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NOTE

Throughout the present report, references to the annexes are indicated by a letter immediately followed by a number: the letter denotes the relevant annex and the number the paragraph therein. Within each annex, references to its scientific bibliography are indicated by numbers.

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.

ANNEX B

RADIATION CARCINOGENESIS IN MAN

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I. Introduction

1. The purpose of this survey is to review data on the risk of induction of cancer by ionizing radiations in man, with emphasis on information either new or not discussed in detail in the 1962 report of the Committee[a] to the General Assembly.[1,b]

2. Most of the information available on tumour induction by radiation in man and experimental animals comes from studies of the effects of high doses of radiation, that is, doses of hundreds of rads and greater. From these data it is known that ionizing radiation in high doses may cause or contribute to the induction of cancer in widely diverse types of mammalian tissues, though the susceptibility of the different tissues varies greatly with genetic and physiological factors.

3. Few data are available at low doses of radiation (doses of the order of 10 rads and less), and the extent to which radiation has a general carcinogenic effect at low doses is a matter of speculation.

4. The mechanisms of carcinogenesis in general are not well understood. However, the evidence is that the neoplastic change occurs at the cellular level and is frequently associated with observable modifications in cell structure (particularly chromosomal constitution) and function. A variety of carcinogens, including chemicals and viruses as well as ionizing radiations, produce structural and functional changes which appear to be similar in nature.

5. Among the mechanisms likely to be of importance, which include systemic as well as local factors, are (*a*) direct cellular injuries, including changes in genes and chromosomes; (*b*) promotion of growth and development of cells with malignant potential through local injurious effects on related cellular systems and stroma; (*c*) complex perturbations of cellular and tissue homeostasis; (*d*) systemic influences and effects on distant tissues and cells which may result in altered immunological mechanisms, endocrine disturbances, and changes in metabolism and nutrition.

6. Radio-biological investigations suggest that relatively large doses of radiation are usually required to cause severe systemic effects or produce observable changes in tissue structure and function. Such high-dose effects may play a major role in the production of the neoplasms that are superimposed on chronic radiation-induced tissue changes. However, in so far as cancer may result from low doses of ionizing radiation, the major mechanisms would presumably be more consistent with the production of malignancy as a result of mutations, of chromosomal injuries or possibly of changes enhancing the susceptibility of cells to transformation by viruses.

7. Radiation-induced tumours are indistinguishable in general from cancers arising from other causes. Furthermore, as noted above, there may be common basic mechanisms. These two considerations affect both the type of statistical data that can be obtained in clinical

[a] *Official Records of the General Assembly, Seventeenth Session, Supplement No. 16* (A/5216); hereinafter referred to as the "1962 report".

[b] Superscripts refer to the corresponding entries in the bibliography at the end of the present annex.

and experimental studies and the interpretation of such data.

8. When similar basic mechanisms are involved in the production of radiation-induced and other cancers, the effect of radiation may be either (*a*) to advance in time the control curve of age distribution of tumours or (*b*) to multiply by some factor the age-dependent incidence. When similar mechanisms are not involved, the effect of radiation may be to produce an additional incidence unrelated to the control age incidence. The yield of tumours, in any given interval after the exposure, will be determined by which of these processes or by what combination of them operates and by possible changes in survival time occasioned by the irradiation.

9. Most of the data available in man, and even in experimental animals, are confined to a limited period of time following irradiation. Any attempt to estimate the total lifetime incidence of tumours is likely to involve extrapolation.

10. In making risk estimates for human populations, the difficulties of epidemiological studies must be borne in mind. There is the possibility of large variation in susceptibility in the population because of differences in genetic, physiological and environmental factors. Thus the dose-effect relationship observed in a study of a whole population does not necessarily apply to individuals or to subgroups of the population. When isolated risk estimates are derived from irradiated subjects highly selected for one reason or another and are applied to the general population, this should be done with great caution.

11. In many instances it has been necessary to perform dose determinations long after the irradiation, and since it may be impossible to reproduce the conditions existing at the time of the original irradiation, many of the dose estimates necessarily have a wide margin of uncertainty.

12. In addition, there are problems of terminology and statement of dose. When the body is irradiated non-uniformly (because of limited field size, limited penetration of the radiation, or non-uniform distribution of radioactive nuclides within the body) the irradiation cannot be unambiguously specified by a single number but only in terms of dose distribution. To provide a basis for a particular risk estimate, one must, however, select a single value of a quantity that characterizes the irradiation, even though such a value may be of limited accuracy or significance.

13. The physical quantities most commonly determined for external irradiation are either kerma or exposure in free air,[2] since measurements are frequently performed with devices of minimal mass and without the use of phantoms. Because of the complexity of the physical interactions, there may be a considerable difference between the quantities thus determined and the absorbed dose in the tissues of interest.

14. All empirical risk estimates are valid only for the conditions of irradiation under which they were obtained. Thus, a risk estimate valid for a certain dose delivered in a single exposure probably is not valid for the same dose delivered over a long period of time.

15. For estimation of risk as a function of dose one requires ideally a dose-effect curve established over a wide range of doses. However, in man, information is scanty and when available refers only to a limited dose range. Within this range and within the limitations described above estimates of risk can be made. Outside this dose range it is necessary to make assumptions as to the nature of the underlying dose-effect relationship.

16. One such assumption relates to "threshold dose". For certain types of radiation-induced cancer there may be a threshold dose, but this can be established only from an understanding of the mechanisms. Even statistical studies of cancer incidence in large irradiated populations cannot unequivocally establish the existence of a threshold. In general, therefore, for the estimation of risk at low doses it has to be accepted that there is a finite risk of cancer induction, however small, even at the lowest doses.

17. In most cases in which extrapolation to low doses has been attempted a linear relationship between dose and effect has been assumed. A discussion of the use of the linear hypothesis can be found in the 1962 report. It should be noted that the assumption of linearity is the only one which allows the use of mean doses in estimating risks. In general, the assumption of a linear dose-incidence relationship at low-dose levels is likely to result in an over-estimate of the degree of risk.

18. This is, in general, likely to be true because most known dose-response curves tend to be sigmoid or linear at their lower ends, and because, on theoretical grounds, single-event changes may be expected to predominate at very low doses. Assurance that linear extrapolations are likely to over-estimate the risk is greatest when observation includes the region of rapidly increasing response with increasing dose.

19. An estimate based on the relative increases over the "natural" incidence will be influenced to a large extent by the natural incidence, which in some cases (for example, thyroid or bone cancer) is very low. Absolute risk estimates are a measure of the susceptibilities of different tissues to the induction of cancer by radiation.

20. In this report risk estimates of cancer induction will be presented either in relative terms, as increase relative to natural incidence, or in absolute terms, expressed as the number of cases per unit time and unit dose in a population of given size, for example as number $\times 10^{-6}$ per year per rad. It must be emphasized that these estimates of risk are reliable only in the range of doses, usually high, for which information is available. The use of the estimate at doses outside the observed range may be very much in error, and in the low dose range where a linear extrapolation to zero dose is used, it can in most cases only be taken as an indication of the upper limit of risk.

II. Leukaemia

Leukaemia in Japanese A-bomb survivors

21. The most informative data that are available on the relationship between radiation exposure and leukaemia in man are those obtained from the studies of the survivors of the atomic bombing in Hiroshima and Nagasaki. Even in these studies there are great uncertainties in dosimetry, in the size and characteristics of exposed populations, and in the leukaemia incidence data. Furthermore, the incidence is being observed in a population of survivors, therefore of individuals heavily selected at least at the high dose levels.

22. Some studies have been done on an "open population" in which there may be little accounting for migra-

tion of persons both non-exposed and exposed. To attempt to circumvent the uncertainties that arise in the follow-up of such an "open population", the Atomic Bomb Casualty Commission (ABCC) created the Master Sample, a "closed population" matched by age and sex in segments of the population proximally exposed (0-2,000 metres from hypocentre), distally exposed (2,000-10,000 metres), and non-exposed (beyond 10,000 metres).

23. Watanabe[6] has reported the incidence of leukaemia among Hiroshima survivors ("open population"), including all leukaemia cases for the seventeen years 1946-1962. Recomputations of these data to obtain the leukaemia incidence in the total population, in the non-exposed population (beyond 5,000 metres, presumably including post-detonation entrants), and in the exposed population (within 5,000 metres) are given in table I and figure 1. Estimates of relative risk are given in table II.

24. In table I and figure 1 it can be seen that there was a sharp increase in the reported leukaemia incidence in the exposed (within 5,000 metres) after 1946, reaching a peak eleven times higher than in the non-exposed (beyond 5,000 metres) in 1951. From 1952 to 1959 the incidence in the exposed fluctuated below this peak; from 1960 to 1962 it fluctuated within a still lower range.

25. Brill *et al.*[7] have summarized and compared previously reported findings on leukaemia in atomic bomb survivors in Hiroshima and Nagasaki, as obtained from the ABCC Master Sample or "closed population", up to 1958. Table III presents incidence by distance from the hypocentre for the 89 confirmed leukaemia cases in Hiroshima and the 60 confirmed leukaemia cases in Nagasaki during the twelve-year period 1947-1958.

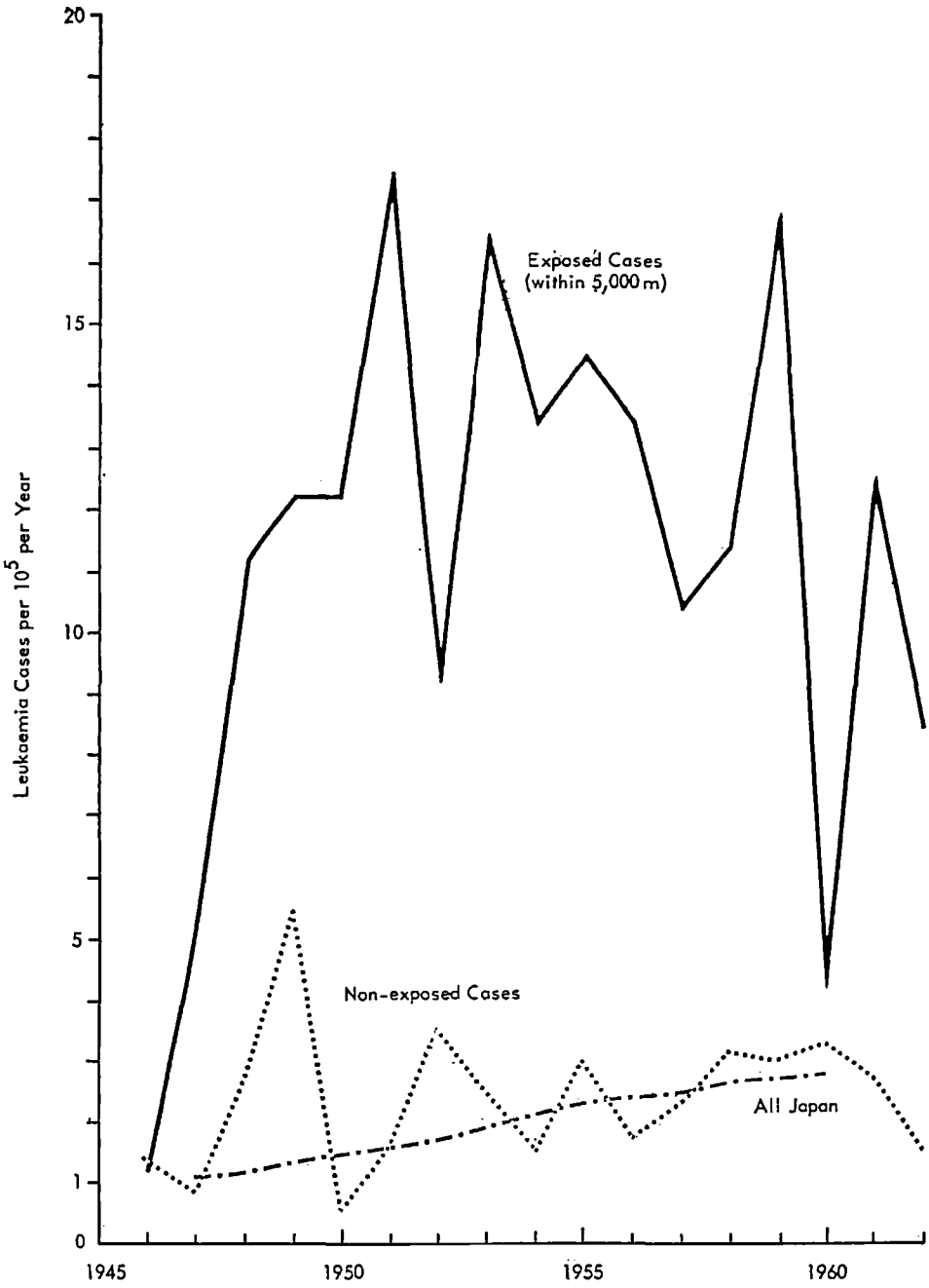


Figure 1. Leukaemia cases in Hiroshima, 1946-1962 (modified from Watanabe[6])

26. The incidence of leukaemia was greatly increased among survivors exposed within 1,500 metres from the hypocentre. Between 2,000 and 10,000 metres the average yearly incidence in Hiroshima ($28/10^6$/y) was regarded by Brill *et al.* as not significantly greater than that expected in Japan where leukaemia rates are reported to be $20\text{-}30/10^6$/y. Nor is the incidence significantly different from the average yearly incidence in the non-exposed Hiroshima population during the same period of time, as deduced from Watanabe's figures. The elevated leukaemia incidence ($37/10^6$/y) in those exposed between 2,000 and 10,000 metres in Nagasaki (table III) is significantly ($P < 0.05$) higher than expected on the basis of the frequency obtaining in the Japanese population.

27. Brill *et al.*[7] also analysed relations between radiation dose corrected for shielding (among those persons for whom knowledge permitted individual dose corrections) and average incidence of confirmed leukaemia during the nine-year period 1950-1958 in the Master Sample in Hiroshima and Nagasaki. Figures 2 and 3 provide a general guide to neutron and gamma radiation doses according to distance from hypocentre in Hiroshima and Nagasaki. Figures for attenuation of dose by shielding were based on the average attenuation factors observed during test explosions in the Nevada Desert.[8] For individuals who had been located in the open no attenuation factor for shielding was applied. For those partly shielded a 15 per cent attenuation of the air dose was assumed for gamma radiation and 25 per cent for neutrons. For persons inside houses of light Japanese style construction an attenuation of 30 per cent of the air dose was assumed for gamma radiation and of 50 per cent for neutrons. Persons located in other shielding categories were not taken into account because the corresponding attenuation factors were not known. This resulted in further reduction of the sample and of the number of leukaemia cases. Gamma and neutron estimates were added in a 1:1 ratio, assuming an RBE of 1 for neutrons. If the RBE were in actual fact higher than 1, then using a 1:1 ratio, as is done here, would yield a higher estimate of risk of leukaemia per unit dose, at least in Hiroshima.

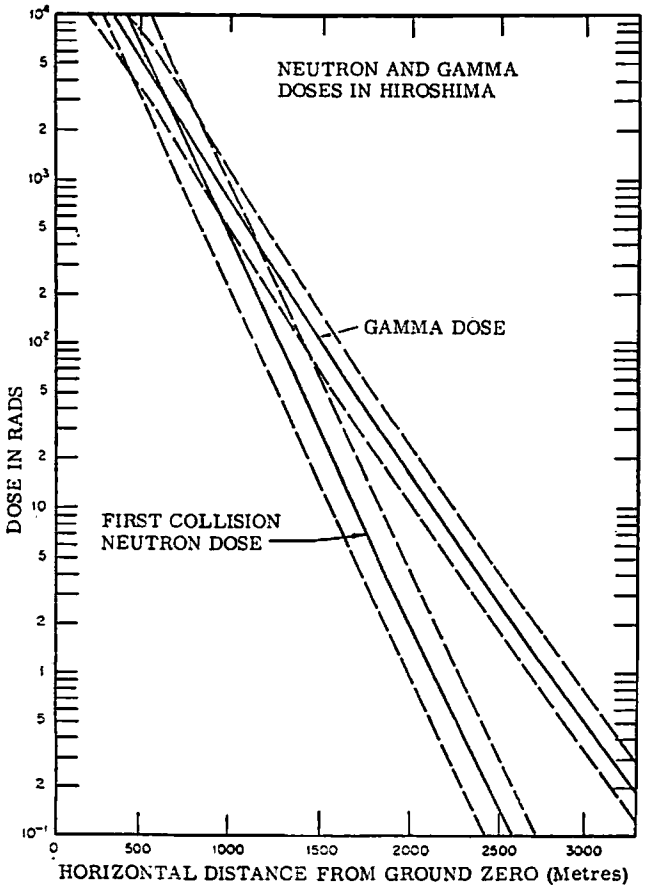


Figure 2. Estimates of neutron and gamma air doses in Hiroshima as a function of horizontal distance from ground zero (modified from York[3])

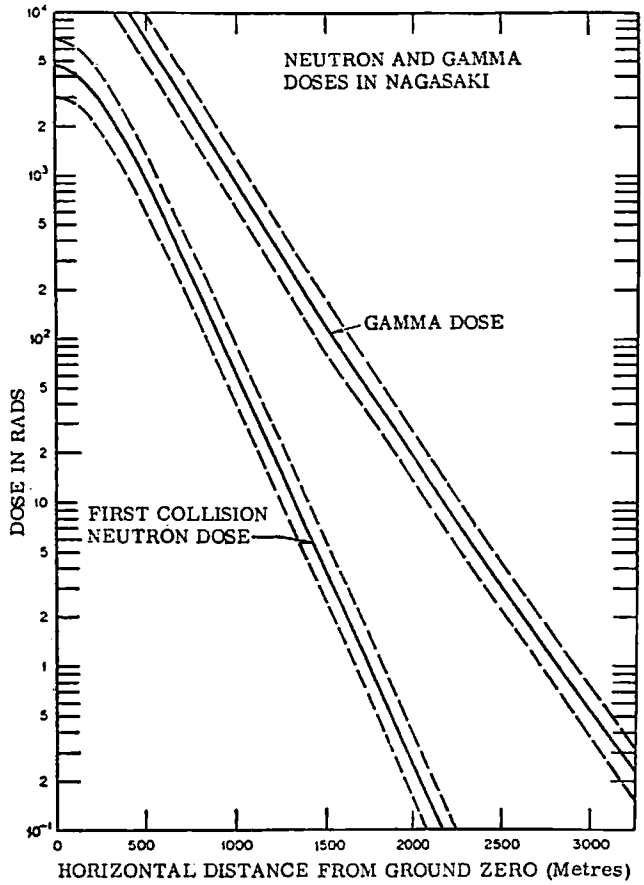


Figure 3. Estimates of neutron and gamma air doses in Nagasaki as a function of horizontal distance from ground zero (modified from York[3])

28. Table IV presents data on confirmed leukaemia incidence according to absorbed dose as obtained by these procedures for 51 cases in Hiroshima and 25 cases in Nagasaki during the nine-year period 1950-1958. The yearly leukaemia incidence according to dose is shown graphically in figure 4.

29. For Hiroshima the relation of dose to annual leukaemia incidence in the nine-year period 1950-1958 can be described by a straight line over the dose range of about 100-900 rads. Between 10 and 100 rads the incidences in each dose group, though consistent with the same straight line, do not differ significantly from one another.

30. The data indicate that at least in the range between 100 and 900 rads the average rate of increase of the incidence with dose was 1.1 cases/10^6/y/rad at Hiroshima and 1.6 cases/10^6/y/rad at Nagasaki, or between 1 and 2 cases/10^6/y/rad in both cities. Since in Nagasaki the exposed population was smaller and the cases of leukaemia fewer, the estimate for that city is statistically less reliable. However, the major cause of uncer-

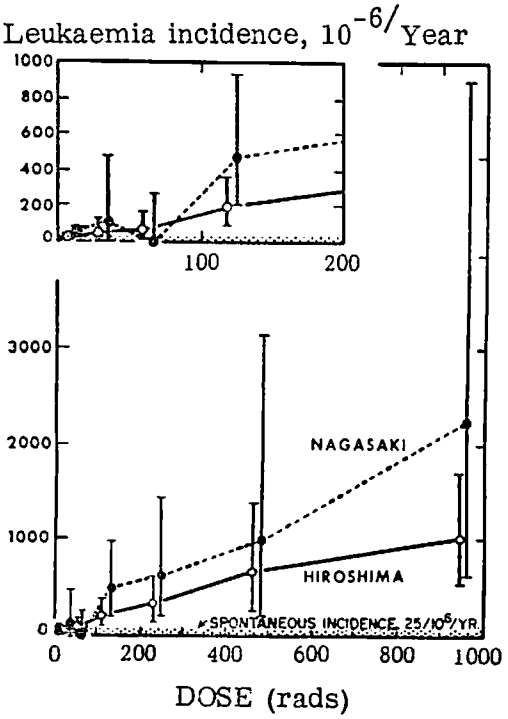


Figure 4. Average incidence of confirmed leukaemia in the master sample, proper plus reserve, 1950-1958, light shielding, by relative radiation dose (modified from Brill *et al.*[7])

tainty affecting both estimates probably lies in the limitations of the dosimetry rather than in the inherent variability of the data.

31. In both Hiroshima and Nagasaki taken together there is moderate correlation between year of onset of leukaemia and distance from the hypocentre. In both cities the group with symptoms of radiation sickness was closer to the hypocentre and had a significantly increased leukaemia incidence over the group without radiation symptoms.

32. The predilection of the various types of leukaemia for specific age groups does not appear to have been markedly altered as a result of irradiation. The rarity of chronic lymphocytic leukaemia in Japan was confirmed. The types of leukaemia observed to be increased most in survivors under 1,500 metres were chronic granulocytic and acute leukaemia. The acute leukaemias occurred predominantly in people under ten years of age at the time of exposure. There is normally a strong predilection for this type in the young. In the Japanese survivors, although chronic granulocytic leukaemia has occurred predominantly in the middle age groups, it has also been seen with increased frequency in children. Acute leukaemias—including granulocytic, myelomonocytic and unclassified types—also have occurred with increased frequency.

33. The incidence of leukaemia of various haematologic types has varied systematically in relation to age at the time of irradiation,[7] so that the age-incidence curves for the irradiated and control populations are nearly parallel.[135] Because the natural incidence of certain types varies with age by as much as an order of magnitude or more, the numbers of cases of induced leukaemia of these types have varied correspondingly with age at the time of irradiation. A given amount of radiation may thus be inferred to have increased the probability of the disease by a given percentage of the natural age-adjusted rate rather than by a given number of additional cases, a distinction of practical as well as theoretical importance.[135]

Leukaemia in early post-detonation entrants in Hiroshima

34. The data from the report of Watanabe[6] on leukaemia cases developing between 1950 and 1962 (thirteen years) in persons entering Hiroshima soon after the detonation have been recomputed and presented in table V. Although the incidence was higher than expected from data on non-exposed persons, the difference between the earliest entrants and later entrants was not statistically significant.

35. Estimates of radiation exposure from fall-out and from neutron-induced radio-activity have been published[4,5] (figure 5), but their reliability cannot be assessed.

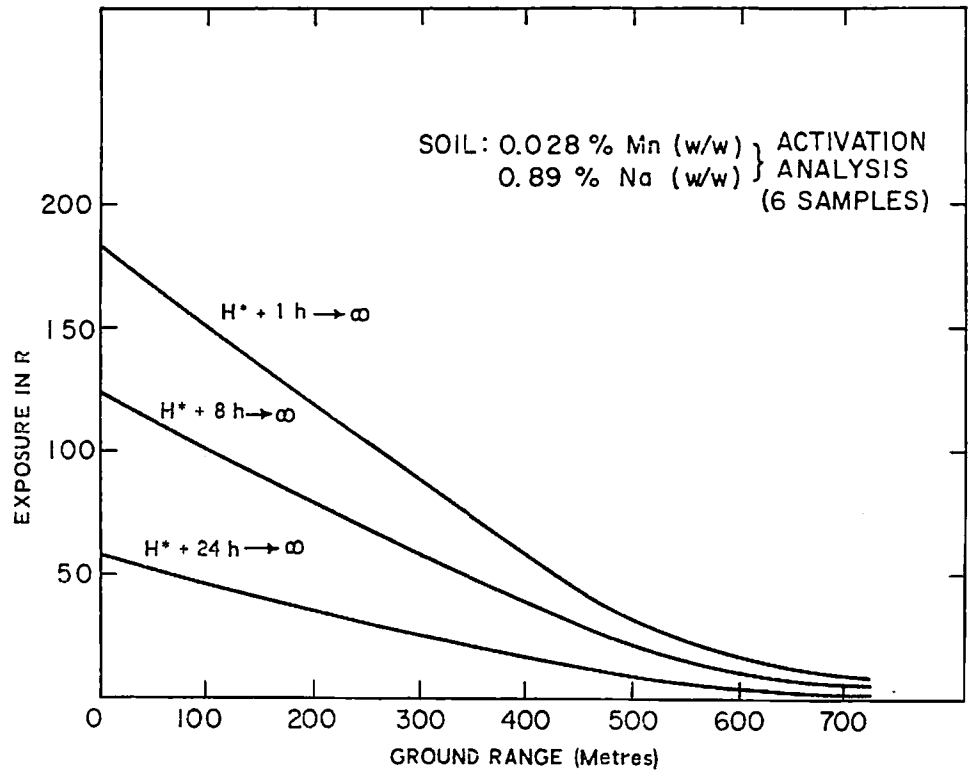
36. The locations of the early post-detonation entrants during the first days after entry are not known. In view of the extensive destruction and the long-lasting fire storm near the hypocentre which broke out within a few hours of the explosion, it has been considered probable that very few persons might have been close to the hypocentre for substantial periods of time during the first day after detonation.

Leukaemia in American radiologists

37. Earlier studies, already discussed in the 1962 report, are summarized in table VI. Since the 1962 report Lewis[9] has reviewed the 425 death certificates of registered specialists in radiology dying between the ages of thirty-five and seventy-four during the fourteen-year period 1948-1961. In table VII the observed numbers of deaths for which the main cause was leukaemia or a related disease are compared with the corresponding expected numbers calculated by applying to the number of living radiologists at risk the death rates (standardized with respect to sex, race, age and year of death) due to each relevant cause. The estimated number of male radiologists, thirty-five to seventy-four years of age, increased from 2,167 in 1948 to 4,713 in 1961; in the fourteen-year period the number of man years at risk at these ages was 47,348. The mortality ratio for leukaemia was 3.0, with 12 cases observed among the radiologists as compared with 4.02 cases expected. The average annual incidence of death from leukaemia in radiologists during these fourteen years was $253/10^6$/y, as compared with an expected incidence of $85/10^6$/y, giving an excess incidence of $168/10^6$/y. About 4.4 of the twelve leukaemia deaths in the group of radiologists were expected to be of the lymphocytic type (predominantly chronic), but only 1 case of lymphocytic leukaemia was observed, and it was of the acute type. Therefore, all 12 cases of leukaemia in the radiologists were of types known to be increased by irradiation.

38. Based on the risk estimates from Hiroshima, the excess leukaemia incidence observed in the radiologists would result from a single acute whole body exposure of about 100 rads. Little is known about the magnitude and distribution of the dose received by the early radiologists, but the evidence available indicates that doses far in excess of 100 rads were received chronically over periods of up to forty years, and this would suggest that long-term radiation exposure is less effective than short-term exposure in inducing leukaemia.

39. For Hodgkin's disease, lymphosarcoma, and lymphoblastoma, the observed numbers of deaths among



*H = Time of detonation.

Figure 5. Neutron-induced ground activity—Hiroshima (modified from Borg and Conard[5])

radiologists were in reasonable agreement with the expected numbers (table VII). On the other hand, in the population at risk there were five deaths from multiple myeloma where one was expected, and four deaths from aplastic anaemia where 0.2 was expected. While the increased incidence of aplastic anaemia was not surprising, the association of multiple myeloma with radiation had not been substantiated before.

Leukaemia in ankylosing spondylitis patients

40. There have been no new data on leukaemia incidence in relation to dose in patients X-irradiated therapeutically for presumed ankylosing spondylitis since Court Brown and Doll[12,13] in England studied the case records of 13,352 patients treated in 81 treatment centres from 1 January 1935 to 31 December 1954. Only cases of leukaemia found before 1955 were considered in the analysis. This study was discussed in the 1962 report. However, for purposes of comparison with studies of dose-incidence relations in other irradiated populations, it is discussed here also in somewhat modified form.

41. In the evaluation of the dose-incidence relationship, the cases used included 32 with an established diagnosis ("A" series) and 5 probable cases ("B" series). Since only 1 certain case of leukaemia was recognized among the 2,065 irradiated women (total incidence $48/10^5$), the analysis was confined to men, and the population at risk was defined as the 11,287 males in the study series.

42. The patients had been subjected to total cumulative exposures ranging from 112 R to more than 3,000 R in from one course of fractionated exposures (over about a month) to eight courses of therapy with separations by as many as eight years. The majority of patients given only one course had been treated since 1950, and most of the patients given multiple courses had been followed for a longer period. Young men were given, on the average, more courses of treatment than older men. The patients included boys of fourteen years of age to men well over fifty-five years of age.

43. In over 90 per cent of the patients the radiation fields were confined to limited areas of the body which included the affected joints. Fields with generous margins were used over the spine, sometimes including the pelvis and other joint areas. Details of X-ray exposure were obtained from a sample of approximately one in every six of the patients (1,878 men). Both exposures to spinal bone marrow (roentgens) and whole body integral exposures (megagramme-roentgens) were estimated. The spinal exposure was estimated in two different forms: as mean exposure to the marrow throughout the whole length of the spine, and as maximum exposure at a point in the spinal marrow. Finally, the mean spinal marrow exposure was estimated separately for those patients receiving only spinal irradiation. Eighteen of the 37 leukaemia cases were patients receiving only spinal irradiation.

44. Since the patients did not receive all their radiation treatment on one occasion, and since the proportions of patients given various exposures did not remain constant throughout the period under review, it is not possible to measure the incidence of leukaemia in relation to the size of the exposure simply by relating the numbers of patients with leukaemia following a given exposure to the estimated total numbers of patients given the same exposure. Court Brown and Doll met this difficulty by estimating the population at risk for each level of exposure from the sum of the number of years the patients survived after receiving an individual exposure and before receiving additional radiation treatment which would place them in the next, arbitrarily defined, exposure category.

45. The accuracy of this method depends much on the limits of latent period for the radiation-induced leukaemia. On the basis of 10 cases receiving only one course of treatment it appeared that the latent period would be seldom less than two years, more frequently of the order of three to five years, and less commonly, longer. However, in their analysis the authors postulated that leukaemia was equally likely to appear at any time after irradiation with the exception of the first year. Since many patients were treated during the last few years of the study, the study may be incomplete with respect to recording the total incidence of leukaemia.

46. The incidence of leukaemia in irradiated spondylitics increased with age from $11/10^4$/y in those less than twenty-five years of age to $56/10^4$/y in those fifty-five years of age or older, consistent with the age-dependent increase in incidence of comparable forms of leukaemia in the general population of England and Wales.[136] The excess of leukaemia, which was of the order of a tenfold increase in the "natural" age-adjusted rate, was present irrespective of the age at which radio-therapy was started but was slightly greater when treatment was begun late in life. For a given exposure, therefore, at least five times as many cases of leukaemia were induced in the elderly group as in the young group, although the natural age-dependent rate was increased by a similar, or only slightly different, percentage in both groups. The greater increase in the elderly cannot be ascribed to differences in exposure because there was a tendency to give older patients less radiation treatment rather than more.

47. A significant excess of deaths from all types of leukaemia occurred in the irradiated spondylitics, as compared with the expected numbers in a non-spondylitic, non-irradiated population, with ratios of 4.6 for lymphocytic, 6.1 for myelocytic, 11.8 for monocytic, and 52.4 for other and unspecified leukaemia.

48. Since adequate data are not available on the incidence of leukaemia in male spondylitics not treated by irradiation nor in non-spondylitics receiving spinal irradiation, the expected rates of leukaemia used in this study were those for the general male population of Britain standardized for age.

49. A certain possibility of error exists in the use of this control population in view of the fact that an association between leukaemia and rheumatic diseases has been observed.[15] Also, the existence of hereditary factors in ankylosing spondylitis and rheumatoid arthritis has been reported.[14] Another cause of concern is the possibility that some of the other forms of therapy used for ankylosing spondylitis may also be leukaemogenic. Agents such as antipyrine, gold salts, and phenylbutazone have been known to depress the bone marrow activity.[16] Bean[17] has reported the development of leukaemia in six non-irradiated patients who had received phenylbutazone. Three of these had ankylosing spondylitis.

50. In the survey of Court Brown and Doll[13] the case records did not provide enough detail for a special study of the use of drugs. These authors pointed out that butazolidine could hardly have played any part in the development of the cases of aplastic anaemia found, as it was not in general use until 1952. The authors indicated that gold had been used for many years, as had many types of analgesics, including amidopyrine. That drugs were largely responsible for the development of leukaemia did not seem reasonable to the authors, but decisive data were not provided in their report.

51. The numbers of men receiving various exposures of radiation to spine alone or spine plus extraspinal regions, given in terms of mean exposures to spinal marrow, and the numbers of man years at risk at twelve levels of estimated exposures, are given in table VIII. The exposures are the total exposures received less those received in the twelve months preceding the diagnosis of leukaemia. The data on the leukaemia patients are summarized in table IX, along with the crude and standardized incidence rates.

52. The annual leukaemia incidence increased from $0.5/10^4$/y in the standard control population to $72/10^4$/y following an exposure of 2,250 R or more. Below 500 R 2 of the 4 cases of leukaemia were lymphatic.

53. The mean exposure received by the spinal marrow was believed by Court Brown and Doll to be the most satisfactory measure of radiation exposure under the conditions of the investigations. However, they pointed out that it failed to take into account the considerable exposure to the extraspinal marrow in some of the patients. Therefore, they considered separately the patients who received treatments to the spine and sacro-iliac regions only. These data are given in table X.

54. Patients whose treatment was initially confined to the spine and sacro-iliac joints but who subsequently received extraspinal (including wide field) irradiation were included in the group only for that part of their life between initial treatment and the first extraspinal treatment. Although this improved the accuracy of dose estimates, the data became limited in value because of the consequent reduction in the number of leukaemia cases.

55. A regression line fitted through the incidences observed at exposures in the range between approximately 300 and 1,500 R to the spine, has a slope of $0.5/10^6$/y/R. Extrapolation of the line below 300 R is not warranted. It will be recalled that the straight line describing the relation between dose and incidence of leukaemia in the Hiroshima population of survivors to the A-bomb explosion has a slope between 1 and $2/10^6$/y/rad in the range from 100 to 900 rads. The characteristics of the irradiated population and the conditions of irradiation in Hiroshima were very different from those obtaining in the spondylitics. Not only had the Hiroshima survivors received an instantaneous burst of radiation while the spondylitics had received several courses of treatment, but most of the Hiroshima survivors had presumably been exposed to whole body irradiation, whereas in the spondylitics only parts of the body (probably involving one-third to one-half of the bone marrow) were irradiated. The similarity of the two slopes suggests that a common risk estimate may apply to both populations.

Leukaemia in children irradiated therapeutically for "enlarged thymus"

56. There have been a number of epidemiologic studies of the incidence of leukaemia in children who received therapeutic X-irradiation during childhood for benign conditions.[18-26] These studies have been discussed in the 1962 report. Among these studies, those by Hempelmann and his colleagues are the largest and the only ones which have shown an increased incidence of leukaemia.

57. The most recent reports on the Hempelmann survey are those by Pifer *et al.*[27] and by Toyooka *et al.*[28, 29] The numbers of leukaemia cases observed, of cases expected in infants treated with X-rays for "thymic enlargement", and of sibling controls in both Series (I and II), are given in table XI. All children were con-

sidered to have been at risk from birth until 31 December 1960, or until death.

58. In Series I most of the children were treated between 1926 and 1946, and treatment techniques and reasons for treatment varied greatly. In Series II the children were treated between 1940 and 1957, and treatment methods were more uniform. Many of the children irradiated in the earlier years were given relatively large doses to large areas, and posterior as well as anterior positioning of ports was often involved. The children more recently irradiated were usually given smaller doses to relatively small areas, with anterior positioning of ports. In Series II the X-ray energies, the numbers of treatments and the total period of treatment were usually less than in Series I.

59. The 6 cases of leukaemia observed in Series I included four lymphocytic and two acute undifferentiated types. The data do not make it possible to study the regression of incidence with dose.

60. These data are inadequate to distinguish between the influence of (*a*) the irradiation and (*b*) the condition, so-called "thymic enlargement", or the underlying basis for the diagnosis which served as the indication for therapy. Conti *et al.*[22] reported no cases of leukaemia in a group of 1,564 children and 96 per cent with no evidence at treatment of the condition called "thymic enlargement". Eighty-eight per cent of the children were treated through relatively small ports with exposures of 75 to 300 R, averaging 150 R, to the thymic region, and 12 per cent of them received 200 to 450 R. One case was expected. These children (90 per cent) were studied from eleven to eighteen years after the therapy.

61. Murray *et al.*[21] found 2 cases of leukaemia in seventy-five children treated for pertussis, 1 case in 1,073 persons treated to the head and neck mainly for lymphoid hyperplasia of the nasopharynx, and no leukaemia deaths in 2,460 children treated with superficial X-rays for benign skin lesions.

Leukaemia in children irradiated *in utero*

62. Several retrospective studies of children irradiated *in utero* have been carried out and their results are summarized in table XII.

63. In the retrospective study by Stewart *et al.*[30-32] of the incidence (mothers' memory) of pre-natal abdominal diagnostic irradiation among mothers of 780 children dying under ten years of age of leukaemia (during the years 1953-1955) and mothers of 1,638 control live children matched for age, sex, and location, there was a relative risk for leukaemia of about 1.83. Excessive maternal age was also related to an increased risk of leukaemia and an increased incidence of Down's syndrome. The incidence of *post-natal* diagnostic or therapeutic exposure was almost twice as high in the leukaemic children as in the control group for the first three years of life, and the frequency of *post-natal* acute pulmonary infections and severe injuries was also significantly increased in children who subsequently died of leukaemia.

64. The controls in these retrospective studies varied considerably. Stewart *et al.*[32] used live children matched for age, sex and location. Ford *et al.*[33] used children dying under ten years of age of causes other than cancer during the same period of time as the treated children. Here, the information about radiation exposure during the last trimester of pregnancy was obtained from obstetricians and hospital records. Kaplan[34] employed two control groups—closest siblings and most habitual playmates. Polhemus and Koch[35] used children attending the same hospital during the same period (consecutive surgical admissions) matched for age, socio-economic and geographic factors. In Kjeldsberg's study[30] the controls were healthy children born at a time different from that of the leukaemic children and therefore not experiencing the same likelihood of antenatal X-ray examination. In the study by Murray *et al.*[21] there were three control groups—children dying of non-malignant disease during the same period, siblings, and live siblings of the deceased controls. Finally, Lewis[37] used as controls all of the children born at the hospital in which the leukaemic children had died.

65. Court Brown *et al.*,[36] in an extensive prospective study of women who were irradiated during pregnancy between 1945 and 1956, found that among 39,166 live-born children who had received antenatal irradiation, nine had died of leukaemia before the end of 1958. The expected number was 10.5. None of the children of the 750 women irradiated in the first three months of pregnancy had developed leukaemia during an average follow-up of over six years. No correlation was found between incidence of leukaemia and the amount of antenatal exposure.

66. MacMahon[39,40] designed an extensive prospective study to examine this problem by a method which utilized objective evidence of intra-uterine X-ray irradiation. The study population consisted of 734,243 children born in, and discharged alive from, any of thirty-seven large maternity hospitals in the north-east United States in the years 1947-1954. The frequency of intra-uterine X-ray irradiation in the population was estimated by review of the records of a 1 per cent systematic sample. Abdominal or pelvic X-rays were recorded in 370 (10.6 per cent) of the 7,242 single pregnancies in the sample. Children dying of leukaemia before the end of 1960 were identified by review of death and birth certificates. After correction for indirect associations with birth order and other complicating variables, it was estimated that leukaemia mortality was about 40 per cent higher in the X-rayed than in the non-X-rayed members of the study population, giving a relative risk of 1.4, with 95 per cent confidence limits 1.0 and 2.0.

67. No estimates of dose were obtained in any of these studies. However, in MacMahon's study, X-ray cases were divided into three categories ranked in order of probable (relative) dose, according to the probable numbers of films involved in the diagnostic procedures. Although there was a minor trend toward higher cancer risk in the more heavily exposed categories, it was far from significant. It was shown that neither the higher risk of leukaemia in first births nor the higher frequency of pre-natal X-ray in first births explained the association between X-ray irradiation and increased leukaemia incidence. It remains to be demonstrated whether or not the association between irradiation and leukaemia explains the high frequency of leukaemia in first births. The ratio of mortality in first-born to that in later-born was as great in the separate X-ray categories (1.5 in the X-rayed, 1.3 in the non-X-rayed) as in the combined data, 1.4. The birth-order differential was also as great among children in specific relative dose categories (pelvimetry) as in the total.

68. The report[39] which included deaths to the end of 1960 of children born during the years 1947-1954, dealt with children predominantly over five years of age and showed a higher frequency of intra-uterine X-irradiation in cases of leukaemia and cancer deaths, as compared

with the 1 per cent sample of the population. It is of interest that an earlier report,[40] which included only deaths prior to 1958, showed little or no difference in frequency of intra-uterine irradiation between the two groups. It is possible that differences in young children have been similarly under-estimated in some other studies as a result of insufficient follow-up time for a significant portion of the population. The small relative risk and the occurrence of the peak risk after five years of age are two characteristics of the association which may go far towards reconciling this view with the negative results reported in a number of surveys.

69. Wise[41] has studied first-born children who had died of leukaemia during the period 1953-1955. In a group of 306 such cases ten birth cohorts were represented (1945-1954), and in nine of these the mean age at death of cases with a history of pre-natal irradiation was four months greater than the mean age at death of the non-X-rayed cases. Only two cohorts had been followed from birth to one year of age (1953-1954), and only one had been followed from birth to two years of age (1953).

70. Stewart and Hewitt,[42] studying 628 children born between 1952 and 1956 who died of leukaemia and lymphosarcoma before the age of five years, found that the percentage of X-rayed cases varied significantly with age at death and increased from age zero to age four. Assuming that none of the leukaemia cases dying within about fourteen months after exposure, i.e., before the age of one year were radio-genic, these authors also suggested that radio-genic cases had a different age distribution than spontaneous cases, and that, over this age range, the radio-genic cases had a tendency to develop later than "spontaneous" cases. The proportion of controls X-rayed (8.3 per cent) was almost the same as that for the youngest—"spontaneous"—leukaemia cases (8.5 per cent), and according to this hypothesis the "extra" X-rayed cases in the older age groups are attributable to the intra-uterine exposures.

71. According to MacMahon[43] the probability of death from leukaemia for white children in the United States up to the age of ten years is 46 per 10^5 persons. Assuming that 10 per cent of these children were X-rayed *in utero*, and that the X-rayed have a 40 per cent higher risk than the non-X-rayed, it follows that the over-all risk of $46/10^5$ is made up of a risk of $62/10^5$ for the 10 per cent X-rayed and $44/10^5$ for the 90 per cent not X-rayed. The difference, $18/10^5$, is the excess risk in the irradiated children. This would be compatible with extrapolated estimates from post-natal irradiated groups of 2 cases per million per rad per year only if the foetal dose received was 9 rads. This is probably at least twice the average dose received.

72. While individual studies of the incidence of leukaemia in children irradiated *in utero* have yielded different risk estimates, these are of different reliability on purely statistical grounds as indicated by their confidence limits. As discussed later in this annex, it has been shown[108] that there is no inconsistency in the findings of eleven surveys, five of which involved small samples with large sampling variability and gave estimates of relative risks less than one. The joint maximum likelihood estimate of the relative risk from all these surveys was in fact found to be 1.4 with 95 per cent confidence limits 1.2 and 1.6.

73. Although accurate estimates of doses are not available, it seems difficult to avoid the conclusion that irradiation of foetal tissue gives rise to a greater risk per unit dose than post-natal irradiation, possibly by a factor as high as 5. As in all cases of irradiation for medical reasons, there is no way to separate the leukaemogenic effect of radiation from other possible aetiologic factors connected with the reasons that had prompted the irradiation.

Leukaemia in other groups medically irradiated from external sources

74. Simon *et al.*[44] found, in 71,582 patients treated by radium therapy for carcinoma of the cervix in large treatment centres throughout the world, an incidence of between 6.2 and 11.6 cases of leukaemia per 10^5 persons. Comparing this to the British death rate of $5.8/10^5$ for leukaemia in women fifty-five years old and the incidence of $9.0/10^5$ for a similar group in the United States, they concluded that the incidence was not increased by radium treatment. However, since 25 per cent of the patients did not survive one year and since 60 per cent did not survive five years, the population at risk was greatly reduced before the greatest incidence of radiation-related leukaemia, if it occurred, would have been expected.

75. Faber[45,46], in a study of cases of leukaemia reported in the Danish Cancer Registry during the years 1940 to 1954, found that 34.8 per cent of the 442 acute leukaemia cases, 32.6 per cent of the 307 chronic granulocytic leukaemics, 17.7 per cent of the 861 chronic lymphocytic leukaemics, and 21.3 per cent of the 395 non-leukaemic controls used, had a history of diagnostic or therapeutic X-irradiation. The period between irradiation and development of the disease ranged from ten to sixty months for the acute cases and from ten to one hundred and forty months for the chronic granulocytic cases with no notable peak in the distribution. The relative risks and their 95 per cent confidence limits are: 2.0 (1.7-2.7) for acute leukaemia, 1.8 (1.3-2.5) for chronic granulocytic leukaemia, 0.8 (0.6-1.1) for chronic lymphocytic leukaemia. From the limits it can be concluded that only for acute and chronic granulocytic types was there a significant increase in risk. The doses received and the reasons of irradiation are not known.

76. Neumann[47] reported that from 1954 to 1960, 10 fatal cases of leukaemia were recorded in Stuttgart among tuberculosis patients over fourteen years of age in a sample equivalent to 91,549 person-years, and 5.86 cases were expected in a corresponding sample of the general population of Stuttgart in the same period. This gives a relative risk for leukaemia of 10/5.86 or 1.7 for the tuberculous patients who presumably were exposed more frequently to chest roentgenography than were control subjects. However, this does not differ significantly from unity, and in the ten tuberculous patients who died of leukaemia the exposure was slightly lower than that for the whole sample of tuberculous subjects.

77. Stewart *et al.*[48] in the United Kingdom made a retrospective survey of possible association between exposure to diagnostic or therapeutic X-irradiation and the subsequent development of leukaemia in adults. The frequency of irradiation appeared to be the same in the so-called L group (512 lymphatic leukaemia and lymphosarcoma cases), in a group of 951 cases with tumours of various sites, and in a group of 974 apparently healthy controls. In the so-called M group (511 myeloid and monocytic leukaemia cases) the frequency of irradiation of chest or abdomen was higher and that of the limbs not different from controls. To obtain risk estimates these authors compared frequency of trunk irradiation in their M series with the frequency of trunk

irradiation among all other groups pooled together (standard group), disregarding limb irradiation because the frequency of limb irradiation was not higher than in control groups.

78. In the standard group during the last ten years prior to the survey, 29 patients reported therapeutic irradiation, 1,025 reported diagnostic irradiation, and 1,323 reported no exposure. In the M group (myeloid and monocytic leukaemia) the corresponding figures were: 24 with therapeutic irradiation, 243 with diagnostic irradiation, and 244 with no exposure. The relative risks of leukaemia were 4.5 (95 per cent confidence limits: 8.0-2.5) for therapeutic irradiation of trunk and 1.2 (1.4-1.0) for diagnostic irradiation of trunk.

79. Gunz and Atkinson,[49] in a retrospective study in New Zealand, found that 47 of 590 leukaemia patients had received prior X-ray and/or radio-isotope (various) therapy for a variety of malignant or benign conditions, as compared with 38 of 712 non-diseased controls, giving a relative risk of 1.5 (1.0-1.9). They also found that 7 of 122 cases of myelomatosis (5.7 per cent) had previously been irradiated therapeutically (relative risk 1.1, limits 1.7-0.7). Prior radiation therapy was found in 25 of the 355 acute leukaemia cases (relative risk of 1.3, limits 2.1-0.8), 9 of the 78 chronic granulocytic leukaemias (relative risk 2.3, limits 5.0-1.0), and 13 of the 157 chronic lymphocytic cases (relative risk 1.5, limits 2.9-0.8).

80. In the same study the frequency of diagnostic irradiations received in the previous ten years was also investigated. Significant differences in the frequency of diagnostic irradiation among the various groups were apparent. No conclusion can be drawn with regard to the relative risks involved because the effect of diagnostic doses cannot be separated from that of the presumably much higher therapeutic doses received by a fraction of the same sample.

81. While therefore there is evidence that, as expected, therapeutic irradiation in adults may give rise to a detectable increase of risk of leukaemia, the question of the effect of diagnostic irradiation remains open. The results of Stewart *et al.*[48] are open to question as they barely reach statistical significance, because in that study leukaemics showed not only higher frequency of irradiation but also a different distribution, compared to controls, of diseases that might themselves lead to an increased risk of leukaemia, and because irradiations of the limbs, though they must have involved substantial doses to the bone marrow, were disregarded. More intensive investigations and better dosimetry are required before meaningful estimates of risk from diagnostic irradiation of adults can be obtained.

Leukaemia after I^{131} therapy

82. Pochin,[50] in a study of an estimated 59,000 patients (estimated 221,900 patient-years at risk) treated for thyrotoxicosis with radio-iodine for the twenty years preceding mid-1960 in the main clinics of the United Kingdom, Canada and Austria, and in a number of clinics in the United States, collected 8 published cases and 10 others, as well as 1 case of lymphosarcoma. He estimated from the appropriate national leukaemia rates an expected number of 21 ± 5 cases of leukaemia and concluded that presently available evidence, while giving no support to the possibility of leukaemia induction, neither excluded such induction nor made it possible to set any upper limit to the actual frequency. The average follow-up time in this study was about 3.8 years after therapy.

83. Wald *et al.*,[16] in their 1962 review, listed 2 additional cases of leukaemia and 1 of lymphoblastoma. Of the total of 20 cases there were 19 in which the type of leukaemia was known and 15 were acute. This proportion was higher than anticipated in a normal population of the same age and sex distribution. About 20 per cent only of the patients treated were males, but over 70 per cent of the cases of leukaemia occurred in males. Eight of the 20 cases were diagnosed in less than two years after therapy, and only 5 were diagnosed more than four years after therapy. The mean age of this population was higher than that of hyperthyroid patients in general, probably reflecting the conservative use of I^{131} in the young.

84. Werner *et al.*[51] in 1961 further analysed the data for the patients in the United States (collected by Werner and included in Pochin's report). In this series there were 10 leukaemia cases among 32,000 thyrotoxicosis patients treated with I^{131} with an average follow-up time of 4.44 years. An incidence of 13.8 cases was expected. There were significantly fewer chronic cases (3 as opposed to 9 expected). For males there was a significant excess of acute cases (6 to 1), while for females there was a significant deficit of total cases (2 to 10) and of chronic cases (1 to 6).

85. No information is available on the incidence of leukaemia in thyrotoxic patients not treated with radiation which would make it possible to distinguish the influence of the disease itself on leukaemia incidence from that of I^{131}.

Leukaemia in polycythemia vera patients treated with P^{32}

86. Wald *et al.*[16] in 1962 reviewed 1,238 cases of polycythemia vera cases treated with P^{32}. Among these there had been 41 deaths (3.3 per cent) from acute leukaemia. Since nearly 75 per cent of the patients in the combined series reviewed (observation periods ranging from seven to eighteen years) were still alive at the time the reports were made, complete ascertainment of leukaemia incidence has yet to be made. In the absence of adequate information on leukaemia incidence in polycythemia vera patients not treated with radiation, it is not possible to distinguish the influence of P^{32} from that of the disease. Prior to the advent of radio-phosphorus, as well as since, X-ray therapy has also been used frequently. There is some evidence among patients not treated with radiation suggesting that the condition of polycythemia may predispose to leukaemia or may be a condition closely related to leukaemia.

87. The general concept of myelo-proliferative diseases developed by Dameshek[52] would suggest that the stimulus producing an increased incidence of one form of this general type of disorder, e.g. myeloid leukaemia, might well be capable of the initiation of closely related clinical entities such as polycythemia vera, erythremic myelosis, and myelo-sclerosis. Yamazaki *et al.*[53] found 18 cases of polycythemia vera among Hiroshima atomic bomb survivors (22 per cent of the 81 cases reported in all of Japan since 1950). It should also be recalled that Lewis[9] found an increased incidence of multiple myeloma in United States radiologists.

Leukaemia and environmental radiation exposure

88. Craig and Seidman[54] have reported that the incidence of leukaemia in the one hundred and sixty-three

metropolitan areas of the United States bears no demonstrable relationship to differences in the amounts of cosmic radiations received.

89. Court Brown and Doll,[55] in a study of the four principal cities of Scotland, five rural areas, and the rest of Scotland found that, from 1939 to 1956, leukaemia mortality was highest in Aberdeen (mainly excess of acute and chronic myeloid) and in Edinburgh (mainly excess of chronic lymphocytic leukaemia). The average gamma radiation background in Aberdeen was 90 mrads per year and in Edinburgh 57 mrads per year. It was thought that the excess leukaemia mortality found was partly the result of better case finding in the large cities.

III. Thyroid neoplasms

THYROID CARCINOMA IN JAPANESE A-BOMB SURVIVORS

90. Socolow *et al.*[56] have reviewed the cases of carcinoma of the thyroid that were detected through routine medical examination, between 1 July 1958 and 1 July 1961, in matched groups of exposed and non-exposed subjects included in the long-term medical investigations (Adult Health Study) of the Atomic Bomb Casualty Commission (ABCC). The sample used in the Adult Health Study consisted of four components balanced for age and sex: group 1 (proximal), exposed within 2,000 metres of the hypocentre (reported acute radiation symptoms); group 2 (proximal), exposed within 2,000 metres (reported no acute radiation symptoms); group 3 (distal) exposed 3,000 to 3,499 metres; and group 4 (non-exposed), beyond 10,000 metres or not in the city at the time of the bombing. The review by Socolow *et al.* includes 10,780 subjects in Hiroshima and 4,589 in Nagasaki.

91. During the three-year period of this study 355 patients were found to have enlarged thyroid glands in Hiroshima and Nagasaki. Biopsies were recommended in 114 cases in Hiroshima and 17 in Nagasaki, corresponding to 37 and 38 per cent, respectively, of patients with thyroid enlargement. Seventy biopsies were performed, 64 in Hiroshima and 6 in Nagasaki. While there was a random distribution of three types of thyroid enlargement among the four component groups in Nagasaki, single nodules were diagnosed more often among patients of exposure group 1 in Hiroshima. Biopsy was recommended in about 80 per cent of cases with single nodules, 50 per cent with multi-nodular glands and 3 per cent of cases with diffuse goitre. That there was some degree of uniformity of sampling is suggested by the fact that the percentages of patients with single nodules of the thyroid who were biopsied were fairly constant (range 42-45 per cent) within the four exposure groups in Hiroshima. A similar analysis cannot be made in Nagasaki in view of the smaller number of cases and fewer biopsies performed.

92. Twenty-one patients with histologically confirmed thyroid carcinomas were seen. Seventeen cases were diagnosed as a result of a routine Adult Health Study medical examination and 4 cases were diagnosed elsewhere just before the inception of the current study in July 1958.

93. In Hiroshima, exposure group 1 contained 10 of the 18 thyroid cancer cases seen in that city, a finding which is moderately significant ($0.05>P>0.02$). When the figures for both cities are combined, 10 of the 21 cases fall within group 1, a distribution of doubtful significance ($0.10>P>0.05$). However, if only the 17 cases diagnosed as a result of the Adult Health Study examinations are considered, a different distribution is seen. All 4 cases diagnosed at other hospitals are in the proximal exposed group, and their elimination from the analysis results in a distribution that does not depart significantly from chance ($P>0.30$). Fourteen of the 21 cases occurred within 1,399 metres, a significant increase compared with those at greater distances.

94. According to Socolow *et al.*,[56] although the overall incidence of thyroid cancer in the Adult Health Study may not depart greatly from that cited by others for Japan, the age distribution differed significantly in that the cases in the A-bomb survivors were younger. Of the 21 cases, 8 were diagnosed in the group under the age of thirty-five years. At the time of exposure these patients ranged in age from six to twenty years. The latent period after exposure can only be defined as less than thirteen or fifteen years owing to the fact that all cases in this study were diagnosed between 1956 and 1961. Among cases occurring in the younger age groups, over 80 per cent were exposed within 1,400 metres, whereas in older age groups fewer than 50 per cent were similarly exposed.

95. From the available information it is difficult to define a pertinent population base for these cases or to evaluate the general significance of identified cases. However, if the findings were representative of the incidence in the total exposed and non-exposed populations in this study, the incidence of thyroid carcinoma in the exposed would be 19/14,970 or 0.13 per cent, and in the non-exposed 2/4,992 or 0.04 per cent.

96. In 1964 Zeldis *et al.*[57] reviewed thyroid lesions in autopsy and surgical pathology specimens in Hiroshima A-bomb survivors. From 1 January 1948 to 30 December 1960, thyroid specimens were available in 1,253 of a total of 1,535 adult autopsy cases examined at ABCC. For the same period, a total of 342 surgical thyroid specimens, representing 301 cases, were assembled from all pathology departments in Hiroshima. However, for analysis of the surgical thyroid specimens, it proved impossible to define a pertinent population base for the entire series or to evaluate the general significance of identified cases in the face of the known occult character of many thyroid lesions. Therefore, analysis was made simply of diagnoses in those 70 of the surgical cases which fell into two exposure groups (within 1,399 metres and between 1,400 and 1,999 metres). Table XIII gives the incidence of thyroid cancer and thyroid adenoma in the autopsies and in the 70 surgical thyroid specimens according to distance from hypocentre.

97. The incidence of thyroid carcinoma in the total of 1,253 autopsy cases, in the entire exposed group, or in the group exposed between 2,000 and 9,000 metres, is about 3 per cent, or only about 1.15 times the incidence in the non-exposed. The incidence in the non-exposed is 1.7 times that in the group exposed between 1,400 and 1,999 metres. The incidence in the group exposed within 1,400 metres is about twice that in the non-exposed group. The incidence of thyroid adenoma is more than doubled in the most proximally exposed group and slightly increased in other exposure groups.

98. In the surgical specimens, the incidence of thyroid carcinoma in the group exposed within 1,400 metres was 3.75 times that in the 1,400-1,999 metres group. However, the incidence of thyroid adenoma was 2.6 times greater in the latter group than in the former group.

99. The increased incidence of thyroid carcinoma in the autopsy cases in the group exposed within 1,400

metres was found not to be statistically significant ($P = 0.07$), but the increased incidence in the thyroid cancers in the surgical specimen groups exposed within 1,400 metres was found to be statistically significant.[57]

100. Taken together, both surveys suggest that the incidence of thyroid carcinoma has been increasing in the irradiated population of Hiroshima and Nagasaki, the incidence varying inversely with distance from the hypocentre. Difficulties of ascertainment, due to the fact that the incidence of carcinoma of the thyroid is difficult to record, and the fact that the latent periods are long, make it difficult to set up the surveys that would be necessary to obtain information on the dose-effect relationship and therefore on the risk of induction.

Thyroid neoplasms in patients therapeutically irradiated from external sources

101. Takahashi *et al.*,[58] in a retrospective survey of human cancer in relation to medical exposure in certain hospitals up to 1962 in Japan, found 638 cases of thyroid cancer, of which 29 (4.55 per cent) had histories of therapeutic irradiation with the thyroid within the radiation beam. In control groups of similar age distribution, 9 of 1,535 (0.59 per cent) received irradiation to this neck region. The difference was significant at the 1 per cent level.

102. However, the control group in this study is insufficiently characterized to permit adequate interpretation of the results with respect to the influence of factors other than radiation in the results. The study does not distinguish between (*a*) effects of radiation, and (*b*) effects of the conditions which prompted the irradiation, on the occurrence of neoplasms after irradiation. Furthermore, it is not clear how far back in time the survey of irradiation went. It should be noted also that the data indicate an average dose of 14 rads in the controls.

103. Neglecting these reservations, it is possible to compare the proportion of irradiated subjects among patients developing thyroid cancer and among healthy controls. The relative risk estimate so obtained amounts to 8.4 with 95 per cent confidence limits 14.8 and 4.8, respectively. Dividing the estimate by the excess radiation (160 R) received on the average by thyroid cancer patients compared to healthy controls gives a relative risk per R of approximately 5 per cent. In table XIV are given the proportions of patients with and without thyroid cancer, according to the estimated exposure.

104. In many prospective surveys[18,23-29,60,61] and in numerous retrospective surveys,[63-73] therapeutic irradiation of children has been associated with a subsequent increase in incidence of thyroid tumours. In some prospective studies[22,62] this association has not been found. A number of surveys of thyroid cancer incidence following therapeutic irradiation for benign conditions are summarized in table XVI.

105. In 1962 Hanford *et al.*[59] reported the results of a study of 458 patients who had received therapeutic irradiation for non-malignant disease of the cervical region (thyroid included). Of these patients, 431 patients comprised three main treatment groups, including 43 treated as infants for "enlarged thymus", 92 children and adults treated for toxic goitre, and 296 children and adults treated for tuberculous adenitis. Eight cases of thyroid cancer were found where ~ 0.1 case was expected, 7 of them among the 162 tuberculous adenitis patients followed ten years or longer after treatment, and 1 case among the toxic goitre patients.

106. Data on ages at irradiation and at operation for thyroid cancer, and approximate doses, for the 7 cancer cases in the tuberculous adenitis group are given in table XV. Five of the 7 cases were four to eighteen years of age at the time of irradiation, and the others were twenty-three and thirty-four years of age, respectively. Five of these 7 cancer cases were among 54 patients who had received exposures between 500 R and 1,000 R, and 2 of the cases were among 66 patients who had received exposures of 1,000 R or more. The one patient who developed thyroid cancer after irradiation for toxic goitre had received an exposure of about 2,000 R at sixteen years of age.

107. In the prospective survey by De Lawter and Winship[74] of adult patients X-irradiated for hyperthyroidism or other benign diseases of thyroid, there was no evidence of thyroid cancer in any of the 222 patients followed for an average of 22.5 years.

108. In a retrospective survey of 286 cases of thyroid cancer, Winship and Rosvoll[70] found that 80 per cent of the 286 cancer cases had received prior therapeutic irradiation to head or neck during infancy or childhood, mostly for "enlarged thymus", others for hypertrophic tonsils and adenoids, and some for other benign diseases. The exposures ranged from 180 R to 6,000 R with an average of 600 R. The latent periods averaged 8.6 years, were often less than five years, and in 12 cases there were thyroid tumours at birth which later proved to be carcinoma.

109. In the prospective survey of Pifer *et al.*[27] (see tables XI and XVI and paragraphs 57 and 58 for description of survey) of infants X-irradiated therapeutically for "thymic enlargement", 8 cases of thyroid cancer were found in Series I among patients followed from thirteen to thirty-four years, as compared with 0.09 case expected on the basis of the "natural" incidence. The relative risk was 88.9. In Series I, 21 cases of thyroid adenoma were found, and 0.9 was expected, with a ratio of 23.3. The mean exposure for Series I was 329 R.

110. In Series II, with patients followed only from three to twenty years, only 1 case of thyroid carcinoma was found, and 0.01 case was expected. The mean exposure for Series II was 126 R.

111. The 9 cases of thyroid carcinoma in the two series combined were associated with cumulative exposures ranging from 156 R to 1,092 R, with a mean of 598 R. Seven of these cases had been irradiated with combined anterior and posterior port arrangements, 1 anteriorly only, and in 1 case the port arrangement had not been ascertained. The 21 cases of thyroid adenoma were associated with cumulative exposures ranging from 144 R to 756 R, with a mean of 372 R. The percentages of these adenoma cases in the various exposure positions were similar to those for the carcinoma cases.

112. Toyooka *et al.*,[28] in analysing the data of Pifer *et al.*,[27] found that the incidence of thyroid tumours was considerably higher when a dose was given half anteriorly and half posteriorly than when the same dose was given from an anterior approach only. Including additional thyroid neoplasms found between 1960 and 1964, it was found that 29 of the total of 34 thyroid tumour cases (malignant and benign) occurred among 472 children treated by combined anterior and posterior

approaches, whereas only 5 of the tumour cases developed in the 2,111 children treated anteriorly only.

113. Attempts to demonstrate a dose dependence for these major positional groups were unsuccessful. A decision cannot now be made as to whether the high tumour incidence in children treated anteriorly and posteriorly was a consequence of port position, of statistical variation, or of other factors. The possibility has been demonstrated that the posterior approach, with its attendant difficulties, could have resulted in exposure of larger regions of the neck and head, including the pituitary gland, than was the case when the anterior approach alone was used. In this connexion, there is uncertainty in this and other surveys of children irradiated for "thymic enlargement" as to the extent of the inclusion of the thyroid gland in the radiation beam in many of the patients. Of importance in this study are the facts that many of the older children (irradiated in earlier years) were given relatively large doses to relatively large areas, often with posterior as well as anterior position of ports, and with greater X-ray energies, numbers of treatments and total periods of treatment, as compared with younger children (more recently irradiated).

114. Toyooka *et al.*,[29] in a report of clinical aspects of these thyroid tumour cases, indicated an equal sex distribution of adenomas, but a greater frequency of carcinomas in females. The mean exposure in carcinoma cases was almost three times that for the entire group, and the mean exposure for adenoma cases was almost double that for the whole group. The average latent periods were 16.3 years for carcinomas and 18.2 years for adenomas. There was no relation between latent period and exposure.

115. Saenger *et al.*[24] reported a prospective study of 1,644 patients under sixteen years of age who had received X-ray therapy to the head, neck or chest during the period 1932-1950 for benign conditions, and of 3,777 untreated siblings. Irradiation for "thymic enlargement" accounted for 33 per cent and irradiation for cervical adenitis for 26.9 per cent. Twenty-one per cent of the sample received radiation therapy for two or more presumably unrelated conditions. Exposures ranged from $<$ 50 R to 5,000 R, with 62 per cent receiving less than 400 R and 72.5 per cent receiving less than 600 R. Eleven cases of thyroid cancer were found among previously treated cases who were under twenty-three years of age at the time of cancer development, and 0.12 case was expected, giving a relative risk of about 91.

116. No one of the surveys on the incidence of thyroid cancer among irradiated subjects makes it possible to obtain dose-effect regression. Because of the small number of cases in any individual survey only one point of the dose-response curve can be determined from each of them. Crude risk estimates, however, can be obtained for a number of surveys by determining the slope of the straight line connecting the origin with the points obtained when the observed incidences (cases per man year) are plotted against exposures. The risk estimates are summarized in table XVI.

117. A single straight line can be fitted through the incidences observed in surveys of children when plotted against exposures. Its slope indicates that the rate of increase of the incidence with exposure is 0.9 cases/10^6/y/R. Taking into account the statistical uncertainty of the data and the probably larger uncertainties of the dosimetry, it appears that the joint risk estimate may be between 0.5 and 1.5 cases/10^6/y/R. The estimate is based on an average follow-up time of about sixteen years and is valid for acute exposure of children only in an estimated exposure range of 100 to 300 roentgens.

118. Analogous joint estimates had been obtained by Beach and Dolphin[138] through a different method of estimation and on the basis of more limited and partly different data. Their risk estimate (35 cases/10^6/rad) is a lifetime risk estimate. Assuming that the period of risk for cancer of the thyroid is between fifteen and twenty years, Beach and Dolphin's estimate is slightly higher than the one given in the previous paragraph. Differences in method and in material can easily account for the discrepancy.

119. The validity of an estimate of risk such as is given here is limited, like all empirical estimates, to the range of exposures from which it has been derived—in the present case between 100 and 300 R. It also suffers from the fact that the results were obtained in children irradiated for medical reasons and may therefore be different from the estimate that would apply to a random sample of the population. Finally, the uncertainties in dosimetry are high. Doses have probably been overestimated, thus slightly lowering the risk estimate.

Thyroid neoplasms in patients given I^{131}

120. In 1962 Sheline *et al.*[75] reported on a group of 256 patients with diffuse hyperthyroidism (non-nodular thyrotoxicosis) treated with I^{131} between 1946 and 1953. Eight patients (3.12 per cent) developed multiple nodules in the thyroid glands between five and eleven years after therapy and then had surgery. The nodules occurred in six of eighteen patients (33.3 per cent) under 20 years of age at the time of treatment, and in two of 238 adult patients (0.84 per cent). The ages at time of treatment in these tumour cases ranged from 2.66 to 29 years. One of the children showed evidence of thyroid carcinoma of low grade malignancy.

121. Aside from the above case, no association between I^{131} treatment for thyrotoxicosis and thyroid cancer has been reported.

IV. Neck tumours (excluding thyroid) after therapeutic irradiation

122. Takahashi *et al.*,[58] in their retrospective survey of human cancer in relation to medical exposure in Japan, found 906 cases of cancer of the neck (excluding thyroid cancer), namely, cancer of the pharynx, larynx, root of tongue, cervical oesophagus, parotid gland, etc. Of these, eleven (1.21 per cent) had histories of therapeutic irradiation of the neck, compared with a control irradiation frequency of 8 out of 1,770 (0.45 per cent). The difference was significant at the 5 per cent level and gave an over-all relative risk of 2.7.

123. In table XVII are presented the relative risk values for neck cancer at various ranges of estimated exposure. The relative risk is only 1.22 at the 500-2,000 R range and increases to 4.41 for the 6,000-8,000 R range. The risk of radiation-induced cancers of the neck other than thyroid cancers seems to be less than that for radiation-induced thyroid cancer.

124. These data suggest that relatively large exposures are required to cause substantial increase in incidence of neck cancers other than thyroid cancer. This is in accord with the observation by Goolden[76] in his review of pharyngeal and laryngeal cancers following radiotherapy (which in 75 per cent of patients was given for thyrotoxicosis) that few cases did not show signs of

severe radiation damage to the skin or subcutaneous tissues long preceding the appearance of the cancer. It should be noted that the severity of skin changes depends on a number of radiological and temporal factors.

125. Pifer *et al.*,[27] in their study of 1,451 children treated for thymic enlargement between 1926 and 1946 with exposures averaging 329 R found 3 cases of salivary gland cancer up to 1960, compared with 0.05 case expected, and compared with 0.09 case expected in 2,073 sibling controls and none observed.

V. Skin tumours after therapeutic irradiation

126. Takahashi *et al.*,[58] in their survey of human cancer in relation to medical exposure in Japan noted the increase in relative risk of skin cancer with the exposure received (table XVIII). As in the case of thyroid cancer, though the rising trend is apparent, limits are very wide owing to the paucity of cases.

127. The over-all relative risk was 6.0, with limits 16.3 and 2.2. With an average excess radiation of 240 R in the cancer group the relative risk per roentgen is 2.6 per cent. Most instances of radio-therapy probably involved fractionated exposures and these risk estimates may not apply to single exposures.

128. Clinical and occupational experience suggests that the risk of cancer of the skin is low and that radiation-induced skin lesions usually precede the development of cancer. It may well be, however, that, as the observations are not based on well designed surveys, radiation-induced cancers are recognized as such mainly because of the existence of previous lesions.

129. Two studies have shown the occurrence of skin cancer in 10 per cent[77] and 28 per cent,[78] respectively, of patients with chronic radiation dermatitis. Since the latent period may vary from three to as long as forty-eight years or more,[79] those percentages may reflect incomplete ascertainment. The dependence of the frequency and seriousness of radiation dermatitis on dose has not been studied quantitatively and would in any case complicate the establishment of dose-effect relationships for cancer of the skin. No increase in incidence of skin cancer has been noted yet among the survivors of Hiroshima and Nagasaki.

VI. Bone tumours

Bone tumours after therapeutic irradiation

130. Most of the few cases of bone sarcoma that have been reported after radiation therapy have arisen in areas of bone containing previously either a benign tumour or chronic osteomyelitis.[80] In some instances, however, the site of origin was normal prior to irradiation. Reports of radiation-induced osteogenic sarcoma have in some cases indicated substantial radiation damage of bone and/or marrow persisting before cancer development, while in other cases this has not been detected. The lowest exposure thought to have caused an osteogenic sarcoma[81] is, at the present time, about 3,000 R. Most other reported cases have received larger exposures, usually between 4,000 and 7,500 R, sometimes greater.

131. However, Pifer *et al.*[27] found 9 osteochondroma cases (1.2 expected) up to 1960 in 1,451 (Series I) children treated for thymic enlargement (from 1926 to 1946) with exposures averaging 329 R, and 2 cases of osteochondroma (0.26 expected) up to 1960 in 1,358 (Series II) children so treated (from 1940 to 1957) with exposures in the same range but with a mean of 126 R. The relative risks are 7.5 for Series I and 7.7 for Series II, representing increases per R in the vicinity of 2.0 and 5.3 per cent, respectively. However, it should be noted that all of the 6 cases of osteochondroma given both anterior and posterior treatments (Series I) occurred within the tissues in the primary X-ray beam, whereas 4 of the 5 cases of osteochondroma observed in children irradiated anteriorly (Series I and II) arose in tissues outside the primary beam. In the sibling control groups, 1 case was observed in Series I (1.53 expected), and no case was found in Series II (0.66 case expected).

Bone tumours in persons with radium body burdens

132. Hasterlik *et al.*[82,83] have extended and confirmed the results of earlier surveys which indicated a strong correlation between the frequency of development of bone tumours and the skeletal content of radium. They reported a study of 264 persons sought out and measured for radium content in the Chicago area who had been formerly employed in the radium watch dial industry (219) or as radium chemists (4), or who had received radium as a form of medical therapy (41). With respect to watch dial painters, this study concerned itself almost exclusively with those women whose occupational history antedated 1925. Detailed radiographic studies of the entire skeleton were completed in 236 of the 264 persons. Of the 264 persons measured for radium, there were 23 (8.7 per cent) with a body burden of < 0.001 μCi Ra^{226}, 36 (13.6 per cent) with 0.001—0.01 μCi, 102 (38.4 per cent) with 0.01 — 0.1 μCi, 62 (23.5 per cent) with 0.1 — 1.0 μCi, and 41 (15.5 per cent) with > 1 μCi. The frequencies of different body burdens and the number of cases of bone malignancy are given in table XIX.

133. Three of the 61 radiographed persons (including 43 dial painters) in the 0.1 to 1.0 μCi range (4.9 per cent) revealed malignant neoplasms of or associated with the skeleton. Of the 40 radiographed persons (including 19 dial painters) containing above 1 μCi, 14 (35 per cent) had such malignant neoplasms. Of the 17 neoplasms, 12 were bone sarcomas (0.45 to 6.8 μCi), and the others were epithelial and other neoplasms of mastoid and paranasal sinuses (0.89 to 4.7 μCi). The bone sarcoma case at 0.45 μCi, however, was found to be a person with an exceptionally rapid metabolism and therefore a higher original burden than this figure would indicate.[84]

134. Analyses of these data suffer from the fact that the determinations of radium content of the body have been done at least thirty-six years after the acquisition of the radio-active material. At the present time, the extrapolation of these burdens of radium to radium burdens at early times is difficult and carries large factors of uncertainty. The dial painters may, in addition, have been exposed to substantial gamma doses over the period of their employment at this work. Furthermore, there is great uncertainty as to the relevant radiation dose and its target in terms of production of osteosarcoma, e.g. integration of radiation doses to whole skeleton, to some unit volume of bone, etc. The radiation doses to different units or components of bone vary greatly.

135. However, tentative and very rough estimates of relationships between incidence and body burden have been drawn by Hasterlik[82] who analyzed data in two body burden ranges. In the range of 1 to 10 μCi there was

a total of 41 persons with about 1,300 man years irradiation experience and 14 cases of malignancy. The risk of malignancy per man year of exposure in this group is therefore about 1.06×10^{-2}. In the group of 62 persons (2,200 man years irradiation experience) in the 0.1 to 1.0 μCi body burden range, with 3 cancer cases, the risk is about 1.34×10^{-3}.

136. On the basis of the assumed initial intake of radium, it can be calculated that the risks of development of bone tumours in the two groups are 22 and 33×10^{-6} cases per year per microcurie intake, respectively. The selection of midpoints in the two content ranges for these calculations involves certain assumptions concerning the distribution of patients with different body burdens within the two ranges.

137. Assuming as the Committee did in the past that the cells lining bone surfaces are those that give rise to malignancies when irradiated, crude estimates of risk per unit dose can be obtained from these data and may be taken to be about 4 cases/10^6/y/rad, or a figure of the same order of magnitude as that for leukaemia and thyroid cancer following irradiation from external sources. However, comparison of the figures may be quite misleading in this case, since it is not known how much of the dose that is delivered over several decades is, in fact, responsible for the induction. Also, the doses are average values to the cells lining bone surfaces and do not take account of the highly inhomogeneous distribution of the absorbed dose. Furthermore, the estimate of risk of bone tumour is based on experience within two broad dose ranges only and therefore gives no information on the shape of the dose incidence relationship nor on the effects of lower doses. It may be noted that the general incidence of primary bone tumours is reported to be about 10 cases/10^6/y and may, in fact, be somewhat lower.

138. In these studies[82] only 2 of the 264 patients showed (by X-ray spectroscopy) evidence of the presence of mesothorium as well as of Ra^{226}. This situation is in contrast to the patients studied by other groups in the United States, since the dial painters in other groups ingested paints containing varying mixtures of Ra^{226}, radio-thorium, and/or mesothorium. In the study by Hasterlik *et al.*, most of the dial painters were unselected cases but several of the other subjects were not.

139. Aside from the study described above, Hasterlik *et al.*[83] have found 2 cases (death certificates) of acute myeloid leukaemia in radium patients, one of which was confirmed by their study of the original blood smear made shortly before the patient's death in 1931.

140. Barrer *et al.*[127] have given a preliminary summary of the data from the first 150 cases studied in a large survey in the State of New Jersey, United States. Three (2 per cent) developed osteogenic sarcomas, associated with body burdens of 0.6, 0.9, and 1.67 μCi Ra^{226}. There was 1 case of chronic myelogenous leukaemia associated with a body burden of < 0.0042 μCi Ra^{226}. Of 190 death certificates for deceased radium cases, 64 (33.7 per cent) made mention of malignancies, of which 16 cases were of bone and periosteum (8.4 per cent) and 3 were tumours of the nose and of the paranasal sinuses (1.5 per cent).

141. At the Massachusetts Institute of Technology[85] there have been studies of persons with skeletal burdens of radium or radium-mesothorium mixtures resulting from occupation (dial painters, chemists, physicists), from parenteral injection of radium solutions and from ingestion of radium or radium-mesothorium mixtures.

142. Because many of these patients are exposed to substantial amounts of mesothorium (Ra^{228}) the total radiation from decay of the mesothorium chain has been estimated and the equivalent in terms of radiation from Ra^{226} has been used, the data being expressed in μCi minimum pure radium equivalent (MPRE).

143. In December 1963 Evans *et al.*[124] reported on 237 subjects (of the more than 350 under study) who had had radiological examinations. Of these, 76 cases showed radiological abnormalities associated with body burdens ranging from 0.23 to 44.0 μCi minimum pure radium equivalent (MPRE). Excluding dental abnormalities, which were almost universal in these 76 cases, there were 18 persons with no evidence of abnormality or disease (including body burdens as high as about 3 μCi MPRE), 19 cases of spontaneous fracture (0.6 to 20.0 μCi), 23 cases of osteogenic sarcoma (0.6 to 24.0 μCi), 8 cases of cancer of the paranasal sinus or mastoid (1.0 to 10.0 μCi), and 3 cases of osteomyelitis of mandible or maxilla (15.0 to 44.0 μCi).

144. More recently, Maletskos *et al.*[128] summarized the results of the same survey covering 361 subjects (88 males and 273 females) with skeletal burdens of Ra^{226} and Ra^{228}. Two-thirds of the subjects were dial painters, some of whom had received Ra^{226} alone and others a mixture of Ra^{226} and Ra^{228}. The remainder were persons contaminated as a result of laboratory work or by ingestion or injection of the radio-active materials. Most of the cases studied earlier (before 1957) came to attention because of the symptoms they developed, while the majority of cases studied more recently were investigated after being found by search. There were 299 found by search and 62 by symptoms. The main exposure period of the dial painters was from 1918 to 1925, although a few started as early as 1915. Fourteen of the cases had originally been examined by Martland.[129-131]

145. With regard to the data of Maletskos *et al.*,[128] one of the authors has stated:[86] "At the present stage of the statistical study of these data . . . , no clinically significant signs or symptoms are seen with residual or terminal body burdens of <0.5 μCi Ra (MPRE). With higher residual body burdens, beginning in the neighbourhood of 1 μCi Ra and extending to about 25 μCi Ra, the fraction of the total number of cases which involve either of these types of malignancies (osteogenic sarcomas and carcinomas of the paranasal sinuses and mastoids) amounts to roughly ¼." This statement need not be taken to be in conflict with reports of radiographically observed changes in fine structure of bone such as appear in table XXII associated with burdens below 0.1 μCi. Data on the percentages of subjects in various body burden ranges showing osteogenic sarcomas or cancers of paranasal sinuses or mastoid are not yet available for publication.

VII. Thorium-related neoplasms

146. Thorium dioxide in a colloidal suspension, known as Thorotrast, was widely used in diagnostic radiology between 1928 and 1945, primarily for the visualization of the liver, spleen, cerebral arteries and cavities of the body. The thorium dioxide content of Thorotrast is usually about 25 per cent by weight, but may vary considerably. After intracavitary or extravascular injection, Thorotrast remains largely at the place of injection and may be carcinogenic there. After intravascular injection, the thorium dioxide particles are deposited in phagocytic cells of the reticulo-endo-

thelial system, and by this means they are concentrated in liver and spleen. Immediately a redistribution begins which continues slowly for years and results in change of position of the particles in the organs of concentration and in increasing amounts in the connective tissues of the body.

147. In 1962 Dahlgren[88] reviewed the literature on tumours following administration of Thorotrast. He listed 68 cases of malignant tumours that had been reported, including 3 sarcomas at the site of extravascularly deposited Thorotrast (volume injected 20 ml in 1 case, unknown in 2 cases) with latent periods of six to twenty-five years; 26 carcinomas and sarcomas in a variety of organs (kidney, breast, eyelid, maxillary sinus, bronchi, peritoneum, ovary, seminal vesicle) after deposition of Thorotrast in natural cavities (volume injected known in 4 cases, 10, 24, 30 and 30 ml, respectively) with latent periods ranging from ten to thirty-five years; 33 malignant tumours (sarcomas and carcinomas) of liver and bile-ducts after systemic injection of Thorotrast (volume injected known in 12 cases: 3 cases at 20, 34 and 70 ml, respectively; 5 cases at 75 ml; and 4 cases at 80 ml) with latent periods ranging from three to twenty-four years; and 6 cases of malignant tumours in various organs (colon, lung, spleen, kidney) after systemic injection of Thorotrast (only one known injected volume, 15 ml) with latent periods ranging from thirteen to twenty-four years. The mean latent period for the total cases is 17.7 years, with mean latent periods in the four subgroups above ranging from 16.7 to 18.3 years.

148. In 1963 Blomberg *et al.*[89] reported a study of patients who had received Thorotrast injections in cerebral angiography during the years 1932-1947. They found 6 cases of primary malignant liver tumours (5 hepatic cancers and 1 haemangio-endothelioma) in 908 patients (about 0.66 per cent). Information on the amount of Thorotrast injected was available for 436 of the patients and for 3 of the 6 cases of liver cancer. The 413 patients who had received less than 30 ml showed no tumours of liver, while 18 patients receiving between 30 and 40 ml showed 1 case of liver cancer and 2 among 5 patients receiving more than 40 ml had liver cancers. Of the remaining 3 patients who had received more than 40 ml, 2 died during the first year after the injection and the fifth patient was not traced. The latent periods for the 6 liver cancer cases found in this study ranged from nineteen to twenty-seven years, and the longest observation period was twenty-nine years. Blomberg *et al.*[89] indicate that the order of magnitude of the mean alpha radiation doses to the liver and the spleen after intravascular injection may be hundreds of rads per year.

149. According to Looney,[91] the accumulated mean radiation dose to the liver in Thorotrast-injected patients who developed Kupffer cell sarcoma of the liver (mean latent period 15 $\pm$ 7 years) was of the order of 1,000 to 1,500 rads. The estimated accumulated dose to the liver of one patient who developed an hepatic tumour only three years after 20 ml of Thorotrast was about 100 rads.

150. However, it should be emphasized that there are enormous difficulties involved in attempts to determine dose parameters and the doses relevant to cancer incidence for thorium dioxide. After intravascular injection, the distribution of the material, and therefore of the radiation as well, is extremely non-uniform and changes with time. The radiation, consisting of alpha-, beta-, and gamma radiation in the ratio 90:9:1,[132] is confined largely to a very short radius from the particles of origin and is absorbed to variable degrees by the particles or particulate agglomerations of origin themselves. It should also be mentioned that irritation of tissues by the particles, apart from effects of radiation, cannot be discounted as a factor in the pathogenesis of tumours. Data from experimental mammals,[133] using non-radio-active zirconium hydroxide in colloidal suspension, give some support to that view.

151. According to Wald *et al.*,[16] various case reports and follow-up studies have resulted in the accumulation of about ten instances of leukaemia following thorium injection. In 6 cases for which detailed data were available, the latent period was 12 $\pm$ 7 years. A causal relationship has not been established between leukaemia and Thorotrast injection.

VIII. Lung cancer in miners

152. A review of earlier studies of lung cancer related to radiation in miners has been published by Stewart and Simpson.[92]

153. In 1926 Rostoski *et al.*[93] reported that in miners (pitchblende) in the Schneeberg region of Saxony, dying between 1921 and 1926, about 50 per cent had carcinoma of the lung, with the majority originating in large bronchi, while the incidence of lung carcinoma in the control groups was not noteworthy.

154. Pirchan and Sikl[94] found that about 50 per cent of the miners (pitchblende) of Jachymov, dying in 1929 and 1930, also had carcinoma of the lung. Observations of these miners up to 1939 confirmed earlier findings.

155. Although these mines contain several potentially carcinogenic materials including arsenic and cobalt, these elements are also found in many mines where there is no particularly high incidence of carcinoma of the lung. Radium itself, as a constituent of the airborne dust in the mines, has been suspect, but measurements of the radium content of the lungs of deceased miners have shown no substantial difference from that in the average human of middle age. Silicosis and silicotuberculosis have been considered as contributing causes since at Jachymov nearly half the miners died of either silicosis, tuberculosis, or a combination of the two, and pneumoconiosis was often found at autopsy in the Schneeberg miners as well.

156. The opinion is now generally held that airborne radon in the mines may probably be the most essential factor in the production of lung cancer. The Jachymov and Schneeberg mines have radio-active air and radio-active ore in common.

157. According to Bale[95] the major portion of the radiation dose from Rn^{222} stems from the decay of the short-lived daughters (RaA through RaC') that are carried by the atmosphere in varying degrees of equilibrium with the radon parent and are trapped in the lungs. Radon itself and the daughter products of its decay while in the lungs contribute only about one part in a thousand of the total dose to the bronchial epithelium.

158. Chamberlain and Dyson[96] concluded from experiments that the major portion of the radiation dose to the trachea and large bronchi was attributable to the fraction of RaA preformed in the inhaled atmosphere and unattached to dust or condensation nuclei.

159. Evans and Goodman[97] summarized data on the radon content of the air in the Schneeberg and Jachymov

mines and concluded that the average radon concentration to which the miners had been exposed was about 2.9×10^{-9} Ci/l. They concluded also that prolonged breathing of an atmosphere containing about 10^{-9} Ci/l of radon may have been responsible for the increase in the incidence of lung cancer observed in the Schneeberg and Jachymov miners.

160. In 1945 Mitchell[98] considered it possible that the average radon concentration was higher in the years before the hazard was recognized and regarded a level of about 1.5×10^{-8} Ci/l as a reasonable estimate of average concentration.

161. Assuming a linear relationship between concentration of Rn^{222} and duration of exposure and the lung cancer incidence, and using the Schneeberg and Jachymov experience, Evans and Goodman[97] in 1940, and Mitchell[98] in 1945 suggested MPC (maximum permissible concentration) values for human exposure to airborne Rn^{222} and daughters of 10^{-11} Ci/l and 5×10^{-11} Ci/l, respectively. From the literature Mitchell concluded that the approximate 50 per cent incidence of lung carcinoma in the Jachymov miners was associated with employment of the order of ten years and exposure during working hours to a concentration of radon not less than 2.5×10^{-8} Ci/l. To reduce the incidence of lung carcinoma to about that of the community as a whole, i.e., to the order of 0.1 per cent for ten years, the concentration of radon in the air would have to be reduced to 5×10^{-11} Ci/l.

162. Sikl[99] in 1950 stated that in his experience the average duration of exposure associated with carcinoma of the lung was seventeen years, the shortest thirteen years.

163. Jacoe[100] in 1953 in his search for airborne radon in tunnels and non-uranium mines in Colorado, mostly in areas of little air movement, found a range of concentration from zero (instrumental) to one reading of 2.1×10^{-9} Ci/l. Most of the samples were in the range of 5×10^{-10} to 10^{-11} Ci/l.

164. Harris[101] in his examination of atmospheres in zinc, iron and talc mines in New York, where ventilation was low, found radon concentrations ranging from 4×10^{-11} to 10^{-12} Ci/l.

165. Oosthuizen *et al.*[102] in their measurements of radon concentrations in the air of the gold mines of the East, Central and West Rand, South Africa, found in areas where the uranium content of the ore was too low for economic extraction, average radon atmospheric concentrations in the range from 2.5×10^{-11} Ci/l, to 5×10^{-11} Ci/l, with measured values as high as 2×10^{-10} to 3×10^{-10} Ci/l. In mining areas where the extraction of uranium was economic, radon concentrations in the mines were in the range from 10^{-10} to 5×10^{-10} Ci/l. These authors reported that the incidence of lung cancer in a large group of underground workers was investigated in two independent surveys, and in each the incidence was similar to that observed in a comparable age group of the population at large.

166. Yourt[103] found in dead-end drifts in a number of non-uranium hard-rock mines (gold mines) in Northern Ontario radon concentrations with a median in the range of 1.2×10^{-11} to 1.5×10^{-11} Ci/l.

167. No gross excess of lung cancer has been noted in the miners employed in non-uranium mines in Colorado, New York State or northern Ontario. However, there apparently has not been a study carried out to detect small significant increases in incidence.

168. Earlier calculations of radiation dose received by the bronchi of the Jachymov miners were made by Mitchell,[98] who concluded that the epithelial cells of the main bronchi received about 0.13 rad of alpha radiation in eight hours of exposure, and by Evans,[104] who calculated that the total dose to the bronchus during the duration of underground exposure (average seventeen years) amounted to about 600 rads.

169. Later, Bale,[95] taking into account the short-lived daughter products preformed in the radon-containing atmosphere, calculated the dose rate to the epithelial layer of bronchial tissue from 10^{-10} Ci Rn^{222}/l, 10^{-10} Ci RaA/l and 5×10^{-11} Ci RaC'/l as being 1.0 rad/40-hour week. In comparison with previous calculations of the dose from the same radon concentration, this value is about 2,000 times that predicted by Evans and Goodman[97] in 1940, about 300 times that predicted by Mitchell[98] in 1945, and about 100 times that predicted by Evans[104] in 1950.

170. De Villiers and Windish[105] reported that 23 of the 51 deaths (45 per cent) among miners with one or more years of underground experience in the fluorspar mining community of St. Lawrence, Newfoundland, during the ten-year period 1952-1961 were due to primary lung cancer, chiefly near the hilum of the lungs. A shift in the average age at death of the lung cancer cases to involve younger age groups, and an association between age at entry into risk and age at death, were also observed. The number of deaths expected as a result of malignant neoplasms of trachea, bronchus and lung among the total of 71 deaths from all causes in all St. Lawrence miners during 1952-1960, based on 157 such deaths among 15,264 deaths (less those among St. Lawrence miners) from all causes in males of Newfoundland, was 0.73. The 21 observed cases among the 71 miners dying of all causes was 28.8 times this expected number. The ratios for the four ten-year age groups between 25 and 64, inclusive, were 43.2 (25 to 34 years), 10.6 (35 to 44 years), 16.0 (45 to 54 years), and 8.0 (55 to 64 years). Considerable numbers of deaths from tuberculosis and pneumoconiosis were also found.

171. The most outstanding environmental finding in the mines at St. Lawrence has been the discovery of concentrations of radon and daughters in air, well in excess of suggested MPC levels. On the basis of these concentrations and other considerations, it was suggested that underground workers were probably exposed to an average potential alpha energy to complete decay of between 2.5 and 10 times the previously suggested working level of 1.3×10^5 Mev per litre of air for a forty-hour working week.[134] These levels were measured in mines in which no radio-active ore bodies had been found. The mine water was regarded as the source of the radon.

172. The more important findings relating to St. Lawrence, Jachymov and Schneeberg, and to the uranium mines of South Africa and the United States, are compared in table XX which gives data on radio-activity in various mines and the associated incidence of lung cancer. The incidence of lung cancer at St. Lawrence as a percentage of miner deaths ranges between 33.3 per cent (23 of 69 underground miner deaths 1933-1961) and 45.1 per cent (23 of 51 underground miner deaths 1952-1961).

173. Wagoner *et al.*[125] reported recently on a study of the cancer mortality pattern of a group of United States uranium miners and millers for the thirteen-year period 1950-1962 and compared their age-race-cause-

specific mortality experience with that of the general male population of the Colorado Plateau area. Among white uranium millers, total- and cause-specific mortality did not differ significantly from that expected. Among white uranium miners, 218 deaths were observed as compared with 148.7 expected ($P < 0.01$). Categories in which death significantly exceeded that expected were: (*a*) respiratory neoplasms among uranium miners with five or more years underground experience (11 observed as compared with 1.1 expected or a relative risk of 10); (*b*) "all other causes", in the same group of miners, a reflection of pulmonary fibrosis and its complications; and (*c*) accidents, particularly in mines, regardless of type of employment or duration of underground mining experience. The tenfold increase in respiratory cancer was not attributable to age, smoking, heredity, urbanization, self-selection, diagnostic accuracy, or prior hard-rock mining or other ore constituent, including silica dust. The evidence presently available implicates airborne radiation in the genesis of this increase in respiratory cancer.

174. The data available in miners from Jachymov, Schneeberg, the Colorado Plateau and the St. Lawrence region strongly suggest that cancer of the lung can be induced by inhaled radon and its daughters. Risk estimates cannot, however, be obtained from these groups because only the relative frequency of lung cancer among all cases of death is known, rather than the mortality from lung cancer in the population of miners.

IX. Over-all incidence of neoplasms after total-body irradiation

Japanese A-bomb survivors

175. The 1962 report discussed the report of Harada and Ishida[106] on the incidence of neoplasms among survivors of the Hiroshima A-bomb during the period April 1957-December 1958. The data were obtained from the tumour registry and were not based on the Atom Bomb Casualty Commission (ABCC) closed sample. The incidence of neoplasms varied inversely with distance from hypocentre. The "doubling dose" for cancer incidence was estimated as having been received at about 1,300 metres from hypocentre, where the dose was approximately 400 rads.[8]

176. Studies of the mortality of A-bomb survivors recently reported[107] show that in a subsample of 20,000 persons (ABCC Medical Subsample, Selection I, 1950-1958) there is thus far no evidence of a higher general mortality in the more heavily irradiated groups. When mortality from specific causes was studied, the well-known leukaemogenic properties of radiation were clearly reflected, but for no other causes were radiation effects seen. In this study the non-exposed group was deemed unsatisfactory as a control, at least for the periods in question, since it was characterized by abnormally low mortality in relation to both the exposed survivors and the Japanese population generally, and deaths from tuberculosis and cancer were notably deficient. Therefore, the control of this study relied on comparison of persons exposed at different distances from the hypocentre.

177. Zeldis *et al.*[57] reported recently on the Hiroshima and Nagasaki tumour registry study of cancer incidence covering a further twelve months in Hiroshima in addition to the twenty months already reported by Harada and Ishida[106] (May 1957-December 1959), and on the first thirty-six months in Nagasaki (April 1958-March 1960). Neoplasms diagnosed prior to the beginning of these studies were eliminated, and analyses were based on the more restricted, but known, Life-Span Study population rather than on the total city population.

178. In table XXI are shown crude incidence rates and age-sex-adjusted rates of malignancies (excluding leukaemia) per 100,000 persons. The indicated excess of malignancies in the most proximally exposed group in Hiroshima is not so large as that previously reported on a city-wide basis by Harada and Ishida,[106] but the gradient of incidence with exposure distance is statistically significant. In Nagasaki, with a considerably smaller number of collected cases, variations with exposure distance are not significant. For reasons not understood, the incidence in the non-exposed group in Nagasaki (particularly in males) is significantly greater than in exposed groups.

179. Figures now available[137] allow some comparison to be made between the number of cases of leukaemia and that of all other forms of cancer which may have been induced by radiation. During the years 1950-1959, 36 more deaths from leukaemia (standard error 6.4) occurred amongst the groups of people who had been exposed within 1,400 m of the hypocentre at Hiroshima and Nagasaki than was to be expected from the mortality amongst those exposed to lower doses of radiation at between 1,400 and 2,000 m. During the same period, 30 more deaths from other forms of malignant disease (standard error 13.6) occurred in the former group than were expected on the basis of mortality in the latter group. In this comparison, therefore, the number of deaths from all malignancies other than leukaemia, in excess of those in the comparison population, was 0.8 (standard error 0.4) times the excess number of deaths from leukaemia occurring in the same population and during the same period.

180. It seems probable that the mean latency for radiation-induced leukaemia is less than that for other forms of radiation-induced malignancy for which information is available and, therefore, that within the period of this survey (extending to thirteen years after irradiation) the proportion detected of all deaths that would finally occur would be greater for leukaemia than for other malignancies. For this reason the value of the ratio may be expected to rise somewhat in coming years and cannot yet be assessed accurately. Moreover, these data are based on mortality statistics and not on morbidity records, and so may not accurately reflect even the present incidence of disease. It already seems evident, however, that leukaemia (in acute forms and the chronic myeloid form), which normally accounts for only 2 per cent of all deaths from malignant disease, is increased in its incidence by radiation received under these circumstances, by a much larger factor than is the total of all other forms of malignant disease.

Populations exposed to high levels of environmental radiation

181. Gianferrari *et al.*[111] made a survey of births, deaths and other relevant variables in some communities of the Cervo Valley, Italy, where the background radiation is higher than normal (average total exposure of gamma radiation 15 R per thirty years), and in a nearby area similar geographically, socially and economically except for one-fifth (3 R per thirty years) of the background radiation level. The average uranium content (as U_3O_8) in various alimentary sources in the respective low background and high background areas was:

soil 1.0, 20.8 mg/kg; drinking water 0.06, 0.24 μg/l; vegetables 0.3 17.7 mg/kg; and fodder 0.4, 18.4 mg/kg. In the high radiation area the observed proportion of deaths from cancer was higher than expected in every age group. However, the increase was statistically significant only in the sixty-one to eighty-year age group.

CHILDREN EXPOSED *in utero* TO DIAGNOSTIC IRRADIATION

182. In the first reports of the retrospective study by Stewart *et al.*[30,31] of the relationship of pre-natal diagnostic X-ray exposure to subsequent development of leukaemia and other malignancies in children dying under ten years of age, it was found that more of the mothers of children dying of cancer had received abdominal X-ray examination during the relevant pregnancy than had mothers of control (living) children. Of the twenty mothers X-rayed in the first half of pregnancy, eighteen were mothers of children dying of cancer and only two were controls. The ratio of foetal irradiation in cancer cases to controls was 1.7 for deaths up to the age of four years and 2.5 for deaths from five to nine years of age.

183. The frequency of viral infections and threatened abortions was also significantly higher among the mothers of the dead children. X-ray exposures in infancy, acute pulmonary infections and severe injuries were three *post-natal* events significantly increased in children who subsequently died of leukaemia. Excessive maternal age was related to increased incidence of Down's syndrome and increased risk of leukaemia.

184. More recently, in an extension of the survey, Stewart[32] concluded that most childhood cancers and leukaemias were pre-zygotically determined, that the recent increase in incidence of childhood leukaemia was due to the pre-zygotic form, and that the maximum incidence of that form occurred earlier than the maximum incidence of pre-natal leukaemias.

185. MacMahon's prospective study[39] of this problem utilized a study population of 73,243 children born in the years 1947-1954 and the frequency of intra-uterine X-ray exposure estimated from a 1 per cent systematic sample. Abdominal or pelvic X-rays were recorded in 770 (10.6 per cent) of the 7,242 single pregnancies in the sample, and a total of 584 children born in the study sample who subsequently died of cancer before the end of 1960 were identified. There were 85 (15.3 per cent) of the 556 cancer deaths born of "single pregnancies" which had maternal abdominal or pelvic X-ray recorded, as compared with 770 of the 7,242 (10.6 per cent) single pregnancies in the whole 1 per cent samples ($P < 0.05$). After correction for indirect associations with birth order and other complicating variables, it was estimated that cancer mortality was about 40 per cent higher in the X-rayed than in the non-X-rayed members of the study population. This relationship held for each of the three major diagnostic categories: leukaemia, neoplasms of the central nervous system, and other neoplasms.

186. The excess cancer mortality in the X-rayed group was most marked at ages five to seven years, at which time the relative risk was 2.0. The excess risk was apparently exhausted by age eight years. A trend toward higher mortality in the more heavily exposed children was small and not statistically significant. No significant variation with stage of pregnancy at exposure was evident.

187. The most important determinant of the amount of pre-natal X-ray exposure appeared to be birth order. First births had three times as many exposures, and greater doses, than later births. There was little change with birth order after the first birth.

188. In MacMahon's study the ratio of 556 cancer deaths in 7,242 sample births indicates a total cancer mortality rate of $76.8/10^5$ single live births. Since in both the zero to four and the five to nine-year age groups for United States children born in 1950, leukaemia accounts for about half of all deaths, he regarded it as likely that the probabilities of dying from any neoplastic disease during these age intervals were approximately double the values for leukaemia. Applying these probabilities to the population of his study, he estimated that the study population would be expected to yield 388 cancer deaths in the first five years of life and 246 in the second five years (total 634). The observed numbers were 352 and 197, respectively (total 549). Eighteen other cancer deaths occurred at age ten years or older.

189. A deficit of 20 per cent of the expected deaths for the five to nine-year age group can be accounted for to some extent because the population has so far been followed for only three-fourths of the person-years necessary for complete ascertainment.

190. Using an indirect method of standardization, MacMahon calculated that the cancer mortality rate in the X-rayed population, adjusted for the several variables, was 10.31 per 10,000 live births. Using this value, he obtained a relative risk for all cancers of 10.31/7.8 or 1.42, compared to that of 1.52 without adjustment.

191. MacMahon, in estimating relative risk for malignancy from Stewart's data, excluding twins and taking into account Stewart's figure of 1.16 as the measure of bias in mothers reporting, and including all abdominal X-ray during the relevant pregnancy, derived a figure of 1.65, not very different from that derived in his study.

192. Stewart's data, however, indicate no appreciable decline in relative risk even at the highest ages included, whereas MacMahon's data show no increased risk after the age of seven years.

193. Recently, MacMahon and Hutchison[108] reviewed eleven published studies (to September 1, 1962) on the question of relative risk of malignant disease in children from exposure to X-ray *in utero*. The relative risks in five of these studies[21,36–38,109] were less than one, and in six studies[31,33–35,39,110] were greater than one. However, in view of the great overlap in the confidence limits of all eleven studies, they tested the possibility that all studies were consistent with a single risk value and found the maximum likelihood estimate of this common risk value by computing the weighted mean of the eleven observed relative risks. They concluded that there was no inconsistency in the findings of the eleven studies, and that the five studies reporting relative risks less than one all involved small samples with large expected sampling variability. The maximum likelihood estimate of the risk involved is 1.40, and the true value may be expected to be within the range of 1.20 to 1.64 ($P = 0.05$).

TABLE I. INCIDENCE OF LEUKAEMIA IN HIROSHIMA (1946–1962)
(Computed from data of Watanabe[6])

Onset year	Total population Hiroshima			Non-exposed population Hiroshima[a]			Exposed population Hiroshima (within 5,000 metres)			Excess Cases 10^{-5}	Leukaemia deaths all Japan Cases 10^{-5}
	Persons number	Cases No.	Cases 10^{-5}	Persons number	Cases No.	Cases 10^{-5}	Persons number	Cases No.	Cases 10^{-5}		
1946.....	171,204	2	1.17	72,135	1	1.38	99,069	1	1.01	0.00	—
1947.....	222,434	6	2.70	123,607	1	0.81	98,827	5	5.06	4.25	1.07
1948.....	246,134	15	6.09	147,548	4	2.71	98,586	11	11.16	8.45	1.19
1949.....	262,832	21	7.99	164,498	9	5.47	98,334	12	12.20	6.73	1.37
1950.....	285,712[b]	13	4.55	187,610[b]	1	0.53	98,102[b]	12	12.23	11.70	1.47
1951.....	297,758	20	6.75	199,898	3	1.50	97,860	17	17.37	15.87	1.58
1952.....	321,973	17	5.28	224,355	8	3.56	97,618	9	9.22	5.66	1.67
1953.....	339,432	22	6.48	242,055	6	2.48	97,377	16	16.43	13.95	1.91
1954.....	361,367	17	4.70	264,232	4	1.51	97,135	13	13.38	11.87	2.12
1955.....	360,808	22	6.10	263,915	8	3.03	96,893	14	14.45	11.42	2.28
1956.....	382,011	18	4.71	285,360	5	1.75	96,651	13	13.45	11.70	2.41
1957.....	396,730	17	4.29	300,321	7	2.33	96,409	10	10.37	8.04	2.44
1958.....	412,707	21	5.09	316,539	10	3.16	96,168	11	11.44	8.28	2.65
1959.....	426,564	26	6.10	330,638	10	3.02	95,926	16	16.84	13.82	2.67
1960.....	431,285[b]	15	3.48	335,601[b]	11	3.28	95,684[b]	4	4.18	0.90	2.80
1961.....	459,301	22	4.79	363,859	10	2.75	95,442	12	12.63	9.88	—
1962.....	479,379	14	2.92	384,000	6	1.56	95,379	8	8.42	6.86	—
	TOTALS	288	83.19	TOTALS	104	40.83	TOTALS	184	189.84	149.38	

[a] Non-exposed population presumably includes early entrants after detonation.
[b] Figure from census for year indicated.

TABLE II. RISK OF LEUKAEMIA IN HIROSHIMA A-BOMB SURVIVORS[6]
(1946–1962, open population)

Metres from hypocentre	Estimated dose range[a] (rad)	Exposed population	Leukaemia cases	Cases 10^{-5} exposed	Ratio to expected incidence[b]
0–1,500	> 10,000–200	11,839	127	1,072	26.0
1,500–5,000	200– < 1	87,230	57	65	1.6
0–5,000	> 10,000– < 1	99,069	184	186	4.5

[a] Without correction for attenuation by shielding.
[b] The expected incidence is that observed in the period 1946–1962 in the population beyond 5,000 m., namely 41×10^{-5}.

TABLE III. AVERAGE INCIDENCE OF CONFIRMED LEUKAEMIA IN RESIDENTS OF HIROSHIMA AND NAGASAKI IN 12 YEARS (1947–1958) BY CITY OF EXPOSURE AND DISTANCE FROM HYPOCENTRE. ABCC MASTER SAMPLE
(Modified from Brill et al.[7])

Distance (metres) dose (rad)[a]	Hiroshima			Nagasaki		
	No. leukaemia cases	Man-y at risk 1947-1958	Cases 10^{-5} Man-y at risk	No. leukaemia cases	Man-y at risk 1947–1958	Cases 10^{-5} Man-y at risk
0–999 m. (1,400– > 10,000)	20	14,638	1,366	3	5,330	563
1,000–1,499 m. (200–1,400)	39	126,446	308	20	37,758	530
1,500–1,999 m. (30–200)	9	214,629	42	3	44,197	68
2,000–9,999 m. (< 1–30)	21	747,827	28	34	925,653	37
TOTAL	89	1,103,540	81	60	1,012,938	59

[a] Uncorrected for shielding.

TABLE IV. LEUKAEMIA INCIDENCE IN ABCC MASTER SAMPLE IN 9 YEARS (1950–1958) BY RADIATION DOSE (CORRECTED FOR LIGHT SHIELDING) IN HIROSHIMA AND NAGASAKI
(*Modified from Brill* et al.[7])

	Hiroshima				*Nagasaki*			
Dose in rads	*No. leukaemia cases*	*Man-y at risk 1950–1958*	*Cases 10^{-4} Man-y at risk*	*Ratio to expected incidence*[a]	*No. leukaemia cases*	*Man-y at risk 1950–1958*	*Cases 10^{-4} Man-y at risk*	*Ratio to expected incidence*[a]
> 1,280.....	5	3,204	1,561	78	0	387	0	—
641–1,280.....	10	9,999	1,000	50	3	1,341	2,237	112
321–640.....	5	7,623	656	33	2	2,043	979	49
161–320.....	7	21,888	320	16	4	6,408	624	31
81–160.....	7	37,278	188	9	6	12,681	473	24
41–80.....	3	48,798	61	3	0	11,565	0	—
21–40.....	2	48,402	41	2	1	9,981	100	5
0–20[b].....	12	547,839	22	1	9	217,782	41	2
TOTAL	51	725,031	70	3.5	25	262,188	95	4.8

[a] The expected incidence is the estimated yearly incidence in Japan in the period 1950–1958, namely 2×10^{-4}.
[b] Includes A-bomb survivors exposed between 2,000 and 10,000 metres.

TABLE V. INCIDENCE OF LEUKAEMIA (1950–1962) AMONG EARLY ENTRANTS INTO HIROSHIMA AFTER A-BOMB EXPLOSION
(*Modified from Watanabe*[6])

	Cases entered within 3 days	*Cases entered 3–7 days after*	*Cases entered 7–14 days after*	*Cases entered within 2 weeks*
Population.....	25,799	11,001	7,326	44,126
No. of leukaemias developed....	27	5	7	39
Incidence per 100,000 per year[a].	8.05	3.50	7.35	6.79

[a] Average yearly incidence of leukaemia for 13 years (1950–1962) in non-exposed population (beyond 5,000 metres) in Hiroshima, computed from data of Watanabe,[6] was 2.34×10^{-4}.

TABLE VI. INCIDENCE OF DEATH FROM LEUKAEMIA IN PHYSICIANS [16]

Occupation	*Time*	*Place*	*Total deaths*[a]	*Leukaemia deaths*	*Incidence*	*Ratio of incidences radiologists: all physicians*	*General population incidence*	*Reference*
Radiologist.....	1929–43	USA	175	8	4.57%			March[114]
Non-radiologist.....	1929–43	USA	50,160	221	0.44%	10.3:1		
All physicians.....	1933–42	USA	26,788	143	0.53%		0.39%	Henshaw and Hawkins[116]
Radiologist.....	1938–42	USA	95	5	5.30%	10.6:1		Dublin and Spiegelman[117]
All specialists.....	1938–42	USA	2,029	19	0.94%			
All physicians.....	1938–42	USA	12,419	62	0.50%			
Radiologist.....	1944–48	USA	124	6	4.84%			March[115]
Non-radiologist.....	1944–48	USA	15,637	113	0.72%	6.7:1		
All physicians.....	1947–51	USA	11,481	133	1.20%		0.52%	Peller and Pick[118]
Radiologist.....	1949–58	USA	296	11	3.71%			Cronkite[121]
All physicians.....	1949–58	USA	23,393	221	0.77%	4.8:1		
Radiologist.....	1897–56	G. Brit. Eire	463	3	0.65%			Court Brown[113]
Radiologist.....	1938–42	USA	205	8	3.90%			Ulrich[119]
Non-radiologist.....	1938–42	USA	34,626	158	0.44%			
Radiologist.....	1952–55	USA			3.57%	3.6:1		Melville in Schwartz and Upton[112]
Non-radiologist.....	1952–55	USA			1.00%			
Radiologist.....	1930–54	USA			3.65%		0.39%	Warren[120]
Non-radiologist with X-ray.....	1930–54	USA			2.33%		(1950)	
Non-radiologist without X-ray..	1930–54	USA			0.63%			

[a] With known diagnosis.

TABLE VII. MORTALITY AMONG RADIOLOGISTS: DEATHS ATTRIBUTED TO CANCERS OF THE LYMPHATIC AND BLOOD-FORMING TISSUES AND FROM APLASTIC ANAEMIA. ONLY DEATHS OCCURRING BETWEEN THE AGES OF 35 AND 74, INCLUSIVE, IN THE 14-YEAR PERIOD, 1948 TO 1961, ARE INCLUDED [9]

International code rubric	*Principal disease*	*Number of deaths*		*P*[a]	*Mortality ratio (M.R.)*	*95% Confidence M.R.*
		Observed	*Expected*			
200	Lymphosarcoma	4[b]	2.4	> .05	1.7	0.5 to 4.3
201	Hodgkin's disease	1	1.6	> .05	0.6	0.02 to 3.5
202, 205	Lymphoblastoma	1	0.38	> .05	2.6	0.07 to 14.6
203	Multiple myeloma	5	1.01	.004	5.0	1.6 to 11.6
204	Leukaemia	12	4.02	.001	3.0	1.5 to 5.2
292.4	Aplastic anaemia	4	0.23	.0001	17.0	4.7 to 44.5

[a] Probability that the observed number of deaths, or a larger number, would occur by chance.
[b] Includes two deaths from lymphosarcoma, one from reticulum cell sarcoma, and one from malignant lymphoma.

TABLE VIII. NUMBER OF MEN RECEIVING THERAPEUTIC RADIATION TO THE SPINAL MARROW BY 31/12/54, AND MAN-YEARS AT RISK FOLLOWING EACH LEVEL OF EXPOSURE THROUGHOUT THE PERIOD OF OBSERVATION: STUDY SERIES

Mean exposure to spinal marrow (roentgen)	*No. of men exposed by 31/12/54*	*No. of man-years at risk following exposure*	*Mean exposure to spinal marrow (roentgen)*	*No. of men exposed by 31/12/54*	*No. of man-years at risk following exposure*
Less than 250	1,153	8,184	1,750–1,999	305	1,550
250–499	1,708	10,339	2,000–2,249	172	939
500–749	1,912	10,126	2,250–2,499	118	509
750–999	2,268	11,654	2,500–2,749	44	283
1,000–1,249	2,124	10,632	2,750 or more[a]	45	151
1,250–1,499	938	5,098			
1,500–1,749	500	2,437	TOTAL	11,287	61,902

[a] Average exposure—3,043 R.

TABLE IX. THE NUMBERS OF PATIENTS WHO DEVELOPED LEUKAEMIA, AND THE CRUDE AND STANDARDIZED INCIDENCE RATES, AFTER DIFFERENT MEAN EXPOSURES TO THE SPINAL MARROW: MALE "A" AND "B" CASES, EXCLUDING CO-EXISTENT CASES [13]

	Mean exposure to spinal marrow (R)													
	0[a]	*Less than 250*	*250–499*	*500–749*	*750–999*	*1,000–1,249*	*1,250–1,499*	*1,500–1,749*	*1,750–1,999*	*2,000–2,249*	*2,250–2,499*	*2,500–2,749*	*2,750 or more*	*Total*
No. of men developing leukaemia														
"A" cases	—	1	2	6	3	7	2	3	1	2	3	1	1	32
"A" and "B" cases	—	1	3	6	4	8	3	3	1	2	4	1	1	37
Crude incidence per 10,000 men per year														
"A" and "B" cases	0.49	2.16		4.59		6.99		12.18			63.65			5.98
Standardized incidence per 10,000 men per year														
"A" and "B" cases	0.49	1.98		4.66		7.21		14.44			72.16			5.98

[a] The rate given for "zero" therapeutic exposure is the corresponding rate among men of the same age-distribution and observed over the same period, calculated from the mortality from leukaemia experienced by the whole male population of Britain.

TABLE X. THE INCIDENCE OF LEUKAEMIA AFTER DIFFERENT MEAN EXPOSURES TO THE SPINAL MARROW: MALE "A" AND "B" CASES GIVEN ONLY SPINAL IRRADIATION, EXCLUDING COEXISTENT CASES [13]

	Mean exposure to spinal marrow (R)										
	0	*Less than 250*	*250–499*	*500–749*	*750–999*	*1,000–1,249*	*1,250–1,499*	*1,500–1,749*	*1,750–1,999*	*2,000 or more*[a]	*Total*
No. of man-years at risk following exposure	—	5,404	7,673	6,573	8,262	7,411	2,782	897	566	679	40,247
No. of men developing leukaemia											
"A" cases	—	0	2	4	3	4	0	2	1	1	17
"A" and "B" cases	—	0	2	4	3	5	0	2	1	1	18
Crude incidence per 10,000 men per year											
"A" and "B" cases	0.49		1.53		4.72	6.75[b]		8.12[c]			4.47
Standardized incidence per 10,000 men per year											
"A" and "B" cases	0.49		1.44		4.83	6.82[b]		8.70[c]			4.47

[a] Average exposure, 2,290 R.

[b] For the group receiving 1,000–1,499 R the crude incidence is 4.91; standardized incidence 5.06. For the group receiving 1,000–1,749 R the crude incidence is 6.31; standardized incidence 6.82.

[c] For the group receiving 1,500 R or more the crude incidence is 18.68; standardized incidence 19.86. For the group receiving 1,750 R or more the crude incidence is 16.07; standardized incidence 16.82.

TABLE XI. OBSERVED AND EXPECTED NUMBERS OF LEUKAEMIA CASES IN CHILDREN IRRADIATED FOR "THYMIC ENLARGEMENT"
(*Modified from Pifer* et al.[27])

Series group	*Series I*		*Series II*	
	Treated	*Siblings*	*Treated*	*Siblings*
Number of persons	1,451	2,073	1,358	2,256
Average age (yrs.) at observation	18.5	—	8.1	—
Leukaemia cases (total)	6	0	0	1
Cases expected[a] (local)	0.96	1.27	0.51	0.87
Ratio obs./expected	6.25	—	—	1.15
Mean exposure (R) for cases	336 (150–684)	—	—	—
Mean exposure for series	329	—	126	—
Cases < 200 R	4	—	0	—
Cases > 200 R	2	—	0	—

[a] Cases expected on the basis of records for upstate New York, the area in which the children were treated.

TABLE XII. RELATIVE LEUKAEMIA RISK IN RETROSPECTIVE STUDIES OF CHILDREN DYING OF LEUKAEMIA AFTER DIAGNOSTIC IRRADIATION *in utero*

Reference	*Age (years) of leukaemics at death*	*Years of death for leukaemics*	*Percentage of mothers receiving abdominal irradiation during pregnancy*		*Relative risk, 95% limits in brackets*
			Leukaemics	*Controls*	
Stewart[33]	< 10	1953–55	96/780 (12.3%)	117/1,638 (7.1%)	1.8 (2.4–1.4)
Ford *et al.*[33]	< 10	1951–55	20/70 (28.6%)	48/247 (19.4%)	1.7 (2.9–0.8)
Kaplan[34]	?	1955–56	37/150 (24.7%)	24/150 (16.0%)	1.7 (3.7–1.0)
Kaplan[34]	?	1955–56	34/125 (27.2%)	27/125 (21.6%)	1.4 (2.5–0.7)
Polhemus and Koch[35]	?	1950–57	72/251 (28.7%)	58/251 (23.1%)	1.3 (2.0–0.9)
Kjeldsberg[36]	?	1946–56	5/55 (9.1%)	8/55 (14.5%)	0.6 (2.0–0.2)
Murray *et al.*[21]	< 20	1940–57	3/65 (4.6%)	3/65 (4.6%)	1.0 (12.0–0.6)
Murray *et al.*[21]	< 20	1940–57	3/65 (4.6%)	7/93 (7.5%)	0.6 (2.4–0.1)
Murray *et al.*[21]	< 20	1940–57	3/65 (4.6%)	2/82 (2.4%)	1.9 (40.0–1.1)

TABLE XIII. THYROID TUMOURS IN AUTOPSIES AND SURGICAL THYROID SPECIMENS IN JAPANESE A-BOMB SURVIVORS ACCORDING TO DISTANCE FROM HYPOCENTRE
(*Hiroshima ABCC, 1948–1960*[57])

	Metres from hypocentre			
	< 1,400	*1,400–1,999*	*2,000–9,999*	*Non-exposed*
Number of autopsies	124	188	397	544
No. and per cent carcinoma	7 (5.6%)	3 (1.6%)	12 (3.0%)	15 (2.7%)
No. and per cent adenoma	9 (7.2%)	7 (3.7%)	18 (4.5%)	15 (2.7%)
Number of surgical specimens	35	35	—	—
No. and per cent carcinoma	15 (42.8%)	4 (11.4%)	—	—
No. and per cent adenoma	5 (11.1%)	10 (28.6%)	—	—

TABLE XIV. RELATIVE RISKS FOR THYROID CANCER AT VARIOUS EXPOSURE LEVELS AFTER THERAPEUTIC IRRADIATION (EXTERNAL SOURCES) TO NECK REGION
(*Computed from data of Takahashi* et al.[58])

Estimated exposure (roentgen)	*Proportion of thyroid cancer cases* %	*Proportion of controls* %	*Relative risk, 95% limits in brackets*
0	95.45 (609)	99.43 (4,044)	—
500–2,000	0.94 (6)	0.25 (10)	4.0 (1.2–13.2)
2,000–4,000	2.04 (13)	0.25 (10)	8.6 (4.3–15.4)
4,000–6,000	0.78 (5)	0.05 (2)	16.6 (3.1–89.0)
6,000–8,000	0.47 (3)	0.02 (1)	19.9 (2.0–200.0)
8,000–10,000	0.16 (1)	—	—
> 10,000	0.16 (1)	—	—

TABLE XV. AGES AT IRRADIATION AND AT OPERATION, LATENT INTERVAL, AND THYROID EXPOSURE IN 7 CASES OF THYROID CANCER FOLLOWING RADIO-THERAPY FOR TUBERCULOUS ADENITIS [59]

Cases	*Age at irradiation years*	*Age at cancer operation years*	*Interval years*	*Approximate exposure (roentgen)*
1	4	17	13	1,500 (rt. lobe) 1,000 (isthmus)
2	9	27	18	700 (both lobes)
3	15	26	11	500–700 (rt. lobe)
4	18	45	27[a]	500 + (over 8 years)
5	18	42	24	650 (rt. lobe)
6	23	40	17	1,000 (each lobe)
7	34	44	10	700 (rt. lobe)
Means	17.3	34.4	17.1	

[a] From first radiation treatment.

TABLE XVI. THYROID CANCER FOLLOWING THERAPEUTIC IRRADIATION

Author	Age at irradiation	Man-y at risk	Average exposure (roentgen)	Cases	Cases × 10^{-6}/y	Risk estimate (c × 10^{-6}/y/R)
Conti[22]	Children	21,896	168	0	0	0.0 (0.0–1.1)[a]
De Lawter[74]	Adults	5,000	2,100	0	0	0.0 (0.0–0.03)
Hanford[59]	Children, Adults	5,711	900[b]	8	1,400	1.6 (0.7–3.1)
Latourette[23]	Children	15,130	214	1	66	0.3 (0.01–1.7)
Pifer[27], Series I	Children	26,843	329	8	298	0.9 (0.4–1.8)
Pifer[27], Series II	Children	11,000	126	1	91	0.7 (0.01–4.0)
Saenger[24]	Children	24,871	330	11	442	1.3 (0.9–2.3)
Simpson[60,c]	Children	18,829	520[d]	10	531	1.0 (0.5–1.9)

[a] In brackets, approximate 95% confidence limits of the estimate.
[b] Mean exposure to largest group (65%).
[c] Partly overlaps Pifer's Series I.
[d] Mean exposure to cases developing cancer.

TABLE XVII. RELATIVE RISKS FOR NECK CANCER (EXCLUDING THYROID) AT VARIOUS EXPOSURE LEVELS AFTER THERAPEUTIC IRRADIATION (EXTERNAL SOURCES) TO NECK REGION
(*Computed from data of Takahashi* et al.[58])

Estimated exposures (roentgen)	Proportion of cancer cases %	Proportion of controls %	Relative risk, 95% limits in brackets
0	98.79 (895)	99.43 (4,044)	—
500–2,000	0.33 (3)	0.25 (10)	1.5 (0.4–16.0)
2,000–4,000	0.66 (6)	0.25 (10)	2.7 (0.9–7.0)
4,000–6,000	0.11 (1)	0.05 (2)	2.2 (0.2–24.0)
6,000–8,000	0.11 (1)	0.02 (1)	4.5 (0.3–74.0)

TABLE XVIII. RELATIVE RISKS FOR SKIN CANCER AT VARIOUS EXPOSURE LEVELS AFTER THERAPEUTIC IRRADIATION (EXTERNAL SOURCES)
(*Computed from data of Takahashi* et al.[58])

Estimated exposures (roentgen)	Proportion of cancer cases %	Proportion of controls %	Relative risk, 95% limits in brackets
0	95.45 (294)	99.43 (4,044)	—
500–2,000	0.97 (3)	0.25 (10)	4.1 (1.2–9.6)
2,000–4,000	0.97 (3)	0.25 (10)	4.1 (1.2–9.6)
4,000–6,000	0.65 (2)	0.05 (2)	13.7 (1.8–100.0)
6,000–8,000	0.65 (2)	0.02 (1)	27.4 (2.5–300.0)
8,000–10,000	0.97 (3)	—	—
> 10,000	0.32 (1)	—	—

TABLE XIX. LONG-TERM EFFECTS OF RADIUM DEPOSITION IN MAN (CORRELATION OF CLINICAL AND RADIOGRAPHIC FINDINGS WITH CURRENT BODY BURDENS OF Ra^{226})
Hasterlik et al.[82]

Body content (μCi)	*Number radio-graphed*	*Radiographic changes in skeleton attributable to radium deposition*					
		None	*Minimal*	*Mild*	*Moderate*	*Advanced*	*Malignant*
<0.001	17	14	3	0	0	0	
0.001–0.01	28	28	0	0	0	0	
0.01–0.1	90	80	8	1	1	0	
0.1–1.0	61	25	13	9	9[a]	5[b]	3
> 1.0	40	1	2	5	4	28[c]	14
TOTAL	236	148	26	15	14	33	17

[a] MsTh present in two cases.
[b] Severe tooth changes only in one case.
[c] Based on film taken elsewhere in two cases.

TABLE XX. COMPARISON OF ST. LAWRENCE, JACHYMOV AND SCHNEEBERG, COLORADO PLATEAU AND SOUTH AFRICA DATA [105]

	Fluorspar Mines		*Uranium Mines*			
	St. Lawrence		*Jachymov & Schneeberg*			
	Non-working areas	*Working areas*	*Abandoned mine*	*Working mine*	*Colorado Plateau Working mines*	*South Africa Working mines*
Radon (picocuries per litre)						
Average				2,900		
Range	270–25,000[a]	5–1,510	?–59,000	?–18,000	70–59,000	25–500
Radon daughters (multiples of 1.3×10^5 Mev per litre per working week)						
Average	53	2.5–10[b]				
Range	4.2–193	0–12				
Gamma radiation (mR/h)	0.03–0.50					
Incidence of lung cancer as % of miner deaths	33 (1933–1961)		43 (1875–1939)[c]			
	45 (1952–1961)		52 (1921–1939)[c]		11.4[d]	3.5[e]
Duration of underground exposure (years)						
Average and range	12.5 (5.5–21.3)		17 (13–23)[f]		7, 8, 9, 10, 12	17.3 (3–30)[h]
Induction period (years)						
Average and range	19.1 (11.5–25.0)		25 (15–43)[f]			
Age at death (years)			50 (40–67)[f]			
Average and range	46.8 (33.56)		55 (37–69)[g]			58.2 (45–73)

[a] Calculated on basis of highest radon daughter concentration found.
[b] Estimated.
[c] After Lorenz (1944).[122]
[d] Miners with 3 or more years underground experience—5 cases—Archer and others (1962).[122]
[e] Based on an autopsy series—23 cases among 650 autopsies—Oosthuizen and others (1958).[102]
[f] Nine cases—Pirchan and Sikl (1932).[94]
[g] Thirteen cases—Rostoski and others (1926),[93] as quoted by Lorenz (1944).[122]
[h] Based on 14 of 23 cases reported by Oosthuizen and others (1958).[102]

TABLE XXI. INCIDENCE OF MALIGNANT NEOPLASMS EXCLUDING LEUKAEMIA, HIROSHIMA AND NAGASAKI TUMOUR REGISTRIES, 1957–1959 (SEXES AND AGES COMBINED) [57]

	Distance from hypocentre in metres				
	500–1,499	*1,500–2,499*	*2,500–9,999*	*Non-exposed*	*Total*
Hiroshima (32 months)					
No. of cases	79	183	151	120	533
Crude rate per 10^5	978.1	829.2	773.4	625.1	774.0
Age- and sex-adjusted rate	953.3	819.7	758.6	650.1	774.0
Nagasaki (30 months)					
No. of cases	19	47	29	36	131
Crude rate per 10^5	635.9	608.1	475.5	697.1	596.0
Age- and sex-adjusted rate	846.4	667.1	600	915.2	735.4

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