that this is almost certainly a consequence of the appearance in culture of second and subsequent mitoses which result in increasing the proportion of undamaged cells. The usual standard fixation time of seventy-two hours used in many laboratories is not only too late to find many first division cells but may also be on the border-line between waves of second and third mitoses in culture so that small differences in timing

and in culture conditions can be expected to have exaggerated effects on the aberration frequency. Information on the rate of decline in aberration yield with increasing culture time suggests that estimates of aberration yield made at this late time of seventy-two hours may be too low by as much as a factor of two.

143. Second, it has been suggested that differences in the methods used to handle the cells (and, in general, differences in culture techniques) might conceivably contribute to variation in aberration yield. This suggestion needs to be explored, and the various techniques must be compared within laboratories. Moreover, because of the present lack of knowledge concerning possible subtle effects of minor variations in technique, it is of the utmost importance for workers in this field to define clearly the conditions of culture being used, including temperature, centrifugation methods and cytological techniques.

144. Finally, it cannot be over-emphasized that laboratories should endeavour to standardize scoring methods and presentation of data, giving, where possible, the maximum amount of information on the frequencies of all the various aberration types as outlined in paragraphs 24 to 34.

IV. The relationship between aberration yield and dose

A. Introduction

145. In considering the relationship between radiation dose and aberration yield and the significance of the aberrations in terms of their potential hazard, it is important to note that a statistically significant increase in chromosome-type aberrations is observed in the peripheral blood leucocytes of individuals exposed to low doses of diagnostic radiation. The human chromosome complement is, therefore, sensitive to aberration induction.

146. Reference was made earlier (paragraph 96) to the relationship that exists between absorbed dose and aberration yield in a wide variety of organisms and cell types. A similar relationship between aberration yield and dose must also exist in the case of man's cells, and it is this relationship, coupled with the high sensitivity of the human chromosome complement, that forms the basis of the possible use of aberration yield in dosimetry.

147. Interest in the potential application of aberration yields to estimate dose was largely stimulated by early observations that the peripheral blood leucocytes of persons exposed to radiations, either accidentally or for therapeutic purposes, contained chromosome aberrations.[3] It was generally suggested that, in the case of accidental exposure, determining chromosome aberration yields in an exposed individual might provide not only a simple but also a much more valid alternative to dose estimates based on physical measurements and would make possible some sort of direct estimate of the degree of biological damage incurred.

148. The merits and possible disadvantages of "chromosome aberration dosimetry" are considered in paragraphs 326 to 340. The present section is more concerned with the kinds of data that have been obtained from experiments, from radio-therapy treatments and from incidents where aberration frequencies were determined under conditions where some kind of physical estimate of dose was available. The available data can be separated into two categories, namely, those that have been obtained in *in vitro* experiments where accurate physical estimates of dose were available and those obtained following *in vivo* (whole-body or partial-body) exposure where physical dose estimates were, in general, rather less accurate.

149. There are three principal reasons why studies on the effects of irradiation *in vitro* are very important in the context of any biological dosimetry technique that involves using aberrations produced *in vivo*. They are as follows:

(*a*) Chromosome damage sustained by leucocytes *in vivo* can only be readily observed following short-term *in vitro* culturing of the cells. As has already been seen, studies on aberrations induced *in vitro* are providing a means for determining the optimum conditions for sampling and for defining the types of observations that are required and the conditions under which they should be made.

(*b*) Since many of the fundamental aspects of aberration induction, such as the kinetics of response and the influence of radiation quality and of exposure time, etc., are similar in different species and in *in vitro* and *in vivo* exposures in organisms other than man, the response of human cells exposed *in vitro* is not expected to be different from the response obtained *in vivo*.

(*c*) Various authors[130, 225] have concluded that the x-ray-induced aberration rates in mammalian cells *in vitro* are very similar to those seen *in vivo*. There is, thus, a strong possibility that the sensitivity of the peripheral blood leucocytes *in vitro* may be similar to that *in vivo*.

150. Bender's conclusion was arrived at following comparisons between the response of chromosomes in Chinese hamster bone-marrow cells[151] and corneal epithelium cells[226] and, more particularly, between *in vivo* exposure of bone-marrow cells of the spider monkey (*Ateles* spp.) and *in vitro* exposure of continuously cultured kidney cells of the same species.[12]

151. It might be expected that the *in vitro* irradiation of freshly drawn human whole blood, as opposed to irradiation studies on established human cell culture lines, might closely approximate the irradiation of these cells while they are circulating in the peripheral blood system. As yet there is only a small amount of direct information on this point.[227]

152. In line with this suggestion are the recent preliminary and unpublished studies of Cleminger[228] on rabbits. In this work, blood was taken from animals and given a total gamma-ray dose of 300 or 500 rads from cobalt-60 following which the animals themselves were given either of these doses. Within each dose level, the aberration yields in blood cells exposed *in vitro* and in cells from blood sampled ten minutes after whole-body irradiation were found to be closely similar.

153. In the *in vivo* radiation studies made on man, a considerable amount of data has been accumulating on aberration yields in peripheral blood lymphocytes of individuals exposed to radiations, although a great deal of these data, as is the case in much of the *in vitro* work, comes from cultures grown for seventy-two hours or more. Since the conditions of *in vivo* exposure are so diverse and the information obtained is so varied, the *in vivo* studies will be considered separately according to type of exposure.

B. *In vitro* STUDIES

1. *X rays and gamma rays*

154. Dose-response data from *in vitro* x-irradiation studies on peripheral blood leucocytes have been obtained by fourteen groups of workers. These data appear in twenty-three separate publications,[34, 35, 125, 137, 138, 140, 156, 211, 229, 238] only thirteen of which report data on cells cultured for less than fifty-four hours. In assessing these data, there are at least three important differences in experimental conditions that are of importance. These are (*a*) the use of different culture times; (*b*) the irradiation of whole blood prior to culture as opposed to the irradiation of blood in culture; and (*c*) the use of different qualities of x rays.

155. In the original data of Bell and Baker,[140] terminal deletions and exchange aberrations both increased approximately linearly with increasing x-ray exposure, and the yield of exchange aberrations was dose-rate dependent. For instance, at 200 roentgens, 2.1 exchanges per cell were recorded when the exposure rate was 160 roentgens per minute but only 1.0 exchange per cell when the exposure rate was 1.6 roentgens per minute. In these experiments, however, the cells were cultured for 100 hours, and, in addition, in some of the experiments, radiation was given at various times after culture initiation. No firm conclusions on response with dose can, therefore, be drawn from these data.

156. The data of Bender and his colleagues[125, 229] were obtained by irradiating whole blood with up to 200 roentgens (250 kV x rays, HVL 2 mm Cu) and culturing separated leucocytes by using the buffy-coat technique. In Bender's laboratory, cells were sampled at seventy-two hours so that the aberration yields reported may be under-estimates. Coefficients of aberration production were given as yield per cell-roentgen in the case of deletions and yield per cell-roentgen squared in the case of dicentrics and rings. In two experiments, values of 0.9 and 1.1 10^{-3} deletions per cell-roentgen and 5.2 and 6.0 10^{-6} dicentrics + rings per cell-roentgen squared were obtained.

157. It has been claimed[156, 211] that Bender's dicentric + ring data give a best fit to the relationship $y = kD^{1.4}$ rather than to $y = kD^2$, where y = yield, k = a constant and D = dose. A very relevant point of interest in these data is the fact that, in the first experiment of Bender and Gooch, a culture was grown for fifty-four hours in addition to parallel cultures grown for seventy-two hours. In the fifty-four-hour culture, the aberration yield was 50 per cent higher than in similarly irradiated cells grown for seventy-two hours. This is in accord with the expectation that the coefficient for aberration production obtained from seventy-two-hour samples may be too low.

158. Kelly and Brown[137] irradiated whole blood (200 kV x rays, HVL 1.5 mm Cu) and cultured separated leucocytes for seventy to ninety-six hours after exposures of from 100 to 1,600 roentgens. The data were analysed according to the equation $y = kD^2$, but they were not uniform. Over the full dose range the coefficient for the yield of dicentrics was 0.9 10^{-6} per cell-roentgen squared and was considerably lower than that obtained by Bender and his colleagues. If the data obtained at exposure above 200 roentgens were omitted, a coefficient of 5.6 10^{-6} per cell-roentgen squared (i.e., similar to that obtained by Bender) was obtained. Clearly, culture time played a very important part in these experiments, and no firm conclusion on the relationship between dose and yield can be drawn from these data.

159. The original data of Norman and his colleagues[239] were obtained from lymphocytes that were irradiated in whole blood (100 kV to 1.9 MeV x rays) and then cultured, after separation by centrifugation, for seventy-two to ninety hours. Doses of up to 1,200 rads were used, and dose rates ranged from 10 to 200 rads per minute. No effect of dose rate was observed, and a coefficient for the production of dicentrics of 2.7 10^{-6} per cell-roentgen squared was obtained. These data for dicentrics gave an excellent fit to the equation $y = kD^2$, and the coefficients obtained in these data are approximately one-half of those obtained by Bender's group. No significant differences were observed between the effects of these two radiations of different qualities.

160. In the very recent publications from Norman's group,[34, 240] cells have been cultured for fifty hours as well as seventy-two hours, and doses of up to 5,000 rads have been used. In these experiments, higher aberration yields were observed at fifty hours, and the coefficient for dicentrics and rings in these shorter term cultures was 5.7 10^{-6} per cell-roentgen squared, almost identical with that obtained by Bender and his colleagues. These data were obtained with x rays from a linear accelerator giving a mean photon energy of 1.9 MeV, although it should be noted that Bender's data were obtained with the more efficient 240 kVp x radiation.[241]

161. Visfeldt[242] in his *in vitro* work has used only three dose levels of up to 200 rads of cobalt-60 gamma radiation and has reported higher aberration yields than Norman *et al.* and Bender *et al.* In Visfeldt's work, leucocytes were separated without resort to centrifugation, and cultures rather than whole blood samples were irradiated. Cells were sampled after forty-eight hours in culture, and it is of interest to note that these gamma-ray data from irradiated cultures approach the high yields obtained with x-irradiated whole blood microcultures. It is important to note here also that the RBE for chromosome-aberration production is about 0.8 for cobalt-60 gamma rays relative to 250 kV x rays.[243, 244]

162. Mouriquand *et al.*[138] have exposed separated leucocytes (gravity sedimentation) in autologous serum to x irradiation (160 kV, 7.5 mA, 100 R per min) prior to culture and have sampled cells seventy-two hours later. The yields of dicentric aberrations obtained by these workers were higher (coefficient of 8.2 10^{-6} per cell R^2) than those obtained by other authors who irradiated whole blood. The data of Mouriquand *et al.*[138] were very probably obtained from a mixture of first and second division cells, and their yields closely approach those obtained in x-irradiated microcultures sampled at seventy-two hours[115] and are about 25 per cent lower than the yields obtained in microcultures sampled at fifty-four hours.

163. Evans[156, 211, 212] has reported data from five experiments on whole blood x-irradiated (250 kV HVL 1.2 mm Cu) prior to or during culture, using doses of up to 460 rads and dose rates of from 17.5 to 230.5 rads per minute. These experiments differ from the others in that whole blood microcultures were used. The cells were sampled at fifty-four hours, and no differences were observed between cultures exposed at different dose rates. In these experiments, the dicentric

and ring aberrations did not increase in proportion to the square of the dose but give a best fit to the equation $y = kD^{1.2}$. The pooled data from all experiments analysed as a quadratic, i.e., $y = k + \alpha D + \beta D^2$, give $\alpha = 3.42\ 10^{-3}$ and $\beta = 3.5\ 10^{-6}$.

164. Bajerska and Liniecki[231] have recently reported experiments on x-irradiated cultures (180 kV with 1.05 or 1.8 mm Cu filtration) and have obtained results somewhat similar to Evans. In these experiments, using a dose range of up to 415 rads given at dose rates of around 100 rads per minute, the yields of dicentric aberrations best fit the equation $y = kD^{1.3}$, and the total yields are similar to those reported in the other published data on x-irradiated cultures (figure 4).

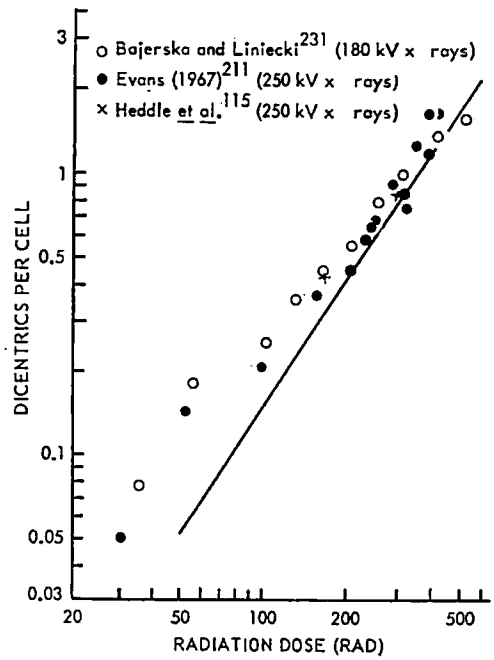

Figure 4. Dose-effect relationship for dicentric aberrations (irradiation with 180 and 250 kV x rays *after* PHA stimulation)[a]

[a] Whole blood x-irradiated *in culture*. Cultures grown at 37° C for *fifty* to *fifty-four hours*. Regression line fitted to data obtained from blood cells irradiated with 180 to 300 kV x rays *prior* to culture (figure 8).

165. Up until very recently the x-ray *in vitro* data appeared to be very confusing. Within individual laboratories, consistent and repeatable results were obtained, but little uniformity in the form of the relationship between aberration yield and dose existed between laboratories. Recently acquired experimental data have markedly improved the picture, however, particularly if separate consideration is given to data obtained using different techniques and radiations of differing quality.

166. Studies by a number of workers have now clearly demonstrated that 2 MeV x rays are less efficient than 180 to 300 kVp x rays, the RBE being 0.8[232, 234-236] when comparisons are made between samples handled in the same way with regard to irradiation technique and culture sampling time. The data of Sasaki[234] on the dose-response relationship of dicentrics + rings for radiations of differing qualities are shown in figure 5. These data were obtained using irradiated whole blood cultured for fifty hours prior to sampling, and the constants and dose exponents for the

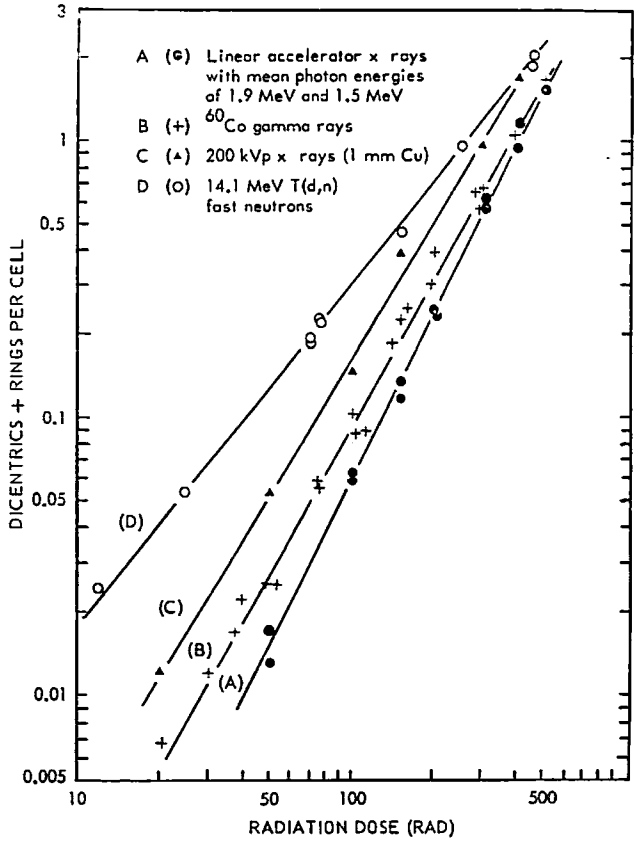

Figure 5. Dose-response relationship for dicentrics plus rings for different qualities of radiation[a]

[a] Cells irradiated *prior* to culture and cultured for *fifty* hours.[234]

fitted lines are as follows: 1.9 MeV and 1.5 MeV x ray, $y = 8.50\ 10^{-6}\ D^{1.94}$; cobalt-60 gamma rays, $y = 25.5\ 10^{-6}\ D^{1.78}$; 200 kV x rays (HVL 1 mm Cu), $y = 81.14\ 10^{-6}\ D^{1.60}$; 14.1 MeV T(d,n) fast neutrons, $y = 1.039\ 10^{-6}\ D^{1.24}$. The D^2 relationship for the 1.9 MeV x rays confirms the earlier studies[34, 240] using radiation of this quality.

167. Sasaki's data on the cobalt-60 gamma rays are very similar, both in terms of absolute yield of dicentrics and of dose kinetics, to recent data obtained with this radiation, under similar culture conditions, by Sevankayev and Bochkov[237] (figure 6). Both these sets of data differ, however, from Visfeldt's[242] results and from some recent data of Scott *et al.*[234] In these latter studies, cells were sampled after forty-eight to fifty-four hours in culture, but the cultures themselves (stimulated cells) rather than the freshly drawn whole blood (unstimulated cells) were irradiated. In this context, it is of interest to note that all the data on x- or gamma-irradiated cultures give lower dose exponents than do the data on irradiated whole blood, the difference being largely a consequence of higher yields at low doses in the irradiated cultures (figures 4 and 7).

168. Recent data from five different laboratories on the yields of dicentric aberrations in cells irradiated in whole blood prior to culture for up to fifty-four hours, with x rays of peak kilovoltage ranging from 180 kV to 300 kV, all give consistent results. These data are shown in figure 8, and the slope of the fitted line gives a dose exponent of 1.53. The aberration yields in these five sets of data are higher than the yields reported by

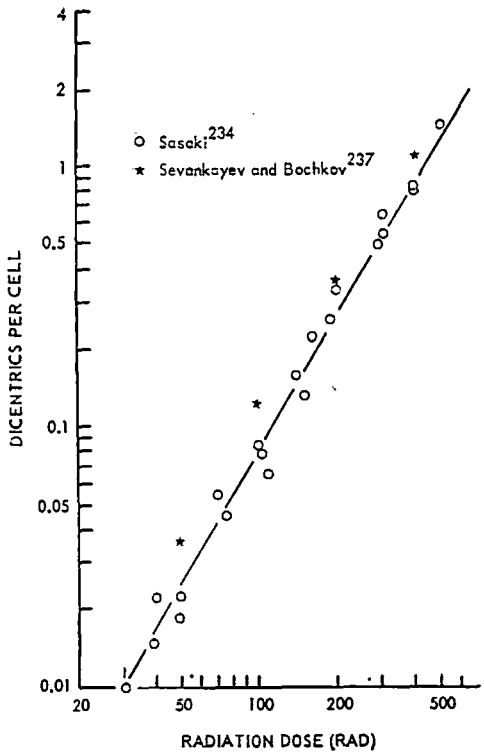

Figure 6. Dose-effect relationship for dicentric aberrations (irradiation with ^{60}Co gamma rays *before* PHA stimulation)[a]

[a] Whole blood irradiated *prior* to culture and cultured for *fifty* to *fifty-four* hours.

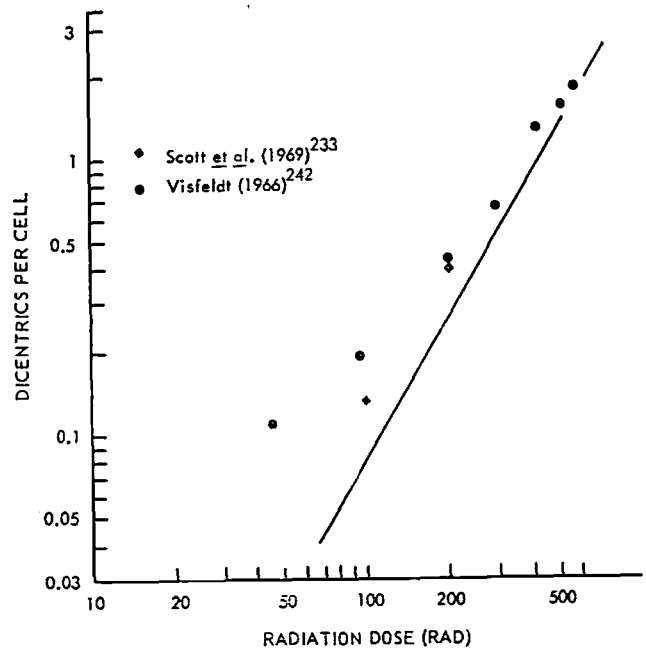

Figure 7. Dose-effect relationship for dicentric aberrations (irradiation with ^{60}Co gamma rays *after* PHA stimulation)[a]

[a] Whole blood irradiated *in culture*. Cultures grown at 37° C for *forty-eight* to *fifty* hours. Regression line fitted to data obtained from blood cells irradiated with ^{60}Co gamma rays *prior* to culture (figure 6).

other authors using longer culture periods; for the purpose of comparison, some of these latter data are plotted in figure 9.

169. It would appear, therefore, that, in the case of irradiated whole blood sampled after fifty-four hours

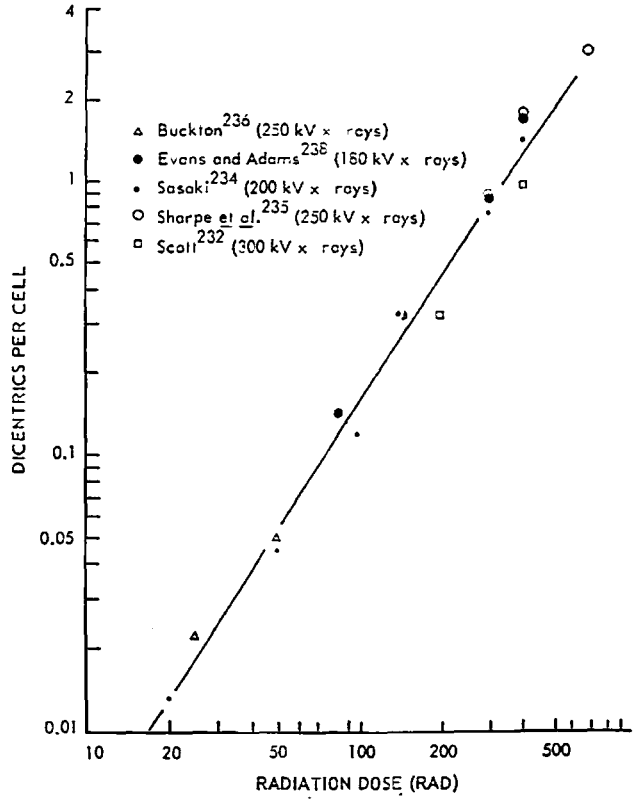

Figure 8. Dose-response relationship for dicentric aberrations (irradiation with 180 to 300 kV x rays *before* PHA stimulation)[a]

[a] Whole blood x-irradiated *prior* to culture and cultured for *fifty* to *fifty-four* hours.

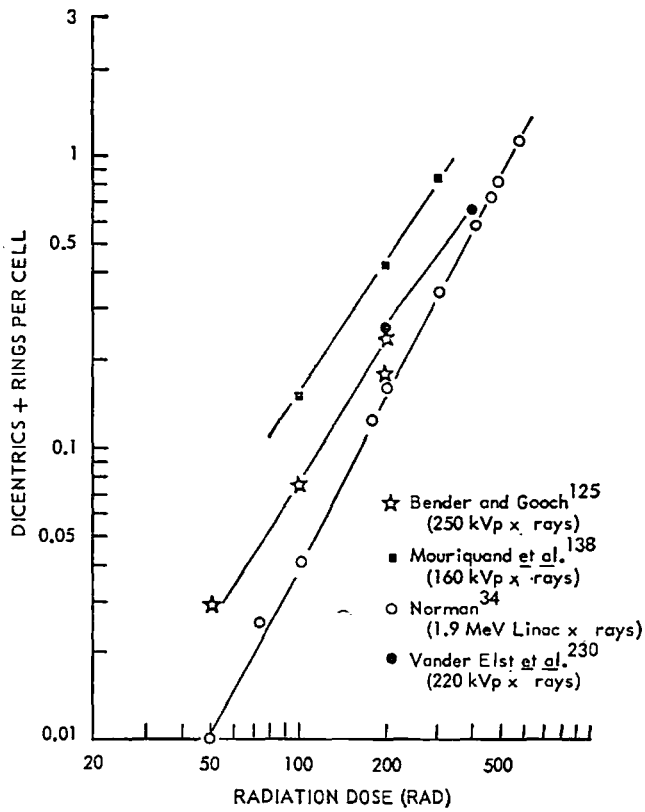

Figure 9. Dose-response relationship for dicentrics plus rings[a]

[a] Cells irradiated with various qualities of x rays *prior* to culture and cultured at 37° C for *seventy-two* hours.

in culture or less, the interchange aberrations induced by high-energy x rays are predominantly a consequence of the interaction between two lesions produced by independent tracks. However, over the same aberration yield range (up to about two dicentrics per cell) a significant fraction of the exchange aberrations induced by conventional x rays (150-300 kVp) are the result of the interaction between two lesions produced by a single track. The importance of this one-track contribution will, of course, decrease with increasing dose level.

170. Despite the excellent agreement between sets of data recently obtained quite independently in different laboratories, the difference in response, particularly at low doses, between irradiated cultures and irradiated whole blood requires further investigation.

2. *Fast neutrons*

171. Dose-response data from peripheral blood leucocytes exposed to fast neutrons *in vitro* have been reported by three groups of workers, namely, in the United States, the United Kingdom and Japan.

172. Gooch *et al.*[229] in the United States irradiated whole blood with 14.1 MeV DT and 2.5 MeV DD fast neutrons with doses of up to 200 rads, and the separated leucocytes were cultured for seventy-two hours before determining the induced aberration yields. With the 14.1 MeV neutron dose delivered at 6 rads per minute, it was found that "chromosome breaks" (terminal deletions + intercalary deletions?) increased slightly more than with the first power of the dose and that dicentrics plus rings increased as approximately the square of the dose (apparently the best fit to the equation $y = kD^n$, for dicentrics + rings gives a value[245] of $n = 1.42$). The coefficient of aberration production for deletions was 2.0 10^{-3} deletions per cell-rad and for dicentric and rings 12.1 10^{-6} aberrations per cell-rad squared.

173. It has been argued[156, 211] that the curvilinearity of these dicentric and ring data with 14.1 MeV neutrons might be due to the sampling of predominantly second and third division cells at low doses and, as a result of mitotic delay, to sampling of an increasing proportion of first division cells with increasing dose. There is no direct information on this possibility, but previous experiments with this quality of radiation on chromosome-aberration induction in plant cells have shown that all the aberration types increase approximately linearly with increasing dose.[246-249] However, it is important to note that, in the more recent studies of Sasaki[234] in Japan, using 14.1 MeV neutrons but with the cells sampled after fifty hours in culture, a dose exponent for dicentric aberrations of 1.24 was obtained.

174. Gooch *et al.*[229] compared their 14 MeV fast neutron data with those obtained with 250 kV x rays and obtained an RBE for these neutrons of approximately two. Preliminary data with 2.5 MeV DD neutrons yielded a linear dose response for all aberration types and an RBE of approximately four to five for deletions. It is of interest to note here that these authors derived an estimated RBE from *in vivo* exposure of three men to fission spectrum neutrons during a criticality accident. These estimates were arrived at after making certain assumptions, and an RBE value of the order of five was obtained (figure 10).

175. Scott *et al.*[245] in the United Kingdom exposed whole blood to fast neutrons of 0.7 MeV mean energy using doses of up to 150 rads. The cells were exposed prior to or following their introduction into whole blood microcultures. Continuous irradiations were given over periods of up to twenty-four hours and involved dose rates of 6.75 rads per hour and 3.41 rads per hour, and short-term irradiations were given at the approximately thousandfold higher dose rate of 50 rads per minute. No differences in efficiency between chronic and short-term exposures were found, and in both cases all aberration types increased linearly with increasing neutron dose. Comparisons with 250 kV x-ray data (doses of up to 500 rad) gave an RBE value for these 0.7 MeV fission neutrons of around three (figure 10).

176. In two of the five sets of 0.7 MeV neutron-dose-response data, some indication of a saturation in aberration yield was indicated at doses of above 100 rads in the chronic low dose-rate experiments. In these two experiments, the data also indicated a higher yield (of up to 10-20 per cent) in those cells irradiated while in the G_1 phase in culture (PHA-stimulated blood cells), as opposed to those cells irradiated prior to culture (i.e., unstimulated blood). The possibility of differences between the response to irradiation of stimulated and unstimulated cells has already been commented on (paragraph 171).

177. It has been suggested that the saturation effect results from a preferential loss of damaged cells due to "interphase death" under conditions of continuous irradiation in culture. This possibility again raises the question of preferential cell loss both prior to and during culture. It is of interest to note here that, in parallel to the higher yields of x-ray-induced aberrations observed by Scott *et al.* relative to those observed by Gooch *et al.*, similar, but rather more pronounced, increases in yield have been observed with the neutron data. This difference must, of course, partly be the consequence of differences in culture times and partly of differences in radiation quality. The difference is such that, at equivalent dose levels, the yields of dicentrics and rings with the 0.7 MeV neutrons is some ten times higher than the yields reported with the 14.1 MeV neutrons (figure 10). Further work is most certainly necessary here.

3. *The variation in response between blood samples obtained from different individuals*

178. Perhaps the only consistency among laboratories which has emerged from the *in vitro* studies is the indication that the variation between the *in vitro* response of blood cells obtained from different adult donors of both sexes is very small.[125, 131, 143, 229, 250] Five donors have been used by the Oak Ridge group, and data have been presented in two publications.[125, 229] In no case did the responses to the same dose level of cells obtained from different donors differ significantly.

179. In the Harwell studies,[250] seven donors were used, and all yielded closely similar aberration yields when exposed to similar doses. Moreover, cells from one donor were used for much of the x-ray dose-response work, and cells were, therefore, sampled at various times throughout a three-year period. Throughout this period, there was no significant change in the aberration yield at any given dose.[211]

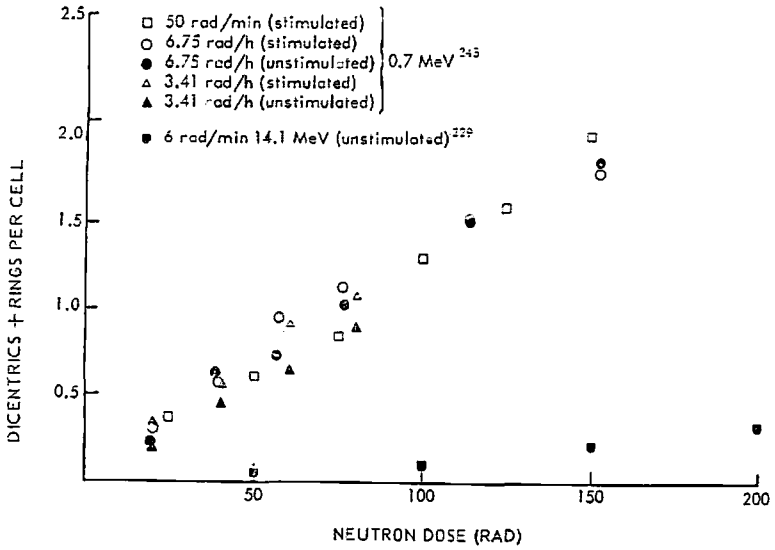

Figure 10. Dose-response data for *in vitro* fast neutron irradiation[245]

180. Recent work in the Soviet Union[251, 252] has indicated that the yield of x-ray-induced chromosome aberrations in peripheral blood lymphocytes irradiated *in vitro* may be slightly higher in cells taken from infants and from elderly people than in cells taken from other healthy adults. However, Migeon and Merz[253] had previously reported no significant differences between the responses of lymphocytes from infants and adults. Bochkov *et al.*,[254] in a study of fifty-nine individuals, reported that there was an influence of age on the frequency of spontaneous structural rearrangements in these individuals. The possibility of an influence of age of donor on radiation response clearly merits further study.

181. Studies on plant and animal cells (see references 17 and 255) have shown that, in a given species, the presence of an extra chromosome or chromosomes over and above the normal diploid complement results in an increased aberration frequency in these cells. The induced aberration frequency at any given dose level is, therefore, closely correlated with chromosome number as well as with chromosome size and chromosome morphology.[255]

182. Because of the disparity in size between the X and Y chromosomes in man,[256] it might be expected that, at a given dose, the frequency of chromosome aberrations in normal females might be very slightly greater than the aberration frequency in normal males. This expected very small difference between sexes has not yet been demonstrated, but, in line with expectation, a small increase in aberration yield in *in vitro* x-irradiated leucocytes from individuals trisomic for chromosome 21 (Down's syndrome), as compared with normal individuals, has been reported by three groups of workers.[143, 145, 257]

183. The constancy between individuals, and within individuals over a period of a few years, in the response of their blood cells to *in vitro* radiation exposure is heartening. Nevertheless, it must be strongly emphasized that the number of donors that have been compared to date is extremely small. Bearing in mind the influence of age and of sex on aneuploidy (paragraph 78), it is clear that more information is required from a larger number of donors of both sexes encompassing a wide age range. Such studies are currently in progress in a number of laboratories.

C. *In vivo* STUDIES

184. Quantitative studies on aberrations induced *in vivo* are beset with a number of difficulties additional to those considered in the *in vitro* work. These difficulties will be considered in some detail in this section as well as in paragraphs 341 to 343. Nevertheless, a discussion of the *in vivo* data cannot be initiated without emphasizing that difficulties with regard to physical dosimetry and to biological sampling are inherent in all the *in vivo* work. For instance, many studies have involved partial-body irradiation, and a variety of qualities of radiation has been used. Estimates of absorbed dose in such cases may not be very meaningful, and, in fact, difficulties with regard to the non-uniformity of absorbed dose exist even in the case of so-called uniform whole-body irradiation. Sampling problems are present because of the distribution, life span and mobility of the small lymphocyte within the body. These difficulties should, therefore, be borne in mind throughout the following discussion.

1. *Clinical exposure*

185. A number of instances have been recorded where an increased frequency of chromosome-type aberrations has been observed in peripheral blood leucocytes of individuals following the exposure of these individuals to diagnostic x rays. Although, to date, all the observations have been made on cultures grown for seventy-two hours or more (and, hence, some of the chromosome-type aberrations observed could have been derived following duplication of chromatid-type aberrations produced in culture—paragraphs 67 and 93), control data, where they exist, were also obtained from cultures grown for a similar period. The increases, therefore, must be a real consequence of radiation exposure.

186. The first observation of a possible effect of diagnostic x rays in inducing aberrations was made by Stewart and Sanderson[258] who reported the presence of two cells containing a dicentric out of a total of thirty-one cells scored in a patient with Klinefelter's syndrome. This patient was subjected to a skeletal survey involving a skin dose of less than 2 rads from 60 kV x rays, and blood samples were taken eight hours after exposure. Unpublished evidence[259, 260] on

the yield of spontaneous aberrations in Klinefelter patients who have not been exposed to diagnostic x rays shortly prior to study has indicated that the spontaneous yield in these individuals is no higher than in normal individuals (table I).

187. Observations similar to those of Stewart were made by Conen *et al.*[261, 262] who found two dicentric aberrations in 121 blood cells of an infant examined one week after exposure to a series of diagnostic x rays giving a total dose of 0.8 rad. Bloom and Tjio[263] did not detect any dicentric aberrations in blood cells from six patients given diagnostic chest x rays involving exposures of from 20 to 80 milliroentgens, but four dicentric aberrations were observed in 300 cells of five patients subjected to gastro-intestinal examination using fluoroscopy. The exposures of these five patients ranged from 12 to 35 roentgens, and blood samples were in all cases taken thirty minutes after irradiation.

188. Further indications of what appears to be a significant elevation in aberration yield are seen in the data of Court Brown[264] on ankylosing spondylitis patients subjected to diagnostic x rays (columns *b* and *c* in table I). Moreover, Sasaki *et al.*[265] have reported that, in a scan of over 7,000 cells taken from a total of eleven individuals, dicentrics were only found in one man who had received a number of lumbar spinal x-ray examinations some five years previously.

189. These observations suggest that very low-dose partial-body x irradiation at low (diagnostic) kilovoltage is capable of inducing a detectable frequency of chromosome-type aberration. The fact that we can detect the effects of such small doses of x rays is a consequence, first, of the relatively high sensitivity of human peripheral blood leucocytes to the induction of chromosome damage by radiation, and, second, of the extremely low frequency with which chromosome-type aberrations are found in individuals not exposed to ionizing radiations.

190. More recently, information has become available from patients treated with Thorotrast, a stabilized colloidal suspension of the dioxide of thorium-232. Thorotrast is taken up by the reticulo-endothelial cells and deposited in liver and spleen, and, to a lesser extent, in bone marrow and lymph nodes. Only minute quantities are excreted so that these tissues are subjected to continuous irradiation, much of which is due to densely ionizing alpha particles.

191. Ishihara and Kumatori[182, 266] reported that a significant yield of aberrations was to be found in blood leucocytes of persons given Thorotrast injections some twenty-five years prior to observation. The residual body burdens of these persons were estimated by whole-body counting, but no definite correlation was found between body burden and aberration yield.[267] Similarly, Buckton *et al.*,[224] in a cytogenetic study of thirty-six patients who received intra-arterial injections of Thorotrast some eleven to thirty-one years prior to study, reported a marked increase in aberration yields in the leucocytes of these patients as compared with those of control individuals. The cells in this latter study were cultured from forty-eight to fifty-two hours, and 9.2 per cent of the cells were found to contain unstable (asymmetrical) aberrations and 5.7 per cent stable (symmetrical) aberrations. It is of interest to note that, in this work, a very high frequency of tricentric aberrations was found (3.8 per 100 cells) and that many cells contained more than one aberration. This high aberration frequency in damaged cells is typical of damage induced by high LET radiation, such as the alpha particles of thorium.

192. The high aberration yields obtained by Buckton *et al.*[224] in their Thorotrast patients are considerably greater than the yields obtained by these authors[16] in patients receiving a whole-body dose of 50 rads of x rays or a partial-body dose of 300 rads. However, in the Thorotrast work, although the volume of Thorotrast administered and the time interval between treatment and observation were known, no relationship between these parameters and aberration yield could be demonstrated.

193. Fischer *et al.*[179, 268] examined blood cells from twenty individuals who had received Thorotrast from nineteen to twenty-seven years prior to sampling, and in these patients estimates of residual body burden were made through whole-body counting. Nineteen of these cases showed a significant increase in aberration frequencies above the background level; the only one that did not show such an increase had undergone a retrograde pyelography and had, thus, retained little radio-activity as was confirmed by the extremely low burden registered by the whole-body counter.

194. In this work, it was shown that, with an increasing amount of Thorotrast (estimated from whole-body gamma-ray counting), there was an increasing amount of chromosome damage and a significant linear correlation between these parameters when the data were weighted by the time interval elapsing between administration and observation. However, we should note that there are several difficulties in assessing these dose-response relationships, since considerable variation exists in the distribution of Thorotrast within the reticulo-endothelial system,[224] and estimates of dose from thorium and its decay products, based on gamma-ray measurements, require that allowance be made for the self-absorption of alpha rays; this is of particular importance if the thorium is not uniformly distributed. Because of these difficulties in physical dosimetry and since, in the work of Fischer *et al.*,[179] the leucocytes were cultured for seventy-two hours, it is difficult to arrive at any meaningful coefficients for aberration production.

195. Since the original paper of Tough *et al.*[15] who reported gross chromosome damage in cells from blood cultures of two patients after x-ray therapy for ankylosing spondylitis, a number of publications dealing with aberrations induced in patients following radiotherapy have appeared. Most of this work has been concerned with aspects of aberration induction (such as the question of the longevity of the small lymphocyte — paragraphs 252-263) other than the quantitative correlation between induced chromosome damage and absorbed dose. However, a limited amount of data on dose response *in vivo* has been obtained, and more should be available in the near future.

196. Norman *et al.*[239] obtained a limited amount of data on two patients receiving doses of 300 rads from 250 kV x rays, using blood samples that were collected immediately after irradiation. No details of the method of exposure were given, and the geometric mean of the aberration yields from the two rather different samples was nearly equal to the yield obtained from normal blood irradiated *in vitro* and receiving a dose of 300 rads. In these cases, all the cultures were grown for seventy-two hours.

197. A more recent paper[34] reports aberration yield data from six patients treated with (partial-body?) radio-therapy for malignant disease. Cultures were grown for fifty hours and seventy-two hours, but no estimate of dose is given. In considering such partial-body exposures, the question, of course, arises as to what significance can be attached to a partial-body dose if such a dose is reported.

198. The aberration yield observed in peripheral blood leucocytes sampled after a partial-body irradiation will depend upon a number of variables including the following: the physical characteristics of the radiation; the region of the body and the volume of tissue exposed; the absorbed dose in this volume and the duration of the radiation exposure; the proportion of the total body lymphocytes that were resident in this volume during irradiation; the proportion of blood lymphocytes that traversed this region during irradiation; the amount of exchange of lymphocytes between the lymphatic tissues and peripheral blood and the time of sampling after irradiation.

199. The question of dosimetry in cases of partial-body exposure is, therefore, complex and will be considered in some detail later (paragraphs 264-273). However, it is pertinent to note here the recent studies by Winkelstein *et al.*[227] on chromosome aberrations in leucocytes of three patients whose blood was exposed to extracorporeal irradiation (ECI) prior to renal transplantation.

200. In this work, blood was passed through a teflon loop outside the body, using a standard Quinton-Scribner shunt, and was subjected to ECI by exposure to beta-emiting ^{90}Sr-^{90}Y sources. Exposure times of up to four to eight hours were used, and the frequency of dicentric aberrations in leucocytes cultured with PHA immediately after the termination of the ECI period was determined. In addition, the frequency of dicentric aberrations in *in vitro* studies on blood put through the radiation applicator in a single passage was also determined.

201. In these ECI studies, physical dose estimates to the blood cells were made on the basis of patient blood volume, flow rate through the applicator and duration of irradiation exposure. Although no detailed data on aberration yields were given, the relationship between calculated physical doses (integrated over the whole blood volume) and the doses estimated on the basis of dicentric aberration yields in sampled blood leucocytes were compared. The dose was estimated from the aberration yield through the use of the proportionality constant (paragraph 160) of dicentric yield being equal to $5.7 \pm 0.5\ 10^{-6}$ per cell-rad squared as determined from previous *in vitro* studies[34, 240] of this group. A very close correspondence between physically and biological estimated dose was found (table II), provided that samples were taken after no more than a four- to eight-hour ECI exposure so that blood leucocytes were not replaced by populations of leucocytes from the unirradiated lymphoid tissues.

202. In an ECI study carried out by Sharpe *et al.*[243] on a patient with reticulum cell sarcoma, it was found that the relationship between estimates of dose based on blood flow rate and on total blood volume of a patient and of those based on the yield of dicentric aberrations differed by a factor of 2.7. The data obtained indicated that, in a treatment lasting three and a half hours, several cells made many transits through the irradiator and that there was a fairly rapid exchange between leucocytes of peripheral blood and those in much larger pools in extravascular sites.

203. Sharpe *et al.*[269] have recently reported on some further ECI studies made on a patient with Hodgkins disease. This work has confirmed and very much extended their earlier findings, and the results are somewhat at variance with the conclusions of Winkelstein *et al.*[227] In this recent study,[269] it was found, as previously shown by others,[227] that the yield of dicentric aberrations (0.83 per cell), in a sample of the patient's blood taken prior to ECI treatment and receiving an *in vitro* dose of 300 rads from 2 MeV x rays, was closely similar to the dicentric yield (0.87 per cell) obtained from blood allowed to proceed through one transit of the radiation coil (320 rad from a caesium-137 source) over an exposure period of four seconds. However, in blood samples taken from the patient after one and a half, three and twenty-four hours, continuous ECI-treatment, dicentric yields of less than 0.09 per cell were obtained.

204. From these data and from studies on the distribution of aberrations between cells, Sharpe *et al.*[269] concluded that there is a rapid exchange between lymphocytes in blood and lymphocytes in the extravascular pool. It was estimated that the peripheral blood contained 3 grammes of lymphocytes, whereas the extravascular pool contained between 800 and 1,070 grammes. Two independent estimates of the mean residence time of lymphocytes in blood gave values of 4.7 and 7.5 minutes.

205. The results of the ECI studies by these two groups of workers, although somewhat conflicting, are most interesting, and further work in this field will be particularly rewarding both from the point of view of yielding information on the population structure and movements of the leucocytes and in providing information applicable to the possible use of chromosome aberrations in dosimetry.

206. Following up on its original studies[15] on aberrations induced by x irradiation of spondylitis patients, the Edinburgh group has recently reported[16] data on the relationship between aberration yield and radiation dose in these patients and in patients suffering from neoplastic disease. With the spondylitis patients, single partial-body doses of 100 to 700 rads (250 kV x rays, HVL = 2.7 mm of Cu) were given and the cells cultured for forty-two to fifty hours. At all doses, blood samples were taken twenty-four hours after exposure, but, in some instances, samples were also taken at earlier and later times. The data indicate a slightly lower aberration yield in cells cultured immediately after exposure than in cells sampled for culture twenty-four hours later. A summary of the data obtained is given in table III.

207. Although we cannot define the absorbed doses in these cases for whom data are given in table III, there is evidently a clear relationship between skin dose and aberration yield. The data are somewhat variable, and for dicentric and ring aberrations the aberrations appear to increase in proportion to the 1.5 to 2.4 power of dose, at least for doses up to 300 rads. If the data from one patient given a partial-body dose of 700 rads is included in the kinetic analysis, then this high dose yield reduces the dose-squared component considerably. Extrapolation from the data shown in table III shows that these yields are higher

than those obtained by Millard[126] from patients exposed to partial-body (lower abdomen) radiation following orchidectomy. In Millard's data (2 MeV Van der Graff x rays), 20 per cent of the cells showed aberrations after doses between 925 and 1,550 rads and 32 per cent after doses between 3,100 and 4,330 rads. These latter data, however, were obtained from peripheral blood cells that were allowed to grow for seventy-two hours, and, moreover, the radiation treatment was spread over a period of thirty-six to seventy-four days.

208. Similar observations to those of Millard have been made by Dubrova[270] on two myeloma patients receiving radiation therapy. In this work, patients were treated with an accumulated partial-body exposure of 9,000 roentgens, and up to 42 per cent of the leucocytes cultured for forty-eight hours were found to contain chromosome aberrations. High aberration yields were also observed in blood cells of a similar patient sampled thirty-two months after the completion of a similar course of treatment.

209. Spondylitis patients were also given ten partial-body x-ray dose fractions over a period of twelve to fourteen days;[16] blood samples were collected immediately after each treatment. Again, there was a clear relationship between radiation dose and aberration yield, the data giving a very good fit to a linear relationship (figure 11). In these data, each fraction

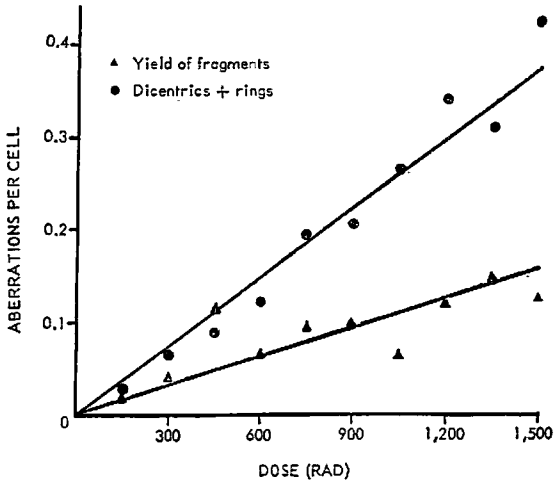

Figure 11. Yield of fragments and dicentrics plus rings in ankylosing spondylitis patients exposed to doses of up to 1,500 rads (250 kV x rays) given as a series of fractions of 150 rads[16]

of 150 rads (partial-body dose) gave an average yield of 3.6 dicentrics and rings per 100 cells analysed.

210. Buckton *et al.*[16] also reported preliminary data, summarized in table IV, on aberration yield in seven men suffering from bronchial carcinoma who received low doses (25 or 50 rad) from whole-body x irradiation (2 MeV Van der Graff). In contrast to the data obtained from patients exposed to partial-body irradiation (table III), no differences in aberration yields were found between bloods sampled immediately after exposure and twenty-four hours later (however, see paragraph 211). Moreover, the dose response for dicentrics and rings after whole-body irradiation was linear (n in the equation $y = c + aD^n$ being equal to 0.92 with 90 per cent confidence limits of 0.5 to 1.4). From the data presented, it would seem that the aberration yield obtained following a whole-body dose of 50 rads to the cancer patients was equivalent to the yield obtained with a partial-body dose of 250 rads to the ankylosing spondylitis patients.

211. The Edinburgh group has recently extended its studies on whole-body irradiation of patients with bronchial carcinoma and has now reported[271] data obtained from a further nine patients exposed within the dose range 17 to 50 rads. The dicentric and ring aberration frequencies in fifty-three-hour cultures of blood cells sampled immediately after irradiation and twenty-four hours later are summarized in table V for each of the sixteen patients.

212. In these data, there is a significant increase in aberration yield in bloods sampled twenty-four hours post-treatment as opposed to bloods sampled immediately after exposure in patients receiving doses of 50 rads. This observation is entirely in line with the earlier observations made by this group of workers on ankylosing spondylitis patients exposed to partial-body irradiation (paragraphs 206 and 210).

213. Analysis of the data obtained from these whole-body exposures revealed that the yield of dicentric and ring aberrations in blood sampled immediately after irradiation increased as the 1.13 power of dose ($n = 1.13$ with 95 per cent confidence limits of 0.52 to 1.74), whereas, in blood sampled twenty-four hours later, the yield increased as the 1.88 power of dose ($n = 1.88$ with 95 per cent confidence limit of 1.24 to 2.50). These two sets of data are shown in figures 12 and 13.

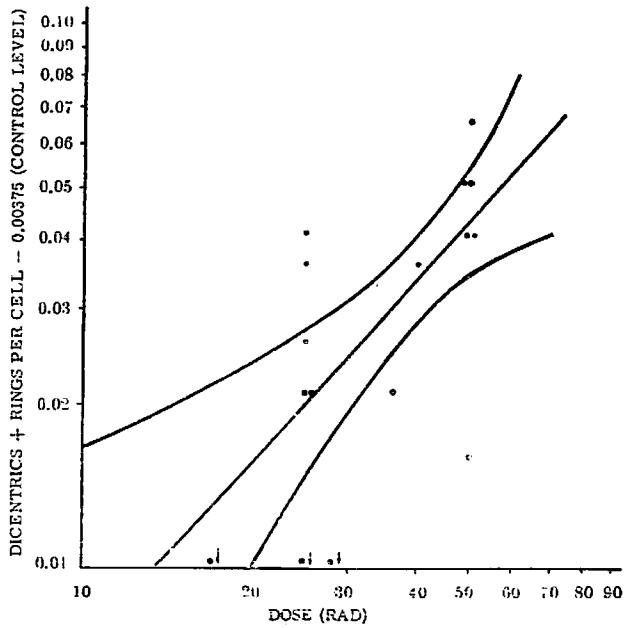

Figure 12. Relationship between yield of decentrics plus rings per cell and uniform whole-body dose in patients exposed to 2 MeV x rays[271 a]

[a] Data from blood samples taken immediately after radiation exposure. Points are from data given in table V, and curved lines represent the 95 per cent confidence limits of the regression line.

214. It is of interest to compare the 25-rad and 50-rad whole-body irradiation data with data obtained using similar doses (but with various qualities of radiation) by other authors in *in vitro* studies. These

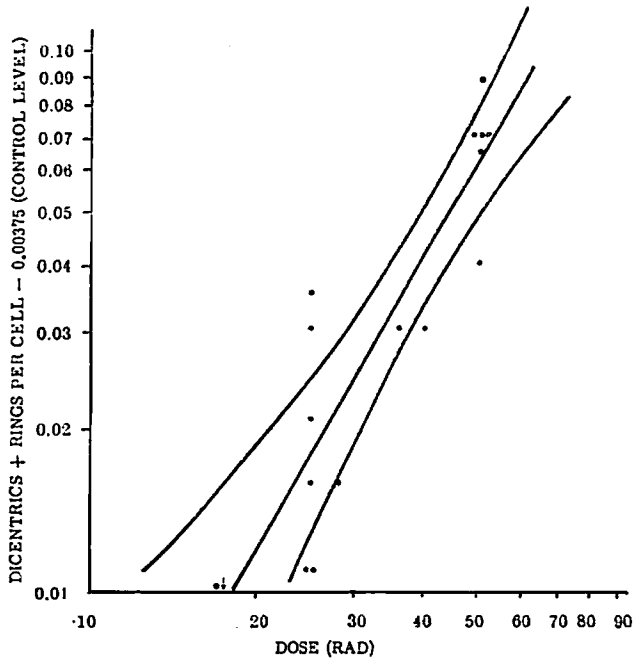

Figure 13. Relationship between yield of dicentrics plus rings per cell and uniform whole-body dose in patients exposed to 2 MeV x rays[271 a]

[a] Data from blood samples taken twenty-four hours after radiation exposure. Points are from data given in table V, and curved lines represent the 95 per cent confidence limits of the regression line.

comparisons are set out in table VI where it may be seen that scores obtained in the *in vivo* work fall in between the lowest and highest yields reported for the same absorbed doses in the *in vitro* studies. It is disappointing to note that, in the only *in vitro* work where a radiation quality similar to that used in the *in vivo* studies was used and where the cells were cultured for fifty hours, the aberration yield at a dose of 50 rads was four times lower than that found in the *in vivo* studies. However, the observations were made in different laboratories where techniques were not entirely comparable.

215. In addition to the data on therapeutic exposure to external radiation sources, there is some information on aberration yields in patients to whom radio-active materials had been administered internally for therapeutic purposes. Boyd *et al.*[272] initially reported that types of chromosome damage similar to those reported by Tough *et al.*[15] were to be found in blood cells of patients treated with radio-active iodine. It was suggested that, in quantitative terms, the effects of 100 millicuries of radio-iodine were similar to the effects of a partial-body dose of 250 rads of x rays and that a 10-millicurie dose of radio-iodine was probably sufficient to produce recognizable chromosome damage. Similar findings with radio-active iodine were also reported by other authors,[172, 273-275] and, in one report,[274] a significant yield of aberrations was observed fourteen years after completion of treatment.

2. *Occupational exposure*

216. A number of workers have reported the presence of chromosome-type aberrations in individuals receiving chronic low doses from external sources.[127, 132, 136, 165, 168, 239, 263, 265, 268, 276-280] Norman and his colleagues[265] observed seven dicentrics in 5,138 cells from ten hospital radiation workers who had received dose equivalents of up to 88 rems accumulated at an average rate of from 1 to 3 rems per year, whereas in ten control individuals no dicentrics were observed in 4,219 cells. Later studies[167] were carried out on thirty-six radiation workers who had received cumulative doses of from 10 to 98 rads with a median annual dose rate of 1.45 rads per year. In this later work, fourteen dicentrics were observed in 14,839 cells, whereas in twenty-three control individuals no dicentrics were observed in 5,784 cells. Observations similar to these have recently been made by Lisco and Lisco[277] and by Gorizontova.[278]

217. Studies somewhat similar to those of Norman and his colleagues have been reported by Court Brown *et al.*[276] and Buckton *et al.*[132] These authors studied sixty-seven adult males working in atomic energy establishments and divided their sample into five groups: (*a*) a control group that had received a cumulative dose of less than 1 rad; (*b*) a group with an average accumulated dose of 3.8 rads, with a range from 1 to 10 rads; (*c*) a group with an average accumulated dose of 27 rads, with a range from 23 to 34 rads; (*d*) a group with an average accumulated dose of 24 rads, with a range from 15 to 37 rads; (*e*) a group with an average accumulated dose of 84 rads, with a range from 75 to 98 rads. The irradiated groups differed not only in the doses received but also with respect to the time over which the exposures occurred. The control group did not differ cytologically from a control population drawn from outside atomic energy establishments, but all the irradiated groups showed a highly significant increase in aberration yield. Although yields of dicentric and ring aberrations of as high as eight per 1,000 cells were observed, no correlation between dose and yield could be discerned.

218. Visfeldt[127] studied aberration yields in peripheral blood cells of ten members of the staff of the Copenhagen Radium Institute who had received cumulative doses ranging from 1 to 116 rads over a period of ten years. Again, a clear increase in aberration yield was observed in irradiated (thirteen dicentrics plus rings in 950 cells) personnel as opposed to control (zero dicentrics plus rings in 300 cells) personnel, but the data are once more too meagre to show any correlation with the dose received.

219. El-Alfi *et al.*[279] analysed blood cells from twelve radiation workers, exposed over periods as long as four years, who received cumulative dose equivalents of up to 1,110 millirems of x, gamma or beta rays or up to 9,722 millirems of neutrons. No details on the quality of the radiation nor on the kinds of exposures were given, but significant increases in aberration yields were observed in the six individuals exposed to neutrons when compared with nine control individuals.

220. Data somewhat similar to those of Visfeldt's have recently been reported by Wald *et al.*[136] These authors studied aberration yields in six nuclear industry workers who had received external body dose equivalents ranging from 25 to 55 rems at an average accumulation rate of 4.3 rems per year. A significant increase in the frequency of stable and unstable aberrations in irradiated as opposed to control personnel was noted, but no relationship with the various dose levels could be discerned, and no detailed cytogenetic data are given.

221. A number of studies have been carried out on persons who have worked in the luminizing industry

and who have, as a consequence, high body contents of radium-226. These studies also have shown a significant increase in aberration yields in exposed versus unexposed individuals, even in individuals having body burdens well below the maximum permissible level.[167, 281] With these internal emitters, there is some evidence of a consistent gradient of increasing aberration yield with increasing radium body burden.[282] In the data of Boyd *et al.*[282] on individuals who accumulated body burdens between 0.10 and 0.56 microcuries of radium-226 eighteen years prior to study, some 3.2 per cent of the cells were classed as "unstable" and found to contain asymmetrical aberrations. In this work, the total occupational dose equivalent from external gamma rays averaged about 90 rems. There was no association between these low-level external exposures and aberration yield.

222. These data on occupationally exposed individuals all show significant increases in aberration yield in persons exposed to very low dose levels. This is, of course, in line with the earlier observations on the effects of low doses of diagnostic radiation. Moreover, it should be emphasized that, in those cases where accurate physical dosimetry has been carried out, it is possible to state that significant aberration yields have been observed in individuals receiving doses below the permissible levels.

3. *Accidental exposure*

223. Bender and Gooch[128, 129] studied aberration yields in peripheral blood cells of eight men exposed accidentally to mixed gamma and fast neutron radiation. The doses were estimated to range from 23 rads to 365 rads, with the neutrons comprising some 26 per cent of the total dose. No chromosome-type aberrations were found in five control individuals (total of 458 cells), but dicentrics and rings were present in all five individuals exposed to doses calculated to be over 200 rads. Blood samples were first collected twenty-nine months after the original exposure and then a year and a half later. Aberrations were present in all individuals except the person exposed at the lowest dose level. In one individual who received an estimated 339 rads, the frequency of dicentric and ring aberrations was 0.166 per cell (table VII). All the cultures in these cases were grown for seventy-two hours. Goh[283] followed up these observations and examined cells from blood samples, cultured for seventy-two hours, taken from six of these men seven years after the original accident. Cells from bone marrow were also sampled. Aberrations were observed both in cells from the marrow and in cells from peripheral blood, but dicentric aberrations were absent in marrow cells. Although the over-all frequencies of aberrations in peripheral blood cells had declined with time after exposure, significant yields of dicentric and ring aberrations were observed on each of the three occasions when samples were taken. The published data on dicentric and ring aberrations in these studies are summarized in table VII.

224. In a later criticality accident,[131, 229] three men received estimated doses of 12, 22.5 and 47 rads of mixed radiation (gamma and fission neutrons), the neutrons contributing, in the different individuals, 25-50 per cent of the total dose. In these cases, blood was sampled from four hours up to two years after exposure, and the cultures were grown for seventy-two hours. Dicentric aberrations were observed in all three individuals, their frequency showing a clear increase with increasing dose. A reasonable correlation between estimated physical dose and aberration yield was observed with some 3 per cent of the cells being affected at the highest dose level. Using these data, previous *in vitro* information and certain assumptions, it was suggested that the RBE for fission-spectrum neutrons versus gamma rays was of the order of five to one.

225. Biola and Le Go[284] have described studies on blood samples taken from an individual four days after a highly non-uniform exposure to mixed gamma and neutron radiation in an incident at Mol, Belgium. Physical estimates of dose suggested that the individual had received a mid-line exposure of around 500 rads. In parallel with the studies on the blood sample from the irradiated individual, studies were also made on blood cells taken from a normal individual and then exposed to cobalt-60 gamma rays with doses of 400 and 600 rads. For comparison with the data of Gooch and Bender,[229] all cultures were harvested at seventy-two hours or ninety-six hours, although it was evident that at seventy-two hours at least 10 per cent of the cells were in their second mitosis in culture. The aberration yields observed, therefore, were clearly an under-estimate of the true yield, but, since cultures of the blood of the irradiated individual and of the cells irradiated *in vitro* were handled in exactly the same way, valid comparisons could be made. The actual yields observed *in vitro* were similar to those obtained by Gooch and Bender[229] at the lower dose levels and to those obtained by Kelly and Brown[137] at the higher doses. The *in vitro* yield at a dose of 450 rads was equivalent to the yield obtained in the cultures from the irradiated individual so that a good correlation existed between physically estimated and biologically estimated dose.

226. More recently, Buckton *et al.*[132] analysed cells from two men who accidentally received whole-body doses of 17 and 18 rads, the men having additionally accumulated 10 and 9 rads, respectively, as an occupational exposure over several years of routine employment. Dicentric and ring aberrations were present in the blood cells of both men at levels up to a maximum of 3 per cent, depending on whether blood was taken at forty-eight hours or at one or three months following exposure. One of the two controls who had received occupational exposures of approximately 2 to 3 roentgens had a dicentric and ring frequency of approximately 1 per cent on two out of the three occasions on which his blood was sampled. The data here are too scanty to draw any conclusions on dose relationship.

227. Sugahara *et al.*[285] have reported data obtained from two men exposed to external irradiation from 250 kV x rays and cobalt-60 gamma rays, with estimated exposures of, respectively, 66 and 40 roentgens, and studied ten and twelve months after exposure. In addition, data were obtained from a further three men who inhaled uranyl fluoride and from whom blood cells were taken forty days after the accident. The amounts of uranyl fluoride (estimated from urine excretion) taken up ranged from 2.2 milligrammes to 3.9 milligrammes, representing an inhalation of between 2.6 and 4.6 10^{-3} microcuries.

228. In blood cells obtained from all five men in this study,[285] significant increases in aberration yields, as compared with those in cells obtained from control individuals, were noted, and dicentric and ring aberra-

tions were present in cultures from all but one of the individuals. The authors point out that the frequency of aberrations in the x- and gamma-irradiated individuals were in the range expected from earlier observations of other workers[128, 131] but that almost equivalent yields were obtained in two of the three men who had inhaled uranium (3.2 per cent enriched uranium). The cumulative, external, occupational dose equivalents of these men were small, ranging from 128 to 936 millirems. The observations made on these three men were comparable with those reported by Boyd *et al.*[282] on luminous dial painters (paragraph 219).

229. Wald *et al.*[136] have carried out cytogenetic studies on a group of seven workers who accidentally inhaled iodine-125 and whose body burdens were measured by direct counting methods. Body burdens ranging from 1.2 to 111 microcuries were determined. These workers had also been exposed to external sources and had accumulated dose equivalents ranging from 1 to 18.8 rems at an average rate of 1.4 rems per year. No details of the qualities of the external radiations were given. The data clearly show a significant increase in the frequency of cells carrying unstable aberrations over controls, but no breakdown of the aberration data is given.

230. Observations similar to those reported above have been made by Lejeune and his colleagues[286] on four individuals, one of whom received an estimated maximum dose of 33 rads of neutron and gamma rays (following an accidental exposure to a proton beam), and the others were exposed to unknown quantities of gamma rays, although in one individual the estimated dose was between 35 and 50 rads. Significantly increased aberration yields relative to controls were observed in samples taken at various intervals up to one year after irradiation. The aberrations included dicentrics and rings as well as a number of symmetrical changes, and the cells were cultured for seventy-two hours prior to preparation. In the individuals in whom physical estimates of dose were available, it was shown that the aberration yields observed were reasonably consistent with those predicted on the basis of the aberration-yield coefficient quoted by Bender and Gooch[229] (paragraph 156). The authors were careful to point out, however, that the data were insufficient to draw any firm conclusions on the relation between aberration yield and dose in these individuals.

231. Lisco and Lisco[287] have recently examined peripheral blood leucocytes (forty-eight-hour and seventy-two-hour cultures) of two radiation workers who exposed their right hands to mixed gamma-beta radiation from an iridium-192 source. The exposure was for a ten-minute period, and the physically estimated dose to the hands was 3,000 rads, 10 per cent of which was from gamma radiation. Eleven days after exposure, the yield of dicentric and ring aberrations in cells of both individuals was around 0.05 per cell (equivalent to that observed with a 50-rad whole-body dose from x rays), and high aberration yields were noted in each of the follow-up studies carried out at intervals up to three years after the accident. No aberrations were observed in bone-marrow cells.

232. The rather sparse data obtained from, fortunately rare, accidents underline the earlier statement that one of the complications in accidental exposure is the difficulty of obtaining good physical estimates of dose, particularly in those cases of mixed radiation exposure. In general, the cytological data that have been obtained are not inconsistent, but they are still too scanty to draw any firm conclusions on the usefulness of aberration yield for biological dosimetry in these particular cases.

4. *Nuclear explosion*

233. A number of studies[133-135, 168, 175, 182, 221] have been made on survivors at Hiroshima and Nagasaki who were exposed to radiation from nuclear explosion in 1945. The data of Ishihara and Kumatori,[135, 175] obtained from blood cells of persons who were between 500 and 2,000 metres from the hypocentre and who were studied nineteen years later, show a significant increase over control individuals in the yield of asymmetrical and symmetrical aberrations.

234. Bloom *et al.*[133, 134, 288, 289] carried out surveys on survivors in different age groups. In the first study[133] on ninety-four exposed individuals and ninety-four matched controls, all the individuals sampled were under the age of thirty years at the time of the bombings in 1945. Chromosome aberrations were found in 0.6 per cent of the peripheral blood leucocyte cells in the exposed individuals, whereas only 0.01 per cent of the cells contained aberrations in control individuals. In the control individuals, no dicentric aberrations were observed in the 8,847 cells scored, but nine such aberrations were found in 8,283 cells from the irradiated population sampled twenty years after exposure.

235. In the second survey by Bloom *et al.*[134] observations were made on seventy-seven heavily exposed (estimated dose greater than 200 rad of mixed gamma-neutron radiation) survivors and eighty control individuals, all of whom were over the age of thirty years at the time of the bombings. Sixty-one per cent of the heavily exposed survivors and 16 per cent of the controls were found to contain aberrations at a frequency of 1.5 per cent in cells of exposed individuals as opposed to 0.3 per cent in cells of control individuals. One dicentric aberration was detected in the 7,188 cells scored from controls, and this was observed in a cell from an eighty-year-old male. In the irradiated individuals, eight dicentrics were found in the 6,778 cells studied.

236. The relative frequencies of the asymmetrical dicentric, ring and fragment aberrations in the survivors of the two different age groups were very similar. However, the symmetrical translocations and inversions were found to be more frequent in the older exposed survivors than in the younger ones. In parallel with this latter observation, it was noted that symmetrical aberrations were also more frequent in the older of the two control groups. These observations once more raised the question of whether the sensitivity to aberration induction by radiation might be related to age, a problem that requires urgent attention.

237. The most frequent aberrations observed by Bloom *et al.*[134] in the exposed older survivors were translocations which were present in seventy-two of the 6,778 cells scored. It was noted, however, that twenty of these cells containing a translocation were detected in four individuals, and these represented five different types of translocation or five possible cell clones.

238. Estimates of the dose sustained by the exposed older survivors ranged from 204 to 991 rads of mixed gamma and neutron radiation. A preliminary attempt

to correlate aberration frequency with physically estimated dose suggested that the aberrations increased approximately linearly over the dose range studied, the over-all aberration frequency being about 1 per cent at 200 rads and increasing by approximately 0.5 per cent per 100-rad increment. It should be noted, however, that, in this work, the leucocytes were cultured for a period ranging from 66 to 70 hours, and, of course, samples were studied twenty years after an original radiation exposure.

239. Workers at the Atomic Bomb Casualty Commission [289] have analysed the karyotypes of 128 individuals who were born after at least one of their parents had received a minimum exposure of 100 rads as a result of the atomic bombings at Hiroshima and Nagasaki. Control studies were carried out on fifty-seven sibs of these individuals who were born before the time of the bombings. Particular attention was devoted to the 103 individuals who were born in the first five years after parental exposure, but no significant increase in chromosomally abnormal individuals could be detected. However, a detailed study of thirty-eight *in utero* exposed survivors,[288] whose mothers had been exposed to more than 100 rads (estimated range 104-477 rad) at the time of the bombings, revealed a small but significant increase in the frequency of lymphocytes with complex chromosomal rearrangements (0.52 per cent) as compared with matched control individuals (0.04 per cent).

240. Sasaki and Miyata[221] re-opened the question of the relationship between aberration yield and estimated physical dose in the atomic bomb survivors and presented a considerable amount of detailed data obtained from the scoring of over 80,000 cells from exposed and control individuals. Chromosome analysis was carried out on fifty-one Hiroshima survivors and eleven controls twenty-two years after the original exposure. Care was taken to score only cells dividing for the first time in culture, and the cultures were terminated after fifty hours. The aberrations were classified as outlined in paragraphs 24 to 34, and it was found that the mean number of dicentrics and rings in the exposed individuals (201 in 73,996 cells) was 0.0024 per cell as compared with 0.0002 per cell (2 in 9,510 cells) in the controls. It was also shown that the frequency of cells carrying stable symmetrical rearrangements (largely reciprocal translocations) was 0.40 per cent in exposed individuals as compared with 0.07 per cent in controls.

241. A significant yield of aberrations was observed among nineteen survivors who were more than 2.4 kilometres from the hypocentre and who, as was estimated on the basis of physical considerations, had received a dose of the order of 1 rad. Eleven of these individuals entered the bombed area within three days after the bombing, and the frequency of dicentrics and rings in these individuals was 0.0013 per cell as compared with a frequency of 0.0006 per cell in the eight individuals who did not enter the bombed zone.

242. The exposed individuals were divided into four groups based on distance from the hypocentre at the time of the bombing and on whether they were directly exposed or shielded by wood or by concrete. Proportionally more cells with aberrations appeared in survivors exposed at the shortest distance from the hypocentre, and, at a given distance, the aberration yield was highest in those directly exposed, intermediate in those shielded by wood and lowest in those shielded by concrete.

243. Since the observations were made twenty-two years after the original exposure, Sasaki and Miyata[221] used two different methods in an attempt to obtain dose estimates. Studies by other workers[33, 44, 290] have shown that the proportion of peripheral blood lymphocytes carrying stable chromosome rearrangements (C_s cells) observed many years after an irradiation exposure remains unchanged from the proportion observed shortly after exposure. The ratio of C_s cells to normal cells could, therefore, be used as an end-point in these Hiroshima survivors, and the relationship between this end-point and distance from the hypocentre is shown in figure 14.

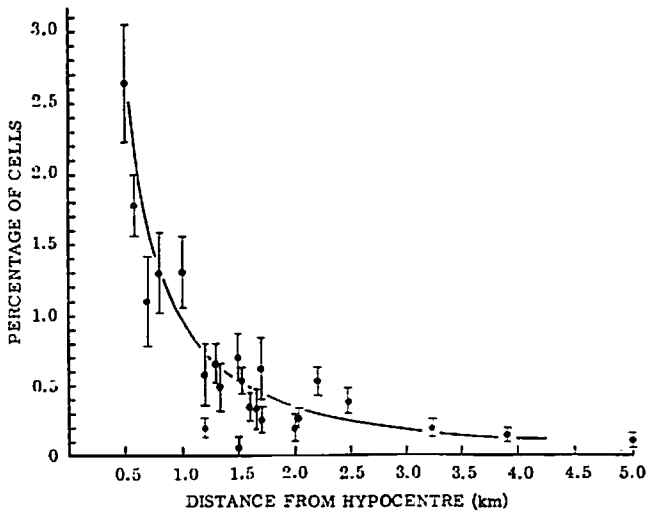

Figure 14. Frequency of C_s cells as a portion of all (except C_u) cells plotted against distance from hypocentre[221]

244. Asymmetrical aberrations would, of course, have been largely eliminated over the twenty-two years since exposure so that the total frequencies of dicentric and ring aberrations in individuals at different distances from the hypocentre would not offer a good method of relating aberration yield to absorbed dose. However, the distribution of chromosome aberrations within X_1C_u cells which had not divided since exposure should be the same as that existing immediately after exposure. In figure 15 are shown the number of dicentric and ring aberrations in C_u cells in relation to distance from the hypocentre.

245. Using the proportion of C_s cells to normal cells and the number of dicentric-plus-ring aberrations in C_u cells, Sasaki and Miyata[221] obtained absorbed-dose estimates simply by relating the values given in figures 14 and 15 to equivalent yields obtained with measured doses of 2 MeV x rays in *in vitro* studies. Figure 16 shows the dose estimates obtained in this way (without attempting to make corrections for shielding or for quality of radiation, etc.) plotted against distance from the hypocentre. The dashed line in this figure shows a recent[201] indirect physical estimate of air dose for comparison with the dose arrived at by using the biological methods.

246. The estimates based on chromosome aberration yields compared with the physical estimates (figure 16) are low in the survivors exposed close to the hypocentre and high in the remotely exposed people. The authors[221] suggest that these differences may reflect a selective mortality over the twenty-two-year period in the population exposed near the hypocentre and that

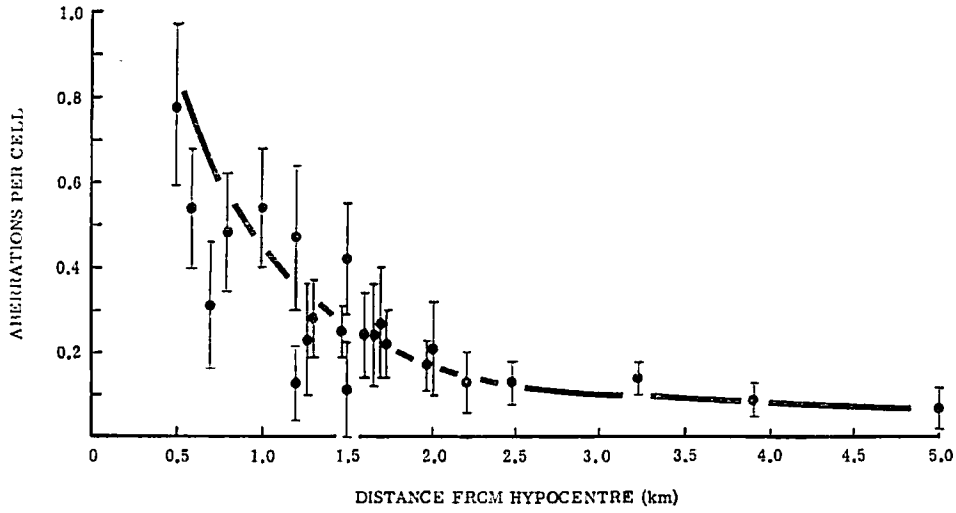

Figure 15. Number of dicentrics plus rings per X_1C_u cell versus distance from hypocentre[221]

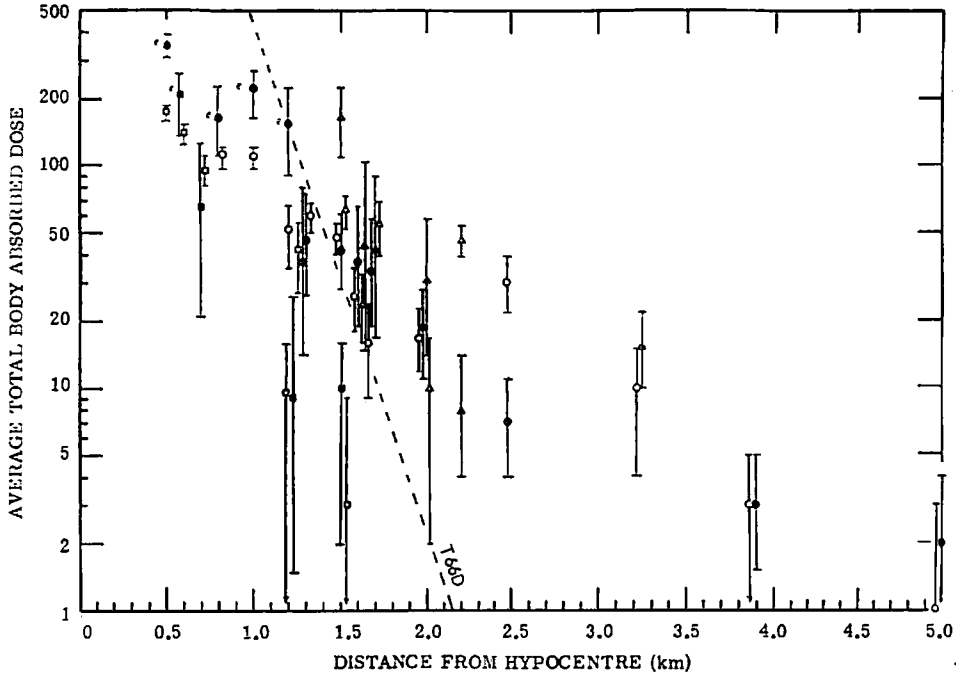

Figure 16. Average total-body absorbed dose estimated from the frequency of chromosome aberrations in Hiroshima survivors[221] [a]

[a] Vertical lines through points represent 50 per cent confidence limits, and dashed line, T66D, gives estimate of air dose derived from physical considerations. Estimates of absorbed dose based on the C_1 cell data (figure 14) are those given as open symbols, and estimates based on dicentric and ring aberrations in X_1C_u cells (figure 15) are given as closed symbols. Triangles, circles and squares represent directly exposed survivors and survivors shielded by wooden or concrete houses, respectively. Subscript *e* indicates those survivors who had epilation.

individuals who were more than 2.4 kilometres away might have received radiations from sources other than the primary rays.

247. Three papers describe observations on peripheral blood chromosomes of individuals accidentally exposed to radiation from radio-active fall-out due to the explosion of a thermonuclear device at Bikini in 1954.

248. Ishihara and Kumatori[135, 292, 293] studied cells obtained from eighteen of the twenty-two fishermen whose external exposure resulted in doses estimated to range from 220 to 660 rads and who had also received an unknown contribution from internally deposited radio-active material. Samples were first taken ten years after exposure and repeated sampling has continued since that time. In the original study[135] it was found that the aberration yield in the irradiated individuals was significantly above controls and that dicentric aberrations were present, but it was not possible to correlate aberration yields with physically estimated doses. However, when the individuals were divided into three groups according to the degree of damage indicated by the lowest neutrophil levels reached shortly after exposure, it was found that the mean frequencies of cells containing aberrations in these three groups were correlated with the extent of damage indicated by the original haematological findings. Follow-

up studies showed that three individuals possessed clones of cells with chromosome abnormalities in their bone marrow, and it was noted that these three persons were, in fact, in the group who had the lowest neutrophil counts shortly after exposure.

249. Lisco and Conard[294] have recently studied blood cells obtained from fifty-one Marshallese, of whom thirty had received an estimated whole-body gamma-ray dose of 175 rads, thirteen had received approximately 70 rads, and eight had not been exposed and served as controls. The results are curious in that more acentric fragments were found in controls than in irradiated individuals. However, if we consider only the dicentric and ring aberrations, a difference between exposed and unexposed individuals is observed. In the controls, no asymmetrical exchange aberrations were found in the 400 cells analysed, but three dicentrics and rings were found in 650 cells from the 70-rad group and six in 1,500 cells in the 175-rad group. A similar difference between control and exposed individuals was found for symmetrical exchange aberrations.

250. These data from individuals exposed to radiation following nuclear explosions all show significant aberration yields in the survivors studied. Moreover, the observations confirm earlier studies which showed that radiation-induced chromosome aberrations can be detected in leucocytes of individuals exposed to radiation for clinical reasons up to twenty-two years prior to observation. Most of these earlier studies did not permit quantitative conclusions relating aberration yield to absorbed dose, but the recent extensive data and analyses on Hiroshima survivors suggest that a fair measure of agreement exists between dose estimates based on the yields of chromosome aberrations and indirect estimates of air dose arrived at through the use of physical methods.

251. From the data discussed thus far it is evident that the aberration yield must decline with increasing time interval between irradiation and blood sampling, and the influence of this factor on aberration yield should now be considered.

5. *Time of sampling after radiation exposure*

252. Since the first publications[44, 128] demonstrating that a significant yield of aberrations could be observed in blood cells of individuals exposed to radiation many years earlier, virtually all of the publications on *in vivo* exposure present data confirming these observations.

253. In the original work of Buckton *et al.*[44] it was shown that the frequency of cells carrying asymmetrical aberrations ("unstable" C_u cells) showed an approximately exponential decline with increasing time after exposure, whereas the frequency of cells with symmetrical changes ("stable" C_s cells) stayed roughly constant with time (paragraph 243). Cytological evidence indicated that many of these aberrant cells with asymmetrical changes were in their first post-irradiation mitosis when sampled so that these data offered a means of determining the average *in vivo* life span of the dormant non-dividing leucocytes (small lymphocytes). Further studies by Buckton *et al.*[33, 295] and by Norman *et al.*[290, 421] have extended and refined the analysis and led to the conclusion that the mean life span of this cell lies somewhere between 500 and 1,500 days in accordance with the tritium-labelled thymidine data on these cells obtained by Little *et al.*[193]

254. Goh[283] has suggested that not all the aberrations observed in peripheral blood leucocytes many years after exposure are aberrations induced at the time of irradiation. The evidence in support of this suggestion is meagre and is open to an alternative interpretation. It is known, however,[296] that chromatid-type aberrations can be induced in human fibroblasts by exposure to extracts of allogenic lymphocytes, and Goh presents evidence[297] for a small, but significant, effect of irradiated human plasma in inducing aberrations in peripheral blood leucocytes, an observation supported by the independent work of Hollowell and Littlefield.[298] In Goh's experiments, the cultures were incubated for seventy-two hours and, from the figures in the published account, it is evident that most of the aberrations observed were chromatid-type changes with some "derived" (paragraph 74) chromosome-type fragments; no chromosome-type dicentrics or rings were noted. Hollowell and Littlefield[298] used plasma from patients given doses up to 4,500 rads from 2 MeV x rays and observed chromatid-type and chromosome-type changes in blood cells from normal individuals cultured in the presence of such plasma. Five dicentrics and rings were observed in 476 cells, but these aberrations were probably of the "derived" type. Unpublished works of other observers[299-301] have shown either no discernible effect or a small increase in chromatid aberration yields in first divisions of cultured cells exposed to irradiated plasma.

255. It is of interest to note here reports[302, 303] indicating that the long persistence of chromosomally damaged lymphocytes so clearly demonstrated in man and Rhesus monkey may not occur in certain other mammals. Studies on PHA-stimulated blood cells from monkey, rat, guinea pig and pig have shown that unstable chromosome aberrations are not observed for more than a few hours after irradiation except in the monkey where C_u cells were observed for as long as the animals were observed (seven months). This rapid loss of C_u cells in these animals is of particular interest, since, at least in the rat, *in vivo* studies with tritium-labelled thymidine[304, 305] have clearly demonstrated the presence of long-lived lymphocytes in unirradiated animals.

256. From the point of view of biological dosimetry, there is normally little interest in samples of blood cells taken from irradiated individuals many years after radiation exposure. However, follow-up studies will, of course, be of importance in connexion with the possible somatic risks that may be associated with the presence of aberrations. Chromosome studies on bone-marrow cells in particular will be of paramount importance with regard to leukæmia risks. In the case of the peripheral blood leucocyte (small lymphocyte), the composition of this cell population in peripheral blood (as well as in extravascular areas) will change with time simply because of the role played by this cell in immunological response.[306] The work of Nowell[218, 302] suggests that the aberration yields observed in leucocytes many weeks, months or years after exposure will be dependent upon the number and type of antigenic stimuli received by the individual between the time of exposure and the time of sampling.

257. Although these small lymphocytes are involved in immune responses, they are, nevertheless, normally non-dividing so that, in man, there should be no preferential loss of cells carrying chromosome damage in samples taken many hours, days or possibly weeks after exposure, provided the cells are not involved in

an immune response. Support for this concept has come from the *in vitro* studies of Scott *et al.*[245] and of Kozlov[307] who have compared aberration yields in peripheral blood leucocytes placed in a culture medium containing PHA immediately after irradiation with cells held for twenty-four hours post-irradiation or less in a culture medium devoid of PHA. In both these studies, using fast neutrons[245] (paragraphs 176-177) and cobalt-60 gamma rays,[307] the general finding was that an increased time between irradiation and mitotic stimulation had little or no influence on the aberration yield.

258. There is little information, however, on the variation in life span of the small lymphocyte and on the multiplicity of populations present throughout the body. Nevertheless, on the basis of information available, it would seem that, within any particular defined subpopulation, the aberration yield should remain constant until that population becomes involved in an immunological response. The difficulty is, of course, that of defining a subpopulation or compartment in a mixed population of morphologically identical but functionally diverse cells which migrate throughout the body.

259. In terms of biological dosimetry, the location, distribution and population density of lymphocytes throughout the body is a problem of no importance if an individual receives a uniform whole-body exposure to a radiation of high penetrating power. This problem could, however, be of great importance in the case of an individual receiving partial-body exposure or when the exposure is to radiation of low penetrating power or of mixed quality. The problem may be minimized if a sufficient cell mixing within the population occurs between the time of irradiation and sampling.

260. When blood is sampled *immediately* after an acute exposure to radiation, then leucocytes that were in the peripheral blood vessels at the time of exposure will presumably be the only population that is sampled. However, if sampling is delayed for a sufficient but unknown time, then leucocytes that were in various lymphopoietic centres at the time of irradiation may have been mobilized into the blood stream. The data obtained in the extracorporeal studies[227, 243, 244] suggest that this time interval is not greater than eight hours and may, in fact, be of the order of a few minutes (paragraphs 199-204). At later sampling times, some of the leucocytes observed in peripheral blood will not have been directly exposed to radiation but will have been derived from irradiated stem cells.

261. To date, there is not a great deal of information on the change in aberration yield in blood samples obtained at frequent intervals throughout the first two or three days following exposure. In the data of Bender and Gooch[131] obtained from three men receiving up to 47 rads of mixed gamma and neutron radiations in a criticality accident, there appeared to be a little difference in aberration yield in samples taken four hours, two weeks and four weeks after exposure.

262. In some more recent work of Buckton *et al.*[16] which involved the partial-body exposure of ankylosing spondylitis patients to various doses of x rays, it was observed that higher aberration yields were obtained from blood samples taken twenty-four hours after exposure than from samples obtained immediately after exposure (table III). More detailed studies were then carried out by these authors on patients who had received a partial-body exposure of 300 roentgens. Samples were taken from these patients at zero, three, six, twelve, twenty-four and forty-eight hours after exposure. The aberration yield increased with sampling time up to twenty-four hours and then declined at forty-eight hours. At zero hours and forty-eight hours, the frequency of "unstable" cells was approximately one-half the maximum yield that was observed in the twenty-four-hour samples. There was no significant difference between yields observed in the six-, twelve- and twenty-four-hour samples.

263. The very limited data on whole-body exposure in the criticality accidents, often involving uneven exposure, are insufficient to make any pronouncements on change in aberration yield in the first few hours following exposure. What few data exist do not contradict the expectation of no change in yield with time of sampling with this kind of exposure. However, the recent whole-body x-ray studies[271] support the observations made in the earlier partial-body x-ray work (paragraph 212 and table V). In the partial-body and in the extracorporeal blood exposures, there is clear evidence that the aberration yield changes with time even in the first twenty-four hours following exposure. There is but little information on the amount and rate of change and no information on whether these parameters are influenced by dose level, site of exposure, age and health of the exposed individual.

D. Conclusions

264. It is evident from the studies carried out on patients receiving low doses from diagnostic x rays and on individuals receiving chronic low doses as a consequence of their occupation that doses of the order of a few rads from x or gamma rays result in a significant increase in the yield of aberrations in blood leucocyte cells. This increase is particularly impressive when dicentric and ring aberrations, that are extremely rare occurrences in the blood cells of unexposed individuals, are considered. Thus, in terms of its possible use in biological dosimetry, it is clear that this particular system is a very sensitive one.

265. A knowledge of the form of the relationship between aberration yield and radiation dose is essential in any attempt to extrapolate from one to the other. Until very recently, the *in vitro* data that were available seemed rather disappointing, since considerable differences were evident when data obtained in different laboratories were compared. Nevertheless, within any one laboratory, when the same techniques were employed, the results were consistent and highly repeatable (paragraphs 178-179). The more recently available data on the response to radiations of differing quality reveal a high degree of consistency between laboratories when similar conditions of irradiation and of duration of culture are used.

266. The main factors contributing to differences in results between laboratories are (*a*) the use of different culture times; (*b*) the irradiation of whole blood prior to culture as opposed to the irradiation of blood in culture; and (*c*) the use of different qualities of radiation. It is evident that the aberration yields obtained in cultures maintained from forty-eight to fifty-four hours are generally higher than in cells irradiated and cultured under the same conditions but sampled at seventy-two hours. Higher aberration yields are also reported, particularly at dose levels below approximately 150 rads of x or gamma rays, if blood cells are irradiated after culturing rather than as whole

blood prior to culture. As a consequence of this, the dose exponents from experiments with irradiated cultures are somewhat lower than from experiments using cells irradiated prior to culture. The reason for these differences is not clear, and further work is certainly necessary in this area. Large differences in response are observed between radiations of differing quality, and the RBE for 2 MeV x rays as compared with 250 kVp x rays is 0.8.

267. Studies on the yields of dicentric aberrations in whole blood irradiated with 2 MeV x rays, cobalt-60 gamma rays or 150 to 300 kVp x rays, and cultured from forty-eight to fifty-four hours, show that the dose exponent, n, in the equation $y = kD^n$, is 1.9 to 2, 1.7 to 1.8 and 1.5 to 1.6, respectively. For blood cells irradiated in culture with 180 to 250 kVp x rays and cobalt-60 gamma rays, the dose exponents are reduced to around 1.2 to 1.3. These data indicate that exchange aberrations induced *in vitro* by 2 MeV x rays are predominantly a consequence of the effects of two separate tracks. With conventional x rays (150-300 kVp), however, up to dose levels yielding less than two dicentrics per cell, a considerable proportion of the exchange aberrations is the consequence of single track events. Studies with 2 to 5 MeV DD neutrons and 0.7 MeV (mean energy) fission neutrons indicate that with these radiations there is a linear relationship between dose and aberration yield over a wide range of doses. In the case of 14.1 MeV neutrons, the relationship is not linear, the dose exponent lying between 1.2 and 1.4. Further information on the effects of fast neutrons, particularly in relation to the influence of irradiation and culture conditions and technique, is required.

268. In the *in vivo* studies on the relationship between aberration yield and dose, much of the data have been obtained from individuals exposed to partial-body doses. Here, numerous complications arise, and most of the data indicate that the aberration yield changes with time within the first day or so after exposure. These changes reflect alterations in the number, distribution and mobility of the different leucocytes within and between the exposed and unexposed regions of the body at the time of exposure and the degree of mixing that occurs between the time of irradiation and the time of sampling from peripheral blood. It is clearly difficult to derive a measure of absorbed dose under these circumstances.

269. In view of the complications referred to above, there can, of course, be no simple standard dose-response relation for aberration yield in cases of partial-body irradiation. In those cases where defined areas of the body have been exposed to radiation for therapy purposes and blood samples taken at short defined intervals after exposure, an increase in aberration yield with increasing skin dose has been noted. In these cases, the relation between the yield of dicentric and ring aberrations and "skin dose" may be almost linear ($y = kD^{1.2}$) or approximately follow a dose-squared ($y = kD^2$) relationship.

270. In the whole-body studies in which patients received from 17 to 50 rads from 2 MeV x rays, the yield of dicentric and ring aberrations increased approximately linearly with dose in blood samples taken immediately after exposure ($y = kD^{1.13}$) but increased approximately in proportion to the square of the dose in samples taken twenty-four hours later ($y = kD^{1.68}$). This increased dose exponent in the later samples was a consequence of significant increases in the yields obtained in two of the patients given a dose of 50 rads.

271. A number of laboratories are now studying aberration yields in patients exposed to uniform whole-body irradiation so that more data on the relationship between aberration yield and radiation dose and quality should become available in the near future.

272. In the criticality accidents in which individuals were non-uniformly exposed to mixed gamma-neutron radiation (paragraph 225), the data are naturally difficult to evaluate because of the complications of dose distribution, radiation composition and RBE. However, in the individual that received a physically estimated dose of 47 rads (47 per cent of which was estimated to be due to gamma rays) the yield of dicentrics and rings was 0.033 per cell in cells sampled between four hours and four weeks after exposure and cultured for seventy-two hours. This yield is somewhat lower than that (0.056 dicentrics and rings per cell) observed following forty-eight-hour cultures of blood from individuals exposed to whole-body irradiation of 2 MeV x rays with a dose of 50 rads (paragraphs 210-213, and table V.)

273. The limited data on whole-body exposure indicate that the aberration yield could serve a useful purpose in dosimetry in such cases, but more information is certainly required. In this respect, we have pointed out that results from samples taken shortly after (within the first few hours or days) uniform whole-body irradiation may not be influenced by the distribution, etc. of the leucocytes at the time of irradiation or sampling. On the other hand, in the case of follow-up studies or where the first samples are taken many weeks or months after an original exposure, the aberrations will be studied in a selected population of long-lived cells. The primary aberration yields in surviving long-lived damaged cells will, however, be a reflection of the dose received in the original exposure (see the Hiroshima data referred to in paragraphs 240-246), and it may still be possible to make estimates of absorbed dose from such cells. However, much more work in this area is necessary, and a great deal more information is required on the rate of decline in aberration frequency with time and possibly, under various conditions, in the months or years following exposure.

V. Possible biological significance of the aberrations

A. Introduction

274. The possible biological significance of chromosome aberrations, particularly with reference to their presence in germ cells, has been the subject of continued review by the Committee.[2,3] There are no direct data on the genetic consequences of radiation-induced chromosome aberrations in the germ cells of man, although information on the genetic consequences of radiation-induced chromosome anomalies in laboratory mammals and on constitutional chromosome anomalies in man is available. Most of this information was reviewed in detail in the 1966 report[3] so that only a very brief consideration of the little new material will be attempted here.

275. The significance of chromosome aberrations in somatic cells has been the subject of much speculation. The idea that aberrations might be causal factors in certain somatic disease states in man has been considered since the early suggestion by Boveri[308] that abnormalities of chromosome constitution might be

significant causal factors in neoplasia. The fact that neoplasms can be induced by ultra-violet, ionizing radiations and chemical carcinogens, that these agents induce chromosome aberrations and that such aberrations are to be observed in many tumours has naturally provided a good deal of incentive to examine the possible relationships involved. This has been further stimulated by the more recent studies on virus-induced neoplasia in mammals and on virus-induced chromosome aberrations and also by the discovery of a specific chromosome change in bone-marrow cells of humans suffering from a particular form of leukæmia.

276. This section will, therefore, examine the mutational importance of chromosome aberrations in relation to metabolic effects, cell killing, life-shortening, neoplasia and immunological deficiency, effects which have all been suggested to be a consequence, at least in part, of genetic imbalance.

B. Aberrations in germ cells

277. The varieties and incidence of constitutional aneuploidy in man were considered in detail in the 1966 report[3] of the Committee, and there is only little new information of relevance to be considered here. In that report, reference was made to two well characterized syndromes causally related to a loss of autosomal chromosome material, the "cri du chat" syndrome (a deficiency in the short arm of chromosome 5)[309] and a congenital anomaly resulting from a deficiency of the long arm of chromosome 18 (18q —).[310, 311] Another deletion syndrome, first reported by Lejeune *et al.* in 1964,[312] was shown to be associated with a deletion of chromosome 21 (giving a partial monosomy), the syndrome showing many signs that appeared to be the reverse of those characteristic of Down's syndrome. Since that time, a number of cases of a syndrome[313] have been reported in which the affected individuals are completely monosomic for a group G chromosome[176-178] (generally considered to be chromosome 21). Further evidence is, therefore, accumulating that indicates that certain deficiencies in certain chromosomes and even the loss of a group G chromosome (presumably chromosome 21) may not be incompatible with life, although all appear to be associated with gross physical and mental abnormality.

278. Consideration was also given in the 1966 report[3] to the incidence of chromosome anomalies in spontaneous abortion and still-born, and reference was specifically made to the work of Carr.[314, 315] In this work, it had been shown that the incidence of 45X zygotes in man occurs at a frequency of about 8.3 per 1,000 conceptions; the majority of such XO conceptions abort,[316] one estimate indicating that only one in forty reach full term.[317] In the mouse, XO individuals are viable fertile females, and the average incidence of this condition in the mouse is around seven per 1,000 births[318, 319] (annex C, table VI, of the 1966 report[3]). The probable incidence of the XO condition at the time of conception in man and mouse may, therefore, be very similar, and it is of interest to note that, in the mouse, depending on the stage of development of the germ cells at the time of irradiation, it has now been shown that the incidence of XO offspring may be increased up to three or four times following an exposure of 100 roentgens of x rays.[318, 321]

279. In the last three years, considerable interest has been aroused in individuals having an XYY chromosome constitution, since they have been reported to occur with relatively high frequency in patients with "dangerous, violent and criminal propensities" in state hospitals[322] and in prison populations.[323, 324] Jacobs *et al.*[322] reported that 3 per cent of 314 patients in a state hospital in Scotland for the mentally sub-normal had an XYY chromosome constitution and that the mean height of such patients was significantly in excess of the mean height of men in the hospital with an XY chromosome constitution. It had previously been reported[325] that XYY individuals were fertile.

280. The possible significance of an extra Y chromosome with regard to criminal behaviour has not yet been clarified, as a number of conflicting reports[326, 327] have appeared since the original suggestion of this association.[322] Good estimates of the incidence of XYY males in "normal" populations are only just becoming available. It is reported[328] that only one XYY male was discovered in a survey of over 2,000 Edinburgh males examined prior to the state hospital and prison surveys. Recent studies in Canada[329] indicate a frequency of XYY males among new-born of two in 1,000, and a frequency between one and two in 1,000 in the general population is suggested by a survey carried out in France.[330]

281. Five sexually abnormal patients have been reported[331-334] to contain chromosome complements with an apparent dicentric Y chromosome, and it has been suggested[335] that some isochromosomes for the long arm of the X chromosome are dicentrics. These are referred to here simply to point out that, in those rare instances when the two centromeres of a dicentric chromosome are very clearly juxtaposed, the dicentric may behave in a manner functionally similar to a normal monocentric chromosome at anaphase of mitosis and, hence, be transmitted to all the descendant cells.

282. It was concluded in the 1966 report[3] that chromosome anomalies are to be observed in the somatic cells of about ten per 1,000 live new-born infants and that half of these abnormalities are accounted for by translocations. This estimate of five individuals with translocation per 1,000 live new-born is certainly a minimum estimate, and better estimates will not be available until considerably more work on meiotic cells is carried out. For this reason, it is relevant to consider here some new data[331] obtained from a highly selected population comprising fifty males attending a subfertility clinic.

283. These individuals were selected on the basis of being chromatin-negative and having a sperm count of less than 20 10^6 per millilitre; a proportion were azoospermic. The observation of interest here is that four of the men were found to be translocation heterozygotes on the basis of meiotic studies, but in only two of these men could the translocations be discerned at mitosis in somatic cells. This result serves to underline the inefficiency of translocation detection in somatic cells (see paragraph 38 where it is concluded that only approximately 20 per cent of the radiation-induced translocations can be detected in somatic cells) and points to a very high incidence of translocation heterozygosity in subfertile men. This observation is in itself significant, since it is usually assumed that the semi-sterility that is to be found in insects or laboratory mammals that are translocation heterozygotes will be of little consequence in man because family-size falls short of the fecundity of the species.

284. A study has recently been reported [338] on the incidence of constitutional chromosome anomalies in offspring of mothers exposed to abdominal diagnostic radiation (estimated maximum gonadal dose up to 7 rad) prior to conception, and the authors interpret their results as indicating an increased risk in such offspring. However, in this study, the frequency of trisomic offspring in matched-control unirradiated mothers was unexpectedly low, and, moreover, the incidence of still births in this control group was significantly higher than in the irradiated group. The Committee is continually reassessing this problem, but these new data do not alter its opinions stated in the 1962 and 1966 reports,[2, 3] that is, that exposure to ionizing radiations might result in an increase in the prevalence of developmental congenital malformations but that no quantitative estimates can be made at this time.

C. Aberrations in somatic cells

285. There has been much speculation concerning possible relationships between radiation-induced chromosome aberrations in somatic cells and various diseases in man. To date, however, almost no data have been obtained which permit precise statements relating a particular chromosome aberration to a particular lesion or a given yield of radiation-induced aberrations to a predictable incidence of a specific disease in man or other mammals. Nonetheless, the postulated relationships between chromosome changes and such disorders as neoplasia, auto-immune disease, and non-specific aging are worth reviewing if only to stimulate further work.

1. *Somatic mutation and metabolic effects*

286. One general hypothesis has suggested that radiation-induced chromosome aberrations may be an important mutational mechanism by which cellular alteration or depletion takes place in mammalian organs with increasing age leading to disease or death, but few corroborative data are available.[339, 340] Deleterious metabolic changes in mammalian parenchymal cells surviving radiation injury have not been directly related to induced chromosome changes. Material for such studies is possibly available in the clones of cells with chromosome aberrations which repopulate the peripheral blood and the hæmatopoietic tissues of humans and rodents surviving large doses of radiation.[131, 135, 222, 341-344] To date, however, the alterations of specific functional capacity of the enzyme activity of these chromosomally abnormal cells have not been compared to those of non-irradiated populations, although superficially, at least, these cells appear to be functioning normally.

287. In human chronic granulocytic leukæmia, including those cases believed to be radiation-induced, alkaline phosphatase levels are consistently reduced in leukæmic leucocytes which also carry an abnormal chromosome 21 (the Philadelphia chromosome).[345] Whether this enzymatic deficiency has any deleterious effect on the cells involved is not known.

288. Only very sketchy data are available on enzyme changes associated with constitutional chromosome abnormalities in man (these conditions were reviewed by the Committee in its 1966 report).[3] Trisomy 21 (Down's syndrome) is associated with increased levels of a number of leucocyte enzymes[346-348] as well as with alterations in tryptophane metabolism,[349] but these may reflect a general alteration in control mechanisms for RNA or protein synthesis rather than involvement of specific structural loci.[350] Abnormalities in hæmoglobin and haptoglobin synthesis have been reported in constitutional anomalies involving group D chromosomes (chromosomes 13-15), but again it is not clear whether structural genes or regulatory mechanisms are involved.[351, 353] In abnormalities of the human X chromosome, specific metabolic alteration in affected cells has not been recognized; apparently the abnormal X is consistently inactive genetically in such cells.[354] The metabolic effects of specific chromosome abnormalities in human cells thus remain almost totally unknown.

2. *Somatic mutation and cell killing*

289. With respect to the relationship between radiation-induced chromosome aberrations and cell killing, more extensive information is available. These data largely involve reproductive cell death *in vitro* (for example, inability to complete mitosis or to proliferate sufficiently to produce a viable clone) as opposed to interphase death (for example, death of non-proliferating cells), and this may be of importance in considering the relevance of such studies to the effects of radiation in the human body. In general, the x-ray dose-response curves have been similar for both cell reproductive survival and production of chromosome abnormalities in a number of cell systems,[149, 355] and there is good evidence that certain types of chromosome aberrations may result in cell killing (paragraphs 24-50).

290. However, discrepancies have been observed in some experiments, both in the shape of the curves, with consequent considerations of recovery and repair mechanisms, and in the effect of modifying factors. Thus, in some instances, mechanisms not involving chromosome aberrations can apparently cause reproductive cell death following radiation injury.[149, 197] Both somatic mutation and cell killing may underlie various somatic effects of ionizing radiation in the mammalian organism, and chromosomal damage may be visible evidence of the primary site of injury, but any quantitative statements, based on presently available data, attempting to relate these phenomena may subsequently prove to be oversimplified.

3. *Somatic mutation and life-shortening*

291. There has been considerable speculation about the role of chromosome aberrations as mediators of the aging process. The fact that radiation results in life-shortening has long been well documented in experimental animals with extensive consideration of a variety of radiation parameters,[356] but whether reduced life span results simply from radiation-induced increases in certain specific diseases or from acceleration of some generalized non-specific aging process has been debated. Where radiation-induced life-shortening is clearly related to increased tumour incidence, the same concepts of the role of chromosome aberrations would apply, as will be discussed in the next section. If some non-specific aging phenomenon is to be postulated, the possible significance of chromosome aberrations depends on the particular senescence theory being proposed. If radiation-induced aging of tissues and organs is considered to result from mutational events leading to death or diminished function of non-replaceable cells or to reproductive death of cells needed for renewal,

chromosome aberrations might obviously play a central role. Similarly, aging attributed to auto-immune mechanisms mediated by "forbidden clones" arising through somatic mutation (paragraph 317) could also have a chromosomal basis.[357, 359] On the other hand, theories of aging based on extracellular, degenerative changes, such as increased cross-linkage of collagen,[360] would seem unrelated to chromosome alterations.

292. Attempts to approach these questions experimentally have been relatively few. Curtis, in a series of studies in mice,[340] extending concepts and techniques of earlier workers,[339, 361, 362] has demonstrated a direct correlation between life-shortening and frequency of chromosome aberrations in liver cells. This relationship was observed after various types of radiation exposure and also in strains of mice differing naturally in life span. Curtis has cited these data to support the somatic mutation theory of aging, postulating radiation-induced life-shortening as the direct result of radiation-induced chromosome aberrations. This conclusion has been challenged on various grounds, including the lack of correlation between liver chromosome change and hepatic dysfunction and the failure of chemicals which produce liver chromosome aberrations in mice to induce life-shortening.[363] Kohn[360] has suggested that the observed aberrations might be the consequence, rather than the cause, of altered metabolic states or of diseases associated with life-shortening.

293. Comparable data are not available in man, although an increased incidence of aneuploidy with age has been observed in peripheral blood lymphocyte cultures from a large human population (paragraph 78). The incidence of such alterations is always low, however, and no increase in structural aberrations has been reported. In the absence of a generally accepted definition of biological aging, the relationship between radiation-induced life-shortening in experimental animals and age-related processes in the human population is difficult to assess. Even if such a relationship is accepted as valid, additional experimental evidence is required that specifically relates radiation-induced aging to chromosome aberrations as opposed to other possible mechanisms.

4. *Somatic mutation and neoplasia*

294. The most extensive evidence relating radiation-induced chromosome changes in somatic cells to significant biological effects in man would appear to be in the area of neoplasia. It has been recognized for many years that ionizing radiation produces chromosome aberrations and also tumours in both man and animals. Since chromosome changes have been demonstrated in nearly all tumours studied by modern cytogenetic techniques, older concepts concerning the causal role of chromosome aberrations in neoplasia[308] have been revived, and it has been tempting to speculate that radiation-induced tumours result directly from radiation-induced chromosome aberrations. Much evidence has accumulated which at least indirectly supports this hypothesis, but, at the same time, it has proved extremely difficult to demonstrate precise quantitative relationships, following radiation, between aberration frequencies and subsequent tumour incidence. In the following paragraphs, the evidence relating chromosome aberrations and tumours is briefly summarized, and some limitations of available data and concepts are indicated.

295. It is certainly well documented that many agents and conditions which produce chromosome aberrations also cause tumours. Not only ionizing radiation, but also ultra-violet light, a number of oncogenic viruses and several carcinogenic chemicals have been shown to have this capacity (paragraphs 53 and 56).

296. Both DNA and RNA tumour viruses, including Rous virus, adeno-viruses, SV40 and polyoma,[92, 98, 101, 364] have produced chromatid aberrations in human and animal cell cultures (paragraph 56). It is of interest that, while the Schmidt-Ruppin strain of the Rous virus causes chromatid abnormalities in human leucocyte cultures and also tumours in experimental animals, the Bryan strain of the Rous virus, under similar circumstances, produces neither chromosome changes nor neoplasia.[103]

297. Benzene, perhaps the best documented leukæmogenic chemical in man, also appears capable of causing chromosome changes in human cells.[365, 367] Carbon tetrachloride and other hepatic carcinogens have been shown to produce both tumours and chromosome aberrations in the rodent liver.[368, 370] Although a number of other mutagenic chemicals have recently been shown to yield chromatid alterations in human cells (paragraph 53), their carcinogenicity remains to be demonstrated.

298. It is also now clear that there is an increased incidence of leukæmia and lymphoma in several rare human diseases (Bloom's syndrome, Fanconi's syndrome, and perhaps ataxia-telangiectasia and xeroderma pigmentosum) in which there is a constitutional propensity for increased spontaneous chromosome aberrations observed as chromatid aberrations in leucocyte cultures.[340, 371, 372] Such data, involving a variety of agents and conditions, have suggested that genetic damage, as indicated by chromosome aberrations, might be a common mechanism by which most, if not all, carcinogens act.

299. The frequency of chromosome abnormalities in tumours has been used to support this argument. Certainly most neoplasms, radiation-induced or not, do show chromosome aberrations. Numerous studies in recent years[373, 381] have demonstrated that, except for some human acute leukæmias and some virus-induced rodent leukæmias, nearly every mammalian tumour, by the time it reaches macroscopic size, is characterized by chromosome changes.

300. Furthermore, the neoplastic cells bearing these abnormalities frequently appear as stemlines or clones, particularly in the leukæmias, but in many solid tumours as well. The entire neoplasm often consists of a single clone with all cells showing the same alteration in karyotype, or of a small number of clones, usually with related chromosome changes. This clonal phenomenon has suggested that a tumour may consist entirely of the progeny of a single aberrant cell,[344, 382] a cell having a proliferative advantage as a result of its altered karyotype. Subsequently, additional clones may appear and even come to predominate as further karyotypic changes confer additional selective advantages. Sequential studies in human neoplasms have supported this concept of the important role which chromosome alterations play in the progressive development of tumours.[382, 386]

301. However, it is still debatable whether the chromosome changes observed in mammalian neoplasms are primary or secondary phenomena and whether they

are involved in the initiation of the tumour or only in its subsequent progression. The alteration observed in one tumour is usually different from that observed in the next even when the two neoplasms are clinically and histologically identical.[373, 381] In general, each type of mammalian neoplasm has *not* been characterized by a specific chromosome abnormality. This, plus the occurrence of some leukæmias and even a few solid malignancies[373, 380, 387] without any demonstrable chromosome changes, has led many investigators, but not all,[373, 379] to conclude that the chromosome changes seen in most tumours are secondary phenomena superimposed on an already neoplastic process. This conclusion does not rule out genetic alteration, or alterations,[388] as the initiating event in neoplasia; it simply suggests that it may be submicroscopic.

302. The first example of a neoplasm *with* a specific chromosome change is human chronic granulocytic leukæmia, where, in 90-95 per cent of the typical cases, the karyotype is characterized by the same abnormality, namely, a chromosome 21 lacking approximately half of its long arm, the so-called Philadelphia chromosome (Ph^1). This is not an inborn change but rather an acquired abnormality,[405] ordinarily limited to the neoplastic hæmopoietic cells (myeloid, magakaryocytic and erythroid) and not present in lymphocytes or other tissues of the body.[374] (In irradiated individuals without leukæmia, the Ph^1 chromosome has occasionally been observed in extramedullary tissues (paragraph 309), and in two incompletely documented instances it may have occurred as a familiar abnormality).[389, 390]

303. When present in neoplastic cells, the Philadelphia chromosome is associated with chronic granulocytic leukæmia, although it has been, on rare occasions, observed in related myeloproliferative disorders such as polycythaemia vera.[389] It persists throughout the course of the disease with additional karyotypic changes frequently superimposed in the late stages. During remission, when immature myeloid cells disappear from the peripheral blood, the Ph^1 may not be demonstrable in peripheral leucocyte cultures, but it is still observable in dividing marrow cells.[375]

304. The constancy of the association between the Philadelphia chromosome and chronic granulocytic leukæmia has suggested that, in this instance, a chromosome change is a primary phenomenon and that the occurrence of this aberration in a marrow stem cell is directly involved in the initiation of the neoplasm.

305. A similar suggestion might also be made for the relatively few other human and animal tumours in which some of the cases have apparently demonstrated a characteristic chromosome change.[393, 397] These include such neoplasms as Waldenstrom's macroglobulinemia, Burkitt lymphoma, multiple myeloma, certain human ovarian and testicular tumours and several leukæmias in rats and mice. In the first three instances, for example, a number of cases have shown a large abnormal "marker" chromosome, similar to a group A chromosome (chromosome 1-3) in the Burkitt and Waldenstrom's tumours, and similar to a large D chromosome (chromosome 13-15) in multiple myeloma.

306. In none of these various human and animal tumours, however, has the constancy of the particular chromosome change noted in each instance approached that of the Ph^1 in chronic granulocytic leukæmia. For most of these tumours, the abnormality characteristic for the particular neoplasm has been found in less than half of the cases examined. In these disorders, therefore, it is much more difficult to postulate a primary role for the chromosome alteration observed.

307. In truth, of course, one cannot currently make an absolute statement about the primary nature of any chromosome change in any tumour. Only when specific chromosome changes can be related to specific metabolic abnormalities (and we also know what metabolic changes are critical in the initiation of neoplasia) will such a statement be made with assurance. In our present state of knowledge, one may perhaps only suggest that the changes observed in most neoplasms, because of their apparent inconstancy from case to case, seem likely to be evolutionary phenomena important in progression, while the Philadelphia chromosome, because of its constant and specific association with chronic granulocytic leukæmia, is probably involved in the initiation of that disease.

308. Radiation-induced tumours have proved to be no exception to these general concepts of the significance of chromosome alterations in neoplastic cells. Apparently all, or nearly all, radiation-induced tumours show chromosome changes, but, as with most other tumours, these vary from case to case.[344, 345, 366, 376, 398, 399] In addition, not all cell clones with radiation-induced chromosome aberrations are necessarily neoplastic. Heavily irradiated humans and animals have been found to have clones of cells marked by radiation-induced chromosome aberrations which are apparently non-neoplastic and functionally normal and persist in their hæmatopoietic tissues for long periods of time after recovery.[131, 135, 222, 341-344] The frequency of such non-leukæmic clones has made it impossible to use chromosome studies to predict which irradiated individuals will eventually develop leukæmia, although in non-irradiated individuals a clone of marrow cells with a chromosome abnormality appears to be a good indication that a preleukæmic disorder is in transition to a frank leukæmia.[341]

309. The Philadelphia chromosome is present in those cases of chronic granulocytic leukæmia which appear to be radiation-induced,[345, 400-404] as well as in those with no radiation history. In irradiated individuals *without* leukæmia, the Ph^1 chromosome has been observed (both in single cells and in clones) in peripheral lymphocytes and in skin cells,[135, 406] but, with one possible exception,[223] it has not been reported in the bone marrow. Since only in a marrow stem cell does the Ph^1 appear to have a role in initiating a malignancy, those individuals in which it is found in such a cell will be of particular interest to follow to determine if leukæmia subsequently develops.

310. In addition to these considerations, lack of quantitative conclusions on the role of chromosome changes in radiation carcinogenesis has also resulted from the difficulty of obtaining precise dose-response curves for either aberrations or tumours, although, in general, both show an increasing incidence with increasing dose. The induction of tumours by ionizing radiation is a complex problem which was extensively reviewed by the Committee in its 1964 report.[392] In addition to the important modifying effects on tumour incidence of such variables as radiation quality, dose rate, and non-uniform dose distribution over the body, one must also consider possible indirect mechanisms involved in radiation carcinogenesis.[407-410] Activation of oncogenic virus, depression of the immune response,

alteration of hormone levels and non-specific cell killing and regenerative stimulation may all be radiation-induced effects in the body which play an important role in carcinogenesis.

311. At the level of the individual cell, one must, of course, consider not only direct genetic damage by radiation but also the possibility of the cell previously damaged by radiation being more susceptible to attack by an oncogenic virus.[408] Such a radiation-damaged cell may also have a greater propensity for subsequent "spontaneous" chromosomal rearrangements during mitosis or other "spontaneous" genetic alterations[286] and may as well be more liable to reproductive cell death.[409] The evidence incriminating viruses in many radiation-induced tumours has recently become particularly strong,[410] but all of these various factors have contributed to make it extremely difficult to predict with confidence the tumour incidence subsequent to a given radiation exposure.

312. Similarly, radiation quality and dose rate are important modifying factors, although some *in vivo* data and many *in vitro* data now make it possible to relate quantitatively radiation doses to chromosome-aberration yields in human, as well as in animal, cells. In addition, the quantitative results of *in vivo* studies may also be affected by the frequency of cell division in the irradiated host of the particular cells studied.[218, 302]

313. Taking these variables together, it is perhaps not surprising that no data, either animal or human, are yet available on which to establish precise quantitative relationships involving a given radiation exposure, the resultant aberration yield and the number or kind of tumours to be subsequently expected. It is of interest that the RBE for neutrons versus x rays appears to be comparable for tumours[407] and chromosome aberrations, at least in some circumstances. Also, several studies have indicated that Thorotrast, through its primary localization in the reticulo-endothelial system, produces both leukæmias and hemangioendotheliomas as well as demonstrable chromosome alterations in lymphocytes, whereas radium, localizing in bone, produces osteogenic sarcomas more frequently than leukæmias and yields fewer chromosome changes in lymphocytes.[179, 224, 268, 411, 412]

314. However, very few experiments have approached directly the quantitative relationships between chromosome aberrations and tumour incidence. In one study that compared the effects of high and low dose radiation on the mouse liver,[413] the chromosome aberration yield was *higher*, but the subsequent incidence of hepatomas *lower*, after exposure to a high dose rate than it was after exposure to a low dose rate. The authors postulated a cell-killing effect of the high-dose-rate radiation, associated with visible chromosome aberrations, which removed potentially neoplastic cells from the surviving population.

315. *Summary.* In both man and animals, radiation-induced chromosome aberrations and radiation-induced neoplasms regularly appear together. The chromosome changes may represent visible evidence of intracellular alterations involved in the neoplastic process. However, the mechanism of radiation carcinogenesis is still far from clear, and the number or type of radiation-induced chromosome aberrations observed in an irradiated individual cannot at present be confidently used to predict the risk of his later developing a neoplasm, except perhaps in the case of chronic granulocytic leukæmia.

5. *Somatic mutation and immunological deficiency*

316. Both mutational events and cell depletion have been cited as possible mechanisms for immunological disorders and deficiencies, and both could result from radiation-induced chromosome aberrations.

317. Although radiation can produce acute immunological deficiency through its cell-killing effects on the lymphoid system,[414] how much of this effect is mediated through chromosome aberrations is not known. Nor is it known if the tendency towards increasing immunological deficiency with advancing age is due to either cell depletion or genetic alterations in the immune system. In a system, however, in which cell division is apparently required for the initiation of its specific functions, deleterious effects of chromosome aberrations can be readily visualized.

318. It has been postulated that human auto-immune disorders might stem from somatic mutations in the lymphoid system. For instance, statistical study of the age and sex distribution of rheumatoid arthritis, lupus erythematosus, multiple sclerosis and other possible auto-immune diseases has led Burch,[357] extending the concepts of Burnet[415] and others, to suggest somatic mutation as a source of "forbidden clones" of lymphoid cells capable of reacting against "self" and producing clinical disease. Although such theories do not necessarily require either radiation as the mutagen or visible chromosome aberration as the form of genetic change, such possibilities obviously exist.

319. Among the group of rare human diseases which have recently been shown to be characterized by increased chromosome fragility,[366, 371] it is of interest that at least one of them, ataxia-telangiectasia, is also associated with immunological deficiency.[416] Immune defects have not been prominent in either Fanconi's anæmia or Bloom's syndrome, the other two disorders showing excessive spontaneous chromosome breakage in lymphocyte cultures, but neither disease has been extensively studied from this standpoint.[417]

320. It must be stated, in summary, that at present there is neither epidemiological nor experimental evidence directly relating immunological disorders or deficiencies in man or animals to chromosome aberrations known to be induced by radiation.

D. Conclusions

321. In relation to aberrations in germs cells, there is little to add to the conclusions arrived at by the Committee in its 1966 report.[3] The only point worthy of extra emphasis here is the need for more information on human meiotic cells so that better estimates of the spontaneous level of translocations in man and a better understanding of their genetic consequences can be obtained.

322. At the somatic cell level, although attempts at relating certain constitutional chromosome abnormalities in man with specific metabolic deviations from the normal are continually being made, as yet there is little direct information relating alteration or loss of gene function with alteration or loss of a particular chromosome or chromosome segment. The demonstrations of the existence of clones of cells containing abnormal karyotypes in the peripheral blood leucocytes of individuals previously exposed to radiation now offer an opportunity for detailed metabolic studies on a wide variety of chromosomally aberrant cells. No

such studies have yet been reported, but work in this area will not only clarify the variety of detrimental effects that are to be expected to result from the presence of aberrations in somatic cells but will also provide information for the genetic mapping of the human chromosome complement.

323. It is to be expected on *a priori* grounds that certain kinds of chromosome aberrations will be cell-lethal and so will contribute to cell depletion. However, it is not possible to state in quantitative terms the relative importance of the variety of chromosome aberrations in contributing to cell killing in human somatic cells.

324. If one attempts to relate specific somatic effects, such as immunological deficiency or life-shortening, to chromosome changes, the problem becomes even more complex. Hypotheses have been advanced relating these disorders to radiation-induced somatic mutations, but strong, supportive, experimental evidence is lacking, and non-mutational mechanisms have also been advocated.

325. The significance of the role played by chromosome aberrations in the aetiology of neoplastic disease is also far from clear. In the case of chronic myeloid leukæmia, the evidence strongly implicates a specific chromosome aberration (the Ph^1 chromosome) as playing a significant role in the initiation of this disease. Although the possibility remains open that other specific chromosome abnormalities may be involved with other types of neoplastic change, the presence of a wide variety of chromosome aberrations in most tumours, and their complete absence in a few, militates against the notion of a simple causal relationship. The inconsistencies that have been observed may well be a consequence of there being many different pathways that lead to a common biological end-point. If neoplasia is a multi-step process, the possibility exists that a radiation-induced alteration of the genome may provide a more favourable environment for the development of additional essential alterations, through increased susceptibility to an oncogenic virus, or greater liability to "spontaneous" mitotic errors, or through some other mechanism. Until the basic mechanisms of radiation carcinogenesis are better understood, it will be difficult to define more clearly the role of chromosome aberrations in this process.

VI. Conclusions

A. Application of aberration yields for biological dosimetry

326. The possibilities of estimating the absorbed dose received by individuals through biological rather than (or where possible, in addition to) physical methods have an obvious interest, particularly in those cases where accidental exposure has occurred. Attempts to make rapid estimates of dose based on film badges worn by radiation workers are liable to error, especially if assumptions have to be made regarding shielding by objects intervening between the exposed individual and the radiation source. Moreover, the degree of radiation exposure is frequently not uniform over the whole body, and this leads to complications if the dosimetric device is in essence a point receiver.

327. In cases of criticality accidents, physical measurements made at a later time usually involve an experimentally contrived incident in an attempt to obtain a reasonable approximation of the dose received during the accident. Alternative biological techniques that have been studied from the point of view of their use as dosimeters have so far proved disappointing. A number of possibilities have been investigated.[276, 118] including studies of metabolic products excreted in the urine and of the frequency of lymphocytes with bilobed or double nuclei or of neutrophils carrying particles with specific staining properties. However, none of these biological parameters has been shown to vary consistently with radiation dose.

328. Considered in qualitative terms, there is no doubt that the presence of a significant number of chromosome aberrations, more particularly of the dicentric- and ring-type, may be indicative of a previous radiation exposure. This follows, since it has been shown that the spontaneous *in vivo* occurrence of a dicentric or ring aberration is an extremely rare event in the blood cells of the many hundreds of individuals that have been examined from this aspect. Such aberrations occur, at most, once in every 2,000 cells taken from unirradiated subjects, whereas 20 ± 5 such aberrations would be expected in 2,000 cells from an individual, or individuals, that had received a whole-body x-ray dose of 10 rads or its equivalent. The frequency of these aberrations would appear to be uninfluenced by previous exposure to infectious agents or (except in certain specific cases) to chemical agents. The frequency of dicentric and ring aberrations in a population or in an individual is, therefore, a good qualitative screening test for a previous radiation history. Moreover, because of the long life span of at least a proportion of the lymphocyte population, aberrations can be observed in these cells many years after the original radiation exposure.

329. A good example of the use of chromosome-aberration yield in this qualitative context is afforded by a recent report[16] of an examination of an individual who, on the basis of film badge measurements, was assumed to have received a dose of 300 rads. It was possible to state after chromosome analysis that a significant dose of radiation had not, in fact, been received by this individual, since no chromosome abnormalities were seen in cultured blood or even in direct preparations of bone-marrow cells. The badge was, therefore, assumed to be faulty or to have been exposed independently of the individual. In circumstances such as this, where there is no way of reconstructing the conditions under which the exposure occurred and thereby of checking the validity of the film badge information, information from chromosome analysis can be of great value.

330. The main advantages of a biological method as opposed to physical methods of measuring absorbed dose in man would follow from the directness and permanent availability of the biological method, from the fact that information on and extrapolation from the relative biological efficiencies of a spectrum of radiations received in a mixed exposure is not required and because a biological dosimeter is in itself one step nearer to the problem of assessing immediate damage and future risk. In the particular case of a chromosome-aberration dosimeter, it may be added that chromosome aberrations are believed to be responsible for a certain proportion of the cell killing following radiation exposure; they are mutational events and they are generally believed to play some part at least in the development of late somatic effects. However, it should be emphasized here that, in the current state of our

knowledge, aberration yields cannot be related to a biological effect and that the presence of a low frequency of aberrations in the peripheral blood cells of an individual can, therefore, in no way be regarded as constituting a medical risk.

331. The starting points for considering the possible use of chromosome aberrations as opposed to other possible biological systems as indicators of dose are (*a*) the high sensitivity of the human chromosome complement and the high resolution of the method, since the effects of doses of around 5 rads or less can be detected, and (*b*) the fact that the yield of chromosome aberrations induced is closely correlated in a specific manner with the dose of radiation received.

332. It was concluded (paragraphs 138-144) that, from the cytological viewpoint, by far the best system for use in chromosome-aberration dosimetry was the peripheral blood leucocyte system, provided chromosome-type aberrations were scored, preferably at the first mitosis following radiation exposure. Moreover, there is little doubt that a measure of the radiation damage incurred by leucocytes (more particularly the small lymphocytes) that are widely distributed throughout most tissues and areas of the body should be a good indicator of the effect of radiation on the individual as a whole. There are, however, a number of disadvantages to the system, although it should be noted that many of these disadvantages also apply to physical dosimetric systems.

333. Dosimeters require calibration, and the calibration with the peripheral blood leucocyte system will almost certainly require an accurate correlation between the response of these cells *in vitro* and their response when exposed *in vivo*. This cross reference to the *in vitro* system seems necessary, since opportunities for analysing cells from individuals exposed to various levels of whole-body radiation are fortunately rare. Thus, good *in vivo* dose-response curves, particularly from healthy individuals accidentally exposed to radiation, will be difficult to obtain. However, recent studies (paragraphs 199-205), including the use of the technique of extracorporeal irradiation, indicate that the response *in vitro* is equivalent to that obtained *in vivo*, although further work here is clearly necessary.

334. In the *in vitro* work, despite the fact that accurate physical estimates of dose are available and that, within most laboratories, a repeatable quantitative relationship between aberration yield and dose is always found, differences in results are, nevertheless, to be found between laboratories in both the absolute aberration yields at given dose levels and in the shape of the dose-response curves. Some of the explanations for these differences have now become clear. When factors such as radiation quality, methods of irradiation and duration of culture are taken into account, good interlaboratory agreement is obtained. Further studies on these factors are, however, necessary before the prospect of obtaining standard sets of coefficients relating aberration yield to radiation dose can be realized.

335. *In vitro* studies on the influence of dose rate on aberration yields induced by x rays have been carried out by a number of laboratories, and it can be concluded from the results obtained that there is little dependence of aberration yield on exposure time over times ranging from one to thirty minutes. This is, of course, a feature of some importance in attempting to relate aberration yields with dose. Similar studies with fission neutrons show that the yield of aberrations induced by these particles is, as expected, independent of dose rate and exposure time, and that fission neutrons (mean energy 0.7 MeV) and fast neutrons (2.2 MeV and 14 MeV) are two to five times as effective per rad as 250 kV x rays in inducing aberrations.

336. In the *in vivo* work, in only one study have individuals been exposed to accurately measured uniform whole-body radiation (2 MeV x rays). In this study, the yield of dicentric and ring aberrations in peripheral blood cells was shown to increase approximately linearly with exposure over the dose range studied (0-50 rad) if samples were taken immediately after radiation exposure, the coefficient of yield for these aberrations being 0.001 per cell-rad. Uniform whole-body exposure to a penetrating radiation, so that all cells receive a similar dose, is the ideal state for the purpose of biological dosimetry. Such a state is, of course, rarely encountered, and most of the *in vivo* work that has been done relates to partial-body or non-uniform exposures, and it is here that the greatest dosimetric problems arise.

337. In the case of acute partial-body exposure, the aberration yield in peripheral blood leucocytes will depend upon a variety of factors. These include (*a*) the amount of radiation energy deposited in that area of the body that is exposed and the duration of the exposure; (*b*) the area and volume of the body that is irradiated; (*c*) the proportion of peripheral blood leucocytes that are exposed to radiation and the time that they spend in the irradiated area during exposure; (*d*) the proportion of leucocytes (lymphocytes) in extravascular areas within the exposed region; (*e*) the amount of exchange of lymphocytes between peripheral blood and the extravascular pools; and (*f*) the time at which blood is sampled after the radiation exposure. Since there is evidence indicating that there is an appreciable exchange of lymphocytes between the blood vessels and extravascular sites in the first few hours following irradiation (paragraph 204), it is not yet possible to make any reasonable estimates of physical dose from an analysis of chromosome-aberration yields in partial-body exposures.

338. The question of what is meant by dose, in terms of biological effect or biological consequence, is itself not very meaningful in the case of partial-body irradiation. This follows, not only because aberration yields may be very much dependent upon the regions of the body that are exposed, but also because aberration frequency cannot be related to any given somatic effect. It should be noted, however, that the difficulties encountered with the type of biological dosimeter under discussion may be far less than the difficulties encountered with a point receiver measuring physical dose. Studies on individuals who received partial-body exposures at varying dose levels over similar regions (and areas) of the body have, in all cases, revealed a strict proportionality between physically measured skin dose and aberration yield. However, it is not possible simply to relate the aberration yield to skin dose and area or region exposed, since, because of cell mixing, the measured aberration yield varies with the time at which blood is sampled in the first twenty-four hours after radiation exposure.

339. It can only be concluded from this discussion that, in the case of partial-body exposure, a great deal more knowledge is required about the structure of the

populations (and subpopulations) of small lymphocytes and about the distribution, mobility and longevity of the cells before it is possible to equate an aberration yield observed at any given time to the dose absorbed in the lymphocytes. It should be noted that, in any case, within the limitations of existing knowledge, any given aberration yield in these cells can only be related in physical terms to an "equivalent whole-body dose".

340. It should be re-emphasized here that the difficulties that confront us in the case of partial-body exposure do not exist in the case of uniform whole-body exposure. With uniform whole-body exposure, there is no doubt that the yield of chromosome-type aberrations in peripheral blood leucocytes can be used as an accurate measure of dose received. In the case of accidental, non-uniform, whole-body exposure, the aberration frequency in peripheral blood cells can yield but little information on the degree of non-uniformity of the exposure but may more readily provide an estimate of an "equivalent whole-body dose".[423] Care should be taken to note, however, that dose estimates require the use of dose-yield kinetics obtained in *in vitro* studies and possibly also information on the form of the distribution of aberrations between cells.

B. Assessment of risks

341. There is no new information about the estimated frequency of aberrations induced in germ cells by radiations and the consequent risk to individuals and to offspring. These risks have been fully discussed in the 1966 report,[3] and the only new point to add is the preliminary observation of a possible association between translocation and subfertility in the human male. In this connexion, however, further data are required before any real assessment can be made.

342. In somatic cells, information on the yields and types of chromosome aberration does not as yet provide either a new approach to or a better estimate of risk, except in one specific case. With existing information, knowledge of chromosome-aberration yield in peripheral blood leucocytes does not enable us to make any quantitative statement regarding the risk of developing neoplastic disease, immunological defects and shortening of life span, etc. As a consequence, no information of clinical significance can be obtained from the presence of aberrations. Little can, therefore, be added to the statements on assessments of risk of somatic disease that have already been made by the Committee in its earlier reports. From the point of view of assessing risks, the only direct use of the aberration yield is when this is the only parameter from which a "physical" estimate of the dose can be obtained. Clearly, where physical dose estimates can be made, the aberration yield may serve as a valid supplement to the physical data.

343. The exception mentioned in the above paragraph relates to the association between chronic granulocytic leukæmia and the presence of the Ph^1 chromosome in cells of the bone marrow. The presence of such an abnormal chromosome in bone-marrow cells is, apart from one possible exception,[223] always associated with a blood dyscrasia—in almost all the cases with chronic granulocytic leukæmia and, in the others, with a disorder such as polycythaemia vera. It has not yet been shown whether a Ph^1 chromosome can be observed in bone-marrow cells prior to the development of overt hæmatological disease. However, its presence in a bone-marrow cell of any irradiated individual must, on present knowledge, be taken as indicating an extremely high risk for the individual of developing leukæmia. On the other hand, it should be stressed that Ph^1-like chromosomes have been observed in single cells and in clones in peripheral blood lymphocytes and skin cells of irradiated individuals, but their presence in such cells has not, to date, been associated with any kind of neoplastic change.

C. Recommendations for further study

344. Human cytogenetics is still a relatively new and vigorously developing field, and it is evident that there are large gaps in our knowledge both of the response of human chromosomes to radiation and of the consequences of radiation-induced chromosome aberrations in human germ cells and somatic cells. Some of the more immediate requirements and questions that need answering and some of the more general longer-term problems that require further attention are outlined in the following paragraphs.

345. Further studies should be undertaken on human meiotic cells, particularly from the point of getting better information on the frequency and possible genetic consequences of symmetrical spontaneous aberrations that cannot be detected in somatic cells.

346. A better understanding of the effects of culture conditions on aberration yield in peripheral blood leucocytes should be achieved, the aim being to develop a standardized technique for interlaboratory use so that standard coefficients for the yields of the various aberration types can be obtained.

347. Further *in vitro* studies on the effects of dose rate and exposure time with radiations of low LET and on the relative efficiencies with which aberrations are produced by radiations of different quality should be made.

348. Very much more information is required to define to what extent there exists a range of sensitivity to aberration induction in a human population and regarding the influence of age on response. These studies can be carried out by measuring the response of blood cells to *in vitro* exposures.

349. Further work should be undertaken on the relation between *in vivo* and *in vitro* responses, including studies on laboratory mammals and, where possible, on humans exposed to extracorporeal radiation treatments.

350. Further information is needed on the influence of various patterns of non-uniform radiation exposure and a better understanding required of the lymphocyte populations in the body, their distribution, age structure and turn-over.

351. Further data on the rate of decline of aberration yield with time following exposure under a variety of radiation régimes should be acquired. Attention should be devoted, in this respect, not merely to long-term changes occurring over periods of weeks, months or years after exposure, but to changes that occur in the first few hours and days. Consideration should also be given to the importance of immune response and other possible factors in such work.

352. Where possible, the utmost effort should be made to obtain data from individuals undergoing uniform whole-body irradiation.

353. Further work on the qualitative and quantitative differences between aberrations induced by chemical and infectious agents in relation to ionizing radiations and studies on the response of peripheral blood leucocytes (and bone-marrow cells) to radiation whilst in the S and G_2 phases of the cell cycle should also be undertaken, since current information on chromatid-type aberrations induced in these cells is minimal.

354. Future advances in all aspects of population cytogenetics will be greatly facilitated by the introduction of automation into the processes involved in cytogenetic analysis. In the case of surveys of populations exposed to mutagens that induce chromosome abnormalities, although a considerable amount of valuable information will continue to be obtained through conventional methods, automatic systems should provide powerful tools for the cytologist, and their development should be fostered.

355. A continued effort should be directed at attempts to relate both yields and types of chromosome aberrations to specific somatic diseases. In this connexion, follow-up studies on individuals exposed to radiations are desirable, and continued studies of irradiated individuals possessing Ph^1-like chromosomes and other clonal changes in their proliferating cells are essential.

356. Further studies on the possible relationship between the incidence of aberrations on the one hand and neoplasia on the other, both in man and in experimental animals, are required. In this connexion, it should be pointed out that there is no direct information whatsoever on a possible synergistic interaction between oncogenic viruses and radiation-induced chromosome damage. Experimental attack on this problem is now possible.

357. There is an absolute dearth of information relating radiation-induced aberrations to biological endpoints. It should, therefore, be emphasized that the existence of clones of cells containing abnormal karyotypes in the skin, bone marrow and peripheral blood leucocytes of individuals previously exposed to radiation now offers an opportunity for detailed metabolic study on a wide variety of chromosomally aberrant cells. In this context, human-animal hybrid cells[419, 420] may provide a useful tool. Such studies will provide valuable genetic information as well as information on the detrimental effects to be expected from certain kinds of aberrations.

358. A follow-up of the studies indicating a possible difference in the *in vivo* response of lymphocytes to chromosome-aberration induction in different laboratory mammals should be made.

359. Further studies on the radiation response in different tissues and the radio-sensitivity of different cell types, together with the possibility of utilizing materials other than blood cells to measure aberration yields, should be carried out.

360. Studies on the frequency, types and consequences of constitutional chromosome anomalies in man should be continued.

TABLE I. FREQUENCY OF DICENTRIC ABERRATIONS IN "NORMAL" SUBJECTS NOT EXPOSED TO RADIATION OTHER THAN ROUTINE DIAGNOSTIC EXPOSURE

The forty-seven individuals in column *c* were patients with ankylosing spondylitis, and the samples were taken prior to any therapy, but *shortly after* the individuals had received diagnostic radiation exposures. The thirty-eight individuals in column *b* were individuals from a general population and served as controls for population *c*

Authors	*Norman* et al.[165]	*Ishihara and Kumatori*[175]	*Evans and Speed*[422]	*Norman*[24]	*Bloom* et al.[183]	*Court Brown*[201]			*Sasaki and Miyata*[221]
						a	*b*	*c*	
Number of individuals in sample	23	20	200	?	94	438	38	47	11
Number of cells scored	5,784	2,875	2,400	2,295	8,847	12,420	1,060	2,269	9,510
Number of dicentrics observed	0	0	0	0	0	7	0	3	2
Frequency of dicentrics per cell	<1 in 5.8×10^3	<1 in 2.8×10^3	<1 in 2.4×10^3	<1 in 2.3×10^3	<1 in 8.8×10^3	<1 in 1.8×10^3	<1 in 1×10^3	<1 in 0.76×10^3	<1 in 4.7×10^3

TABLE II. PHYSICAL DOSES AND ESTIMATED DOSES BASED ON YIELD OF DICENTRIC ABERRATIONS IN PERIPHERAL LEUCOCYTES IN BLOOD CELLS OF PATIENTS[227]

A—Exposed to one passage through a ^{90}Sr-^{90}Y extracorporeal irradiator

B—After several passages through the irradiator

	Total calculated physical dose (rad)	*Total dose estimated from dicentric aberration frequency (80 per cent confidence)*
A *In vitro* studies: blood sampled after a single passage at a flow rate of 3.0 to 15.7 ml-min	450[a]	440–490
	565[a]	510–565
	295[a]	245–310
	148[a]	115–175
B *In vivo* studies: blood sampled immediately after a four- to eight-hour extracorporeal irradiation	120[b]	145[c]
	120[b]	180[c]
	240[b]	230[c]

[a] Physical dose calculated on the basis of flow rate and volume of blood passed through irradiator.

[b] Physical dose estimated on the basis of blood volume, flow rate and duration of irradiation.

[c] Estimated dose based on frequency of dicentric aberrations in 200-300 metaphase figures in blood leucocytes immediately after completion of irradiation.

TABLE III. ABERRATION YIELDS FOLLOWING A SINGLE PARTIAL-BODY EXPOSURE OF ANKYLOSING SPONDYLITIS PATIENTS TO X RAYS (250 KV)[16]

A cells—Undamaged cells
B cells—Cells containing chromatid-type aberrations
C_u cells—Cells with unstable chromosome-type aberrations (rings, dicentrics, fragments)
C_s cells—Cells with stable chromosome-type aberrations

Skin dose in rads	Time of sampling post-exposure in hours	Total cells analysed	A cells			B cells		C_u cells		C_s cells		Ring plus dicentrics		Fragments	
			Modal	Non-modal											
			No.	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
100	0	300	256	13	4.3	22	7.3	6	2.0	3	1.0	5	1.7	2	0.7
	24	300	266	8	2.7	14	4.7	5	1.7	7	2.3	3	1.0	2	0.7
150	0	400	349	14	3.5	16	4.0	13	3.3	8	2.0	8	2.0	7	1.8
	24	500	408	18	3.6	30	6.0	32	6.4	12	2.4	20	4.0	13	2.6
200	0	250	205	12	4.8	11	4.4	17	6.8	5	2.0	15	6.0	5	2.0
	24	300	240	7	2.3	21	7.0	27	9.0	5	1.7	16	5.3	13	4.3
250	0	300	218	8	2.7	33	11.0	24	8.0	17	5.7	11	3.7	14	4.7
	24	300	221	7	2.3	30	10.0	32	10.7	10	3.3	20	6.7	20	6.7
300	0	400	319	14	3.5	14	3.5	41	10.3	12	3.0	28	7.0	19	4.8
	24	350	240	23	6.6	13	3.7	67	19.1	7	2.0	55	15.7	27	7.7
700	24	100						29	29.0			30	30.0	18	18.0

TABLE IV. ABERRATION YIELDS FROM SEVEN PATIENTS EXPOSED TO SINGLE WHOLE-BODY DOSES OF X RAYS (2 MEV)[16]

A cells—Undamaged cells
B cells—Cells containing chromatid-type aberrations
C_u cells—Cells with unstable chromosome-type aberrations (rings, dicentrics, fragments)
C_s cells—Cells with stable chromosome-type aberrations

Dose in rads	Time of sampling post-exposure in hours	Total cells analysed	A cells			B cells		C_u cells		C_s cells		Rings plus dicentrics		Fragments	
			Modal	Non-modal											
			No.	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
"O" control		700	618	45	6.4	27	3.9	5	0.7	5	0.7	2	0.3	3	0.4
25	0	600	489	38	6.3	27	4.5	31	5.2	15	2.5	16	2.7	18	3.0
	24	600	499	31	5.1	30	5.0	23	3.8	17	2.8	16	2.7	11	1.8
50	0	800	632	56	7.0	26	3.3	61	7.6	25	3.1	37	4.6	27	3.4
	24	800	637	34	4.3	28	3.5	76	9.5	25	3.1	53	6.6	29	3.6

TABLE V. FREQUENCIES OF DICENTRICS PLUS RINGS IN PERIPHERAL BLOOD CULTURES TAKEN IMMEDIATELY, OR TWENTY-FOUR HOURS AFTER, WHOLE-BODY EXPOSURE OF PATIENTS TO 2 MeV X RAYS AT THE DOSES INDICATED[271]

Case number	*Dose received (rad)*	*Control (190 cells)*	*Immediately after treatment (200 cells)*	*24 hours treatment (200 cells)*
1	25	1	5	3
2	25	0	2	8
3	25	0	9	5
4	25	0	6	7
5	25	0	8	4
6	25	0	5	3
7	50	0	4	15
8	50	0	14	14
9	50	3[a]	10	15
10	50	1	9	9
11	50	0	11	15
12	50	1	9	7[b]
13	17	0	2	1
14	28	0	1	4
15	36	0	5	7
16	40	0	8	7

[a] One cell, containing a dicentric and a tricentric, has been scored as three dicentrics.
[b] Seven rings and dicentrics in seventy-five cells analysed.

TABLE VI. DICENTRICS PLUS RINGS FOLLOWING *in vitro* AND *in vivo* (WHOLE-BODY) IRRADIATION

Authors	*Radiation quality*	*Dose in rads*	*Irradiation*	*Sampling time in hours*	*Culture time in hours*	*Dicentric plus rings per cell*
Evans[212]	240 kV x rays	25	*in vitro*		54	0.065
		50				0.15
Gooch *et al.*[229]	250 kV x rays	25	*in vitro*		72	0.003
		50				0.017
Langlands *et al.*[271]	2 MeV x rays	25	*in vivo*	0	53	0.029
		25		24		0.025
		50		0		0.05
		50		24		0.07
Mouriquand *et al.*[138]	160 kV x rays	25	*in vitro*		72	0.025
		50				0.05
Norman and Sasaki[240]	1.9 MeV x rays	50	*in vitro*		50	0.014
Vander Elst *et al.*[230]	220 kV x rays	25	*in vitro*		72	0.009
		50				0.021
Visfeldt[242]	^{60}Co λ rays	50	*in vitro*		48	0.02

TABLE VII. FREQUENCIES OF DICENTRICS PLUS RINGS PER CELL IN PERIPHERAL BLOOD LEUCOCYTES AT VARIOUS INTERVALS AFTER EXPOSURE OF INDIVIDUALS TO MIXED GAMMA AND FAST NEUTRON RADIATION (CULTURES GROWN FOR SEVENTY-TWO HOURS; OBSERVED NUMBERS IN PARENTHESES)

Case	*Estimated dose (rad)*	*Time after exposure*		
		29 months[128]	*42 months*[129]	*7 years*[283]
A	365	0.01 (1)	0.04 (4)	0.02 (2)
B	270	0.01 (1)	0.02 (2)	0.03 (3)
C	339	0.166 (24)	0.02 (2)	0.018 (2)
D	327	0.04 (4)	0.023 (2)	0.07 (2)
E	236	0.013 (1)	0.03 (3)	0.05 (5)
F	68.5	0	0	0
G	68.5	0	0	—
H	22.8	0	0.01 (1)	—

No dicentrics or rings were observed in 900 cells from control individuals[129]

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422. Evans, H. J., R. M. Speed, Personal communication.

423. Dolphin, G. W., A review of methods of biological dosimetry with particular reference to chromosome aberration analysis. IAEA, Vienna. In press.

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Annex D

LIST OF REPORTS RECEIVED BY THE COMMITTEE

1. This annex lists reports received by the Committee from Governments and agencies of the United Nations between 8 June 1966 and 16 May 1969.

2. Reports received by the Committee before 8 June 1966 were listed in annexes to earlier reports of the Committee to the General Assembly.

Document No.	*Country and title*
A/AC.82/G/L.	
	UNITED STATES OF AMERICA
1101	Radiological Health Data and Reports, volume 7, No. 4, April 1966.
1102	Terrestrial and freshwater radioecology (A selected bibliography—Supplement No. 4). TID-3910.
1103	The extent of radioactive equilibrium between radon and its short-lived daughter products in the atmosphere. Report NRL 6374 (1966).
	UNITED KINGDOM
1104	The assessment of the possible radiation risks to the population from environmental contamination.
	UNITED STATES OF AMERICA
1105	Fallout program quarterly summary report, July 1, 1966. HASL-172.
1106	Flight data and results of radiochemical analyses of filter samples collected during 1965 under Project Stardust, July 1, 1966. HASL-176.
	DENMARK
1107	Environmental radioactivity in Denmark in 1964. Risö report No. 107.
1108	Environmental radioactivity in the Faroes in 1964. Risö report No. 108.
1109	Environmental radioactivity in Greenland in 1964. Risö report No. 109.
	SWEDEN
1110	Gamma radiation at ground level in Sweden during 1960-1965.
	UNITED ARAB REPUBLIC
1111	Fallout programme in U.A.R. during 1964. Report U.A.R.S.C.E.A.R. vol. 7-1, June 1965.
1112	Sr^{90} and I^{131} content of certain food items in U.A.R. during 1964. Report U.A.R.S.C.E.A.R. vol. 7-2, June 1965.
	UNITED STATES OF AMERICA
1113	Radiological Health Data and Reports, volume 7, No. 6, June 1966.
1114	Radiological Health Data and Reports, volume 7, No. 5, May 1966.
A/AC.82/G/R.	
	UNITED STATES OF AMERICA
225/Add.12	Supplement to NYO-4700—Manual of Standard Procedures, August 1965.
A/AC.82/G/L.	
	AUSTRALIA
1115	Strontium-90 in the Australian environment during 1964.
	UNITED ARAB REPUBLIC
1116	Environmental radioactivity in U.A.R. in 1965. Report U.A.R.S.C.E.A.R. vol. 8-1, June 1966.
	ITALY
1117	Data on environmental radioactivity collected in Italy (July-December 1964). Report PROT.SAN/06/65.
	UNITED STATES OF AMERICA
1118	Fallout program quarterly summary report, October 1, 1966, HASL-173.
1118/Add.1	Appendix to HASL-173.
	NEW ZEALAND
1119	The genetically significant dose to the population of New Zealand from diagnostic radiology.
	MEXICO
1120	Strontium 90 content in milk in Mexico.
	UNITED STATES OF AMERICA
1121	Cosmic-ray ionization in the lower atmosphere.
	UNITED KINGDOM
1122	Annual report 1965-66. ARCRL 16.
1123	Assay of strontium-90 in human bone in the United Kingdom. MRC Monitoring report No. 13 (1966).
	SWEDEN
1124	Effects of some radioprotective substances upon pre-natal survival of offspring to roentgen irradiated male mice.

Document No.	Country and title
	UNITED STATES OF AMERICA
1125	Fallout program quarterly summary report, January 1, 1967. HASL-174.
1125/Add. 1	Appendix to HASL-174.
	INDIA
1126	Measurements on airborne and surface fallout radioactivity in India from nuclear weapon tests. Report A.E.E.T.-247.
	BELGIUM
1127	La retombée radioactive mesurée à Mol. Année 1965. Rapport d'avancement.
	UNITED KINGDOM
1128	Radioactive fallout in air and rain: Results to the middle of 1966. Report AERE-R 5260 (1966).
	UNITED STATES OF AMERICA
1129	Frequency of live births among survivors of Hiroshima and Nagasaki atomic bombings.
1130	Some further observations on the sex ratio among infants born to survivors of the atomic bombings of Hiroshima and Nagasaki; and A cohort-type study of survival in the children of parents exposed to atomic bombings.
	AUSTRALIA
1131	Fall-out over Australia from nuclear weapons tested by France during July 1966.
	UNITED STATES OF AMERICA
1132	1966 Annual report of the Radiobiology Laboratory. Report UCD 472-113.
	SWEDEN
1133	^{222}Rn in milk.
1134	Observed levels of ^{137}Cs in Swedish reindeer meat.
1135	Observations on the ^{137}Cs/^{90}Sr ratio in dairy milk from different parts of Sweden.
	UNITED STATES OF AMERICA
1136	Fallout program quarterly summary report, April 1, 1967. HASL-181.
1136/Add.1	Appendix to HASL-181.
1137	Manual of standard procedures, second issuance 1967. NYO-4700.
1137/Add.1	Addendum to Manual of standard procedures. NYO-4700.
1138	Filter pack technique for classifying radioactive aerosols by particle size. Part 5—Final report. NRL report 6520.
1139	Cytogenetic investigation of survivors of the atomic bombings of Hiroshima and Nagasaki.
1140	Testicular changes in atomic bomb survivors.
1141	Radiation-induced leukemia in Hiroshima and Nagasaki 1946-1964. II. Observations on type-specific leukemia, survivorship, and clinical behavior.
1142	*In utero* exposure to the Hiroshima atomic bomb. An evaluation of head size and mental retardation: Twenty years later.
	AUSTRALIA
1143	Concentration of caesium-137 in Australian rainwater during 1964 and 1965.
1144	Concentration of caesium-137 in Australian milk during 1965.
	UNITED KINGDOM
1145	Agricultural Research Council Radiobiological Laboratory. Annual Report for 1966. ARCRL 17.
	FRANCE
1146	Retombées radioactives à la suite des tirs nucléaires en Polynésie — juin-décembre 1966.
	SWEDEN
1147	Influence of gestation and lactation on radiostrontium-induced malignancies in mice. I. Incidence, distribution and characteristics of ^{90}Sr-induced malignancies.
1148	Influence of gestation and lactation on radio-strontium-induced malignancies in mice. II. Retention of radiostrontium and relation between tumour incidence and excretion rate.
	FAO/IAEA
1149	Dietary levels of strontium 90, caesium 137 and iodine 131 for the years 1965-67 (Interim report for the period 1.1.65-31.3.67).
1149/Add.1	Addendum to the report on dietary levels of strontium 90, caesium 137 and iodine 131 for the years 1965-67.
	UNITED STATES OF AMERICA
1150	Fallout program quarterly summary report, July 1, 1967. HASL-182
1150/Corr.1	Corrigendum to HASL-182.
1150/Add.1	Appendix to HASL-182.
	INDIA
1151	Estimates of biospheric contamination and radiation dose from fallout for all the pretreaty tests of nuclear weapons.
	UNITED KINGDOM
1152	Assay of strontium-90 in human bone in the United Kingdom, results for 1966, Part I. MRC Monitoring report No. 14.

Document No.	Country and title
	UNITED STATES OF AMERICA
1153	Strontium 90 concentrations and stratospheric transport.
	AUSTRALIA
1154	Fallout over Australia from nuclear weapons tested by France in Polynesia from July to October 1966.
1155	Strontium 90 in the Australian environment during 1965.
1156	Iodine-131 levels in milk in Australia during the period July-December 1966.
	FAO/IAEA
1157	The reliability of world-wide monitoring in the light of accuracy in low level radiochemical analysis.
	UNITED STATES OF AMERICA
1158	Strontium-90 deposition in New York City.
	SWEDEN
1159	The fallout situation in Denmark, Finland, Norway and Sweden in 1965-1966: report from a meeting of Scandinavian experts on radiation protection, Helsinki, May 11-12, 1967.
	UNITED STATES OF AMERICA
1160	Fallout program quarterly summary report, October 1, 1967. HASL-183.
1160/Add.1	Appendix to HASL-183.
	SWEDEN
1161	Effects of radiostrontium and roentgen rays on germ cells of male mice.
	UNITED ARAB REPUBLIC
1162	Fall-out and radioactive content of food chain in U.A.R. during the year 1966.
1163	Changes in the quenching effects of animal plasma and sera with the radiation dose.
	INDIA
1164	Gamma activity of the food samples in India during the period 1963-65. Report A.E.E.T.273.
1165	Cesium-137 and potassium in milk. Report BARC-278.
	UNION OF SOVIET SOCIALIST REPUBLICS
1166	Об искусственной радиоактивности атмосферных аэрозолей.
1167	Содержание стронция-90 и цезия-137 в водах Атлантического океана и его морей в августе-ноябре 1963 г.
1168	Содержание стронция-90 и цезия-137 в водах Атлантического океана и его морей в апреле-июле 1964 г.
1169	Распределение стронция-90 и цезия-137 по профилю почв в природных условиях в 1964 г.
1170	О загрязнении растительности продуктами деления тяжелых ядер.
1171	Накопление искусственных радионуклидов на земной поверхности в районе г. Ленинграда в 1954-1965 гг.
1172	Выпадение продуктов деления в окрестностях Ленинграда в 1957-1965 гг.
1173	Исследование радиоактивного загрязнения воды некоторых водоемов Ленинградской области и Северо-Западного бассейна СССР в 1961-1966 гг.
1174	Распределение радиоактивных и стабильных изотопов щелочных и щелочноземельных элементов в надземных органах сельскохозяйственных растений.
1175	О влиянии природных условий на содержание и распределение радиоактивного стронция в почвенном покрове.
1176	Распределение радиоактивного стронция в почвах различных природных зон.
1177	Результаты определения стронция-90 в водах Индийского океана в 1962 г.
1178	Стронций-90 в водоемах солоноватоводного и пресноводного типа (1966 г.).
1179	Некоторые аспекты тканевой дозиметрии радия-226.
1180	Дозиметрические характеристики инкорпорированного мезотория-228.
1181	Некоторые радиационно-гигиенические аспекты микроклимата строений.
1182	Радиоактивность тканей жителей отдельных районов Советского Союза.
1183	Статистические параметры обмена цезия-137 глобального происхождения у жителей Арктических районов.
1184	Стронций-90 в костной ткани населения Советского Союза.
1185	Цезий-137 в организме жителей г. Москвы.
1186	Поступление стронция-90 и цезия-137 с пищевым рационом населению Советского Союза в 1965-1966 гг. в результате стратосферных выпадений, и Дозы облучения населения СССР от стратосферных выпадений в 1964-1965 гг.
1187	Особенности миграции глобального цезия-137 из дерново-подзолистых песчаных почв по пищевым цепочкам в организм человека.
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	выпадений в приарктических районах СССР в 1959-1966 гг.
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1191	Исследование распространения радиоактивного загрязнения, обусловливаемого сбросом радиоактивных отходов в Ирландское море.
1192	Радиоактивность атмосферного воздуха и некоторых продуктов питания в г. Москве в 1965 и 1966 гг.
1193	Содержание цезия-137 и калия у населения СССР в 1962-1966 гг.
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1194	Стронций-90 в водорослях, цветковых растениях, моллюсках, ракообразных и рыбах Черного моря (1965-1966 гг.).
1195	Цезий-137 и стронций-90 в тюленях и океанических рыбах.
1196	Определение концентраций кадмия-109 в приземном воздухе и выпадениях в некоторых пунктах Советского Союза в 1964-1966 гг.
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1201	Уровни радиоактивного загрязнения приземного слоя атмосферы и поверхности земли продуктами ядерных взрывов в 1963-1965 гг. в Подмосковье.
1202	Сравнение результатов измерений атмосферных выпадений стронция-90 в разных странах.
	ITALY
1203	Data on environmental radioactivity collected in Italy, January-June 1965.
1204	Data on environmental radioactivity collected in Italy, July-December 1965.
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1205	Fallout program quarterly summary report, January 1, 1968. HASL-184.
1205/Add.1	Appendix to HASL-184.
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1206	La retombée radioactive mesurée à Mol. Année 1966. Rapport R.2429.
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1207	Irradiation induced asymmetry of the thymus in mice.
1208	The radiosensitivity of offspring of an irradiated mouse population. II. The effects of acute or fractionated doses of X-rays on male offspring.
	UNITED KINGDOM
1209	Assay of strontium-90 in human bone in the United Kingdom. Results for 1966, Part II with some further results for 1965.
	MEXICO
1210	Analisis radioquimicos en muestras ambientales en Mexico durante 1966.
	UNITED KINGDOM
1211	Radioactive fallout in air and rain: results to the middle of 1967. Report AERE-R 5575.
	SWEDEN
1212	Protective effect of cysteamine at fractionated irradiation. II. Shortening of life span.
	FAO/IAEA
1213	Dietary levels of strontium-90, caesium-137 and iodine-131 for the years 1965-68. Second interim report covering period 1.1.65-10.2.68.
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1214	Iodine-131 concentrations in Australian milk resulting from the 1967 French nuclear weapon tests in Polynesia.
1215	Fallout over Australia from nuclear weapons tested by France in Polynesia during June and July 1967.
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1218	Environmental gamma radiation from deposited fission products, 1960-1964.
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1219	Strontium-90 in the Australian environment during 1966. Suppl. for January-June 1967 attached.
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1220	Data on environmental radioactivity collected in Italy (January-June 1966).
1221	Data on environmental radioactivity collected in Italy (July-December 1966).
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1222	Concentrations of caesium-137 in rainwater and milk in Australia during 1966.

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1223	Strontium-90 and caesium-137 in some Australian drinking water supplies—1961-1965.
	SWEDEN
1224	Pathologic effects of different doses of ^{90}Sr in mice. Development of carcinomas in the mucous membranes of the head.
	FRANCE
1225	Premier bilan de sept années de recherche sur les niveaux de la contamination du milieu ambiant et de la chaine alimentaire par les retombées radioactives sur le territoire français. Rapport SCPRI N° 115.
	DENMARK
1226	Low dose X-irradiation and teratogenesis. A quantitative experimental study, with reference to seasonal influence.
	UNITED STATES OF AMERICA
1227	Fallout program quarterly summary report, July 1, 1968. HASL-197.
1227/Add.1	Appendix to HASL-197.
	UNITED KINGDOM
1228	Annual report, 1967. ARCRL 18.
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1229	Terrestrial and freshwater radioecology. A selected bibliography. TID-3910, Suppl. 5.
1230	Chromosome aberrations in leucocytes of older survivors of the atomic bombings of Hiroshima and Nagasaki.
1231	Variation in the human chromosome number.
1232	Lens findings in atomic bomb survivors.
1233	Spleen shielding in survivors of the atomic bomb.
1234	Leukemia in offspring of atomic bomb survivors.
1235	Fallout program quarterly summary report. HASL-200, October 1, 1968.
1235/Add.1	Appendix to HASL-200.
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1236	11. Bericht der Eidg. Kommission zur Uberwachung der Radioaktivität für das Jahr 1967 zuhanden des Bundesrates.
	UNITED STATES OF AMERICA
1237	Cytogenetic study of the offspring of atomic bomb survivors.
1137/Add.2	Health and Safety Laboratory Manual of standard procedure, NYO-4700. Revised pages, August 1968.
1238	Effects of ionizing radiation from the atomic bomb on Japanese children.

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	DENMARK
1239	Strontium-90 in human bone. Denmark 1964-1967.
	UNITED KINGDOM
1240	Radioactive fallout in air and rain—results to the middle of 1968.
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1241	Fallout program quarterly summary report, 1 January 1969. HASL-204.
1241/Add.1	Appendix to HASL-204.
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1244	Стронций-90 в костной ткани населения Советского Союза (1957-1967 гг.).
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1246	Математическое описание динамики процессов радиоактивного загрязнения морских организмов из водной среды.
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1248	Содержание стронция-90 и цезия-137 в некоторых объектах внешней среды и в организме людей в 1958-1967 гг.
1249	Стратосферные выпадения радиоактивных продуктов ядерных взрывов на материки и океаны в умеренных широтах северных полушарий.
1250	Экспоненциальный источник как модель радиоактивных загрязнений почвы.
1251	Трех- и четырехкамерная модель метаболизма цезия у крыс и человека.
1252	Некоторые закономерности загрязнения объектов внешней среды стронцием-90 в период стратосферных выпадений.
1253	О методике исследования поведения радиоактивного стронция в почвах различных геохимических ландшафтов.
1254	Радиоэкологические процессы накопления и динамики водных масс в морях и океанах.
1255	Некоторые изменения в двигательной сфере у лиц, работающих в условиях хронического лучевого воздействия.
1256	Характер распределения цезия-137 по глубине почвы в некоторых районах Советского Союза в 1966-1967 гг.
1257	Концентрация цезия-137 в волосах человека как индикатор количества этого изотопа в организме.

Document No.	*Country and title*
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1259	Радиометрическая установка для определения содержания стронция-90 в морской воде.
1260	Полоний-210 в организме и окружающей среде.
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1262	Оседание радиоактивной пыли и ее удаление из атмосферы осадками.
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1264	О действии ионизирующих излучений на нервную систему человека. Часть 1.
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1266	Lung cancer following atomic radiation.
1267	Breast cancer after exposure to the atomic bombings of Hiroshima and Nagasaki.
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1268	Strontium-90 in the Australian environment during 1967.
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1269	Radioactivité naturelle de 250 sources hydrominérales françaises. SCPRI N° 117.
	BELGIUM
1270	La retombée radioactive mesurée à Mol. Rapport d'avancement du Département "Mesure et Contrôle des Radiations", année 1967. Rapport R. 2468.
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1271	Atmospheric and precipitation radioactivity in India.
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1274	Dietary levels of strontium-90, caesium-137 and iodine-131 for the years 1965-68.
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1276	Retombées radioactives à la suite des tirs nucléaires en Polynésie (Années 1967 et 1968).
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1277	Strontium 90 yield of the 1967 Chinese thermonuclear explosion.
1278	Health and Safety Laboratory fallout program quarterly summary report, 1 April 1969. HASL-207.
1278/Add.1	Appendix to HASL-207.
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1279	Soil calcium maps of Africa, South America and parts of Asia.
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1280	Strontium-90 levels of fallout and of food diet in U.A.R. during the year 1968.
1281	Levels of potassium and caesium-137 in man in U.A.R. during year 1968.

Annex E

LETTER SENT AT THE REQUEST OF THE COMMITTEE BY ITS SECRETARY TO STATES MEMBERS OF THE UNITED NATIONS AND MEMBERS OF THE SPECIALIZED AGENCIES AND OF THE INTERNATIONAL ATOMIC ENERGY AGENCY ON 30 APRIL 1968

Sir,

I have the honour to inform you that the Scientific Committee on the Effects of Atomic Radiation, which was established by the General Assembly at its tenth session, has completed its eighteenth session during which it has reviewed, among other things, the information that it currently requires to assess levels of radiation resulting from nuclear tests.

The Committee noted that in the past it had received from a number of countries a large amount of information on radio-active contamination of the environment from nuclear tests. It expressed its appreciation of those comprehensive survey data that have greatly assisted it in its evaluations. Although there are large areas of Africa, South America and Asia, encompassing nearly two thirds of the world population, from which information has been fragmentary, nevertheless the Committee has been able to make reasonable estimates of the average exposure of the world population.

However, to guard against the possibility that population exposures in certain areas, and therefore their contribution to world-wide population averages, may have been underestimated owing to lack of information, the Committee felt that it would be valuable to have some measurements of bone contamination in a few selected locations. Extensive surveys in these areas are not needed for the assessment of the average world population exposure, but more information on environmental transfer mechanisms would be useful for estimating local exposures in possible future situations of environmental contamination.

For those areas from which most of the information has come, the general principles governing the transfer of radio-active material to man through food chains are now better understood than when the last request for measurements was made by the Committee in 1960. In the past, radio-active contamination has been largely by direct deposition on the above-ground parts of plants, but rates of deposition of the radio-active material are now relatively small and, unless large-scale atmospheric testing is resumed, the future mode of entry of long-lived nuclides into food chains will mainly be by root absorption of the deposit accumulated in the soil. Opportunities for quantitative study of this mechanism, as well as of the behaviour of long-lived radio-nuclides in the soil, have been limited in the past, and the Committee expressed the hope that surveys would continue in the future to provide information on this problem.

The Committee considered that this information can be obtained from surveys conducted in only a limited number of countries where agricultural practices and dietary composition are representative of those of a wider area, and recommended that those countries which have reported survey data on contamination of both diet and human tissue since 1961 or earlier continue to do so in the future. The measurements needed by the Committee are, as before, the total amounts of individual long-lived nuclides in food and human tissue, levels of external radiation from deposited radionuclides and levels of contamination by short-lived nuclides in food.

The Committee's specific requirements on continuing survey measurements are the following:

(*a*) The Committee's estimates of the total amount of individual nuclides in the atmosphere and in soil have so far been based on the results of two continuing world-wide surveys. The Committee expressed the hope that the results of these surveys would still be available to it in the future.

(*b*) With regard to levels in food, the Committee requires the results of measurements of Sr^{90} (in pCi/g Ca and pCi/kg) and Cs^{137} (in pCi/g K and pCi/kg) contamination in dairy produce, cereals and vegetables. The Committee also expressed interest in obtaining a few representative measurements of the levels of stable strontium in the same food-stuffs.

(*c*) Tissue levels include (i) body contents of Cs^{137} and (ii) Sr^{90}/Ca ratios in the skeleton. As it is anticipated that the distribution of Sr^{90} in adult bones will become more uniform in the next few years, the Committee recommended that intercomparisons of contamination levels in various types of bone and in whole skeleton be made more regularly than hitherto. The Committee also noted that an increasing number of persons were now entering adult life who had been exposed to Sr^{90} contamination during their growing years and in whom the distribution of Sr^{90} within the skeleton will be different from those who have only been exposed as adults. The Committee therefore recommended that the results obtained from adults should be reported separately for those between twenty and thirty years of age and for those older than thirty in 1967, and that for the next few years results for children should be presented by years of age up to four years and as a group from five to nineteen years. Because of its importance in assessing the long-term behaviour of Sr^{90} in the human body, the Committee would also be interested in obtaining measurements of stable strontium in bones of both juveniles and adults from those populations where comparable data for diet are also available.

(*d*) Levels of external radiation from deposited radio-nuclides have been recorded continuously at a few sites, and the Committee recommended that these recordings be continued and that other measurements making it possible to improve the accuracy

of estimates of external gamma doses from Cs^{137} and short-lived nuclides should also be made.

(*e*) The Committee has a continued interest in levels of I^{131} in milk and vegetables because of the high concentration of iodine in the thyroid gland, relative to other tissues, and of the resultant local radiation doses, which can be of particular importance in infants and children.

(*f*) The Committee is also interested in data on other internal emitters in local areas, when these emitters make a substantial contribution to radiation exposure from environmental contamination.

The Committee's requirements on information from areas not covered by continuing surveys are as follows:

Limited investigations only, rather than continuing surveys, would be adequate for the purpose of obtaining information from those areas of the world from which data are yet scant. Measurements of Sr^{90} in bones from selected areas need to be carried out only once in the near future. The areas of greatest interest to the Committee are those where the main calcium contribution to the diet is from cereals such as rice and maize, or from pulses and nuts. The Committee believes that one effective way of carrying out such a limited collection of samples is by agencies within the United Nations system and by existing national laboratories.

The Committee emphasized that it had outlined the information at present required for its own purposes only and noted that its requirements might need a further revision if massive injections of radio-active material into the atmosphere through nuclear tests were to be resumed, and that the requirements would in any case be revised as soon as sufficient additional knowledge accumulated.

Accept, Sir, the assurances of my highest consideration.

(*Signed*) Francesco SELLA

Secretary

United Nations Scientific Committee on the Effects of Atomic Radiation

APPENDIX I

LIST OF SCIENTIFIC EXPERTS, MEMBERS OF NATIONAL DELEGATIONS

The scientific experts who took part in the preparation of the present report while attending Committee sessions as members of national delegations are listed below.

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Dr. R. Motteram

BELGIUM

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BRAZIL

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CANADA

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Dr. W. E. Grummitt
Dr. J. B. Sutherland

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FRANCE

Professor L. Bugnard (Representative)
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Dr. A. Benazet
Dr. R. B. Coulon
Professor J. W. de Grouchy
Dr. M. H. Dousset
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Professor J. Lejeune
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Dr. J. G. Terrill
Dr. C. A. Tobias
Dr. P. C. Tompkins

APPENDIX II

LIST OF SCIENTIFIC EXPERTS WHO HAVE CO-OPERATED WITH THE COMMITTEE IN THE PREPARATION OF THE REPORT

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Dr. E. I. Komarov
Professor B. Larsson
Dr. T. J. Leith
Dr. J. Liniecki
Dr. P. C. Nowell
Dr. F. Sella
Dr. A. B. Tsypin
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