IONIZING RADIATION: LEVELS AND EFFECTS

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Annex H

RADIATION CARCINOGENESIS IN MAN

CONTENTS

Introduction

1. It is generally accepted that cancer is the major long-term somatic effect of radiation on human beings. The Committee discussed the subject of human cancer induced by radiation in its 1958, 1962 and 1964 reports (161-163). In view of the substantial increase in knowledge about radiation carcinogenesis in man since the Committee's latest report. this annex will review this subject again.

2. The carcinogenic effects of radiation, as indeed the effects of any environmental factor implicated in the causation of human cancer, are best evaluated by human population studies. Because of the great differences in susceptibility to cancer induction between human beings and other species, studies with experimental animals provide information of more qualitative than quantitative significance. The mechanism of carcinogenesis in general and specifically the role of radiation in carcinogenesis are certainly not well enough understood to deduce from first principles the extent of radiation effects on human beings. It is therefore essential to obtain empirical information from epidemiologic studies.

3. In the evaluation of such studies, the following inherent difficulties must be borne in mind:

(*a*) Populations of sufficient size who were exposed to a sufficiently high dose of radiation are few, and their number has been decreasing as radiation hazards have become increasingly understood;

(*b*) In retrospective, or case-history, studies, quantitative estimates of radiation dose received are often very difficult to obtain, especially when radiation exposure has occurred repeatedly. The fact that a number of years are required for the development of cancer after irradiation makes it particularly difficult to determine radiation exposure that has occurred years earlier;

(*c*) The long latent period for cancer induction is also a drawback in prospective or cohort studies unless, at the initiation of the study, an exposed population or a cohort can be selected on the basis of exposure in the distant past;

(*d*) When there is a low natural incidence of cancer of a specific type, a large population must be followed in order to obtain an adequate number of cancer cases;

(*e*) In most studies cancer frequencies are measured, for practical reasons, in terms of mortality. This practice requires great caution, since mortality statistics can be an unreliable measure of incidence, as when cancer of a specific site has unreliable death notification or shows a low fatality;

(*f*) The data on patients who were exposed to medical irradiation also must be evaluated with caution, since the effects of irradiation may well be confounded both with the effects of the primary disease that prompted the therapeutic irradiation, and with the effects of other treatments given to the patients. In addition, such data are biased in most instances toward specific sex and/or specific age group, thus making it difficult to apply the results to the general population;

(*g*) The relative susceptibility of different organs and tissues is of great interest, and this can best be ascertained if different tissues and organs receive the same amount of radiation. Uniform whole-body irradiation, however, has practically never occurred except for fœtus exposure;

(*h*) Comparison of the results of different investigations are made difficult by the fact that the doses received were often from radiations of differing qualities delivered at differing rates.

4. In the present annex, the risk of cancer induction by radiation will be expressed as absolute and/or relative risk. The absolute risk of a certain type of cancer at a stated dose of radiation of a certain quality is the excess incidence due to that dose of radiation. In practice this is estimated from the difference between the incidence rates of the exposed and the non-exposed population. The absolute risk may for instance be expressed as the excess number of cases per million per year for a given dose. The relative risk for a given dose is the ratio between the incidence rates in a population exposed to that dose and that in a non-exposed population which, ideally, should be comparable to the exposed population with respect to all factors affecting the incidence of the effect studied, except radiation.

5. Relative risks are preferred to absolute risks in epidemiologic studies in assessing whether there exists a causal, rather than a mere fortuitous, association between exposure and the disease (93). Once the association is accepted as being casual, absolute risk is a better index of the impact that a successful preventive programme might have. Therefore, the absolute risk has been the estimate of risk of radiation effects adopted by the Committee in its 1964 report and by the International Commission on Radiological Protection (69). Another consideration is that if, under any circumstances, equal doses of radiation increase the risk in proportion to the natural occurrence of cancer (either in different populations for a given form of cancer, or for different forms in a given population), relative risks may provide more general estimates of the effects of radiation. If, on the other hand, the radiation risks are unrelated to the natural probability of cancer occurrence, and the excess risk is a function of the dose of radiation only, then the absolute risk is a better estimate of the effects of radiation. In the present annex radiation risks will be given both in absolute and in relative terms.

6. Estimates of risk per unit dose derived from epidemiological investigations are valid only for the doses at which they have been estimated and they can be applied to a range of doses only if there is a linear relationship between dose and incidence since extrapolations beyond that range may lead to gross errors. Particular care should be exercised in estimating risks from data on people exposed to mixed neutron and gamma radiation. Radiobiological experiments indicate that the RBE of neutrons varies with dose (see annex G) so that, if these results are applicable to human beings, the incidence of various effects cannot be proportional to absorbed dose for both gamma rays and neutrons and estimates of risk in terms of incidence per unit dose need to be clearly qualified.

7. Another serious problem at the present time arises from the fact that present knowledge of cancer induction by radiation is based on the experience of a limited number of years after exposure, thereby making risk estimates for an entire life span impossible. Because of this incompleteness of follow-up period, information is lacking, particularly about the later part of human life during which the natural incidence of cancer greatly increases over rates at younger ages.

8. In terms of man-year experience, the cohort followed by the Atomic Bomb Casualty Commission (ABCC) with the collaboration of the Japanese National Institute of Health (JNIH) is of far greater significance than the other cohorts under study. However, even the experience of this cohort at present gives only part of the information as to the whole risk of cancer induction. The proportion of cancer deaths to deaths from all causes ranged roughly from 10 to 20 per cent in the past 20 years in Japan. If the average figure of 15 per cent is applied to the ABCC cohort, 15,000 cancer deaths would be expected by the time all persons in the cohort had died. Although the extensive follow-up of the ABCC has revealed about 4,000 deaths due to cancer for the period 1950-1970, these deaths constitute only 27 per cent of the deaths to be eventually expected in the absence of radiation.

9. Jablon and Belsky (71) and Jablon *et al.* (75) have reported that the children who were exposed at ages less than 10 years show now, many years later, an unusually high risk of developing cancer at various sites. Children exposed to irradiation at, for example, 5 years of age and then followed for 20 years, will only be 25 years old at the termination of the follow-up period. At that age the natural risk of cancer is still extremely low. Therefore, a long follow-up is particularly advisable, although practically difficult, for

people who are irradiated at young ages. A follow-up of half a century or so may be needed to measure the whole risk of cancer.

10. The above consideration may not necessarily apply to all forms of cancer. If the risk of cancer induction is assumed to follow a unimodal distribution, follow-up is necessary only until the risk, having passed its peak, approaches the level of natural occurrence. At present, leukæmia is the only type of malignancy belonging to this category. The excess of other types of malignancies due to irradiation of the cohorts that are currently being followed up may still be increasing with time after exposure and it is entirely unknown whether the excess risk reaches a peak with time. Nor is it known what the magnitude of the peak, or the modal induction period, etc., are.

11. Since the 1964 report, a substantial amount of new information on radiation carcinogenesis in man has emerged. This will be reviewed here by type of malignancy. The over-all incidence of malignancies, including those about which statistical information is still too limited to warrant separate discussion, will then be reviewed.

12. The physical radiation quantities that are significant in radiation epidemiology have been variously defined and named. In this annex the recommendations of the International Commission on Radiation Units and Measurements (68) are followed. The quantity employed to specify the radiation field at any position in free air is the tissue kerma in free air (K). This quantity has been variously termed "T65D dose", "air dose", "first collision dose" or simply "dose". The quantity employed to specify energy absorption in irradiated tissues is the absorbed dose (D). This quantity has been variously termed "tissue dose", "radiation dose" or "dose". Both kerma and absorbed dose are measured in rads.

I. Leukæmia

A. A-BOMB SURVIVORS (ABCC-JNIH STUDY)

1. *Material and methods*

13. The cohort of A-bomb survivors and their controls in Hiroshima and Nagasaki (Japan) that was selected by the ABCC for the Life Span Study Sample consists of the residents of both cities who had stated in the 1950 National Census that they were in Hiroshima or Nagasaki at the time of the respective A-bomb explosion (12). All those who were within 2.500 metres of the hypocentre at the time of the bombing (ATB) were included in the sample. A comparison group, consisting of those located between 2.500 and 10.000 metres from the hypocentre, was matched by age, sex, and city to the survivors within 2.000 (not 2,500) metres. A second comparison group, similarly matched to the survivors within 2.000 metres, consisted of persons either not in the cities (NIC) or who were more than 10,000 metres from the hypocentre ATB. As a whole, this cohort amounts to about 100.000 individuals, categorized in table 1 by sex, city, and exposure. Information on nearly 100 per cent of the mortality experience of this cohort was obtained from the Japanese family registration system.

14. An attempt was made to procure autopsies on all deaths in the sample of 100.000 being traced for mortality occurring after 1961; the autopsy rate was about 40 per cent (70).

15. From the Life Span Study Sample of 100.000, a sub-sample of 20,000—the Adult Health Study Sample—was drawn to obtain information about conditions that do not lead to death or that do so only after many years. Biennial physical examinations were made on this sub-sample of 20,000. The sample consists of the following four groups: all survivors between 0-1,999 metres ATB with acute symptoms due to irradiation, those between 0-1,999 metres without such symptoms, those between 3,000-3,499 metres, and those beyond 10,000 metres or not in the city. To the first group, that small number of survivors who were closest to the hypocentre and had acute symptoms, equal numbers of individuals were sampled from each of the other three groups and matched by sex, age and city.

16. The risk of cancer induction was formerly related to distance from the hypocentre. While precise estimates of the absorbed doses received by the survivors are not yet available, not only have estimates of the tissue kerma in free air as a function of distance been published for both cities (5, 54), but estimates of the kerma to which the individual survivors belonging to the major ABCC samples were exposed are now available (101). These latter estimates take into account the attenuation due to shielding by the structures surrounding each survivor.

17. The previous kerma estimates (123) which were used by the Committee in its 1964 report have been more accurately re-estimated by Auxier *et al.* (5) with good agreement with the new and independent estimates of Hashizume *et al.* (54). Table 2 compares the kerma-distance curves from the old (T57D) and new (T65D) estimates. At Hiroshima, the new (T65D) kerma estimates 1.0 kilometre from the hypocentre are half the old estimate (T57D), and they are less than a third at 1.5 kilometres. For Nagasaki, the kerma estimates are essentially unchanged. The probable error of the new kerma values is estimated to be about $\pm$ 30 per cent in Hiroshima and $\pm$ 10 per cent in Nagasaki (5). In Nagasaki, about 90 per cent of the kerma is due to gamma radiation; in Hiroshima, gamma rays and neutrons each account for about half of the total kerma.

18. An exhaustive search for the location and shielding histories of each survivor of the ABCC cohort was made. On the basis of this information, and by utilizing kerma-distance curves and the appropriate shielding attenuation factors, Milton and Shohoji (101) were able to estimate the kerma to which the majority of the survivors had been exposed. For about 3,800 survivors estimates could not be made, usually because the survivor was at a distance where the kerma was high but the shielding configuration made it impossible to estimate the attenuation (71).

19. The reliability of kerma estimates for the survivors appears uncertain. As possible sources of error, a number of factors affecting kerma-distance curves, shielding histories, methods of estimating attenuation due to shielding, etc., must be considered. It must also be clearly borne in mind that absorbed doses, particularly to deep tissues, are difficult to obtain from the kerma estimates available, and the fact that a substantial neutron contribution was received by the survivors at Hiroshima introduces additional complications owing to the higher biological effectiveness of neutrons relative to gamma rays.

20. Regarding the material and methodology of the ABCC study, the following conclusions may be drawn:

(*a*) The study cohort of ABCC is generally unbiased with respect to sex, age and pre-existing disease, an advantage compared to other irradiated populations, such as medically treated groups;

(*b*) The mortality study of ABCC is greatly strengthened by the autopsy programme, a very rare feature of studies on radiation carcinogenesis;

(*c*) The morbidity study of ABCC gives valuable information about cancers with long survival times;

(*d*) The survivors were exposed to short-term (instantaneous), whole-body irradiation. The dosimetry shows uncertainties as discussed.

2. *Leukæmia morbidity*

21. In the 1964 report, the review of leukæmogenesis in A-bomb survivors was largely based on the report of Brill *et al.* (18) and showed that little doubt existed about the leukæmogenic effect of A-bomb irradiation. However, numerous problems (e.g., the precise nature of the dose-effect relationship, the relationship of radiation effects to sex, age, time, etc.) remained unsolved.

22. Since the publication of Brill *et al.*, the results of several studies have been published by the ABCC (16, 45, 62, 66, 67). The reports of Ishimaru *et al.* (66, 67) in particular have extensively covered various aspects of leukæmogenesis according to the new kerma estimates (T65D) for each survivor, and have thus provided significant new information about the relation between A-bomb irradiation and leukæmia induction.

23. In the Master Sample of 113,169 survivors (the Life Span Study Sample plus two additional small samples), 117 new cases of leukæmia were found during the 16-year period, 1950-1966. These were primarily detected through the leukæmia registries in Hiroshima and Nagasaki and were confirmed by at least two hæmatologists of the ABCC.

24. The annual incidences based on 88 cases of leukæmia at Hiroshima and 29 at Nagasaki are shown in figures I and II. It is worth noting that the data show a significant excess of leukæmia in the group exposed to kermas ranging from 20 to 49 rads (median 30 rads) at Hiroshima but not at Nagasaki. Regression analysis indicates that between median kermas of zero and 400 rads the rise of the incidence is not inconsistent with a linear kerma-effect relationship, the regression coefficients being 3 and 1.6 cases per million per year per rad at Hiroshima and Nagasaki, respectively.

25. The risk of leukæmia induction for a given kerma is therefore greater at Hiroshima than at Nagasaki. The difference between the two cities is most likely explained by (*a*) uncertainty in the air-dose curve, especially for Hiroshima since the Hiroshima-type of A-bomb was neither produced nor tested again after the Hiroshima explosion and (*b*) differences in the quality of the mixed radiation received in the two cities.

26. The differences between the incidences in the two cities for equal kermas have been used by Ishimaru *et al.* (67) to estimate the RBE of neutrons with

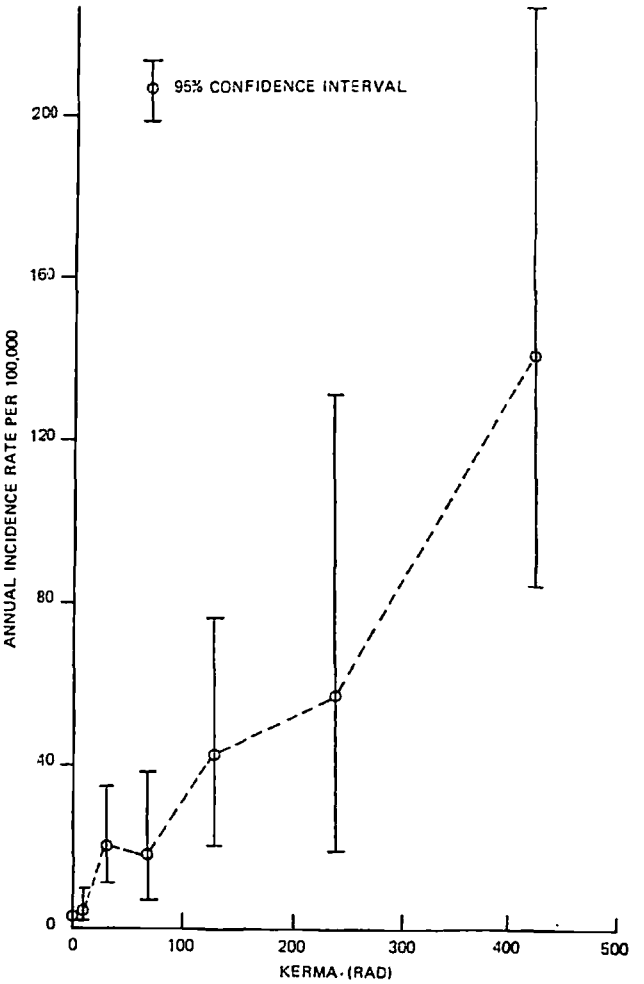

Figure I. Annual incidence rate of leukæmia (all forms) per 100,000 A-bomb survivors in ABCC master sample as a function of exposure at Hiroshima, Oct. 1950-Sept. 1966 (67)

respect to the induction of leukæmia by selecting that value which, applied to the neutron contribution to the kerma, would bring the incidence curves in the two cities to coincide. The closest fit was obtained with an RBE value of five. It has been pointed out (122), however, that the RBE is unlikely to be the same at all doses (see also annex G of this report). Poston *et al.* in fact showed that the data from Hiroshima and Nagasaki on leukæmia induction are consistent with RBE values that vary from four below 100 rads to one at about 400 rads. The implications of assuming that the RBE varies with dose have been mentioned in paragraph 6 and will be further discussed later in this annex.

27. It is worth noting that the data of Ishimaru *et al.* show a significant excess of leukæmia in the group exposed to a kerma as low as 20-49 rads at Hiroshima. However, no leukæmia case is observed at Nagasaki among the survivors exposed to less than 100 rads. The reason for the discrepancy may be due to chance fluctuations resulting from the smaller size of the Nagasaki sample or from differences in the quality of the radiation received in the two cities.

28. Table 3 shows the leukæmia incidence by specific type, kerma, and city. While the excess incidence of leukæmia is primarily seen among survivors having received a kerma of 100 rads or more, no excess is

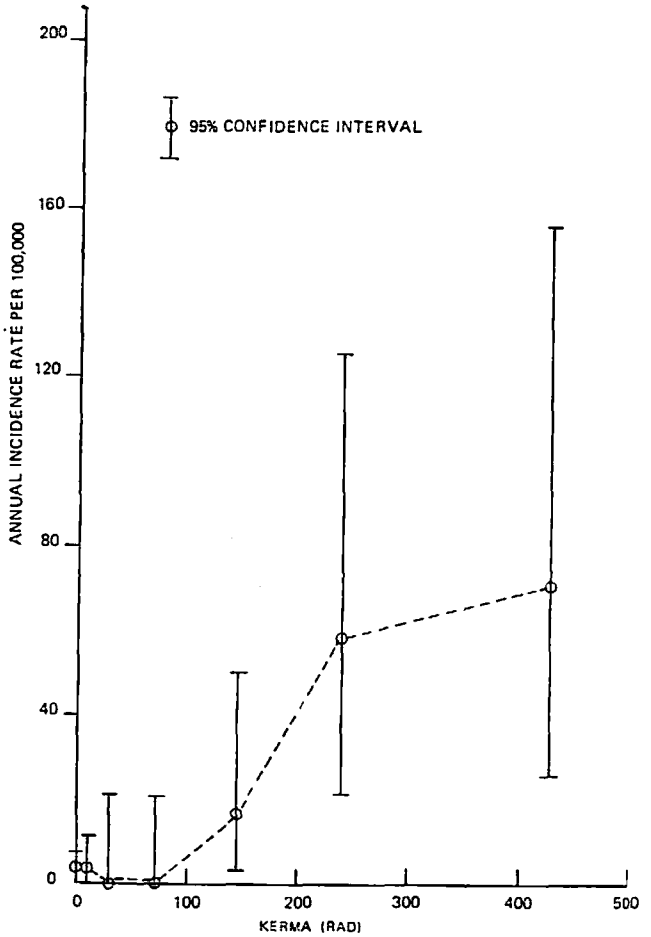

Figure II. Annual incidence rate of leukæmia (all forms) per 100,000 A-bomb survivors in ABCC master sample as a function of exposure at Nagasaki, Oct. 1950-Sept. 1966 (67)

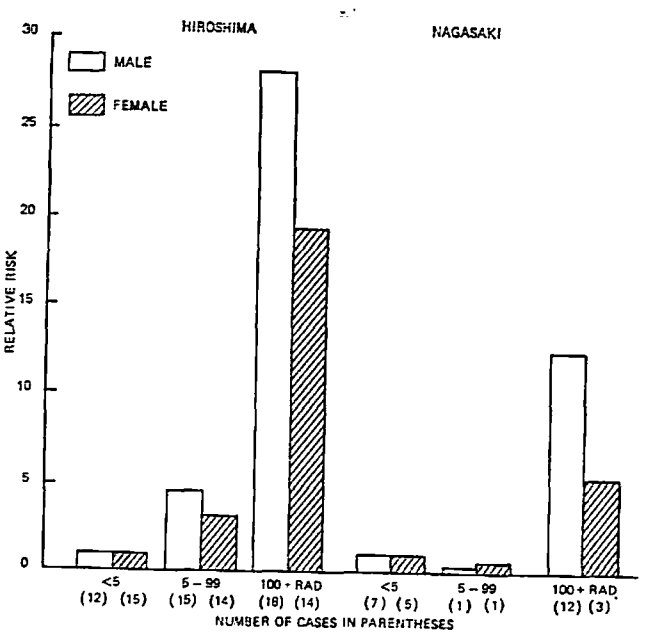

Figure III. Relative risk of leukæmia of A-bomb survivors by kerma, sex and city, 1950-1966 (66)

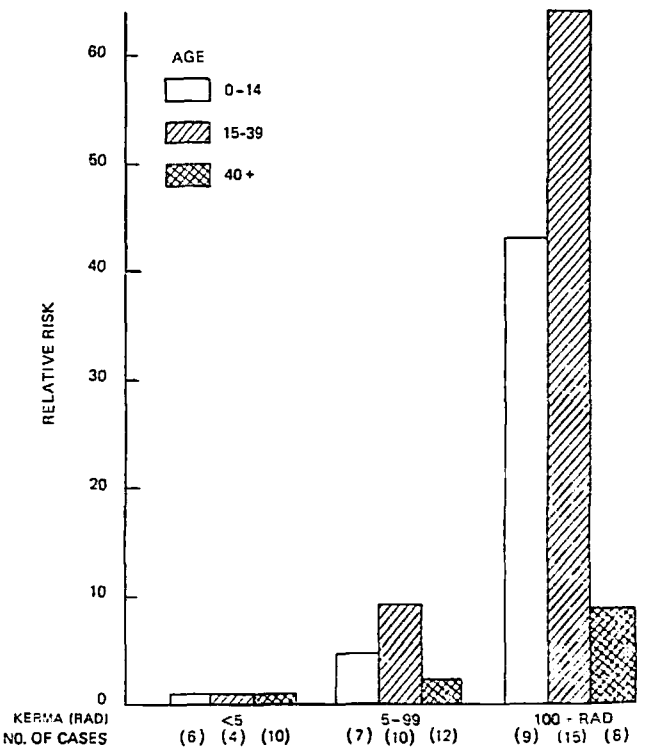

Figure IV. Relative risk of leukæmia of A-bomb survivors at Hiroshima, by kerma and age at exposure (66)

observed, even at 100 rads or more, for chronic lymphocytic leukæmia. In Hiroshima, high risks are noted for acute granulocytic, acute lymphocytic, other acute types, and for chronic granulocytic leukæmia. Although the number of cases is small, the excess in Nagasaki is primarily confined to acute granulocytic and acute lymphocytic leukæmias. This difference in the distribution of excess leukæmias between the two cities may be noteworthy in considering the possible difference between the effects of gamma rays and neutrons. Among younger persons (less than 15 years of age ATB), the risk of acute lymphocytic leukæmia is especially increased.

29. Males seem to be more susceptible to leukæmia induction than females in terms of both relative and absolute risks. Figure III shows a higher relative risk among males than among females in the 5-99 and 100+ rad groups in each of the two cities. Since the natural occurrence of leukæmia (133) is higher in males than in females, the absolute risk must also be greater in males than in females (the male to female ratio is 1.3 for Japan).

30. When the relative risk of leukæmia is examined by age at exposure, both the 0-14-year and the 15-39-year age groups have clearly higher relative risks than the 40+ year age group, as shown in figure IV (only Hiroshima data are presented since the Nagasaki data do not distinguish the 15-39-year and 40+ year age groups). As seen in figures V and VI, leukæmia incidence rates are similar for different age groups in Japan, in sharp contrast to England and Wales and the United States (37)—these three countries being those that have provided the major sources of information regarding radiation leukæmogenesis in man. Thus, the high sensitivity in the younger age groups, as observed on the basis of relative risks, must also be true in terms of absolute risks.

3. *Leukæmia mortality*

31. Table 4, compiled from a report by Beebe *et al.* (10) shows the mortality experience of A-bomb sur-

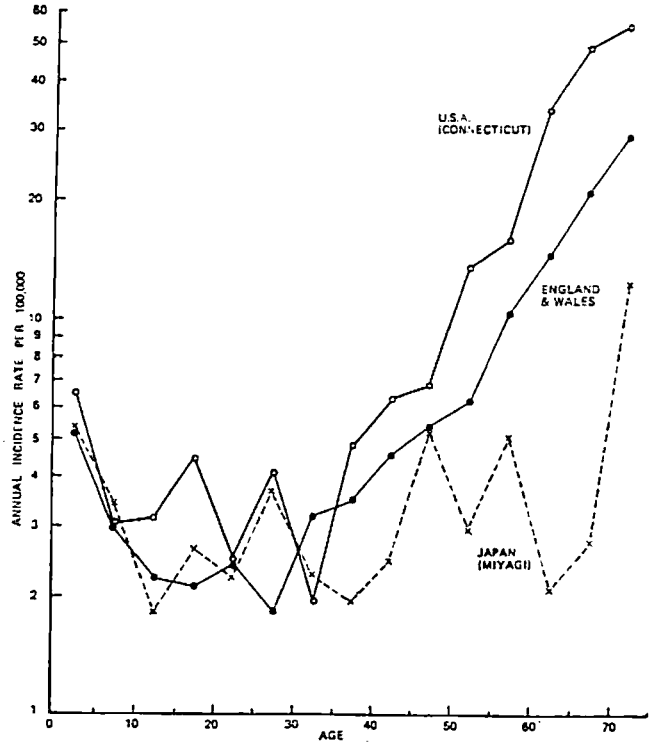

Figure V. Annual incidence rate of leukæmia per 100,000 males in Japan (Miyagi), the United States (Connecticut) and England and Wales in 1959-1960 or 1960-1962 (37)

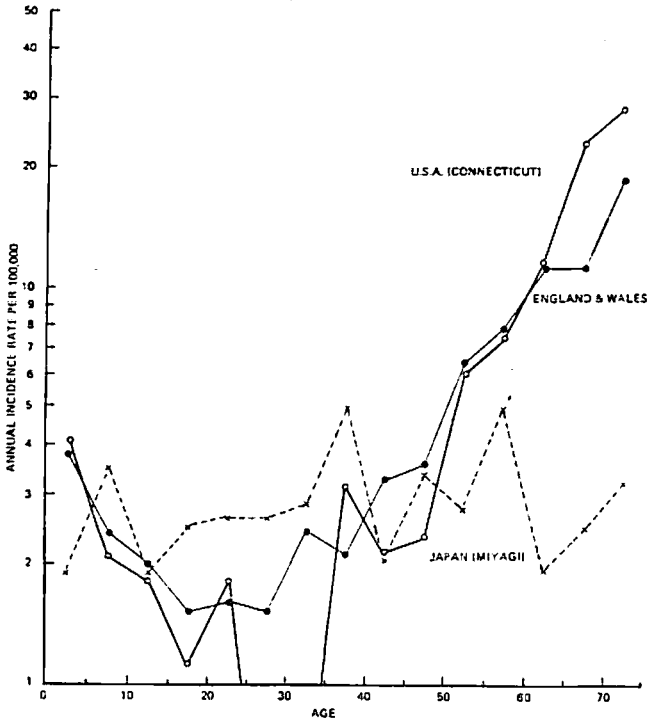

Figure VI. Annual incidence rate of leukæmia per 100,000 females in Japan (Miyagi), the United States (Connecticut) and England and Wales in 1959-1960 or 1960-1962 (37)

vivors in the ABCC cohort (modified Life Span Study Sample) in relation to selected types of cancer for the period 1950-1966. In this tabulation, data from Hiroshima and Nagasaki are pooled together.

32. As seen in table 4, leukæmia mortality clearly increases with increasing dose. For the 1950-1966 period, 116 deaths from leukæmia were observed, which comprised 4.8 per cent of the total malignant deaths of that period. Of the 116 leukæmia deaths, 64, or 55 per cent, may be ascribed to radiation.

33. A more recent mortality study made by Jablon and Kato (73, 74) in the ABCC cohort (modified Life Span Study Sample) has added the new mortality information obtained from 1967 to 1970. Among the five major types of malignancies selected by the authors for analysis—leukæmia, lung, breast, gastro-intestinal tract, and cervix and uterus—the first three show significant excess, and only these three types of cancers are presented in detail in table 5. In this study, the expected numbers were computed from the Japanese national rates by applying to different dose groups the rates specific for age, sex and calendar year. The national mortality rates may be different from those of the unexposed Hiroshima and Nagasaki populations because of geographical differences and because the survivors belong to an essentially urban population. In fact, the ABCC cohort showed a mortality from all causes lower by 8 per cent than the national average. Therefore, two other types of expected numbers of deaths were also estimated, based on the mortality experience of the practically non-exposed populations within the cohort: the 0-9-rad group, and 0-9-rad and NIC groups combined. In the absence of detailed information, these expectations could not be adjusted for sex, age, or calendar year. However, as seen in table 5, the three expected values are in fact very close in all dose groups and for all causes of death.

34. For leukæmia, the Hiroshima survivors show a higher risk than those of Nagasaki, which, as mentioned earlier, may be explained by the different quality of radiation in the two cities. In Hiroshima, the increase of risk is significant even in the 10-49 rad group, but, in Nagasaki, only in the groups receiving more than 100 rads. The excess number of leukæmia deaths in the exposed population (all survivors except the 0-9 rad group) may be estimated as 56.6 at Hiroshima and 18.5 at Nagasaki, when compared to national rates, or 51.8 at Hiroshima and 14.4 at Nagasaki when compared to the 0-9 rad group in the period from 1950-1970.

35. At Hiroshima, the leukæmia mortality rate rose with kerma by about two cases per million per year per rad between 0 and about 450 rads or by about 40 cases per million per rad over 20 years. This is very close to the corresponding figure of 48 cases per million per rad over 16 years of observation that can be obtained from the morbidity study.

36. Because the radiation received at Hiroshima consisted of both gamma rays and neutrons, it would be useful to know the RBEs of neutrons with respect to the induction of leukæmia. Unfortunately, these RBE values are not yet known. Since, however, the neutron contribution to kerma at Hiroshima varied with distance, it must follow that any value (fixed or varying with dose) of the RBE different from one, when applied to the neutron contribution to the dose, must result in a departure of the dose-effect relationship from linearity. For instance, assuming arbitrarily an RBE decreasing from 10 at 5 rads of neutrons to 1 at 100 rads implies that the risk from low-LET radiation varies between 2 cases per million per year per rad at 400 rads to 0.7 case at 60 rads. This could explain why no excess of leukæmia cases is observed

at Nagasaki in the groups exposed to less than 100 rads which received virtually no neutron contribution.

B. A-BOMB SURVIVORS (OTHER STUDIES)

37. In contrast to the ABCC-JNIH study in which investigation was confined to a sample population from the A-bomb survivors, other studies have investigated radiation effects in the unsampled, "open" population of all the survivors living in Hiroshima and Nagasaki. Leukæmia cases among survivors in these cities were ascertained through the leukæmia registry and the size of their parent population living in Hiroshima and Nagasaki was estimated on the basis of periodic census surveys.[1] These studies then have the advantage that radiation effects can be evaluated on all survivors rather than on a sample only. However, a serious disadvantage is that the number of survivors in these cities has become increasingly difficult to estimate accurately with the passage of time.

38. Since the 1964 report of the Committee, several investigators have studied the time trend of leukæmia occurrence (60, 65, 111, 156). Figure VII from

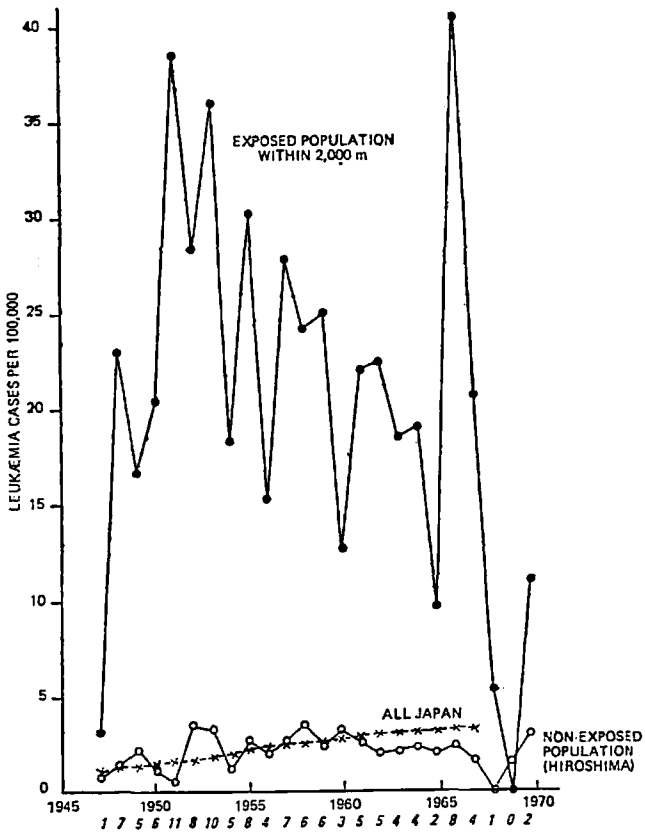

Figure VII. Leukæmia incidence rate in A-bomb survivors in Hiroshima, 1947-1970. In italics, number of cases within 2,000 metres (110, 111)

Ookita's report shows the trend among the Hiroshima survivors in the 1947-1970 period. It is clear from the figure that the Hiroshima survivors within 2,000 metres of the hypocentre ATB had an increase in the rate of leukæmia incidence compared to both the incidence rate in the non-exposed Hiroshima population and the mortality rate from leukæmia of all Japan. The survivors exposed within 2,000 metres were chosen for comparison since radiation dose beyond 2,000 metres was negligible according to the kerma-distance curves.

39. The incidence of leukæmia reached a peak in 1951, six years after exposure, and decreased gradually thereafter with considerable chance fluctuations, particularly in recent years, when the number of cases became small. The observed time trend essentially agrees with that observed among ankylosing spondylitis patients treated by x-irradiation (26), except that the latter showed a more rapid decrease in incidence after a peak was reached 4-5 years following the exposure. The A-bomb survivors had a clear excess risk of leukæmia for even as long as 20 years after exposure.

40. Tomonaga *et al.* (156) analysed the distribution of cell-specific types of leukæmia cases occurring among the A-bomb survivors throughout the country. During the period 1946-1965, 241 cases were found among the survivors exposed within 2,000 metres from the hypocentre. Among these leukæmia cases, the ratio of acute to chronic granulocytic leukæmia was 1.5 in Hiroshima and 2.6 in Nagasaki (the authors did not further classify acute leukæmias into cell-specific type). Among individuals exposed at or beyond 2,000 metres, the corresponding ratios were substantially higher, i.e., 4.9 in Hiroshima and 8.2 in Nagasaki. In the general population of Japan, this ratio was found to be 5.8 in 3,545 leukæmia cases recorded in a nation-wide survey (166).

41. The decrease in the ratio of acute to chronic granulocytic leukæmia among A-bomb survivors, particularly at Hiroshima, was interpreted by Tomonaga *et al.* (156) as a possible specific effect of A-bomb irradiation (neutron irradiation in particular) on the induction of chronic granulocytic leukæmia. A similar decreased ratio was also noted in studies on occupationally exposed populations (103, 165).

42. Consistent with the fact that radiation rarely, if ever, causes chronic lymphocytic leukæmia, no cases of that form of leukæmia were observed among the survivors who were within 2,000 metres of the hypocentre in either city (156).

C. ANKYLOSING SPONDYLITIS PATIENTS TREATED WITH X-IRRADIATION

1. *Material and methods*

43. Court Brown and Doll investigated the mortality experience of ankylosing spondylitis patients in the British Isles treated by therapeutic x-irradiation. Their 1957 report (26) on leukæmia induction was discussed in both the 1962 and the 1964 reports of the Committee. Their studies have since been extended, examining not only leukæmia but also other selected causes of death, including cancer of various sites (28).

44. The 14,554 patients with ankylosing spondylitis treated by x-irradiation in any of the 87 co-operating radio-therapy centres in the United Kingdom during the period 1935-1954 were followed until the end of 1959. The follow-up period was 5-25 years with an average of 10-11 years. The authors also showed the results of an extended but incomplete follow-up to the end of 1962. The duration of the extended follow-up period was 8-28 years, or 13 years

[1] As of 1950, the number of survivors who had been within 2,000 metres of the hypocentre ATB amounted to about 29,000 at Hiroshima and to 8,000 at Nagasaki (62a).

on the average. The study population included only adults, predominantly males (84 per cent). The patients were successfully followed by the end of 1959 with a follow-up rate of 98 per cent.

45. The causes of practically all deaths during the follow-up period were obtained, and the deaths were classified according to the 1957 International Classification of Diseases (ICD). The number of deaths thus recorded was compared with the expected number of deaths derived by applying the national mortality rates specific for age, sex, and calendar year to the person-year experience of the study population.

46. The radiation doses received by the patients were carefully estimated on the basis of the information on radiation exposure available in the medical records of a stratified sample of approximately one of every six patients. The x-ray treatments were from one course of fractionated exposures over a period of about a month to eight courses for periods of up to eight years. Both spinal bone-marrow exposures (roentgens) and whole-body integral exposures (megagramme roentgens) were estimated. The spinal exposures were estimated both as mean exposures to the marrow throughout the entire length of the spine, and as maximum exposures at a point in the spinal marrow.

47. The x-ray treatment of ankylosing spondylitis involved substantial direct irradiation of many organs and tissues in addition to bone and bone marrow. However, precise estimates of the radiation doses received by tissues other than the bone marrow have not yet been obtained.

48. The material and methodology of the ankylosing spondylitis study may be summarized as follows:

(*a*) Among studies of irradiated populations, the ankylosing spondylitis study has the second largest man-year experience next to that of the ABCC study;

(*b*) The results of the ankylosing spondylitis study are applicable only to adult, largely male, populations; the study gives no information on the risk of cancer induction among those exposed to radiation at ages under 15;

(*c*) In evaluating the excess risk of cancer in the ankylosing spondylitis series, it must be borne in mind that certain factors other than radiation (e.g., ankylosing spondylitis itself or other treatments of the disease) should be considered before the excess is simply attributed to the x-ray therapy;

(*d*) Since the ankylosing spondylitis study depends on mortality statistics, the results of the study do not provide information on less-fatal cancers (e.g., thyroid cancer) and cancers known to be unreliable on death notification (e.g., pancreas cancer).

2. *Leukæmia*

49. The major findings of the 1957 report of Court Brown and Doll (26) can be summarized as follows:

(*a*) The leukæmia incidence rises from 50 cases per million per year in the control population to 7,200 cases per million per year following a mean dose to the spinal marrow in excess of 2,250 rads (assuming one roentgen to correspond to about one rad);

(*b*) In the dose range between approximately 300 and 1,500 rads, the relationship between mean exposure to the spinal marrow and leukæmia incidence seems to be linear with a slope of about 0.5 case per million per year per rad;

(*c*) A significant excess of deaths occurs with all types of leukæmia, except chronic lymphocytic leukæmia (only one case of this type of leukæmia was observed);

(*d*) The leukæmia incidence rate increases with age from 1,100 per million for treatment at ages 14-24 to 5,600 per million at ages 55 and above. This age distribution (which is adjusted for the number of treatment courses) is consistent with the age distribution of the spontaneous leukæmia mortality of England and Wales (34).

50. Court Brown and Doll (28) briefly covered the further leukæmia-mortality experience of the ankylosing spondylitics in their 1965 report. In table 6, observed and expected numbers of deaths are presented for every three-year period after the beginning of the observation. Relative risks, the ratio of observed to expected deaths, reach a peak 3-5 years after the first observation and decline thereafter. At observation periods of 12 years and more, the relative risk is erratic because of large chance fluctuations. The extended (although incomplete) follow-up series probably gives more reliable relative risk figures by nearly doubling the man-years experience. At 12-14 years the relative risk is 9.2 (7 observed *versus* 0.76 expected) and at 15-27 years the relative risk is 1.9 (1 observed *versus* 0.54 expected). Because the observed numbers are so small, the above values of relative risk may not be very reliable. But they roughly indicate that the leukæmia risk, after a peak 3-5 years after irradiation, decreases with the passage of time, remaining still higher than that of the non-irradiated population at least up to 15 years after exposure.

51. The excess mortality of leukæmia from irradiation is about 50-55 cases per 15,000 patients (including some probable aleukæmic leukæmia cases mistaken as aplastic anæmia), or 3,000-4,000 cases per million exposed, over a follow-up period averaging 10-11 years from the date of the first observation. The excess mortality may naturally increase with extension of the follow-up period. However, because of the declining trend of the excess, and the already low yearly values, its over-all magnitude is not likely to be much higher than that already observed.

52. In the Committee's 1964 report, a possibility of error in evaluating the leukæmia risk by irradiation of the ankylosing spondylitis patients was pointed out, namely, a possible association between leukæmia and ankylosing spondylitis itself (109), and leukæmia and other therapeutic agents to which the spondylitics must have been exposed (8, 167). The 1964 report therefore stressed the necessity of determining the risk of leukæmia induction in ankylosing spondylitis patients without x-ray therapy.

53. In fact the number of ankylosing spondylitis patients who were not treated by irradiation is very limited. However, Doll (35) has indicated that in a series of nearly 1,000 patients with ankylosing spondylitis who were never treated by radio-therapy, only one case of leukæmia had thus far occurred. The case was one of chronic lymphatic leukæmia, which is known to be rarely, if ever, induced by ionizing radiation.

54. In view of (*a*) the clear dose-effect relationship; (*b*) the characteristic time trend; and (*c*) the specificity of leukæmia type, and also in view of the fact that leukæmia is known to be caused by ionizing radiation in a variety of populations, there can be no doubt today that the excess risk of leukæmia induction among the ankylosing spondylitis patients was largely caused by the x-ray treatment. Assuming that the irradiation involved, on the average, 30-50 per cent of the bone marrow, the slope of the dose-effect curve given in paragraph 49 would correspond to a risk estimate of 1-2 cases per million per year per rad between 300 and 1,500 rads.

D. Radiologist with occupational exposure

55. The results (40, 59, 94, 95, 114, 132, 160, 167, 170) of a number of studies on American radiologists, together with a study on British radiologists, were discussed in the 1962 and again in the 1964 report of the Committee. In addition, the study of Lewis (81) on American radiologists published in 1963 was reviewed in the 1964 report. According to this study, the average annual mortality from leukæmia among radiologists during the 14-year period 1948-1961 was 253 per million per year compared with an expected mortality (based on mortality rates in the United States general population) of 85 per million per year, so that the excess was 168 per million per year.

56. Seltser and Sartwell (134, 135) also studied the mortality experience of American radiologists. Their earlier paper gave the results of a pilot study that examined the practicability of assessing the effects of radiation on American radiologists. The subsequent study published in 1965 included 3,697 male members of the Radiological Society of North America who had entered the Society during the years 1915 through 1954.

57. Compared to the general population, this group of radiologists was certainly selected with regard to education, socio-economic status, etc., and may thus have had a different mortality experience. Therefore, comparison groups were chosen from among the various medical specialties rather than from the general population. The subjects of the comparison groups were: 7,052 male members of the American College of Physicians (ACP) and 6,059 male members of the American Academy of Ophthalmology and Otolaryngology (AAOO). The members of the AAOO were considered the group least exposed to irradiation, and were thus regarded as the group with the lowest risk. The members of the ACP were considered to have received exposures between those of the radiologists and those of the AAOO population. The study and comparison populations were traced successfully to the end of 1958, and the cause of death was secured for 99.3 per cent of those deceased. The number of deaths among the radiologists reached 944 for the years 1935-1958.

58. The mortality of the radiologists was examined in the four disease categories: cardiovascular-renal diseases, leukæmia, all other cancers, and all other causes. In considering all causes of deaths, radiologists in the age range 35-79 showed an excess of 228 deaths by comparison with members of the AAOO. Of this excess, 103.4 (nearly one half) were due to cardiovascular-renal diseases, 11.3 to leukæmia, 48.2 to "all cancers except leukæmia", and 65.3 to "all other causes". The relative risk of death in these age groups (the ratio of the observed number of deaths to the expected number) was the highest for leukæmia (2.5); the next highest were those for all cancers except leukæmia (1.6) and for all other causes (1.6); the lowest that for cardiovascular-renal disease (1.2).

59. Thus, the excess risk of leukæmia among the radiologists compared to the AAOO members was of the order of 200 cases per million per year; this is in accordance with the results of Lewis (81) who compared the mortality of radiologists with that in the general population. Since the radiation dose received by the radiologists over their entire occupational life could not be estimated, it was not possible to derive the risk of leukæmia induction per unit dose. The radiation exposure was obviously heavier in the earlier part of the radiologists' careers as a result of insufficient protection. No cell-specific analysis of leukæmia was reported.

E. Patients exposed to therapeutic irradiation in pelvic region

60. Three major cohort studies on patients exposed to therapeutic irradiation in the pelvic region have been reported since the 1964 report, and a summary of them is presented in table 7.

61. Doll and Smith (38) studied the mortality experience of patients with metropathia hæmorrhagica treated by x-irradiation. The irradiation was confined to the pelvic region and the doses employed, though considerably lower than those used in the treatment of uterine cancer, were sufficient to induce an artificial menopause. Most patients (97.2 per cent) were treated only once by short-term irradiation. The patients —2,068 women—were selected from three radiotherapy centres in the United Kingdom (Aberdeen, Dundee and Edinburgh) in the period 1940-1960 and were followed through 1963. The follow-up period ranged from 3 to 24 years, 13.6 years on average. The follow-up rate was as high as 99 per cent, and the cause of death was ascertained in each case. The observed number of deaths by cause was compared with the expected number computed by applying sex-age-period-specific rates for Scotland to the person-year experience of the study group. An agreement between the observed and expected number of deaths was found for the group of all causes of death (245 observed to 234.56 expected), as well as for several selected subcategories of causes.

62. For leukæmia, although the numbers were small, a significant excess of deaths was noted—6 observed to 1.31 expected ($P<0.01$)—yielding a relative risk of 4.6. The excess was found to occur in the period of five or more years after exposure, the largest excess showing in the 5-9-year range, with a slow decrease thereafter.

63. Among the 2,068 women studied, an excess of 4.69 cases of leukæmia was observed. Ninety-eight per cent of these women were estimated to have received mean doses of between 75 and 174 rads (average 136 rad) to the whole bone marrow. In this range, the risk of leukæmia induction per unit dose may be given as 1.2 cases per million per year per rad.

64. In 1960, Simon *et al.* (140) reported that the risk of leukæmia in a group of about 72,000 patients treated with radiation for carcinoma of the cervix was not increased in comparison with the British or American female population. However, because of

certain problems relating to the methodolgy of this study which were discussed in the 1964 report, Hutchison (63, 64) re-investigated the risk of leukæmia induction in another group of cervix cancer patients who had also received radiation therapy.

65. With the co-operation of 29 radio-therapy centres in nine countries, approximately 28,000 patients were followed by annual or semi-annual physical examinations, which included peripheral blood examinations. Hutchison's 1968 report (63) showed preliminary results of two to five years of observation subsequent to the inclusion of the patients in the study; 49 per cent of the patients were included within one year after radio-therapy, 26 per cent within 1-5 years, and the remaining 25 per cent more than five years after radio-therapy.

66. In 14 per cent of the patients, radio-therapy involved only intracavitary radium, in 8 per cent, only external radio-therapy, and in 69 per cent, external radio-therapy was combined with intracavitary radium. The remaining 9 per cent received no radio-therapy and served as a control group. In three fourths of the patients receiving external radio-therapy, the mean dose to the whole bone marrow was estimated to range from 300-1,500 rads. As with metropathia hæmorrhagica patients, the irradiation was restricted to the bone marrow in the pelvic region which constitutes one third of the total active (red) bone marrow. Therefore the mean dose to the pelvic bone marrow may be estimated to have been 900-4,500 rads. The course of radiation treatment usually ranged from four to eight weeks.

67. The person-year experience of the group of irradiated patients reached about 60,000 at the end of 1965, as against approximately 6,000 person-years in the non-irradiated group. Four leukæmia cases were identified in the irradiated group, with no significant deviation from the expected number of 5.1, computed by applying age-specific incidence rates of leukæmia in the general population to the person-year experience of the patients. The risk of leukæmia was also examined for three different time intervals after exposure (0-3, 4-8 and 9 or more years after exposure), but again no significant excess was observed in any of the three time periods. In the non-irradiated group, one leukæmia case was detected.

68. The continuation of this study (64) showed that, as of 1970, both the number of leukæmia cases and the person-year experience had approximately doubled, so that the incidence remained unchanged. The comparison of the observed number of deaths from leukæmia with the expected number, classified by type of treatment or time interval since irradiation, showed no significant difference. For the entire observation period, there were 10 observed deaths *versus* 10.6 expected in the irradiated group. In the non-irradiated group there were two observed to 0.6 expected deaths. An explanation of the failure to detect any excess risk of leukæmia was sought by the author in the apparent nature of the irradiation. In contrast to both the A-bomb survivors and the ankylosing spondylitis patients, the patients with cervix cancer received a very large dose in a relatively small volume of tissue. The author postulated that this heavy dose might have been more destructive to pelvic bone marrow than stimulative of leukæmogenesis.

69. Wagoner (164) investigated the effects of radiation on patients with benign and malignant gynæcological disorders. A first cohort, taken from Connecticut (U.S.A.), comprised 1,893 patients with benign gynæcological disorders—hyperplasia of the endometrium, fibrosis, etc.—who had been treated by either x rays (993 cases) or radium (900 cases) and 7,835 patients with uterine cancer treated by radio-therapy. A second cohort, taken from Massachusetts (U.S.A.), comprised 1,803 patients similarly treated by radio-therapy for their benign gynæcological disorders. The observation period ranged from 2 to 32 years and the numbers of observed and expected deaths were compared. The expected number of deaths was computed on the basis of incidence (in Connecticut) or mortality (in Massachusetts) rates in the general population, specific for age, sex and calendar year.

70. It is evident from table 7 that heavily-exposed patients had no increased risk of leukæmia. Among the patients who had uterine cancer and who were treated by radio-therapy (estimated mean pelvic-marrow dose of 900-4,500 rad) there was no increase of leukæmia occurrence—9 observed cases *versus* 8.6 expected. This finding is essentially the same as Hutchison's. The patients with benign gynæcological disorders who received relatively heavy radiation dose (300-900 rad) also showed no significant excess of leukæmia occurrence—3 observed cases *versus* 2.4 expected. In contrast to the patients who received a heavy dose of radiation, the lightly-irradiated patients did show an increased risk of developing leukæmia. In the patients with benign gynæcological disorders who received radiation doses of 159-503 rads (the Connecticut group) and 159-318 rads (the Massachusetts group), the relative risk was 3.2 in the former (9 observed to 2.8 expected), and 2.8 in the latter (10 observed to 3.5 expected).

71. Thus, the studies by Simon *et al*, Hutchison and Wagoner all demonstrate that patients with uterine malignancies who have received heavy doses from x-ray and/or radium therapy show no increased risk of developing leukæmia. In addition, the study on patients with benign gynæcological disorders treated by heavy irradiation also showed no increased risk of leukæmia induction.

72. As noted previously, this obvious absence of leukæmogenic effects of heavy irradiation can best be explained by the nature of the exposure. There were reasons to question the methodology of the study of Simon *et al.*, but the more carefully-conducted studies of Hutchison and Wagoner have yielded the same finding regarding leukæmia induction. While the evidence provided by Hutchison's earlier study could have been considered as inconclusive because of the short follow-up period, his newer data (in which the person-year experience had doubled) and the study of Wagoner with its long observation period (2-32 years) show that there is no excess risk of leukæmia. The fact that the irradiation area (that of the pelvic region only) was limited is not likely to account for the absence of effect since Doll's study of metropathia hæmorrhagica and Wagoner's study of patients with benign gynæcological disorders showed an evidently high rate of leukæmia induction although the patients had radio-therapy in the pelvic region only. It looks more likely that the cell-killing effect of high radiation doses far outweighs their leukæmogenic effect.

F. Patients treated with ^{131}I or ^{32}P

73. Pochin (119) investigated the long-term effects of ^{131}I therapy in a group of 215 patients with in-

operable thyroid carcinoma. The patients had been treated during the period 1949-1967, and, through periodic health examinations at intervals of approximately six months or less, the vast majority (96 per cent) were followed up to 1 January 1968.

74. The incidence and mortality from malignant neoplasms found to have occurred in this group of patients were recorded and compared with the expected incidence and mortality computed according to sex and age-group specific rates for the general population. For leukæmia, mortality equalled incidence: 4 observed deaths to 0.08 expected, showing a significant excess ($P<0.005$). Excluding leukæmia from the list of malignancies, the excess of the observed mortality over that expected vanishes. Based on incidence, however, a possible excess risk was noted for cancer of the breast: 4 cases observed to 0.94 expected.

75. To assess the risk of leukæmia, the radiation doses received by blood from circulating radio-iodide and organic radio-iodine and from iodine concentrated in tissues were estimated for each patient. On the assumption that the bone marrow received the same dose as blood, the excess risk of leukæmia was estimated as 14 cases per million per year per rad (total experience 2.7 10^5 man-year-rad). If the bone marrow received 80 per cent (51) or 44 per cent (80) of the blood dose, the estimated risk would need to be increased accordingly.

76. As indicated by the author, caution should be exercised in interpreting the results owing to uncertainties regarding the accuracy of the bone-marrow-dose estimate, the comparability of the patient group with the general population and the fact that the series had been selected for study specifically because of an increased incidence of leukæmia.

77. In its 1964 report, the Committee presented the results of two studies which investigated the risk of leukæmia in patients with thyrotoxicosis exposed to low-dose irradiation from radio-iodine. The study by Pochin (118) showed an observed incidence of 18 cases as opposed to an expected incidence of 21 in an estimated 59,000 patients with thyrotoxicosis treated by ^{131}I. In Werner's study (171), 10 cases of leukæmia were observed as opposed to 13.8 expected among the 32,000 patients with the same disease and receiving the same treatment. In both studies the general population served as the comparison group and as the basis for computing the expected figures.

78. Saenger *et al.* (128) have investigated the incidence of leukæmia in 36,000 patients with hyperthyroidism treated in 26 medical centres by low doses of ^{131}I from 1946 to 1964. The majority (96-97 per cent) of the patients were followed to mid-1967. In this study the risk of leukæmia in patients treated with radio-iodine was evaluated by comparison with those treated surgically.

79. The person-year experience of the ^{131}I group and the surgery group was similar—119,000 and 114,000, respectively; almost identical numbers of leukæmia cases were observed, 17 in the ^{113}I group and 16 in the surgery group. Each of these groups was further subcategorized by sex, type of leukæmia, and differing time intervals following treatment, in an effort to detect an increase in incidence relating with any of these factors. However, no such relationship was discernible among the subcategories.

80. Besides, the leukæmia cases found in this study were compared to the non-leukæmia patients on the basis of administered dosage of radio-active iodine; they were found not to have received radio-iodine in amounts greater than the non-leukæmia patients, i.e., 8.9 millicuries and 10.6 millicuries, respectively. The average bone-marrow dose was believed to have been in the range of 7-13 rads in the leukæmia patients and of 8-15 rads in the non-leukæmia patients.

81. The absence of excess risk of leukæmia in this study might well have been expected in view of the low dose of ^{131}I administered. In fact the rate of 0.7–2.0 per million per year per rad suggested by the studies of Japanese A-bomb survivors for low-LET radiation, when applied to approximately 1.2 10^6 patient-year-rads in the group treated with ^{131}I, leads to an expectation of at most three induced cases of leukæmia. This small excess lies within the range of chance variability, so that even if leukæmia induction had resulted from the exposure of these patients to ^{131}I, no significant excess would have been observed.

82. It is of interest to note that both the ^{131}I group and the surgery group had a higher rate of leukæmia mortality than the general population. This observation might indicate that hyperthyroidism itself may be associated with higher rates of leukæmia. In a group of patients treated with both radio-iodine and surgery, a significant excess of leukæmia cases ($P<0.05$) as compared to the groups treated with either radio-iodine or surgery alone was noted. No clear explanation of this finding was presented.

83. In its 1964 report the Committee also discussed the excess risk of developing leukæmia among patients with polycythæmia vera treated with ^{32}P and pointed out that polycythæmia vera itself might predispose to, or be closely associated with, leukæmia making it desirable to compare the risk of leukæmia in polycythæmics treated by ^{32}P with that in similar patients treated otherwise.

84. Since that report, Modan and Lilienfeld (104) have studied the risk of leukæmia in such patients and shown that it is much higher in ^{32}P-treated patients than in patients not treated by radiation. The authors selected from seven co-operating hospitals in the United States 1,222 patients treated between 1937 and 1955 who met certain diagnostic and demographic criteria. Of these patients, 228 were polycythæmia vera cases treated with ^{32}P only and 133 were cases with the same condition but with no radio-therapy. The majority (98.4 per cent) of the 1,222 cases were followed to 31 December 1961. The frequency of occurrence of acute leukæmia was found to be as high as 25 cases (11 per cent) in the 228 ^{32}P-treated group, in sharp contrast to only one case (0.8 per cent) in the 133 non-radiation-treated group. (Chronic leukæmia was not included because of possible diagnostic uncertainties.) Between zero and 30 millicuries, the incidence of acute leukæmia rose approximately in proportion to the dose of ^{32}P at the rate of about 1 per cent per millicurie of ^{32}P injected, with a mean follow-up time of about eight years. Using a conversion factor of 30 rads to the bone marrow per millicurie of ^{32}P injected (see annex B) this would correspond to a risk of about 40 cases per million per year per rad.

85. In addition to the ^{32}P treatment, several other factors were analysed by the authors in an effort to account for the observed difference in the incidence

of acute leukæmia occurring in the groups, but no plausible factors were identified. Although in this study the control group was adequately chosen from polycythæmia vera patients not treated by radiation, the very high risk of acute leukæmia after ^{32}P may, as the authors themselves pointed out, be the result of an unusually high sensitivity to radiation of the polycythæmic bone marrow.

86. Tubiana *et al.* (159) showed, in a series of 296 patients, that the amount of ^{32}P administered to polycythæmics was larger in those with high initial white counts and enlarged spleens, suggesting that the increased rate of leukæmia may at least in part be due to the biological factors that determine the treatment.

II. Thyroid neoplasms

A. A-BOMB SURVIVORS

87. In the Committee's 1964 report, it was stated that the two ABCC studies that had been published at that time (141, 176) suggested that the incidence of thyroid cancer among A-bomb survivors was inversely related to the distance from the hypocentre at the time of the bombing (ATB).

88. The recent report of Wood *et al.* (173) confirms the earlier findings. It now seems certain that thyroid cancer has increased among those A-bomb survivors who were proximally located to the hypocentre ATB.

89. Thyroid carcinoma is commonly a non-fatal disease. An intensive survey in one country found that the relative five-year survival rate[2] of thyroid cancer in females—thyroid cancer is predominantly a female disease—is 80 per cent for all ages combined and 96 per cent for those under 45 years of age (32). Because of the low fatality rate of thyroid cancer, it is appropriate for the Committee's purpose to measure the risk of the disease in terms of morbidity rather than of mortality.

90. Wood *et al.* (173) based their findings on the Adult Health Study Sample (morbidity sample) of about 20,000 subjects who had routine biennial health examinations from 1 December 1963 to 31 December 1965. In 1964-1965, the examination rate among all living subjects of the Adult Health Study Sample was about 80 per cent for those over 40 years of age and somewhat lower for those under 40 years. The authors believed that examination rates did not differ substantially with exposure status.

91. Among the more than 13,000 persons examined in 1964-1965, 39 thyroid cancer cases were found and histologically confirmed. In addition, 386 individuals showed other thyroid abnormalities, a majority of which (298) were non-toxic goitres. Although the report is not very clear, some of the 39 cancer cases were presumably diagnosed and treated sometime before the 1964-1965 examination. The distribution of these cases in relation to sex, age, and distance from the hypocentre is presented in table 8. Since little difference is noted between Hiroshima and Nagasaki, the data for both cities are combined.

92. From table 8, the following observations may be made:

(*a*) The proximally exposed subjects show much higher rates than those distally exposed. Among females, the difference between the rates in the different exposure categories is statistically significant ($P<0.01$). The number of male cases was too small for statistical tests to be performed. For females of all ages combined, the group exposed within 1,400 metres has a 2.5 times higher rate than the 1,400-1,999-metre group and a 3.9 times higher rate than the 3,000+-metre group. The corresponding figures for males are even higher than for females, i.e., 4.0 and 9.0, respectively;

(*b*) There are indications that thyroid cancer occurs among the survivors more frequently in females than in males. The sex ratio of females to males is 2.2 for the proximally exposed group (within 1,400 m group). However, this does not necessarily mean that females are relatively more sensitive to thyroid cancer induction than males, since the natural occurrence of the disease is known to be much higher in females than in males (37, 78, 102);

(*c*) The age variation in susceptibility to the induction of thyroid cancer by A-bomb irradiation is unclear. Among males within 1,400 metres, all thyroid cancer victims were less than 40 years of age at the time of examination. However, the number of cases is too small (only 5) to conclude that younger men are more susceptible than older men. For females, the cases of thyroid cancer do not cluster in younger subjects: for those within 1,400 metres, the rates are 10.7 for those <40 years of age, 4.4 for those 40-59 years, and 8.5 for those 60 and above.

93. Beside expressing the relation of thyroid cancer risk of induction by irradiation in terms of distance from the hypocentre as shown in table 8, Wood *et al.* also expressed this relation in terms of the new kerma estimates for survivors within 2,000 metres of the hypocentre. As the actual number of cases is not recorded, only the rates per 1,000 examined are shown in table 9. As seen in the table, the risk of thyroid cancer clearly increases with increasing kerma for both sexes. The rates of the 200+ rad group are 9.1 per thousand for females and 4.1 per thousand for males. The figure of 9.1 for females is 3.3 times that of the 0-49 rad group and 1.3 times that of the 50-199 rad group. The corresponding ratios for males are 3.7 and 1.6, respectively.

94. For the purpose of radiation protection, even a rough estimate of the risk of thyroid cancer induction per rad among the A-bomb survivors would be of value. However, because of the inclusion of cases which were detected at an undetermined time prior to the 1964-1965 examination and because of the long duration of thyroid cancer, the period of time during which the observed cases of thyroid cancer developed has been difficult to ascertain. Considering the time interval between exposure to radiation (1945) and examination (1964-1965), that period of time should be less than about 20 years; and because of the long duration of the disease, the time period is likely to be more than 10 years. If the time period ranges from 10 to 20 years and if the difference in the average dose is 100 rads between the 0-49 and the 50-199 rad groups and 200 rads between the 0-49 and 200+ rad groups, then the risk of induction of thyroid cancer in the range 25-200 rads is 1-2 cases per million per year per rad for males and 2-4 cases for females.

[2] The survival rates presented are the adjusted rates which the patients would have experienced had deaths been only from thyroid cancer.

These figures, of course, should be taken as highly tentative, particularly because of wide uncertainties about doses (no allowance having been made for the RBE of the neutron contribution) and about the duration of the observation period. More accurate estimates can only derive from further and more detailed data.

95. Sampson *et al.* (129) have reported on the prevalence of occult thyroid carcinoma in the autopsy series of the Life Span Study Sample. Under the ABCC autopsy programme, 3,067 autopsies were performed during 1957-1968 in Hiroshima and 1951-1967 in Nagasaki. The majority (89 per cent) of the autopsies were performed during 1961-1967, when the autopsy rate was 39 per cent with little bias relating to radiation exposure. Among the 3,067 subjects, 536 cases of thyroid carcinoma were found after histological examination of serial sections of thyroid glands. Almost all of the identified cases were clinically occult (97 per cent). Histologically, 98 per cent were papillary adenocarcinomas.

96. The prevalence of thyroid carcinoma in the autopsy series is shown in figure VIII. The authors

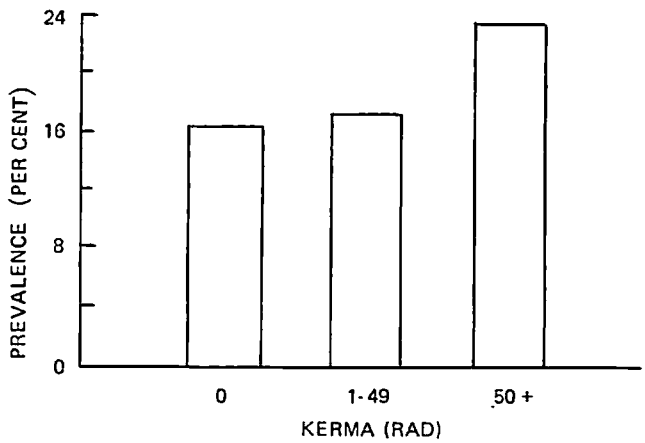

Figure VIII. Prevalence of thyroid carcinoma among autopsied cases of A-bomb survivors as a function of kerma (129)

indicate that the prevalence rate was significantly higher among those exposed to 50 rads or more compared to those exposed to less than 50 rads. The 50+ rad group had a 41 per cent excess, and the 1-49 rad group a 5 per cent excess over the non-exposed group.

97. In spite of the observed dose-effect relation, the meaning of this study is difficult to assess. The relation between clinically apparent thyroid carcinoma and occult thyroid carcinoma has not been clearly established. For occult carcinoma, ratios of males to females are 1.2 in this study and 1.0 in another similar study in Japan (155), whereas for clinically manifest thyroid carcinoma the sex ratios vary from 2 to 3 (36, 78, 102). The observed prevalence rates in this study—15.7 per cent for males and 19.4 per cent for females—are unusually high compared to the rates of clinically apparent thyroid carcinoma—0.8 per cent for males and 1.8 per cent for females (78). For occult thyroid carcinoma the observed rates of 10-20 per cent in the Japanese population in Japan (129, 155) and among Japanese descendants in Hawaii (U.S.A.) (49) are much higher than those reported (56, 105) in the American series (1-3 per cent), although the rates of clinically manifest thyroid carcinoma in Japan and the United States are similar (36, 37). Thus, in view of the unclear role of occult thyroid carcinoma in the development of clinically manifest thyroid carcinoma, the study of Sampson *et al.* is only suggestive of radiation-induced thyroid cancer among the A-bomb survivors.

B. Residents of the Marshall Islands exposed to radio-active fall-out in 1954

98. After the Committee's 1964 report, a substantial body of evidence has accumulated regarding increased risks of the induction of thyroid tumours among residents of the Marshall Islands accidentally exposed to radio-active fall-out in 1954 (23, 24). A comprehensive monograph of Conard *et al.* in 1970 (25) gave detailed information about thyroid-tumour induction in the residents exposed to fall-out.

99. The accidental exposure of these islanders occurred in March 1954 during hydrogen-bomb testing at Bikini Island. The inhabitants of the island of Rongelap were the most exposed, having received an estimated whole-body dose of 175 rads of gamma radiation and a dose contribution from the internal deposition of radio-nuclides such as ^{89}Sr and ^{131}I. The presence of a burden of radio-nuclides was detected by radio-chemical analyses of urine samples and was thought to have probably been brought about mostly by eating and drinking contaminated food and water and to a lesser extent by inhalation. The body levels of the radio-nuclides fell off rapidly, so that six months later radio-activity in the urine was barely detectable. Besides the Rongelap residents, the people of the islands of Ailingnae and Utirik were exposed to substantial internal and external doses.

100. Extensive medical examinations were performed on the exposed population immediately after the exposure, and annual health examinations have been carried out since. The relatives of the exposed individuals of Rongelap island who were away from the island at the time of the accident and who returned thereafter served as an adequate control population in evaluating the late effects of radio-active fall-out.

101. Only thyroid tumours are reported to have been induced in the exposed population. This is probably due to the fact that the thyroid gland was exposed to high doses of radiation from radio-iodine. No cases of leukæmia have been detected.

102. Table 10 shows the frequency of benign and malignant thyroid tumours in the 15-year period 1954-1969, together with estimated external gamma-ray doses and doses from internal deposits of radio-iodine in the thyroid gland. The estimate of the internal deposits was made on the basis of radio-chemical analysis of urine obtained several weeks after the exposure. In addition to ^{131}I, the isotopes ^{133}I, ^{135}I, and to a lesser extent ^{132}I contributed significantly to the thyroid dose. The main source of iodine ingestion was considered to be water, and since the water was being rationed at the time of the fall-out, it was assumed that the same amounts of iodine isotopes were absorbed by each person irrespective of sex and age. As shown in the table, the total estimated thyroid dose from the various iodine isotopes for the Rongelap people was 160 rads for adults and from 500 to 1,400 rads for children, taking into account the smaller size of the children's thyroid glands.

103. The first case with a thyroid lesion was detected in 1963. This case was found nine years after exposure, in the course of an annual health examination which disclosed an asymptomatic thyroid nodule that was later proved by histological examination to be a benign adenoma. Since then, increasing numbers of thyroid abnormalities have been detected in the exposed populations, particularly at Rongelap. As shown in table 10, the number of clinically apparent thyroid lesions reached 21 cases (19 cases of nodular gland and 2 cases of atrophic gland) in the Rongelap population in the 15-year period 1954-1969. Surgical exploration was carried out in 18 of the 19 nodular thyroid glands, and revealed malignant lesions in three of them and benign adenomatous lesions in the remainder.

104. The group of Rongelap children of ages <10 (the group exposed to the highest dose) showed a strikingly high frequency of thyroid lesions (89.5 per cent), in contrast to the absence of lesions in people of the same age in the less exposed and unexposed groups. It was clear that the more exposed group had a higher incidence of thyroid lesions. Three malignant lesions among the 53 Rongelap residents (5.7 per cent) were noted; the expected number on the basis of incidence statistics among the 17,000 Marshallese was 0.056, showing a significant difference at $P<0.01$.

105. Although it is probably impossible to make an accurate dose estimate, the risk of thyroid nodularity in the exposed Marshallese was estimated by the authors to be about 50 cases per million persons per year per rad in a dose range from 500 to 1,400 rads. Based on the one in six proportion of malignant cases revealed by surgical exploration, the risk of nodularity would correspond to a risk of carcinoma close to 10 cases per million per year per rad. This estimate is, of course, subject to the inaccuracy of numerous factors that affect the dose estimates, and therefore may be regarded as a tentative rough index of thyroid cancer induction by irradiation in the exposed Marshallese.

III. Breast cancer

A. A-BOMB SURVIVORS

106. Wanebo *et al.* (168) have investigated the risk of breast cancer among A-bomb survivors in Hiroshima and Nagasaki according to the new (T65D) kerma estimates. Because of the low early fatality of breast cancer (32) the authors assessed the risk in the morbidity sample (Adult Health Study Sample), on which biennial health examinations are performed. The study population comprised 10,357 women in 1958. Of these, approximately 98 per cent had been examined at least once by 1966. No remarkable difference was noted in the proportion of those examined in the different dose groups.

107. Beside the clinical data obtained at the biennial health examinations, the following sources gave additional information: autopsy diagnosis, surgical pathology diagnosis, death certificates, and local tumour registries. From these sources 25 cases of breast cancer were found among the women of the morbidity sample from 1958-1966. Of the 25 cases, 22 were confirmed by tissue examination, and the remaining three cases were designated as possible cases.

108. The distribution of the 22 cases in relation to kerma is shown in table 11. As noted, there is a clear increasing trend in the relative risk of breast cancer with increasing dose. Those who had received 200 rads or more have about twice the risk of those exposed to 40-89 rads and six times the risk of those exposed to 0-9 rads. This increase is statistically significant ($P<0.01$ between the groups of survivors over and under 90 rads). It is noteworthy that even low-dose groups (10-39 and 40-89 rad) show higher risks than the non-exposed population.

109. The excess number of breast cancer cases in the female A-bomb survivors exposed to 10 or more rads may be estimated as 11.5, or approximately 400 cases per million exposed per year. If the mean dose of these survivors is in the range from 100 to 200 rads, the excess risk would be of the order of 2-4 cases per million per year per rad.

110. The mean induction period for definite cases is 15.4 years and the mean age at onset of the disease is about 10 years less at high doses (50+ rad) than at low doses (<50 rad). No clear relation between dose and histologic type of breast cancer was observed. The majority of cases, 78 per cent, were infiltrating duct carcinomas.

111. Breast cancer is known to be associated with such factors as socio-economic status, lactation period, parity, and marital status. The recent international study of MacMahon *et al.* (92)—a case control study covering over 17,000 cases and controls in different countries—indicates that non-parous women have a higher risk relative to parous women. Among the Japanese the relative risk is 1.56.

112. Wanebo *et al.* (168) found that (although statistically non-significant) breast-cancer patients among A-bomb survivors did tend to be unmarried, less parous, and to have lactated for shorter periods. They did not record how such factors related to different exposure categories. Therefore, it is impossible to estimate to what extent the observed dose-effect relationship may be explained by the aforementioned factors. However, it is also obvious that the observed relationship could not be entirely explained by the confounding of extraneous variables. For example, even if all of the women in the 200+ rad group were non-parous and all non-exposed subjects were parous, the relative risk would then still be only 1.56 according to the data of MacMahon *et al.* (92), whereas the observed relative risk is about 6.0.

113. The uncertainty of the study of Wanebo *et al.* may lie in the fact that the observed number of cases is very small (only 9 cases in the 90+ rad group). This small number is likely to have been affected by large chance fluctuations and by the aforementioned variables, or even by the fact that the ascertainment rate of cancer may have been higher in the heavily exposed group if the subjects had appeared more frequently at medical examinations than had those in the less exposed group.

114. It may be concluded that the study of Wanebo *et al.* strongly suggests that the survivors heavily exposed to irradiation are at increased risk of breast cancer, but a definite conclusion will be obtained only after more data have accumulated.

115. In their mortality reports for 1950-1966, Beebe *et al.* (10, 11) dealt with the risk of breast cancer in the Life Span Study Sample. Sixty-seven deaths were ascribed to the disease. No statistically significant

dose-effect relation was observed for the whole 1950-1966 period, and none for any of the four-year periods betwen 1950 and 1966, except for the last one. In the 1962-1966 period, a statistically significant relation between breast-cancer mortality and dose was observed ($P \sim .05$). The authors concluded from the mortality data that the evidence regarding radiation effects on female breast cancer was merely suggestive.

116. The less clear evidence of radiation effects observed in this mortality study as compared to Wanebo's may be more apparent than real. Mortality data are expected to lag behind morbidity data because of the low fatality of the disease; the five-year survival rate of breast cancer is reported (32) to be 50 per cent, and only one third of the breast cancer cases in Wanebo's study was identified through death notification. Besides, radiation effects on breast cancer seem to have become apparent in recent years—the effects were only seen in the 1962-1966 period in the study of Beebe *et al.* Therefore, Wanebo's study covering more recent years (1958-1966) should show a stronger dose-effect relationship.

117. The mortality study of Jablon and Kato (73, 74) has added new mortality data for the period from 1967-1970. In table 5, the number of deaths from breast cancer in 1950-1970 amounted to 104, of which 80 were recorded in Hiroshima and 24 in Nagasaki. Compared to the expected deaths based on national rates, only the 100-199 rad group of Hiroshima, among the various individual dose groups, showed a significant excess ($P<0.05$). However, when all the survivors, except the virtually non-exposed belonging to the 0-9 rad group, are put together, both Hiroshima and Nagasaki show significant ($P<0.05$) excesses—29 *versus* 13.6 in Hiroshima and 12 *versus* 4.6 in Nagasaki. Assuming that the neutron RBE varies from 10 to 1 as in the case of leukæmia (see paragraph 36), the Hiroshima results would suggest tentative risk estimates for exposure to low-LET radiation of 0.3 and 1 case per million per year per rad at 60 and 400 rads, respectively. The lower risk for breast cancer obtained in this mortality study in comparison with Wanebo's morbidity study may be explained at least in part by the relatively low fatality of the disease.

B. Tuberculosis patients exposed to repeated fluoroscopic examinations

118. Mackenzie (87) reported in 1965 that tuberculosis patients exposed to repeated fluoroscopic examinations for pneumothorax treatment were at increased risk of developing breast cancer. This possibility was first suggested by the findings of an apparent radiation dermatitis of the skin over the right chest wall, breast and sternal region in a female patient in whom cancer of the breast had been diagnosed. Her past history revealed that, for the treatment of pneumothorax, she had undergone at least 200 fluoroscopies over a 46-month period some 14-15 years previously. Her radiation reaction was suggestive of an accumulated exposure of over 4,000 roentgens. The artificial pneumothorax was a world-wide common practice for the treatment of lung tuberculosis before the introduction of chemotherapy; in North America, this therapy was common from the 1920s to about 1950. Fluoroscopic examination was made each time (usually before and after) the pleural cavity was refilled with air.

119. The author then searched the Tumour Clinic files of Nova Scotia (Canada), which revealed 50 cases of breast cancer patients with a previous history of pulmonary tuberculosis. Of these, 40 were found to have had artificial pneumothorax therapy accompanied by fluoroscopic examination. In many cases, fluoroscopic examinations had been repeated quite frequently with consequent substantial radiation exposure of the patient: 16 patients had 100-200 fluoroscopies and 9 had more than 200.

120. An accurate estimate of the radiation dose received by the patients could not be made because of the inherent difficulties of dosimetry for fluoroscopic examinations. It is quite likely, however, that in many cases the doses to breast tissue were very high because of features related to the methods of the fluoroscopic examinations. These included orientation of the patients so that the x-ray beam entered anteriorly, the use of x-ray beams with low inherent filtration and little or no added filtration, and high screening currents to compensate for inadequate dark adaptation.

121. The patients tended to have cancer involvement in the breast on the same side as the treated lung. Among 24 cases having unilateral pneumothorax treatment, ipsilateral breast cancer was observed in 15 cases. The location of the tumour in these patients tended to occur in the central or inner half of the chest (72.8 per cent), the area most likely to have been included in the fluoroscopic field. This finding is in marked contrast to the usual distribution of malignant tumours within the breast, where the outer half is predominantly involved (53).

122. The age of onset of breast cancer was compared in two groups of patients classified on the basis of whether they had multiple fluoroscopic examinations or not. The exposed group showed a much younger age distribution than the non-exposed group, and the difference was statistically highly significant. However, this finding is difficult to interpret, since the pneumothorax treatment was introduced only after about 1920 and the number of individuals so treated must have been very limited among those that were at least 60 years old at the time of the report, in 1965.

123. The author also presented the results of a follow-up study comparing the occurrence of breast cancer between two groups of female tuberculosis patients in a sanatorium. Thirteen breast cancer cases were discovered in the pneumothorax-treated group of 271 cases, and only one case in the other group (without pneumothorax treatment) of 510. Although the difference between the occurrence rates of breast cancer in the two groups was impressive, this report lacked information about the extent to which the follow-up was complete, which is undoubtedly essential for the evaluation of the results. Therefore, in this report, even the relative rates of occurrence of breast cancer between the two groups was uncertain, and much more so for the absolute rates of breast cancer occurrence.

124. Myrden and Hiltz (107) studied tuberculosis patients traced up to 1966 who had been treated at the Nova Scotia Sanatorium—presumably the same sanatorium as that used as a source by Mackenzie—during the years 1940 to 1949 inclusive. The period of observation ranged for individual patients from 15 to 25 years after treatment. Among 867 female patients eligible for admission to the study, 783 were traced, with a follow-up rate of 90 per cent. Of those 783 patients, 300 received pneumothorax treatment accom-

panied by repeated fluoroscopies, while the remaining 483 were not so treated. Twenty-two cases of cancer of the breast were observed in the former (7.3 per cent) and only four in the latter (0.8 per cent). The annual incidence in the pneumothorax group was, on average, 0.36 per cent for the entire follow-up period—a strikingly higher rate compared to that of the general female population, which in Nova Scotia was 0.055 per cent in 1965.

125. The average time from the beginning of pneumothorax treatment to the development of breast cancer ranged from 8 to 24 years, or 17 years on the average.

126. There was a clear agreement between the side of the chest exposed to the fluoroscopies and that of cancer involvement of the breasts. In the 22 cases of breast cancer occurring in the treated group, pneumothorax treatment was restricted to one side in 17 of the patients; 14 of these patients were later found to have developed their breast cancer on the side of treatment.

127. When the 22 breast cancer cases with pneumothorax treatment were classified according to the number of fluoroscopies received, the majority of them (19 cases) were found to have undergone more than 75 examinations and, among these, 13 had had over 175 examinations.

128. The estimation of the doses received by these patients is difficult but Mackenzie (87) reported dose rates to the skin of the breast when the patient was facing the x-ray tube. The most probable conditions resulted in exposure rates of 22 roentgens per minute if a one-millimetre aluminum filter was used or 55 roentgens per minute without a filter, and assuming that a five milliampere screening current was used. A 10 second exposure was recommended to the physicians, but Mackenzie infers that higher currents and larger exposures were not uncommon. Assuming that the actual exposures were equivalent to a 10-20 second exposure, the total skin dose to the breasts of a patient examined for an average of 160 examinations would have been in the range 600-3,000 rads depending on the irradiation time and whether a filter was used or not (actual doses to some individuals may have been even up to 10-15,000 rad). The excess of 20 cases of breast cancer in 300 patients followed for an average period of 20 years reported by Myrden and Hiltz (107) would therefore correspond to 1-6 cases per million per rad per year in the dose range just discussed.

129. With regard to risk of cancer induction other than to the breasts, no information was given in the reports of either Mackenzie or Myrden and Hiltz, so that it is not clear whether the tuberculosis patients with repeated fluoroscopies had an excess risk of developing other cancers such as lung cancer, nor whether this possibility had been examined.

130. There have been several case reports (84, 96, 112) of cancer of the breast occurring in patients who had previously undergone radiation therapy. One such case was that of a male who developed breast cancer 35 years after radiation therapy for gynecomastia (84). However, these case reports of one or two patients are only suggestive of breast-cancer induction by irradiation.

131. Mettler *et al.* (100) followed up 606 women treated with x rays for acute post-partum mastitis. The follow-up period in most cases was from 10 to 25 years. Eighty-nine per cent of all patients were traced in a first survey in 1962 and 85 per cent in a subsequent survey in 1967.

132. The radiation treatments were mainly carried out with x rays generated in the 175-250 kVp range. Of the 606 patients, 183 received bilateral treatment. While the mean exposure to one breast field was about 350 roentgens, most of the exposures were in the 100-499-roentgen range but up to about 1,000 roentgens were given in some cases. The average exposure to all the breast tissue (expressing for all patients the mean of the exposures to both breasts even when the contralateral breast was not irradiated) was 211 roentgens.

133. Thirteen confirmed cases of breast cancer were observed in contrast to the expected number of cases, 5.86, the computation being based on the incidence of breast cancer in the female general population of comparable age. For cancer of all sites, this group of patients showed an excess of 6.35 cases (28 observed *versus* 21.65 expected), but the excess could be entirely accounted for by the excess of breast cancer.

134. Although the patient group apparently had a higher risk of developing breast cancer, its causation should not simply be attributed to the previous x-ray treatment. In this study the dose-effect relationship between radiation dose and the risk of breast cancer was not very clear. It is possible that acute post-partum mastitis itself might have been responsible for the high risk of developing breast cancer rather than the previous exposure to radiation. Some of the benign breast conditions are suspected of having had a positive association with breast cancer (83) and acute post-partum mastitis also might be so associated. This possibility could best have been evaluated had a comparison group been chosen from among the patients with acute post-partum mastitis treated by other than x-ray irradiation. However, the number of patients so treated is limited and such a study has not been reported thus far.

IV. Lung cancer

A. A-BOMB SURVIVORS

135. The association of lung cancer with radiation exposure in the A-bomb survivors was first suspected by Beebe *et al.* (9) who observed in the 1961-1965 autopsy material of the Life Span Study Sample a significant excess of deaths from cancer of the lung (16 observed *versus* 9.8 expected, $P \sim 0.05$) among the survivors located at less than 1,400 metres from the hypocentre ATB, whereas such an excess could not be found in the less exposed groups at 1,400-1,999 metres and at 2,000+ metres.

136. Wanebo *et al.* (169) investigated the relation of lung cancer to irradiation by utilizing all available sources at the ABCC in both the Life Span Study Sample and the Adult Health Study Sample through 1966. The authors included among their sources the mortality and autopsy data of the Life Span Study Sample, the clinical data of the Adult Health Study Sample, the tumour registries of Hiroshima and Nagasaki, and surgical specimens sent to the ABCC by private practitioners.

137. During 1950-1966, 188 deaths occurring in the Life Span Study Sample (mortality sample) were

attributed to lung cancer, most of which (154) occurred in the latter half of the observation period. The risk of death from lung cancer appeared to increase with increasing kerma (T65D) and, when all the subjects were classified into either the 90+ rad or <90 rad group, the difference between the two groups was statistically significant ($P \sim 0.001$).

138. In the Adult Health Study Sample (morbidity sample), 66 cases of lung cancer were confirmed by pathologic examinations or thought to be probable cases on the basis of radiological and clinical findings. The distribution of the 66 cases, as with the mortality sample, showed the risk for lung cancer to be increasing with kerma. However, the difference between the 90+ rad and the <90 rad groups was barely significant ($P \sim 0.05$). Information regarding the distribution of lung cancer by histologic type is available for only 52 cases of which 40 per cent were classified as adenocarcinoma, 37 per cent as squamous carcinoma and 20 per cent as undifferentiated carcinoma. No relationship between radiation exposure and histologic type was observed in this small series of subjects.

139. Since smoking is known to be causative of lung cancer, an attempt was made to establish whether smoking was a confounding variable by determining its relationship to radiation dose and lung cancer in the adult health sample. The number of cases was too small to obtain conclusive results, but there was no evidence that the difference between exposure groups was due to different smoking habits in the two groups.

140. In their mortality analyses of various causes of death, Beebe *et al.* (10, 11) reviewed the deaths from lung cancer recorded in the Life Span Study Sample for 1950-1966. Except for minor differences, their results were essentially the same as those of the mortality part of the study of Wanebo *et al.*, because both studies covered the same study period and the same sample.

141. More recently, Jablon and Kato (73, 74) have reviewed the 1950-1970 mortality data from the Life Span Study Sample. The sample now includes 246 cases of lung cancer in Hiroshima and 71 in Nagasaki (table 5). When the deaths occurring in the practically non-exposed population (the NIC and the 0-9 rad groups) are excluded, the number of lung cancer deaths in the exposed survivors are reduced to 79 in Hiroshima and 22 in Nagasaki.

142. As stated earlier, the expected numbers of deaths calculated by three different methods give, in general, similar values for all causes. For lung cancers, however, the expected deaths based on the NIC or 0-9 rad groups are substantially and consistently higher than those, age- and sex-adjusted, based on national rates. The former may be preferred to the latter in comparing with the observed numbers, since the ABCC cohort belongs to an urban population, and the prevalence of lung cancer in urban areas is known to be higher than the country-wide average for Japan (137).

143. In the survivors exposed to more than 10 rads, a significant excess of deaths (observed minus expected) was noted for Hiroshima ($P \sim 0.01$), 79 observed against an expectation of 47.8 (0-9 rad) or 39.5 (national rates). The risk of lung-cancer death in Hiroshima clearly increases with kerma, the observed/expected ratios being 1.81 (10-49 rad), 1.97 (50-99 rad), 2.30 (100-199 rad), and 2.68 (200+ rad). The rate of increase of lung-cancer deaths with kerma, however, appears to decrease in higher exposure categories. Thus, in terms of kerma, the risk per million per year per rad varies according to exposure category as follows: 3.2[3], 1.5, 1.1 and .3.

144. Kerma is not the quantity in terms of which the risk of cancer of deep tissues, including lung, should be expressed, particularly if the risks need to be normalized to those of low-LET radiation, since the radiation incurred at Hiroshima had a substantial neutron component. Although the RBE for lung cancer induction and the depth of the tissue at risk are unknown, it is of some interest to indicate the relationship between effects and the doses that can be obtained on the basis of information on the attenuation of neutrons and gamma rays by body tissues (121).

145. The figures in table 12 give, for each kerma range (K), the mean total kerma ($\bar{K}_T$) and its neutron and gamma contributions ($\bar{K}_n$ and $\bar{K}_g$). From these are derived doses (D_n and D_g) at depth of approximately four centimetres in tissue. Neutron doses are multiplied by the arbitrary RBE values used earlier and added to the gamma doses to obtain the total dose (D_T) at a depth of four centimetres. The excess incidence (E) compared to the 0-9-rad group at Hiroshima is then combined with the dose to obtain risk estimates (R) in each exposure group. The same trend that was observed when excess incidences were related to kerma (paragraph 143) is observed here, although the actual risk estimates are somewhat different.

146. In contrast to Hiroshima, no significant excess of deaths is noted for Nagasaki, 22 observed in the exposed survivors as against 22.8 (0-9 rad) or 14.5 (national rates) expected. The reason for this discrepancy is unknown, although it may at least in part be accounted for by differences in radiation quality.

147. It now seems reasonable to assume that the A-bomb survivors at Hiroshima are at increased risk of dying from cancer of the lung. The risk estimates obtained at Hiroshima (2.3 and 0.6 cases per million per year per rad at 30 and 260 rad respectively), must of course be taken with the greatest caution, both because of the assumptions on which they are based (particularly about RBE values) and because of the negative evidence provided by the Nagasaki survivors. Taken at face value, they would indicate that at low doses (of the order of 30 rads) of low-LET radiation the risk of induction of lung cancer may be three times as high as the risk of leukæmia induction, whereas the opposite may be true at higher doses.

148. It must be noted, however, that, while we have reason to believe that the risk of occurrence of further cases of leukæmia among the survivors is now tapering off, we do not know whether new cases of radiation-induced lung cancer may not yet continue to be recorded and for how long, nor are we sure that estimates derived from the Hiroshima data would apply to a completely non-smoking population.

[3] Computed by dividing the excess deaths of observed over expected (based on the 0-9-rad group) by person-year-rad experience.

B. Ankylosing spondylitis patients treated by x-irradiation

149. In the study on ankylosing spondylitis patients treated by x-irradiation, Court Brown and Doll (28) observed a substantial excess of mortality from lung cancer over that expected in the general population in the United Kingdom. Relative risks and excess mortalities are presented in table 13 for each site of cancer within the x-ray beam. Among these 12 sites, the greatest excess was for lung cancer. The corresponding risk, in absolute terms, amounted to 252.4 cases per million per year and accounted for nearly half of the excess risk of all 12 cancers combined.

150. No estimates of the lung doses received by the spondylitics are available. However, Dolphin and Marley (39), on the basis of the average spinal-marrow dose being 880 rads, have estimated the average bronchial dose to be about 80 rads, which would correspond to a risk of some three cases per million per year per rad, if the excess incidence was all ascribable to irradiation, an estimate not too different from those that could be derived from the Hiroshima data at similar doses.

151. The data do not make it possible to ascertain the role of such factors as smoking habits, the disease itself that had required radio-therapy or the other forms of medication that the patients may have received.

C. Tuberculosis patients

152. Steinitz (148) has reported that tuberculosis patients in Israel were at increased risk of developing lung cancer compared to the general population. This finding was interpreted by some as evidence that diagnostic x-irradiation given to tuberculosis patients was causative of lung cancer.

153. In Israel, a cancer registry as well as a tuberculosis registry is maintained on a nation-wide basis. On the basis of tuberculosis registry, the author estimated the frequency (prevalence) of tuberculosis patients in the country specific for sex and age. The lung cancer cases newly reported to the cancer registry were searched to determine whether they had also been filed in the tuberculosis registry. Incidence rates of cancer of the lung were then estimated among the tuberculosis patients, and showed that the patients were at a 5-10 times greater risk of developing lung cancer than the general population.

154. The author also analysed the risk of lung cancer induction among tuberculosis patients on the basis of mortality records. The number of deaths that occurred in the registered tuberculosis patients were compared with those in the general population for "all causes", "all malignant neoplasms", and "lung cancer". It was noted that the tuberculosis patients had a much higher risk of dying from lung cancer than the general population.

155. Although little doubt remains that the tuberculosis patients in Israel were at increased risk of lung cancer induction, the extent to which irradiation is responsible for that increase is unclear. Information on the irradiation experience of the patients, essential with regard to radiation carcinogenesis, was lacking in the report, so that radiation effects could not be ascertained. The possibility that some people may be especially susceptible to lung diseases—that is, susceptible to both lung tuberculosis and lung cancer—cannot be ruled out. In addition, tuberculosis itself, rather than its treatment, may have facilitated the induction of lung cancer, e.g., scars of healed lesions of tuberculosis may predispose to cancer induction. It may be relevant to note that some other respiratory conditions (e.g., chronic bronchitis) are also suspected of having a causal association with lung cancer (14). Furthermore, since the clinical differentiation between lung tuberculosis and lung cancer is not always clear, some lung cancer patients might have been initially misdiagnosed as having had lung tuberculosis. Thus, further investigations are needed to assess the possible causative role of diagnostic irradiation in lung cancer induction in tuberculosis patients.

D. Workers exposed to high radon levels

156. Workers in certain underground mines, particularly uranium mines, are exposed to high levels of radon present in the mine's atmosphere. ^{222}Rn is a gaseous radio-nuclide that decays into radio-active daughters. These attach to aerosol particles present in the atmosphere. When inhaled, they can remain trapped in the bronchial tree where they deliver high-LET radiation to the respiratory epithelium.

157. Physiological and dosimetric details are considered in annex A of the present report. Here it will only be mentioned that the dosimetry of this situation presents considerable difficulties that have not all been solved. When known, the exposure of uranium miners is measured in "working levels", defined as any combination of short-lived radon-daughter products in one litre of air that will result in the ultimate emission of 1.3 10^5 MeV of potential alpha energy. Depending on the assumptions made on the cells at risk and the physiological and anatomical parameters involved, one working-level-month (WLM: exposure to one working level during 170 hours) corresponds to an alpha dose to the bronchial epithelium of 1-2 rads.

158. Unusually high mortality due to so-called Bergsucht among underground miners in the Krušné Hory (Erzgebirge), in what are now Czechoslovakia on the southern side and the German Democratic Republic on the northern (Saxon) side, had been known for centuries, but it was not until 1876 on the Saxon side and 1926 on the Czechoslovak side that the disease was identified as lung cancer.

159. In 1933, lung cancer in miners was recognized as an occupational disease in Czechoslovakia. As a result, a high rate of autopsies was performed on miners and it became possible to obtain accurate mortality figures. Over a follow-up period of five years there were 53 deaths, 19 of which were due to lung carcinoma, among some 400 miners at risk, or a mortality rate of about 1 per cent per year. Of the 28 carcinomas in that series combined with an earlier one from the same population, 16 were oat-celled and 12 epidermoid (138). In a series of 55 lung-cancer cases in Czech miners collected after the second world war the proportion of oat-cell carcinomas was 70 per cent (61).

160. Increased lung-cancer mortality has also been reported among fluorspar miners in Canada (33), iron-ore miners in Britain (17, 41), tungsten, fluorspar and lithium miners in Czechoslovakia (113a) and, lastly, among underground workers in two Swedish mines (6). In all these reports the miners population

had been occupationally exposed to high levels of radon. By contrast, no increased mortality was detected in a sample of South African gold and uranium miners exposed to apparently much lower levels of radon (7).

161. In none of the instances mentioned above in which increased lung cancer mortality had been reported is it possible to study how the excess mortality is related to the exposure. This, however, can be done on a further group of underground miners, those working in the uranium-ore mines of the Colorado Plateau in the United States. This population had been considered by the Committee in its 1964 report but the data then available were inadequate to permit a full analysis. Much information has now been published on a group of 3,366 white and 780 non-white miners and has been reviewed in a detailed monograph (86).

162. Basically, the study attempted to establish accurately the exposure of the miners in WLM and to follow-up the subjects from the date of first examination to the cut-off date for mortality analysis. The numbers of deaths expected in the various exposure categories were obtained by applying to the groups at risk the rates, specific for age, race, calendar year and cause of death, derived from the vital statistics of the four states in which miners were examined, and were compared with the observed numbers.

163. The major uncertainty affecting the conclusions of this study lies in the assessment of the exposures. This for the most part is due to the fact that large numbers of very small mines had been operating at any one time. Thus, there were 450 mines employing an average of two underground workers in 1950, 850 with three workers in 1957, and 533 in 1966 with an average of five workers (43). In all, the study utilized 43,000 measurements made in 2,500 mines over 27 years. However, while the quality of the measurements was considered to be good, their frequency tended to be very unevenly distributed. Thus, in only five mines were more than five radon-daughter measurements made in 1950 as against 177 in 1962 and 110 in 1968. In many mines only one or two measurements were ever taken, and, the results of early (prior to 1950) measurements not being available for any mine, they had to be inferred from circumstantial evidence collected later and sometimes elsewhere. Likewise, where, as in most mines, uninterrupted series of measurements had not been made, the gaps were made up on the basis of the earlier and later measurements available. Since the amount of radon daughters in air depends on many variables, including ventilation, meteorological conditions and quality of the ore extracted, it is not possible to evaluate the errors that may have been involved in assessing the exposure nor determine whether they gave rise to a systematic bias.

164. The mortality experience of the white underground miners from 1950 to 1968 compared with that expected in the population of the four states shows an excess number of deaths (60 per cent above expectation) essentially due to larger than expected numbers of violent causes (by 145 per cent) and of lung cancers (by almost 500 per cent). The mortality experience of the much smaller group of non-white miners over the same period is insufficient (72 deaths in all) to be informative.

165. The distribution of observed lung cancer deaths among white underground miners according to exposure and the corresponding mortality rates in excess of those expected on the basis of the four-state mortality experience (uncorrected for smoking habits) are given in table 14. Taking the exposure estimates at face value, a simple regression analysis indicates that a straight line adequately fits the data. However, while the data suggest that the risk (excess number of cases per WLM) does not vary significantly over the range of exposures explored, it does not seem appropriate, in view of the uncertainties discussed in paragraph 163 to place much reliance on the exact shape of the curve or on the actual risk estimate (about two cases per million per year per WLM) that can be derived from it.

166. An additional difficulty in interpreting the results arises from the fact that most of the miners included in the study were cigarette smokers (85). The difficulty can to some extent be circumvented by comparing the mortality in the miners with that in the population of the four states adjusted according to smoking habits as well as according to the factors mentioned previously. While the excess mortality over the expected mortality adjusted for smoking was somewhat reduced compared to that given in table 14, the relation of the excess to the exposure remained basically unchanged.

167. The distribution of lung cancer by histologic type was studied by Saccomano *et al.* (127) among uranium miners (121 cases) and controls (138 cases) matched according to age and smoking habits. The relative frequency of small-cell and undifferentiated carcinomas rose from 35.7 per cent in the group exposed to 40-200 WLM (21.4 per cent in matched controls) to 76.7 per cent in the 2,501-9,700 WLM group (10.0 per cent in controls) with little or no increase at all in epidermoid or other types of tumours.

168. It is worth noting that the observations made on the uranium miners are difficult to reconcile with the results of the ABCC study discussed in paragraphs 135 to 148. According to the latter, the excess risk of lung cancer may be decreasing beyond doses around 100 rads, namely, at doses far lower than the cumulative doses likely to have been received by the miners. Likewise, the distribution of histological types of cancer observed among the survivors also differed from that observed among the miners. The conditions of irradiation, however, were quite different in the two groups: (*a*) the exposure of the Hiroshima and Nagasaki survivors was single at high dose rate whereas it was fractionated, protracted over years and at low dose rate in the miners; (*b*) the survivors were exposed to mixtures of gamma rays and neutrons while the miners were exposed predominantly to alpha particles. Not only is the quality of the radiations involved different, but the range of the alpha particles is so much shorter than that of neutrons and gamma rays that different cells might be at risk in either case; (*c*) miners are exposed to high levels of dusts and fumes; (*d*) the smoking habits of the two populations cannot be compared and are likely to be quite different.

V. Bone tumours

A. External irradiation

169. Information on the induction of bone sarcomas (osteo-, chondro-, and fibro-sarcomas) by external radiation is scanty. It consists of clinical case

reports of sarcomas observed after high local doses given for therapeutic purposes and of the results of the surveys of Hiroshima and Nagasaki survivors, and of ankylosing spondylitis patients.

170. Reports of clinical cases are scattered in a number of publications (4, 19, 22, 31, 48, 55, 106, 115, 126, 136, 142, 147). Most of the cases were attributed to radiation merely because the personal histories of the patients showed heavy exposures. No prospective or retrospective survey has been conducted that would give firm indications on the size of the exposed population in which the individual cases were observed.

171. Two important, if crude, pieces of information can, however, be derived from those cases. One is the order of magnitude of the local exposures received. In virtually all cases these were higher than 1,000 roentgens and frequently amounted to several thousand roentgens. Although it is possible that histories of high exposure were recorded more reliably than histories of low exposure, or that low exposures, even if recorded, were not related by the investigators to the observed sarcomas, it is difficult to exclude the possibility that radiation-induced osteosarcomas develop only after very high exposures of external therapeutic radiation.

172. The other point to be noted is that the time interval between irradiation and diagnosis of osteosarcoma is highly variable, with reported extremes 4 and 42 years, but that 73 per cent are less than 15 years and the average (based on 137 cases) is about 11 years. Here, again, a bias cannot be excluded that might weigh the data in favour of shorter time intervals.

173. The Hiroshima and Nagasaki survivors have so far provided negative evidence. In the fixed sample of the Life Span Study, one case of osteosarcoma came to autopsy and four were diagnosed but not seen at autopsy by 1965 (175). Of these five cases, two were not in the city at the time of bombing, two were within 1,400 metres from the hypocentre and one between 1,400 and 2,000 metres. The distribution of these cases by distance was reported to be random. More recently, the total number of bone cancer deaths in the Life Span Study from 1950 to 1970 has been reported (73, 74) as 23, or about the number expected from the Japanese vital statistics.

174. One may assume on the basis of the experience provided by the case reports discussed in paragraphs 169-172 that sarcomas that had been induced by radiation from the 1945 nuclear explosions would have developed clinically during the subsequent 25 years, unless the latency was much longer at the doses received by the survivors. The survival time of bone sarcomas—a few years—is short enough for most cases to have been recorded in the mortality study. It seems therefore clear that, at the doses received by the A-bomb survivors, the risk of induction is orders of magnitude lower than the risk of induction of leukæmia.

175. Among the ankylosing spondylitics (28) 5 deaths from bone tumour were reported, against 1.1 expected, a significant excess. Because local doses delivered in the course of the x-ray treatment were in some cases of the order of thousands of rads, it would be useful to know the dose category to which the cases of bone tumour belonged.

B. Internal irradiation

176. Carriers of radium burdens are among the groups of people exposed to radiation that have been most intensively studied for periods of several years. Of the three major surveys of radium-contaminated subjects, two concern carriers of long-lived ^{226}Ra (half-life 1,622 years), sometimes mixed with ^{228}Ra (half-life 6.7 years), and one involves subjects treated with injections of short-lived ^{224}Ra (half-life 3.64 days).

177. Carriers of ^{226}Ra consist of dial painters, radium chemists and patients that absorbed radium-containing drugs orally or intravenously for therapeutic purposes. The two major groups are known as the MIT group (42) and the ANL-ACRH group (46) and consist of some 500 and 300 subjects, respectively. Until recently these two groups were studied separately by different investigators but the two surveys have now been merged, and only the results of the joint survey (125) will be discussed here.

178. Mean cumulative doses to bone due to alpha radiation were estimated for all subjects included in the surveys. However, it must be underlined that the estimates, based on residual body burdens (themselves not always accurately known) were determined sometimes decades after the initial uptake of radium and are uncertain both because they involve assumptions on the metabolism of radium in bone and because—^{226}Ra and ^{228}Ra being alpha emitters—their dosimetry is very sensitive to the microscopic distribution of the nuclides in bone, which in turn depends on the amount of remodelling that has taken place.

179. Two types of tumour occur with increased frequency among radium carriers—bone sarcomas and antral carcinomas. The latter develop in paranasal sinuses and mastoidal cells. Table 15 and figure IX give the distribution of tumours in the joint survey according to cumulative bone dose averaged over the whole skeleton. It must be pointed out that, the cumulative dose being delivered at a diminishing rate over a period of several years, there is no way to determine which fraction of it is sarcomogenic and which is wasted. On the other hand, the effectiveness per rad might be higher for alpha particles than for x or gamma rays.

180. The most noticeable feature of the data is the apparent discontinuity in the incidence of both types of tumour at around 700 rads. Here also, the data suggest that no tumours are induced until such a dose has been delivered. However, the number of sarcomas expected among those exposed to less than 700 rads ($4.6\ 10^4$ man-rads altogether), based on 51 cases observed in about $1.3\ 10^3$ man-rads, would be 1.8 if proportionality between dose and incidence applied, against none observed. Similarly, 0.7 carcinomas would be expected in the group exposed to less than 700 rads. Much larger samples in the low-dose range would be necessary to make the negative results in these dose groups differ significantly from predictions based on proportionality between dose and incidence.

181. Another important observation is that the frequency of sarcomas and carcinomas does not, above mean doses of 1,000 rads and within a twenty-fold range of doses, increase monotonically with dose. As indicated in figure IX, the observed incidences

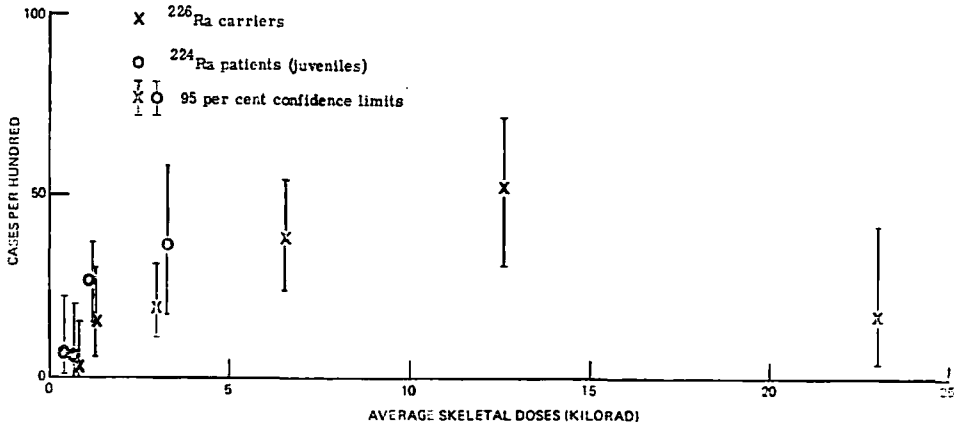

Figure IX. Incidence of bone sarcomas in carriers of ^{226}Ra burdens and in ^{224}Ra-treated patients against average skeletal dose (125, 144)

have a maximum near 12,000 rads and then fall to the same level that is observed near 1,000 rads.

182. Patients treated with ^{224}Ra constitute the third major source of information on the effects of radium exposure (143, 144). The treatment involved intravenous injections of "Peteosthor", a ^{224}Ra-containing preparation that had a period of vogue in Germany between 1944 and 1951, mostly in the treatment of bone tuberculosis and ankylosing spondylitis. Of the approximately 2,000 patients so treated, 802 were investigated and followed up for about 20 years.

183. The observed incidence of bone sarcomas is shown separately for juveniles and adults in table 16 and has been plotted in figure IX for juveniles alone. The main difference between people treated with ^{224}Ra and those with ^{226}Ra burdens lies in the appearance of bone sarcomas at doses about 10 times lower in the former than in the latter. It is as if ^{224}Ra was more effective than ^{226}Ra in inducing the tumours at low doses. At mean bone doses above 1,000 rads the rate appears to be the same in both groups, although it must be recalled that the ^{226}Ra carriers had been, on average, followed up for several more decades than the ^{224}Ra patients.

184. The higher effectiveness of ^{224}Ra at low doses has been attributed to the fact that, owing to its short half-life, ^{224}Ra decays before being incorporated into the bone matrix and therefore delivers to the cells (believed to be those at risk) that line bone surfaces a much higher dose than the same activity of ^{226}Ra, most of which finds its way into deeper bone layers. This explanation, if borne out by the results of continued follow-up of these subjects, would make the results of the study of "Peteosthor"-treated patients particularly valuable, since it would provide information of indirect relevance to the problem of plutonium contamination in man. This is because plutonium, a long-lived alpha emitter, owing to its chemical characteristics, tends to be fixed on bone surfaces and thus to irradiate bone in a manner similar to ^{224}Ra.

VI. Other cancers

A. A-BOMB SURVIVORS

1. *Mortality studies*

185. Table 4 from the study of Beebe *et al.* (11) in the Life Span Study Sample from 1950-1966 shows that, if all malignant neoplasms, except leukæmia, are put together, this combined group has a significant increase of mortality with increasing dose ($P \sim 0.05$). Among the variety of types of cancers included in this group, lung cancer and breast cancer have been discussed already. None of the remaining cancers selected by the authors for tabulation showed a statistically significant dose-effect relationship, although some increased risk in high-dose groups may be noted for stomach cancer, uterus cancer, and the group of other cancers (ICD No. 190-199).

186. The increased mortality from all malignant neoplasms (except leukæmia) with dose has been confirmed by the more recent study of Jablon and Kato (73, 74) which covers the 20-year period 1950-1970 (table 5). In the survivors of the Life Span Study Sample exposed to 10 or more rads, the observed deaths from malignant neoplasms other than leukæmia exceed the expected (national rates) by 144 in Hiroshima and 27 in Nagasaki and exceed the expected deaths from the 0-9 rad group by 113 in Hiroshima and 14 in Nagasaki. At Hiroshima, roughly half of the excess may be accounted for by that of lung and breast cancer.

187. At Hiroshima, the residual group (other cancers in table 5) shows an over-all, highly significant, excess of between 70 and 90 cases, depending on the expectation used. Within the individual exposure groups, the excess is significant only at the highest exposure but the rising trend of the mortality rates with Kerma is highly significant. This trend is not ascribable to any specific site. No significant excess is detectable and no clear-cut trend can be identified at Nagasaki.

188. As with lung cancer, risk estimates are difficult to obtain because the relevant doses are unknown. One may, however, proceed as in the case of lung cancer and use the same notional dose estimates and the same RBE values that were obtained in paragraph 145, for the purpose of showing the possible consequences of crude dosimetric assumptions. The resulting risk estimates then vary from 2 cases per million per year per rad at 30 rads of low-LET radiation to 2.5 cases per year per rad at about 260 rads. However, only the estimate for the group exposed to the highest dose is based on a statistically significant excess number of cases.

2. *Autopsy studies*

189. Several autopsy studies have investigated the role of radiation in the induction of cancer of different sites. Since the autopsy rate has been high (about 40 per cent in recent years in the Life Span Study Sample) and the material is not particularly biased in respect to radiation exposure, the autopsy data may be more reliable than the mortality data for those types of cancer that cannot be identified with sufficient accuracy from death certificates.

190. Schreiber *et al.* (130) have studied primary liver cancer in 2,437 autopsy cases performed from 1961 to 1967. Thirty-four cases were found, but there was no clear relationship between radiation and the disease. In the same autopsy material, Robertson *et al.* (124) found no detectable dose-effect relationship in 31 gall-bladder carcinomas, 14 bile-duct carcinomas and 3 ampullary carcinomas.

191. Yamamoto *et al.* (174) have reported 326 cases of gastric cancer in 2.908 autopsies performed from 1961 to 1968. Again, no clear relationship was observed between the rate of gastric cancer and radiation dose.

192. Nishiyama *et al.* (108) have investigated the relationship between radiation and both malignant lymphoma and multiple myeloma on the basis of a variety of ABCC records including autopsy, death certificate, leukæmia registry, etc. In the extended Life Span Study Sample, 45 cases (37 malignant lymphomas and 8 multiple myelomas) were identified from 1945 to 1965. For multiple myeloma, the number of cases was too small to warrant a study of their relation with kerma. For malignant lymphoma, 26 cases were observed in Hiroshima and 11 cases in Nagasaki. These cases were divided into three broad categories according to exposure and the risks of malignant lymphoma in the high-exposure categories were compared with the risk in the essentially non-exposed category (<1 rad). The relative risks were 0.7 in the 1-99 rad category and 8.0 in the over-100 rad category in Hiroshima; in Nagasaki, the respective figures were 0.7 and 0.6. Thus, only the over-100-rad category in Hiroshima showed an increased risk of malignant lymphoma, and more data appear to be needed to conclude that A-bomb survivors are at an increased risk of developing malignant lymphoma.

B. Cancer mortality among ankylosing spondylitis patients treated with x-irradiation

193. In their 1965 report (28), Court Brown and Doll showed that ankylosing spondylitis patients treated by radio-therapy are at an increased risk of developing a variety of malignancies. Based on the standard course of radio-therapy to the whole spine and to the sacro-iliac joints, all cancers (except leukæmia) were divided into two classes: those occurring inside the beam of radiation (heavily irradiated sites) and those occurring outside the beam (lightly irradiated sites). The lightly irradiated sites included brain and central nervous system, uterus, prostate, testes, kidneys and urinary bladder. All other sites except the colon were classified as heavily irradiated sites (the colon was excluded because of the possible relation of ankylosing spondylitis to ulcerative colitis and, consequently, to colon cancer).

194. As shown in table 17, cancers of heavily irradiated sites, when compared with the numbers expected on the basis of the national mortality rates, show an observed/expected ratio of 1.6 and an excess mortality of 512.9 per million per year during the observation period (5-25 years after the treatment). Cancers of lightly irradiated sites show a slight excess, which is not statistically significant.

195. Table 6 shows the occurrence time of the two categories of cancer in the complete follow-up of the patients to the end of 1960. The results of the incomplete follow-up to the end of 1963 are given in table 18. The excess number of observed deaths from both categories of cancer in the first three years after the first observation is likely to have been due to the inclusion of a small number of cancer patients mistakenly diagnosed as ankylosing spondylitics because of cancerous involvement of the spine.

196. While the leukæmia mortality decreased to nearly the natural rates after the peak in the 3-5-year period since first observation, cancers of heavily irradiated sites have shown no declining trend with the passage of time. In fact the observed/expected ratios increased constantly from 1.1 for the 3-5-year period to 2.3 for the 12-14-year period. For the 15-24-year period the ratio was 1.6 according to the complete follow-up, whereas the incomplete follow-up yields a ratio of 2.2 for the 15-27-year interval since first observation. In contrast to the time trend of cancers of heavily irradiated sites, no mortality increase with time is apparent either for cancers of lightly irradiated sites, or for all causes of death.

197. Among the 200 deaths from cancers of heavily irradiated sites that took place during the 6-27-year observation period, the excess over expectation is significant ($P>0.025$, one-tailed) for a variety of cancer sites: pharynx, stomach, pancreas, bronchi, bones, other lymphatic and hæmopoietic tissues, and others (table 13). The observed/expected ratios in the group as a whole during the 6-27-year observation period is 1.9 while the excess mortality is 561.2 cases per million per year for all cancers of heavily irradiated sites and nearly half of this excess is due to lung cancer.

198. The interpretation of the observed excess of cancers of heavily irradiated sites must be made with caution. As seen in table 17, causes of death (e.g., cerebrovascular disease) with no obvious relation to ankylosing spondylitis or irradiation show a significant excess which was discussed by the authors as follows:

(*a*) The broad disease groups may contain a small proportion of rare conditions which are, in fact, directly related to ankylosing spondylitis;

(*b*) The presence of certain complications may increase the risk of death from other, unrelated, causes;

(*c*) Some deaths related to ankylosing spondylitis are erroneously attributed on death certificates to other causes of death;

(*d*) Ionizing radiation may have non-specific deleterious effects;

(*e*) Other treatment may be harmful; and

(*f*) The computation of the expected number of deaths may be in error because of, for example, a difference of socio-economic class between the patients sample and the general population.

199. Whatever the true reasons, it is conceivable that the excess cancer deaths in these patients might

also be due to reasons other than radio-therapy. The only way to exclude such an explanation would be to determine whether the risk of cancer is higher among spondylitics treated with radio-therapy than among those treated otherwise. However, adequate control groups have yet to be studied. It would be much easier to interpret the excess risk of cancer if dose-effect relationships could be demonstrated as with leukæmia, but no dosimetry for tissues other than bone marrow is currently available. However, the fact that a significant excess of cancers is observed only in heavily irradiated sites and that only for cancers of heavily irradiated sites does the risk increase with time makes it beyond reasonable question that the excess cancer mortality among x-rayed spondylitics is largely due to the radiation treatment.

C. American radiologists

200. Seltser and Sartwell (135) have reported an increased risk of cancer among about 3,700 male American radiologists. During the period 1935-1958, 11.3 excess deaths from leukæmia and 48.2 excess deaths from all other cancers occurred among the radiologists in comparison with the group of ophthalmologists and otolaryngologists (this group was regarded as a virtually non-exposed population). In this study, only combined deaths from cancers of all types (except leukæmia) were presented, so that no analysis of cancer incidence at individual sites can be made.

201. All cancers other than leukæmia showed a relative risk of 1.6 and an excess mortality of about 1,000 per million per year (50 cases in 50,000 person-years). Because the radiation doses received by the radiologists are unknown, the risk per unit dose cannot be derived.

202. Although an apparent excess was noted for all cancers (except leukæmia) in the radiologists, it is not very clear whether the excess was caused by irradiation only. In this study, all deaths were classified into four groups: leukæmia, all other cancers, cardiovascular-renal diseases, and all other causes. Each of the four groups showed an apparent excess when compared to the ophthalmologists and otolaryngologists; e.g., excess deaths were 103.4 in cardiovascular-renal disease, 65.3 in the group of all other causes. If radiation alone were responsible for the observed excess, then it must be assumed that the radiation had deleterious biological effects of a non-specific sort on the American radiologists. Such non-disease-specific effects of radiation, however, have not been observed in a study on British radiologists (27). In addition, Beebe *et al.* (11) could find no such non-specific effects in Japanese A-bomb survivors.

203. A question may be raised as to the appropriateness of the comparison group used in the study of Seltser and Sartwell. In their study, the medical specialists chosen for comparison are obviously more closely related to radiologists than is the general population with respect to such factors as education or socio-economic status: but still the choice of radiology from among the various medical specialties is certainly not random, so that radiologists may indeed have a different mortality experience from the other medical specialists, regardless of their irradiation exposure.

204. Thus, the excess mortality from cancers other than leukæmia among the American radiologists observed by Seltser and Sartwell may not be totally ascribed to their occupational exposure, and definite conclusions should be made only after further data have been accumulated.

D. Patients exposed to therapeutic irradiation in the pelvic region

205. Wagoner (164) studied cancer morbidity in 1,893 patients with benign gynæcological disorders treated by either radium (900 cases) or x-irradiation (993 cases) during the period 1935-1966. Among the various cancers examined, leukæmia showed a significant increase and has been discussed in section I of this annex. The remaining individual cancers were: cancers of stomach, small intestine, large intestine, rectum, biliary passage and liver, pancreas, lung, breast, female genital organs, urinary organs, and lymphatic tissue.

206. Since the radium or x-ray therapy was limited to the pelvic region, most of the selected sites of cancer were outside the main irradiated area. Therefore, as expected, no significant deviation of observed numbers of cases from expected numbers was noted for the majority of cancer sites. The observed numbers were in excess only for cancers of the female genital organs—109 observed cases *versus* 54.87 expected ($P<0.01$)—and cancers of the urinary organs—17 observed cases *versus* 8.50 expected ($P<0.05$). In absolute terms, the excess mortality amounted to 1,532 cases per million per year for cancers of the female genital organs and to 241 cases per million per year for cancers of the urinary tract. The risk cannot be expressed per unit dose of radiation since no estimates of radiation dose received by the organs at risk were made, and it cannot be excluded that the benign gynæcological disorders that had prompted the radiotherapy are associated with an increased risk of cancer of the genital or urinary organs.

207. A study of patients with metropathia hæmorrhagica, was made by Doll and Smith (38) who examined the relationship between the x-ray therapy given to these patients and the ensuing excess mortality from malignancies. Observed and expected deaths (computed from the age-sex-period-specific mortality rates of the general population) in the six disease categories selected for analysis are compared in table 19. The deaths were divided into those that occurred within five years of the radiation treatment and those that occurred later. The former group was regarded as less reliable on the ground that the initial examination (at the time of diagnosis of metropathia hæmorrhagica) was likely to have revealed malignancies that would otherwise have been detected later.

208. As seen in table 19, no significant difference between observed and expected deaths was noted for coronary disease and for the group of other causes. The risk of leukæmia showed a large excess, but this is discussed in section I of this annex. There was a significant deficit in the observed deaths from breast cancer as compared to the expected numbers; this deficit could be explained by the available evidence (44) that artificial menopause tends to reduce the risk of breast cancer. Cancers outside the radiation beam (presented in the table as "other cancers") showed no significant increase of the observed/expected ratios.

209. On the other hand, cancers within the radiation beam (ovaries, large and small intestines, rectum, uterus, other pelvic organs and bladder) showed a significant excess. In the observation period of five or more years after radio-therapy, 31 deaths occurred in comparison with 18.40 expected ($P<0.002$) corresponding to an excess mortality of about 700 per million per year. The excess risk in the group of cancers of heavily irradiated sites was attributable to a variety of cancers (e.g., excess deaths were 5.16 for intestines, 2.66 for rectum, 1.54 for uterus etc.) but the excess cannot be expressed per unit dose of radiation for any of the types of cancer because estimates of the doses to the relevant tissues are not available. The observed/expected ratios were 1.6 in the 5-9-year period after treatment, 1.6 in the 10-14-year period, and 2.1 in the 15-year-or-more period. This time trend seems to indicate a tendency of the risk to increase after exposure.

210. As in the case of ankylosing spondylitis patients (28) and of patients with benign gynæcological disorders (164) the expected numbers of deaths were computed in this study from the mortality rates of the general population. It cannot be excluded that the excess, or part of the excess, observed in the group of cancers of heavily irradiated sites in this study might have been associated with metropathia hæmorrhagica rather than with radio-therapy.

VII. Malignancies in children

A. A-BOMB SURVIVORS

211. As already discussed in section I, the relative risk of leukæmia among the survivors exposed to radiation at ages 0-14 years ATB is known (66, 67) to be higher than that of the older group (ages 40 and over ATB).

212. The risk of cancer also seems to increase among the survivors exposed to radiation at young ages, particularly at ages 0-9 ATB (71, 75). Table 20 shows observed and expected deaths attributed to cancer (except leukæmia) for 1955-1966 among survivors aged 0-9 at the time of exposure. In the group of 20,415 subjects consisting of the survivors aged 0-9 ATB and their matched controls, 22 deaths were attributed to cancer during the period 1955-1969. Before 1955, only one death was reported.

213. In the non-exposed group (not-in-city or <10 rad), the observed number of deaths virtually equalled the expected number. Expected deaths were computed from the 1962 national rates. Eight deaths were observed in contrast to 0.98 expected among those who received more than 100 rads (T65D) or an unknown kerma (undoubtedly high but undetermined since the heavy shielding configuration made dosimetry impossible). Although the numbers are small, the difference is statistically significant. No deaths were observed in the 10-99 rad group, while 3.26 were expected.

214. No specific clustering as to site of origin of these cancers was observed: two stomach cancers, two osteogenic sarcomas, one pancreas cancer, one lymphosarcoma, one prostate sarcoma, one metastatic cancer of the liver. It may be concluded that because of the small number of observed deaths (8 in the exposed group), the evidence relating to increased risk of cancer in this group is still only suggestive and that, to obtain definite conclusions, this group of survivors must be followed for many more years to come.

B. CHILDREN IRRADIATED FOR THE TREATMENT OF *Tinea capitis*

215. *Tinea capitis* is one of the commonest fungal diseases of the scalp in children. For approximately half a century before 1960 epilation by x-irradiation was commonly practised as an effective treatment to free the scalp of fungal contamination. The number of patients so treated throughout the world was estimated (20) to have been 200,000 in the 50 years prior to 1960.

216. Albert *et al.* (1-3) and Schultz and Albert (131) made a follow-up study of *Tinea capitis* patients consisting of a study group treated by x-ray epilation (2,043 patients) and a control, non-irradiated, group (1,413 patients) who visited the New York University Hospital during the years 1940 to 1959. The x-ray therapy given to the patients was according to the Kienbock-Adamson procedure in which the scalp is irradiated in five different fields with 75-100-keV x rays at exposures of 300 to 400 roentgens for each field. After the irradiation, complete epilation followed in two to three weeks and lasted one to two months. On the basis of phantom experiments and theoretical computations, the radiation doses were estimated to have been 70-175 rads to the brain, 450-850 rads to the scalp, and 300-460 rads to the cranial bone marrow.

217. In the patients, males were predominant (86.1 per cent in the irradiated and 78.5 per cent in the non-irradiated groups) and the vast majority were white (about 75 per cent for each of the two groups). For both groups, the average age at the time of the treatment was seven years.

218. An attempt was made to trace the patients by a variety of follow-up methods in order to evaluate possible late effects, including cancer induction, by x-irradiation. During the average follow-up period of 15 years, 85 per cent of the irradiated and 79 per cent of the non-irradiated patients were traced. The patients thus traced were requested to answer a health questionnaire. In the case of tumours, diagnostic confirmation was secured from the treating hospitals or physicians.

219. In the non-irradiated group of about 1,400 patients, only one case of malignancy (Hodgkin's disease) was noted during the average observation period of 15 years. In contrast to this low occurrence, a much larger frequency of malignancies (14 cases) was observed in the irradiated population of about 2,000 patients, i.e., four leukæmias (two acute lymphocytic, one acute myeloblastic, and one chronic myelogenous), one fibrosarcoma of the mandible, two basal-cell carcinomas of the scalp, one submandibular lymphosarcoma, one Hodgkin's disease, one adenosarcoma of the rectum, one acinous-cell carcinoma of the parotid gland, and three brain tumours. Of these 14 cases, four died of leukæmia and one of brain tumour.

220. In view of the far higher occurrence of cancer in the irradiated group in comparison with the non-irradiated, and the fact that all but one of the 14 malignancies occurred in the tissue within the x-ray beam, the majority, if not all, of the observed cancers

can be attributed to the x-ray therapy. Although the number of cases is very limited, it may be of interest to speculate upon the risk of cancer induction per unit dose. For leukæmia, considering the average dose to the whole bone marrow to be of the order of 50 rads, the risk is of the order of three cases per million per year per rad. It is of the order of one case per million per year per rad for brain tumour. The meaningfulness of these estimates is limited by the smallness of the sample on which they are obtained and the fact that data at one dose level only can be used.

C. Children irradiated in the thymic area

221. In the past, thymus enlargement was thought to be a serious medical condition, and after the turn of the century, many children were subjected to x-irradiation for a supposedly enlarged thymus. This practice became less common with the passage of time as medical knowledge increased regarding the hazards of radiation and the non-harmful nature of thymus enlargement.

222. Since the Committee's 1964 report, two cohort studies have been updated (58, 116). The cohort study of Latourette *et al.* (79), already discussed in the 1964 report, was extended by Pifer *et al.* (116). The study population consisted of 958 individuals (59 per cent males and 41 per cent females) who received x-ray therapy for thymic enlargement at the University of Michigan (U.S.A.) mostly in the 1930s. The majority of patients (90 per cent) were treated during the first year of life. After the initial survey in 1958, late effects of x-irradiation were reinvestigated by a mail survey made on 786 persons whose follow-up data were available at the University in 1964-1965. When malignant conditions were encountered, the diagnoses were confirmed from the treating hospitals or physicians.

223. X-ray treatment was given to the anterior chest alone in virtually all subjects, with exposures of 100-199 roentgens in the majority (557) of cases. Thyroid glands were considered outside the main beam and received on the average a tissue dose of approximately 20 rads.

224. During the observation period of nearly 30 years, 9 malignant neoplasms were observed against 5.8 expected, a statistically non-significant excess ($P>0.05$). These nine malignancies were: one thyroid carcinoma, one leukæmia, one lymphosarcoma, two brain tumours, and four others. None of the observed cancers occurred in the tissue within the radiation beam. It may be of interest to note that no cancers of the breast were observed although the breast definitely had been irradiated.

225. In conclusion, the results of this study may be explained as providing no evidence of the induction of malignancies in children at the doses received (20 rad to the thyroid).

226. The authors found 7 cases of benign thyroid neoplasms in contrast to the expected number, 0.13-1.3; however, as the authors recognized, the validity of the expected number was dubious since no reliable data regarding the incidence rates of benign thyroid neoplasms in the general population were obtainable.

227. The Committee's 1964 report cited a follow-up study on children in upstate New York exposed to therapeutic x-irradiation for thymic enlargement (117, 157, 158). This study was updated (57, 58) to include the continuation of the follow-up of the same group of individuals. The study group consisted of 2,876 persons exposed to x-ray treatment for thymic enlargement and of their 5,006 non-irradiated siblings used as controls. The vast majority (90 per cent) was irradiated at less than six months of age. While more males (58 per cent) than females (42 per cent) were treated, the male-to-female ratio was approximately 1:1 in the controls.

228. The follow-up of the individuals was made by mail survey (the third survey), which traced 84 per cent of them. If tumours were recorded on the returned questionnaire, the diagnosis was confirmed by obtaining medical information from appropriate hospitals or physicians. The exposed subjects received x-ray therapy from 1926 to 1957 and, therefore, the observation period until 1963 ranged for individuals from 6 to 37 years.

229. Table 21 indicates the number of observed and expected cases of various malignancies in the treated and the control groups during the observation period. In the non-irradiated control group, the observed numbers were in good agreement with the expected numbers, computed from the incidence rates in the general population. In sharp contrast to the control group, the treated population showed a clear excess of observed malignancies as compared to expected. The most remarkable was the excess of thyroid carcinoma, 19 observed against 0.14 expected. A significant excess was also noted for leukæmia (6 observed to 2.02 expected), salivary gland tumour (4 *versus* 0.08), and all malignancies combined (33 *versus* 8.10). It is of interest to note that no breast cancer developed in spite of the fact that the breasts must have received substantial radiation doses. None of the 19 cases of thyroid carcinoma died from the disease.

230. The authors estimated that the risk of thyroid cancer induction was of the order of 2.5 cases per million per year per rad (50-600 rad); the estimate given in the 1964 report ($1.0\ 10^{-6}\ y^{-1}\ rad^{-1}$) was increased to reflect newly estimated tissue doses to the thyroid gland and the occurrence of further cases. The earlier value was computed according to exposures; as estimates of tissue dose were not available, it was then tentatively assumed that the thyroid glands were within the main beam. When doses to the thyroid glands were eventually estimated, it appeared that in many individuals the thyroid glands were outside the main beam and were exposed only to scattered x rays and so had received only a fraction of the exposure. It was not easy to decide retrospectively whether the thyroid glands were in the main beam since this depended on various factors such as port size, port placement, lead shielding, etc. It must be remembered, therefore, that considerable uncertainties exist in the estimated tissue dose of the thyroid glands and, consequently, in the risk estimate.

231. Previously, types of treatment—AP (anterior and posterior) *versus* A (anterior) irradiations—were suspected to have influenced the risk of thyroid carcinoma, but the latest analysis indicates that this difference could be accounted for simply by the difference of radiation dose accompanying A and AP treatments, without requiring consideration of the possible tumourigenic role of the exposed pituitary gland in the case of AP treatment.

VIII. Malignancies in pre-natally exposed children

232. In the Committee's 1964 report, a number of studies (29, 47, 76, 77, 82, 88, 89, 90, 91, 120, 149, 150, 153, 154) relating to the risk of cancer induction in children exposed to radiation *in utero* were discussed. Most of these studies were of a "retrospective", or "case-control", type in which a study group of cancer cases was matched by sex and age with a control group of healthy children. In the two groups, the proportions of mothers exposed to diagnostic or therapeutic x-irradiation were compared and, on this basis, the risk of cancer induction in the irradiated children as compared with those non-irradiated was estimated. The estimated relative risks varied considerably, ranging from over 1.7 to almost 0.4. MacMahon and Hutchison (91) noted, however, that the studies reporting relative risks less than 1.0 tended to be based on small samples and to show large chance fluctuations, and that the confidence limits of the individual estimates overlapped considerably. The joint maximum likelihood estimate of the relative risk derived from the 10 major studies was 1.40 (1.21, 1.68 as 95 per cent confidence limits) and was within the 95 per cent confidence limits of each of the individual estimates of relative risks.

233. Since the 1964 report, the results of several further studies have been published (50, 52, 72, 151, 152). Graham *et al.* (50) in the United States made a case-control study investigating 319 leukæmia cases and 884 controls. An attempt was made to select all leukæmia cases at ages less than 15 years, based primarily on tumour registry records in upstate New York and the metropolitan and rural areas around Baltimore and Minneapolis-St. Paul. A control group of children in the same age range was also chosen by a stratified selection of households from the same geographical areas. The vast majority of the leukæmia cases and of the controls were interviewed to ascertain a number of demographic and medical risk factors, and the medical information thus obtained was carefully verified against the medical records of relevant hospitals and physicians.

234. The case group included more mothers who had experienced miscarriages or stillbirths prior to the birth of the subjects, the relative risk being 1.4-1.6. The radiation histories of the children before and after birth and of their parents (i.e., of preconception exposure of mothers and fathers) were recorded. Diagnostic radiation experience for mothers prior to conception differed significantly between the case and control groups. The case group included a higher proportion of mothers exposed to radiation (any site of the body) and the adjusted relative risks varied from 1.55 to 1.73 depending on which of the factors such as year of birth, age of mother, birth order, pregnancy order, miscarriage or still-births, were adjusted. From the report it is not clear how many mothers received irradiation to their reproductive organs. Neither dose-effect relationship nor the variation of risk with time interval before conception were well investigated because of small numbers and large chance fluctuations.

235. As to *in utero* exposure, it was found that the mothers of 27 out of 319 cases (8.6 per cent) and those of 54 out of 884 controls (6.3 per cent) had received only abdominal x-irradiation during pregnancy. The relative risk was 1.40 but was not statistically significant. Considering radiation to all sites, rather than to the abdomen alone, the proportions of mothers so irradiated in case and control groups were 29-30 per cent and 22-23 per cent, respectively. The relative risks ranged from 1.40 to 1.59 depending on the selection of adjusted risk factors such as year of birth, age of mother, birth order, and pregnancy order. These values of relative risks were close to the maximum likelihood estimate given by MacMahon and Hutchison (91).

236. As discussed in the 1964 report, Stewart (149) and Stewart *et al.* (153, 154) had reported that a higher proportion of mothers of children dying from leukæmia and other malignancies gave history of x-irradiation during pregnancy than did mothers of control children. Stewart and Kneale (152) confirmed this on the basis of a much larger sample of cases and controls and, in addition, asserted that a clear linear dose-effect relationship was observed between radiation dose and cancer induction.

237. The cases were 7,649 children born between 1943 and 1965 in England and Wales who had died from malignant diseases before 10 years of age. Of these, approximately one half had died of leukæmia. Equal number of controls, 7,649, were selected from live children on the basis of the local birth registers, and were matched with cases according to sex, date of birth, and region.

238. While 1,141 mothers (14.9 per cent) in the case group were found to have had abdominal x-ray examination during pregnancy, the corresponding number in the control group was only 774 (10.1 per cent), and this difference was statistically significant. The vast majority of them had x-ray examination in their third trimester of pregnancy. The x-rayed mothers were further classified according to number of films taken. Comparing the number of such classified mothers between cases and controls, the excess risk of cancer induction was estimated by film-number category. The excess risk appeared to increase linearly with the number of films taken, ranging from about 20 per cent for one film exposure to over 100 per cent for five or more film exposures.

239. The mean fœtal dose per single film exposure was estimated by Stewart and Kneale (152) as varying from 0.46 rad in 1943-1949 to 0.2 rad in 1960-1965. Utilizing these estimates the risk of cancer induction in children under the age of 10 was shown to be in the range 30-80 deaths per million children per year per rad with a mean of 57 deaths and a standard error of 13. Subsequently Stewart and Kneale (152a) showed that if values of 0.72 or 0.89 rad (as derived from the national radiation dose survey carried out in 1960 in the United Kingdom) were used, the estimates would be reduced to 36 or 29 deaths per million children per year per rad, respectively. There is obviously some uncertainty in the values of radiation dose to be used in such retrospective studies. A study of the British literature in the years concerned showed that estimates of fœtal doses were made by a number of authors (13, 21, 98, 99, 113, 145, 146) between 1946 and 1957. From their reports the following average values of fœtal dose per film were derived: 1.8 rads in 1943-1949, 1.0 rad from 1950 to 1954, 0.5 rad from 1955 to 1959, and 0.2 rad from 1960 to 1965. Using these values of dose in conjunction with the incidences reported by Stewart and Kneale, an estimate of 23 deaths per million children per year per rad (in a range 0.2-20 rad) over a 10-year period can be

deduced, to which leukæmias on the one hand and other malignancies on the other contribute in about equal proportions.

240. The results of a study by Jablon and Kato (72) of children whose mothers were pregnant at the time of the A-bomb explosions is difficult to reconcile with the estimates of risk per unit dose given by Stewart and Kneale, even if the revised risk estimate given at the end of the previous paragraph is accepted. Jablon and Kato attempted to interview the mothers of all the children whose births were recorded in Hiroshima and Nagasaki within approximately 10 months after the bombings. Ninety-seven per cent of the 7,720 eligible mothers were interviewed regarding exposure status to irradiation. A sample of 1,292 children was then selected including all 325 children whose mothers were within 1,500 metres of the hypocentres, and randomly sampled comparison groups in the location of 1,500-1,999 metres, 2,000-2,999 metres, and 3,000-3,999 metres from the hypocentres. The comparison groups were matched to the group within 1,500 metres by sex of child, month of birth, and city.

241. The selected children were followed successfully (more than 99 per cent) regarding their survival status and the cause of death was ascertained for those that died during the first 10 years of life. In the irradiated group of children (1,292), only one death from any form of cancer was observed. The case was a cancer of the liver in the group within 1,500 metres. The comparable number of deaths that may have been expected by applying Japanese national rates was 0.75. Thus, no material difference between observed and expected deaths was recorded.

242. The radiation dose received by the children while *in utero* was estimated assuming that the dose to the fœtus was not less than one half of the maternal dose. By taking 50 per cent as a conservative value, the authors estimated that this group of children comprised about 17,500 person-rads in 10 years of life which would have yielded 5.2-13.9 extra cancer deaths if the risk estimate of Stewart and Kneale had applied, or 3.9 on the basis of the revised estimate at the end of paragraph 239. The authors stated that their findings were inconsistent with the model of Stewart and Kneale, and estimated the upper limit of excess risk of leukæmia death consistent with their negative findings to be less than 20 cases per million per year per rad. The discrepancy might be even greater if it were possible to make allowance for the RBE of neutrons received by fœtuses at Hiroshima.

243. While the reason for the discrepancy between the two sets of data is still unknown it must be borne in mind that the excess risk of cancer in children from mothers x-rayed during pregnancy may not be entirely due to x-irradiation. The major form of x-ray examination during pregnancy is pelvimetry, which in most clinics is performed on about 5-10 per cent of pregnant women for such medical indications as poor obstetric history (e.g., prolonged or difficult labour), previous cæsarean section, pelvic abnormalities, fœto-pelvic disproportion, etc. The possibility cannot be excluded that these conditions, rather than radiation exposure, may be associated with the increased risk of developing leukæmia or other malignancies in children born of irradiated mothers. This possibility has been examined with some care by both Stewart and MacMahon who were unable to identify medical conditions that could be responsible for both an increased risk of cancer and prenatal irradiation. Conclusive evidence may come from studies in clinics where pelvimetry has been a routine procedure. The results of such a study were published by Griem *et al.* (52) but the number (1,008) of mothers who had undergone routine pelvimetry was too small to warrant a reliable conclusion.

244. It is well known that precise risk estimates must preferably be derived from cohort studies rather than from case-control studies. However, cancer risk in children of ages less than 10 is extremely rare (e.g., 10^{-4} or so in the United States), so that it is difficult to carry out a cohort study of sufficient size. Most of the studies of *in utero* exposure thus far reported are case-control studies.

245. Thus, although children born from mothers x-rayed while pregnant seem to have an increased risk of cancer after birth, a possibility still remains that the association, or at least part of it, is caused by factors other than radiation and further studies are needed to clarify this point.

IX. Summary and conclusions

246. The information on radiation carcinogenesis in man that has become available since the last report of the Committee and that has been reviewed in the foregoing pages modifies substantially some of the conclusions reached earlier by the Committee. Data currently available make it possible to single out additional tissues and organs, beside the thyroid and the bone marrow, that appear to be particularly at risk and for which tentative risk estimates can now be given. These new additions include lung tissues and the female breast.

247. The advances are mostly due to additional observations made on the two major samples of irradiated people, namely, those of the survivors of the atomic bombings and of ankylosing spondylitis patients treated by x-irradiation. At both Hiroshima and Nagasaki, mortality records in the Life Span Study Sample have been collected up to the end of 1970, 25 years after the bombings, and the British spondylitics have been followed up fully for 10-11 years on average and, in part only, for an average of 13 years. The results of the Life Span Study Sample apply to the general population (approximately 40 per cent males; 20 per cent less than 10 years old at the time of bombing), those of the spondylitics to a largely (84 per cent) male, adult population of patients affected by a specific disease. The conditions of irradiation were different in the two groups. A pulse of mixed radiation in the case of the survivors, with a much larger neutron component at Hiroshima, and fractionated x-irradiation over long periods of time in the case of the spondylitic patients.

248. Revised estimates of the kermas (see paragraphs 16-19) received by the survivors and of their gamma and neutron components are now available both for Hiroshima and for Nagasaki. However, accurate dose estimates have not yet been made and the Committee had to base its assessment of dose-effect relationships on a number of assumptions. These are particularly critical with respect to the RBE values to be applied to the neutron component of the doses. Since the appropriate values are unknown, the Committee was forced to choose arbitrary ones and decided

to use values varying from 10 at low doses to 1 at high doses. The Committee's analyses, however, show that, while the introduction of any RBE value affects the form of the dose-effect relationship, the risk estimates obtained within the dose range that can be explored do not vary by more than a factor of three.

249. While it is hoped that work now in progress on the dosimetry of the survivors may in the future yield more reliable estimates of the doses received, it will not overcome the basic uncertainties concerning the relative effectiveness of neutron and gamma rays. Because the radiations received at Hiroshima and Nagasaki were of different qualities, continued and prolonged observations of the survivors in the two cities may eventually provide realistic indications of the actual RBE values to be used. At present, numerical values as are given in this annex must be taken for what they are, crude estimates that no amount of statistical or mathematical sophistication will protect from the basic uncertainties of the data from which they stem and the simplifying assumption used in deriving them.

A. Leukæmia

250. Among the survivors of Hiroshima and Nagasaki, incidences rise with kerma in each city at the same rate, whether they are based on mortality or on morbidity data. The rise is steeper at Hiroshima, presumably because of the larger neutron contribution. Assuming RBE values varying from 1 to 10 at high and low doses, respectively, risk estimates of 0.7 (at 60 rads) and 2 cases (at 400 rads) per million per year per rad of low-LET radiation can be obtained (see paragraph 36). The estimates derived from the ankylosing spondylitis patients with bone marrow partially exposed to 300-1,500 rads fall within this range. Since both studies indicate that the risk after 20 years is close to that in the non-irradiated population, the estimates correspond to an over-all risk of between 14 and 40 cases per million per rad.

251. A significant excess of leukæmias is seen at Hiroshima after a mean kerma as low as 22 rads of mixed radiation, corresponding to perhaps 50 rads of low-LET radiation. No excess is seen at comparable doses in Nagasaki, possibly because the sample size in that city is about three times smaller, making the expectations liable to wider chance fluctuations, but more probably because of the lower neutron contribution and therefore the much lower doses received.

252. Other studies reviewed in this annex confirm Marinelli's (97) observation that the risk of leukæmia remains within the limits given above, regardless of distribution of dose in space and time over a wide range of doses. At doses of the order of 1,000 rads, however, there is evidence indicating that the leukæmogenic effect of radiation is overshadowed by its call-killing effect, so that the yield of leukæmia per rad decreases.

B. Thyroid cancer

253. Because of its long times of survival, thyroid cancer must preferably be studied through morbidity surveys. One such survey has been carried out among the atomic bomb survivors of both cities and, in the 20-200 rad range, suggests estimates of between one and two cases per million per year per rad in males and twice as many in females (see paragraph 94), values rather higher than those suggested by the Committee in its earlier report from information derived at higher doses. These provisional estimates would correspond to 20-40 and 40-80 cases per million per rad in males and females, respectively, over a period of 20 years. As for all malignancies other than leuæmia, it is not known when the number of induced cases will start to decline.

C. Breast cancer

254. Breast cancer also has relatively long survival times. It is therefore best studied by means of morbidity surveys. The results of such an investigation among the survivors of the atomic bombing show a significant excess among the irradiated but the numbers are too small to obtain meaningful risk estimates. The mortality study (1950-1970) recorded significant excesses in both cities.

255. At Hiroshima, assuming a varying RBE as for leukæmia, the excess mortality of breast cancer among women is about 0.3 case per million per year per rad at 60 rads of low-LET radiation and about 1 case per million per year per rad at 400 rads (see paragraph 117). Because they are based on mortality statistics, these values are probably underestimates of the risk of induction. A survey based on morbidity reports on patients receiving high breast doses of x rays in the course of pneumothorax therapy, suggests that at average doses in the range of 600-3,000 rads the risk may be 1-6 cases per million per year per rad for about 20 years (paragraph 128).

256. While the rates from which the risks have been calculated have not been adjusted for factors such as parity and lactation history that appear to play a role in the occurrence of breast cancer, it does not seem likely that the risk estimates have been significantly distorted as a result. It is not known whether the increased risk will continue in the future or will soon taper off. Based on 20 years of observation at Hiroshima, the excess mortality per rad for the first 25 years after exposure appears to be from 6 to 20 cases per million per rad, depending on the dose. The morbidity survey of women treated by pneumothorax therapy would suggest a rate of induction up to five times higher. Since no breast cancer appears to be induced in males the figures should be halved to apply them to the general population.

D. Cancer of the respiratory tract

257. Significantly increased lung cancer mortality has been reported from Hiroshima (although not from Nagasaki) in the 1950-1970 period at a total mean kerma of 22 rads. Because of the differential absorption of neutrons and gammas by body tissues, this may be fairly close to the tissue dose, even allowing for a neutron efficiency in inducing lung cancer 10 times higher than for gamma rays. The dose-effect curve for the induction of lung cancers at Hiroshima appears to rise with kerma and reach a plateau somewhere between 150 and 450 rads. If crude allowance is made for depth distribution of the doses and the higher efficiency of neutrons, the resulting risk estimates vary from about 2 cases at 30 rads of low-LET radiation to 0.6 case per million per year per rad at 260 rads (see paragraph 147).

258. No dose-effect relationship for lung cancer is obtainable from the surveys of ankylosing spondylitis patients in which lung cancer is the malignancy whose

incidence contributes the largest part of the excess of malignancies of heavily irradiated sites over the incidence of tumours of the same sites in the general population. If, however, following Dolphin and Marley (39), the dose received on average by the bronchi of the patients is assumed to be some 80 rads, the risk of lung cancer is around three cases per million per year per rad (see paragraph 150), not very different from the estimate for low-LET radiation given above. Considering the uncertainties of the data, however, the agreement could well be fortuitous.

259. There is no way to determine for how long the recent rise in the annual incidence of lung cancers among the Hiroshima survivors and the spondylitics will last. The over-all risk (as based on observations from 5 to 25 years after exposure) can only be stated for the first 25-year period after the exposure as being about 40 cases per million per rad (at 30 rad of low-LET radiation) and possibly 12 cases per million per rad (at 260 rad). The estimates, however, are based on very crude assumptions, particularly concerning RBE. Neither among the survivors nor among the spondylitis patients are the data adequate to exclude the possibility that at least part of the radiation risk might be due to confounding of dose with smoking habits or to a synergistic effect of radiation and smoking.

E. Mortality from other malignancies

260. Increases in the mortality from malignancies other than leukæmia, lung cancer and breast cancer have been observed among both the survivors and the spondylitics. At present, only in the survivors can one attempt to study this excess residual mortality according to dose. The over-all excess is not significant at Nagasaki, presumably as a result of the sample being smaller and the average tissue doses (largely from gamma rays) lower than at Hiroshima where the neutron component was substantial. At Hiroshima only at the highest doses (260 rad) is a significant excess of these malignancies to be observed, corresponding to a risk of about 2.5 cases per million per year per rad of low-LET radiation (see paragraph 188).

261. The types of cancer that contribute significantly to this excess cannot yet be identified in the results obtained with the survivors, nor can it be ascertained whether the excess is to be expected in the future and for how long but some clue is provided by the surveys of the spondylitis patients which indicate that pharynx, pancreas, stomach, bone and lymphatic and hæmapoietic tissues might be particularly at risk. Inferences from the observations made in the spondylitics must, however, be made with caution. On the one hand, without knowledge of the tissue doses involved it is extremely difficult to ascertain the extent to which the observed excess mortality are the result of high doses rather than of high tissue sensitivity. Thus, on present information, it is likely that no excess of bone sarcomas will be seen in the survivors since few induced ones are likely to occur 25 years after exposure, whereas the slight excess of bone tumours observed among the spondylitics may have been due to the very high doses received by the spine during treatment, much higher than the highest doses received by the survivors. On the other hand, increases in cancer frequencies at certain sites that are seen in the spondylitics may reflect the effect of factors other than radiation and the possibility that this might be so must be left open until the observations in the spondylitics are borne out by similar ones among the survivors. A case in point is that of gastric cancer which does not seem to increase among the atom bomb survivors and may have done so among the spondylitics as a direct result of the medication that these patients must have received in large amounts for long periods of time, or of a synergistic effect between radiation and medication.

262. Comparison of the complete with the incomplete follow-up of the spondylitics suggests that the excess risk of tumours of heavily irradiated sites may have increased during the additional observation period. Therefore the estimates that can currently be derived from the survivors and from the spondylitics will have to be periodically reviewed. Since it is not possible now to indicate which trends in over-all incidence are to be expected or which specific tumours are likely to contribute to future increases and to what extent, it is imperative that the long-term investigations that have been carried out so far be pursued for several more decades and their results published in detail at suitable intervals, and that no efforts be spared to obtain adequate estimate of tissue doses.

F. Effects of age at irradiation

263. The surveys of the atomic bomb survivors indicate that subjects irradiated before 40 years of age have a higher relative risk of leukæmia than those irradiated later in life. The survivors that were irradiated in childhood (before 10 years of age) have recently (since 1960) shown a sudden increase in tumour incidence. There did not seem to be any specific pattern in the distribution of the types of tumours observed, although it might be of significance that only one pulmonary carcinoma was reported.

264. The observation of this sudden increase in the incidence of malignancies among subjects irradiated in their childhood is not unexpected. Development of malignancies with long latencies have been and are still being observed in a number of surveys of patients having received head or neck irradiation in their childhood. The continued follow-up of the survivors within the ABCC samples, however, is likely to provide in the long run information on the variation of risk with age that would be difficult to obtain reliably by other means, except if the differences were extreme.

G. Tissue irradiation by alpha particles

265. Because of their very short range, alpha particles emitted by nuclides deposited in body tissues give rise to highly inhomogeneous distributions of dose. This, coupled with the particles' high LET and their low rate of emission makes the few cases of alpha irradiation particularly difficult to investigate since their interpretation is seldom assisted by knowledge of the effects of spatially more uniform, short-term, irradiation. The major groups of alpha-irradiated people are miners whose lungs are exposed to high levels of radon and its daughters, and subjects carrying substantial burdens of radium (^{226}Ra, ^{228}Ra) acquired for medical or occupational reasons or treated by injections of ^{224}Ra-containing drugs.

266. Underground uranium miners provide the largest and best studied group of people exposed to high radon levels. The inhaled radon decays while in the res-

piratory tract and its radio-active daughters trapped on the bronchial epithelium, irradiate it and the tissue layers immediately underneath. Lung cancer has been known for a long time to occur with high frequency among these workers and is considered an occupational disease. The incidence appears to rise linearly with cumulative exposure but so many uncertainties attach to the estimates of the exposure that little reliance can be placed on the shape of the curve, except in so far as it fails to bear out the decrease in risk of lung cancer at high doses that the survey of Hiroshima survivors suggests. Because of differences in quality and in time and space distribution of the radiation, and because of the intervention of extraneous factors such as protracted inhalation of fumes and dusts by the miners and of possible differences in smoking habits between the two populations, close agreement between the observations would have been surprising.

267. People with substantial body burdens of long-lived radium (mostly ^{226}Ra) are few but have been followed for long periods of time (40 years on average) and have received on average much higher cumulative mean bone doses (in rads) than the people included in any of the surveys mentioned before. Only a fraction of the cumulative dose received must have been effective in inducing tumours, but its size cannot be ascertained. At cumulative doses above 1,000 rads they show a much higher incidence of bone sarcomas than the general population and a less pronounced excess of antral carcinomas. The incidence of bone sarcomas appears to reach a peak at around 14,000 rads. The size of the sample is too small to exclude that doses lower than 1,000 rads may in fact give rise to bone tumours of the type reported at higher doses.

268. A larger sample of people treated with short-lived ^{224}Ra, but followed up for shorter periods of time, have also shown increased incidence of bone sarcomas. Sarcomas are seen in groups exposed to significantly lower cumulative mean skeletal doses (about 300 rad) than from ^{226}Ra. The apparent higher sensitivity to radiation from ^{224}Ra may be due to the fact that this nuclide decays before it is embedded in the bone matrix so that substantially higher doses of radiation are delivered to the cells at risk.

H. Effects of pre-natal irradiation

269. The 1964 report of the Committee reviewed the results of a number of surveys of malignancies in children irradiated pre-natally for medical reasons which indicated that these children stand a 40 per cent greater chance than non-irradiated children to die of a malignancy within 10 years of birth. More information has now accumulated which is consistent with the earlier results. Estimates of the doses received by the fœtus during pelvimetry and other radiological procedures suggest that the risk of malignancies (50 per cent of them leukæmias) induced by pre-natal irradiation may be of about 20 cases per million per year per rad over a 10-year period (in the range of 0.2-20 rads).

270. This estimate is not borne out by a survey of survivors of *in utero* irradiation at Hiroshima and Nagasaki which did not show the increased cancer mortality to be expected on the basis of the estimate. It is conceivable that at least part of the increased risk seen among children irradiated *in utero* for medical reasons may be associated with the reasons that had prompted the exposure. It may also be that, owing to inaccurate dosimetry, the risk mentioned above is an over-estimate. It is important that further studies be undertaken aimed at securing reliable dosimetric information on a sufficiently large number of children, and at separating unequivocably the several contributions of the various factors that may affect the risk estimates.

I. Conclusions

271. This annex has reviewed in detail the evidence available on the induction of malignancies by ionizing radiation in man, and derived risk estimates for a few of them. These are summarized in table 22. The Committee wishes to re-emphasize that all the estimates apply to short-term exposures at high dose rates and, as discussed in annex G, are likely to be over-estimates of the risks per unit dose that may result from protracted irradiation at low dose rates of low-LET radiation. The estimates given in this annex are all subject to revision, both because the total risk of any malignancy can only be assessed by observing a cohort of irradiated people until extinction, and in no case has there been an opportunity for such prolonged observation yet, but also because of the basic uncertainties of the data.

272. These reflect a still inadequate knowledge of the tissue doses received by all groups of irradiated people, but even more our ignorance of the RBE values that must be applied in obtaining risk estimates from these groups that were exposed to mixed neutron and gamma radiation and that have so far provided the largest amount of information on the induction of malignancies in man.

Table 1. ABCC-JNIH Life Span Study Sample by sex, exposure category, and city (12)

	Total		Exposure category (distance from A-bomb hypocentre)							
			0-1,999 metres		2,000-2,499 metres		2,500-9,999 metres		10,000+ metres or not-in-city	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Hiroshima	30,691	43,665	8,828	12,501	4,775	6,749	8,798	12,477	8,290	11,938
Nagasaki	11,005	14,032	3,059	3,742	2,053	3,091	3,024	3,718	2,869	3,481
Both cities	41,696	57,697	11,887	16,243	6,828	9,840	11,822	16,195	11,159	15,419

TABLE 2. COMPARISON OF T57D AND T65D KERMA ESTIMATES AT 500-METRE INTERVALS FROM A-BOMB HYPOCENTRE (101)

Ground distance (metre)	Gamma rays (rad)			Neutrons (rad)			Total (rad)[a]		
	T57D	T65D	T65D / T57D	T57D	T65D	T65D / T57D	T57D	T65D	T65D / T57D
				Hiroshima					
0	12,000	10,300	0.86	18,000	14,200	0.79	30,000	24,500	0.82
500	4,030	2,790	0.69	4,390	3,160	0.72	8,420	5,950	0.71
1,000	572	256	0.45	321	192	0.60	893	448	0.50
1,500	80.0	21.6	0.27	20.9	10.1	0.48	100	31.7	0.32
2,000	12.1	1.9	0.16	1.4	0.5	0.36	13.5	2.4	0.18
				Nagasaki					
0	27,000	25,100	0.93	5,500	3,910	0.71	32,500	29,000	0.89
500	7,230	7,090	0.98	1,030	703	0.68	8,260	7,790	0.94
1,000	865	889	1.03	61.0	35.9	0.59	926	925	1.00
1,500	113	119	1.05	3.6	1.7	0.47	117	121	1.03
2,000	16.5	17.8	1.08	0.2	0.1	0.50	16.7	17.9	1.07

[a] Gamma and neutron components added without weighting.

TABLE 3. INCIDENCE OF LEUKÆMIA AMONG A-BOMB SURVIVORS IN THE MASTER SAMPLE, BY SPECIFIC TYPE OF LEUKÆMIA, TOTAL KERMA, AND CITY, OCTOBER 1950-SEPT. 1966 (67)

Type	T65D total kerma (rad)							
	Total		100+		5-99		Under 5	
	Cases	Rate[a]	Cases	Rate[a]	Cases	Rate[a]	Cases	Rate[a]
				Hiroshima				
Acute granulocytic	25	2.0	11	24.3	3	1.1	11	1.2
Acute lymphocytic	13	1.1	5	11.1	4	1.5	4	0.44
Acute (other types)	20	1.6	6	13.3	6	2.3	8	0.87
Chronic granulocytic	29	2.4	10	22.1	15	5.7	4	0.44
Chronic lymphocytic	0	0	0	0	0	0	0	0
Chronic (other types) ...	1	0.08	0	0	1	0.38	0	0
TOTAL	88	7.2	32	70.8	29	11.1	27	3.0
Person-years at risk ..... (*thousands*)	1,221.7		45.2		261.4		915.1	
				Nagasaki				
Acute granulocytic	13	3.0	6	16.4	1	0.96	6	2.0
Acute lymphocytic	7	1.6	6	16.4	0	0	1	0.34
Acute (other types)	4	0.91	1	2.7	0	0	3	1.0
Chronic granulocytic	4	0.91	2	5.5	1	0.96	1	0.34
Chronic lymphocytic	1	0.23	0	0	0	0	1	0.34
Chronic (other types) ...	0	0	0	0	0	0	0	0
TOTAL	29	6.6	15	41.1	2	1.9	12	4.0
Person-years at risk ..... (*thousands*)	437.6		36.5		103.9		297.2	

[a] Cases 10^{-5} y^{-1}.

TABLE 4. OBSERVED AND EXPECTED MORTALITY AMONG A-BOMB SURVIVORS OF ABCC LIFE SPAN STUDY SAMPLE (1950-1966), SEXES AND CITIES COMBINED (10)

Cause of death		Total T65D kerma (rad)					
		Total	0-9	10-39	40-179	180+	Unknown
Leukæmia[a]	Observed	116	35	13	24	35	9
	R.R.[b]	—	1.00	1.62	4.98	17.49	3.85
	Excess number[c]	63.9	—	5.0	19.2	33.0	6.7
	M.R.[d]	95.6	43.1	68.9	214.3	764.3	164.0
All malignant neoplasms except leukæmia[a]	Observed	2,276	1,489	365	233	88	101
	R.R.	—	1.00	1.03	1.13	1.27	1.19
	Excess number	72.2	—	10.6	26.8	18.7	16.1
	M.R.	1,875.0	1,832.8	1,993.4	2,080.4	1,921.7	1,840.4
Cancer of stomach	Observed	959	628	153	99	32	47
	R.R.	—	1.00	1.05	1.17	1.11	1.31
	M.R.	790.0	773.0	810.5	883.9	698.8	856.4
Cancer of large bowel	Observed	129	89	22	11	2	5
	R.R.	—	1.00	1.05	0.92	0.54	1.08
	M.R.	106.3	109.6	116.5	98.2	43.7	91.1
Cancer of liver and biliary tract	Observed	249	176	30	25	13	5
	R.R.	—	1.00	0.70	0.98	1.35	0.41
	M.R.	205.1	216.6	158.9	223.2	283.9	91.1
Cancer of pancreas	Observed	61	47	8	3	2	1
	R.R.	—	1.00	0.74	0.46	0.89	0.36
	M.R.	50.3	57.9	42.4	26.8	43.7	18.2
Cancer of bronchus, trachea, and lung	Observed	145	83	25	22	8	7
	R.R.	—	1.00	1.28	1.89	1.98	1.40
	M.R.	119.5	102.2	132.4	196.4	174.7	127.6
Other cancers[e] (ICD 190-199)	Observed	126	80	19	13	5	9
	R.R.	—	1.00	1.01	1.23	1.44	2.05
	M.R.	103.8	98.5	100.6	116.1	109.2	164.0
Cancer of female breast	Observed	67	41	11	9	2	4
	R.R.	—	1.00	1.05	1.54	1.07	2.07
	M.R.	55.2	50.5	58.3	80.4	43.7	72.9
Cancer of uterus	Observed	194	119	39	19	5	12
	R.R.	—	1.00	1.29	1.14	.98	2.27
	M.R.	159.8	146.5	206.6	169.6	109.2	218.7

[a] Significant ($P < 0.05$) linear increase of excess number of cases with dose.

[b] R.R.: Sex and age-adjusted risk relative to that of 0-9-rad dose category. In the 0-9-rad group median dose is zero.

[c] Observed $\times$ (R.R. $-$ 1)/R.R.

[d] M.R.: Average annual mortality rate (crude rate) per million.

[e] Other cancers, ICD No. 190-199: 191 skin, 193 brain and nervous system, 194 thyroid, 195 bone; 199 others and unspecified, etc.

TABLE 5. OBSERVED AND EXPECTED DEATHS FROM SELECTED TYPES OF CANCER 1950-1970 ACCORDING TO T65D TOTAL DOSE. SEXES ARE COMBINED, EXCEPT FOR BREAST CANCER (74).

A. *Hiroshima*

		NIC[a]	*0-9*	*10-49*	*50-99*	*100-199*	*200+*	*Unknown*	*10+*[b]	*Total*
Mean kerma (rad)		0	1	22	70	139	463	—	—	—
Person-years at risk	Both sexes	342,955	795,669	195,448	48,275	30,223	26,708	29,829	330,483	1,469,107
	Females	202,563	472,722	122,761	30,614	17,810	15,223	17,856	204,264	879,549
Leukæmia	Obs.[c]	10	34	17	7	10	27	5	66	110
	(C.L.)[d]	4.8-18.4	23.6-47.5	9.9-27.2	2.8-14.4	4.8-18.4	17.8-39.3	1.6-11.7	51.1-83.9	89-131
	Exp.1[e]	10.1	22.3	5.5	1.4	0.9	0.8	0.8	9.4	41.8
	Exp. 2[f]	—	—	8.4	2.1	1.3	1.1	1.3	14.2	—
	Exp. 3[g]	—	—	7.6	1.9	1.2	1.0	1.2	12.9	—
	Rate[h]	29	43	87	145	331	1,011	168	200	75
Bronchus, trachea, and lung cancer	Obs.	52	115	42	12	9	8	8	79	246
	(C.L.)	38.8-68.2	96-138	56.7-30.3	6.2-21.0	4.1-17.1	3.5-15.8	3.5-15.8	62.6-98.5	215-277
	Exp. 1	41.2	90.4	23.2	6.1	3.9	3.0	3.3	39.5	171.1
	Exp. 2	—	—	28.2	7.0	4.4	3.9	4.3	47.8	—
	Exp. 3	—	—	28.7	7.1	4.4	3.9	4.4	48.5	—
	Rate	152	145	215	249	298	300	268	239	167
Breast cancer	Obs.	11	40	13	4	6	3	3	29	80
	(C.L.)	5.5-19.7	28.6-54.5	6.9-22.2	1.1-10.2	2.2-13.1	0.6-8.8	0.6-8.8	19.4-41.7	63.5-99.6
	Exp. 1	13.6	31.6	8.5	2.2	1.2	1.0	0.9	13.6	58.8
	Exp. 2	—	—	10.4	2.6	1.5	1.3	1.5	17.3	—
	Exp. 3	—	—	9.3	2.3	1.3	1.2	1.3	15.4	—
	Rate	54	85	106	131	337	197	168	142	91
Other cancers	Obs.	587	1,517	388	110	66	73	62	699	2,803
	(C.L.)	540-634	1,441-1,593	349-427	89-131	51.1-83.9	57.3-92.1	47.5-79.6	647-751	2,699-2,907
	Exp. 1	598.4	1,418.1	366.5	95.6	57.3	44.7	45.4	609.5	2,626.0
	Exp. 2	—	—	373.0	91.8	57.6	51.0	56.9	630.3	—
	Exp. 3	—	—	360.5	89.0	55.9	49.4	55.2	610.0	—
	Rate	1,712	1,907	1,985	2,279	2,184	2,733	2,079	2,115	1,908

B. *Nagasaki*

		NIC[a]	*0-9*	*10-49*	*50-99*	*100-199*	*200+*	*Unknown*	*10+*[b]	*Total*
Mean kerma (rad)		0	2	21	71	146	402	—	—	—
Person-years at risk	Both sexes	118,309	209,872	67,649	22,914	23,017	24,349	27,025	164,954	493,135
	Females	65,723	121,986	39,725	13,202	12,677	13,078	14,093	92,775	280,484
Leukæmia	Obs.	3	11	2	0	3	15	3	23	37
	(C.L.)	0.6-6.8	5.5-19.7	0.2-7.2	0-3.7	0.6-8.8	8.4-24.7	0.6-8.8	14.6-34.5	26.1-51.1
	Exp. 1	3.2	5.6	1.8	0.6	0.6	0.7	0.7	4.5	13.3
	Exp. 2	—	—	3.5	1.2	1.2	1.3	1.4	8.6	—
	Exp. 3	—	—	2.9	1.0	1.0	1.0	1.2	7.0	—
	Rate	25	52	30	—	130	616	111	139	75
Bronchus, trachea, and lung cancer	Obs.	20	29	7	1	4	5	5	22	71
	(C.L.)	12.2-30.9	19.4-41.7	2.8-14.4	0-5.6	1.1-10.2	1.6-11.7	1.6-11.7	13.8-33.3	55.5-89.6
	Exp. 1	10.5	18.1	6.2	2.1	1.9	2.0	2.3	14.5	43.1
	Exp. 2	—	—	9.3	3.2	3.2	3.4	3.7	22.8	—
	Exp. 3	—	—	10.1	3.4	3.4	3.6	4.0	24.5	—
	Rate	169	138	103	44	174	205	185	133	144
Breast cancer	Obs.	4	8	6	2	2	1	1	12	24
	(C.L.)	1.1-10.2	3.5-15.8	2.2-13.1	0.2-7.2	0.2-7.2	0-5.6	0-5.6	6.2-21.0	15.4-35.7
	Exp. 1	3.3	6.4	2.2	0.7	0.6	0.6	0.5	4.6	14.4
	Exp. 2	—	—	2.6	0.9	0.8	0.9	0.9	6.1	—
	Exp. 3	—	—	2.5	0.8	0.8	0.8	0.9	5.8	—
	Rate	61	66	151	151	158	76	71	129	86
Other cancers	Obs.	165	281	105	37	19	37	32	230	676
	(C.L.)	140-190	248-314	85-125	26.1-50.9	11.4-29.7	26.1-50.9	21.9-45.2	200-260	626-729
	Exp. 1	154.5	280.3	98	32.1	28.6	28.3	31.2	218.2	653.0
	Exp. 2	—	—	90.6	30.7	30.8	32.6	36.2	220.9	—
	Exp. 3	—	—	91.9	31.1	31.3	33.1	36.7	224 1	—
	Rate	1,395	1,339	1,552	1,615	825	1,520	1,184	1,394	1,361

[a] Not in city at the time of bombing.
[b] Including unknown dose group.
[c] Observed number of deaths.
[d] 95 per cent confidence limits.
[e] Expected number of deaths based on national rates.
[f] Expected number of deaths based on 0-9-rad group.
[g] Expected number of deaths based on NIC + 0-9-rad group.
[h] Mortality rate, per million per year.

TABLE 6. NUMBERS OF DEATHS OBSERVED AND EXPECTED AMONG ANKYLOSING SPONDYLITIS PATIENTS, BY CAUSE AND PERIOD AFTER FIRST OBSERVATION[a] (28)

Cause of death	No. of deaths	Years after first observation 0-2	3-5	6-8	9-11	12-14	15-24	All periods
Leukæmia	Observed	7	19	14	6	5	1	52
	Expected	1.10	1.49	1.32	0.86	0.45	0.27	5.48
	Obs./Exp.	6.4	12.8	10.6	7.0	11.1	3.7	9.5
Cancer of heavily irradiated sites	Observed	33	36	46	46	27	12	200
	Expected	22.48	33.25	31.32	21.16	11.54	7.52	127.27
	Obs./Exp.	1.5	1.1	1.5	2.2	2.3	1.6	1.6
Cancer of lightly irradiated sites	Observed	13	15	13	12	2	5	60
	Expected	10.27	14.09	12.64	8.27	4.28	2.88	52.42
	Obs./Exp.	1.3	1.1	1.0	1.5	0.5	1.7	1.1
All other causes	Observed	234	336	290	191	113	66	1,230
	Expected	139.07	178.56	155.45	102.30	54.22	35.93	665.56
	Obs./Exp.	1.7	1.9	1.9	1.9	2.1	1.8	1.8
Person-years at risk (*thousands*)		35.5	40.7	31.9	19.2	9.6	4.9	141.8

[a] Followed to 1 January 1960.

TABLE 7. RISK OF LEUKÆMIA IN PATIENTS EXPOSED TO THERAPEUTIC IRRADIATION IN THE PELVIC REGION

Disease	Number treated	Follow-up in years	Treatment	Dose[a] (rad)	Leukæmia Observed	Leukæmia Expected	R.R.[b]
Metropathia hæmorrhagica (33)	2,068	3-24	X rays	222-522	6	1.3	4.6
Benign gynæcological disorders (164)							
A. Connecticut	900	2-32	Radium	159-503	9	2.8	3.2
B. Massachusetts	1,803	2-32	Radium	159-318	10	3.5	2.8
C. Connecticut	993	2-32	X rays	300-900	3	2.4	1.3
Uterine cancer (164)	7,835	2-32	Radium / X rays	900-4,500	9	8.6	1.1
Cervix cancer (64)	28,171	2-5	Radium[c] / X rays	900-4,500	4	5.1	0.8

[a] Mean pelvic marrow dose.
[b] Relative risk: observed cases/expected cases.
[c] 14 per cent treated by radium only, receiving 150-450 rads.

TABLE 8. NUMBER OF CASES OF THYROID CARCINOMA AND RATE PER 1,000 EXAMINED BY AGE AT EXAMINATION, SEX, AND DISTANCE IN METRES FROM HYPOCENTRE (173)

Age (year)	Male <1,400 No.	Male <1,400 Rate	Male 1,400-1,999 No.	Male 1,400-1,999 Rate	Male 3,000+[a] No.	Male 3,000+[a] Rate	Male All distance groups No.	Male All distance groups Rate	Female <1,400 No.	Female <1,400 Rate	Female 1,400-1,999 No.	Female 1,400-1,999 Rate	Female 3,000+[a] No.	Female 3,000+[a] Rate	Female All distance groups No.	Female All distance groups Rate
< 40	5	9.7	0	0	1	1.1	6	3.3	10	10.7	2	3.1	1	0.7	13	4.3
40-59	0	0	0	0	0	0	0	0	4	4.4	3	3.7	6	3.7	13	3.9
60+	0	0	1	3.3	0	0	1	0.7	4	8.5	1	2.2	1	1.1	6	3.2
All ages	5	3.6	1	0.9	1	0.4	7	1.4	18	7.8	6	3.1	8	2.0	32	3.9

[a] Includes not-in-city at the time of bombing.

TABLE 9. FREQUENCY OF THYROID CARCINOMA PER 1,000 SURVIVORS EXAMINED BY AGE AT EXAMINATION, SEX, AND KERMA (173)

Age (year)	Male				Female			
	0-49	50-199	200+ (rad)	Total	0-49	50-199	200+ (rad)	Total
< 40	0	6.8	9.8	5.3	5.5	4.0	12.8	7.5
40-59	0	0	0	0	2.5	3.8	7.7	4.1
60+	3.5	0	0	1.4	0	16.4	0	5.3
Total	1.1	2.5	4.1	2.4	2.8	6.8	9.1	5.7
Examined .	928	789	740	2,457	1,806	1,332	1,100	4,238

TABLE 10. THYROID NODULES (PLUS HYPOTHYROIDISM) AND MALIGNANCIES FROM 1954 TO 1969 IN RESIDENTS OF MARSHALL ISLANDS EXPOSED TO FALL-OUT (25)

Island	Age at exposure (year)	Estimated thyroid dose[a] (rad)	Percentage of thyroid lesions[b]	Percentage of malignancies[b]
Rongelap (175 rad)[c]	< 10	500-1,400	89.5 (17/19)	5.3 (1/19)
	> 10	160[d]	8.8 (3/34)	5.9 (2/34)
	all		39.6 (21/53)	5.7 (3/53)
Ailingnae (69 rad)	< 10	275-550	0.0 (0/6)	—
	> 10	55	12.5 (1/8)	—
	all	—	7.1 (1/14)	—
Utirik (14 rad)	< 10	55-110	0.0 (0/40)	—
	> 10	14	5.1 (3/59)	1.7 (1/59)
	all	—	3.0 (3/99)	1.0 (1/99)
Rongelap unexposed	< 10	—	0.0 (0/61)	—
	> 10	—	2.3 (3/133)	—
	all	—	1.5 (3/194)	—

[a] Dose from $^{131, 132, 133, 135}I$.
[b] Based on present population.
[c] Dose from gamma radiation.
[d] Children 10 to 20 years of age at exposure received up to about 500 rads.

TABLE 11. OBSERVED AND EXPECTED BREAST CANCER IN WOMEN EXAMINED IN THE ABCC-JNIH ADULT HEALTH STUDY 1958-1966 BY ESTIMATED TOTAL KERMA (168)

Total kerma (rad)	Number examined	Breast cancer			
		Observed	Expected[a]	Relative risk[b]	Excess rate per 1,000[c]
NIC	2,458	2			
0-9	3,082	3			
10-39	1,262	4	1.14	3.5	2.3
40-89	857	2	0.77	2.6	1.4
90-199	802	4	0.72	5.6	4.1
200+	841	5	0.76	6.6	5.0
Unknown	840	2	0.76	2.6	1.5

[a] Based on rate in NIC and 0-9-rad groups combined.
[b] Risk relative to that of NIC and 0-9-rad dose category.
[c] (Observed-expected)/examined.

TABLE 12. RISK ESTIMATES OF LUNG CANCER INDUCTION BASED ON THE HIROSHIMA DATA

	Kerma range (rad)			
	10-49	50-99	100-199	200+
$\overline{K}_T$	22	70	139	462
$\overline{K}_g$	18	57	109	332
$\overline{K}_n$	4	13	30	130
$\overline{D}_g$	10	35	64	195
$\overline{D}_n$	2	7	15	65
RBE	10	5	2.5	1
$\overline{D}_T$[a]	30	70	102	260
E[b]	70	104	152	154
R[c]	2.3	1.5	1.5	0.6

[a] $\overline{D_T} = \overline{D_g} + \text{RBE} \times \overline{D_n}$.
[b] Excess number of cases per million per year by comparison with 0-9-rad group.
[c] Absolute risk: $R = E/\overline{D_T}$.

TABLE 13. NUMBERS OF DEATHS OBSERVED AND EXPECTED FROM CANCER OF HEAVILY IRRADIATED SITES SIX OR MORE YEARS AFTER FIRST OBSERVATION[a] AMONG ANKYLOSING SPONDYLITIS PATIENTS (28)

Primary site (death certification)	Deaths			Relative risk	Excess mortality per million per year
	Observed	Expected	Difference		
Pharynx	5	1.05	3.95	4.8[b]	23.8
Œsophagus	3	3.37	−0.37	0.9	−2.2
Stomach	38	23.62	14.38	1.6[b]	86.8
Pancreas	12	5.71	6.29	2.1[b]	38.0
Larynx	2	1.81	0.19	1.1	1.2
Bronchi	96	54.20	41.80	1.8[b]	252.4
Ovaries	4	2.16	1.84	1.9	11.1
Skin	0	1.37	−1.37	0.0	−8.3
Bones	5	1.11	3.89	4.5[b]	23.5
Hodgkin's disease	1	2.47	−1.47	0.4	−8.9
Other lymphatic and hæmopoietic tissues	10	3.39	6.61	2.9[b]	39.9
Others	24	6.78	17.22	3.5[b]	104.0
All heavily irradiated sites	200	107.04	92.96	1.9[b]	561.2

[a] Followed to 1 January 1963.
[b] Statistically significant: $P < 0.025$ on a one-tailed test.

TABLE 14. LUNG CANCER MORTALITY AMONG URANIUM MINERS (86)

WLM	Estimated cumulative WLM					
	< 120	120-359	360-839	840-1,799	1,800-3,719	>3,720
Observed number of deaths	1	12	14	12	21	10
Expected number of deaths[a]	1.81	2.57	2.95	2.52	1.43	0.42
Excess		9.43	11.05	11.48	19.57	9.58
Man-years at risk	8,516	9,365	9,045	6,607	3,455	978
Excess mortality rate × 10^3		1.0	1.2	1.7	5.7	9.8

[a] Based on mortality in the population of the four states in which miners were examined. Not adjusted for smoking habits.

TABLE 15. BONE SARCOMAS AND ANTRUM CARCINOMAS IN CARRIERS OF ^{226}Ra (125)

Median dose (rad)	*Sample size*	*Bone sarcomas*	*Antrum carcinomas*	*Total tumours*
23,300	18	3	4	7
12,600	23	12	1	13
6,590	39	15	4	19
2,980	72	14	7	21
1,280	42	6	4	10
756	44	1	0	1
284	80	0	0	0
139	83	0	0	0
65	88	0	0	0
31	139	0	0	0
15	73	0	0	0
5.2	73	0	0	0
0.45	6	0	0	0
TOTAL	780	51	20	71

TABLE 16. BONE SARCOMA IN PATIENTS EXPOSED TO ^{224}Ra (144)

Juveniles (<20 y)			*Adults*		
Mean dose	*Sample size*	*Bone sarcomas*	*Mean dose*	*Sample size*	*Bone sarcomas*
47	5	0	53	210	0
146	7	0	139	229	3
363	35	2	306	214	4
727	76	4	650	55	3
1,345	72	19			
3,329	22	8			

TABLE 17. OBSERVED AND EXPECTED NUMBER OF DEATHS BY CAUSE[a] AMONG ANKYLOSING SPONDYLITIS PATIENTS (28)

Cause of death	*Deaths*				*Excess mortality per million per year*
	Observed	*Expected*	*Excess*	*Obs./Exp.*	
Leukæmia	52	5.48	46.52	9.5	328.1
Cancer of heavily irradiated sites[b]	200	127.27	72.73	1.6	512.9
Cancer of lightly irradiated sites[c]	60	52.42	7.58	1.1	53.5
Causes with no obvious relation to ankylosing spondylitis[d]	752	555.41	196.59	1.4	1,386.4

[a] Followed to 1 January 1960.

[b] Cancer of pharynx, œsophagus, stomach, pancreas, larynx, bronchi, ovaries, skin, bones, Hodgkin's disease, and cancer of other lymphatic and hæmopoietic tissues except leukæmia.

[c] Cancer of brain and central nervous system, mouth, liver and gall bladder, rectum, breast, uterus, prostate, testes, kidneys, and urinary bladder.

[d] Such as peptic ulcer, cerebro-vascular disease, bronchitis, violence, etc.

TABLE 18. NUMBERS OF DEATHS OBSERVED AND EXPECTED BY CAUSE AND PERIOD AFTER FIRST OBSERVATION[a] AMONG ANKYLOSING SPONDYLITIS PATIENTS (28)

Cause of death	Number of deaths	Years after first observation						All periods
		0-2	3-5	6-8	9-11	12-14	15-24	
Leukæmia[b]	Observed	7	19	16	10	7	1	60
	Expected	1.10	1.49	1.59	1.27	0.76	0.54	6.75
	Obs./Exp.	6.4	12.8	10.1	7.9	9.2	1.9	8.9
Aplastic anæmia[b]	Observed	3	7	5	1	0	0	16
	Expected	0.11	0.14	0.14	0.11	0.06	0.05	0.61
	Obs./Exp.	27.3	50.0	35.7	9.1	0.0	0.0	26.2
Cancer of heavily irradiated sites	Observed	33	36	52	67	46	35	269
	Expected	22.48	33.25	38.55	32.52	20.29	15.67	162.76
	Obs./Exp.	1.5	1.1	1.3	2.1	2.3	2.2	1.7
Person-years at risk (thousands)		35.5	40.7	37.4	27.1	15.2	9.8	165.6

[a] Incomplete follow-up to 1 January 1963.
[b] Although all patients were not followed individually until 1 January 1963, the total number of deaths is probably known, as the names of the untraced patients had been checked against a nominal roll of persons dying of these conditions.

TABLE 19. NUMBERS OF DEATHS BY CAUSES AND TIME SINCE FIRST TREATMENT IN PATIENTS TREATED BY X-IRRADIATION FOR METROPATHIA HÆMORRHAGICA (38)

Cause of death	Within 5 years of first treatment			5 years or more after			
	Observed	Expected	Observed / Expected	Observed	Expected	Observed / Expected	P[a]
Leukæmia	0	0.36	0	6	0.95	6.32	< 0.0005
Cancer of heavily irradiated sites	2	6.99	0.29	31	18.40	1.68	< 0.002
Cancer of breast	4	4.42	0.90	5	10.54	0.47	< 0.05
Other cancers	7	6.66	1.05	25	21.65	1.15	—
Coronary disease	1	3.92	0.26	27	28.22	0.96	—
Other causes	48	33.56	1.49	87	98.77	0.88	—
All causes	64	55.94	1.14	181	178.62	1.01	—

[a] One-tailed test.

TABLE 20. OBSERVED AND EXPECTED DEATHS ATTRIBUTED TO CANCER EXCEPT LEUKÆMIA, 1955-1969, AGES 0-9 YEARS AT EXPOSURE (71)

Dose	Survivors, January 1960	Estimated person-years 1955-1969	Deaths		Observed / Expected	P
			Observed	Expected[a]		
Not-in-city or < 10 rad	15,667	235,005	14	13.98	1.00	
10-99 rad	3,650	54,750	0	3.26	0.0	—
100+	799	11,985	6	0.713	8.40	~ 0.0001
Unknown	299	4,485	2	0.267	7.48	~ 0.03
TOTAL	20,415	306,225	22	18.22		

[a] Computed with Japanese national rates of 1962.

TABLE 21. OBSERVED AND EXPECTED MALIGNANCIES IN INDIVIDUALS TREATED BY X-IRRADIATION FOR THYMIC ENLARGEMENT AND THEIR SIBLING CONTROLS (58)

Type	Exposed subjects		Sibling controls	
	Observed	Expected	Observed	Expected
All malignancies	33	8.10	14	14.56
Thyroid carcinoma	19	0.14	0	0.31
Leukæmia	6	2.02	2	3.21
Hodgkin's disease	0	0.47	1	0.80
Salivary gland tumour	4	0.08	1	0.15
Breast carcinoma	0	0.11	0	0.46
Brain tumour	1	1.23	2	2.48
Others	3	—	8	—

TABLE 22. SUMMARY OF RISK ESTIMATES

Irradiated population[a]	*Radiation quality*[b]	*Mean dose or dose range (rad)*	*Observation period*[c]	*Type of data*[d]	*Sex*	*Age at exposure*[e]	*Risk per 10^6 y rad*[f]	*Paragraph*
				Leukæmia				
H	GN	60	5-25	Mt	MF	AC	0.7	36
H	GN	400	5-25	Mt	MF	AC	2.0	36
N	G	10-400	5-21	Mb	MF	AC	1.6	24
S	X	300-1,500	(5.5)	Mt	M	A	1.2	54
P_1	X	0.2-20	0-10	Mt	MF	F	10	239
P_2	GN[g]	25	0-10	Mt	MF	F	NE	241
				Thyroid cancer				
HN	GN[g]	25-200	5-20	Mb	M	AC	1-2	94
HN	GN	25-200	5-20	Mb	F	AC	2-4	94
I	X	50-600	(16)	Mb	MF	C	2.5	230
				Breast cancer				
HN	GN[g]	150	13-21	Mb	F	AC	2-4	109
H	GN	60	5-25	Mt	F	AC	0.3	117
H	GN	400	5-25	Mt	F	AC	1.0	117
N	G	20-400	5-25	Mt	F	AC	0.7[h]	117
T	X	600-3,000	(17.5)	Mb	F	AC	1-6	128
				Lung cancer				
H	GN	30	5-25	Mt	MF	AC	2.3	147
H	GN	260	5-25	Mt	MF	AC	0.6	147
N	G	20-400	5-25	Mt	MF	AC	NE	146
S	X	80	(10.5)	Mt	M	A	3	150
				Other types of cancer				
H	GN	30	5-25	Mt	MF	AC	NE	188
H	GN	260	5-25	Mt	MF	AC	2.5	188
N	G	20-400	5-25	Mt	MF	AC	NE	187
P_1	X	0.2-20	0-10	Mt	MF	F	10	239
P_2	GN[g]	25	0-10	Mt	MF	F	NE	241

[a] H = Hiroshima survivors; N = Nagasaki survivors; S = ankylosing spondylitis patients; P_1 = children irradiated pre-natally for medical reasons; P_2 = children exposed while *in utero* to A-bomb radiation; I = infants irradiated in the cervical region; T = tuberculosis patients.

[b] G = gamma rays; N = neutrons; X = x rays; GN = mixed radiation.

[c] Years elapsed between exposure and beginning and end of follow-up period or, in brackets, average duration (years) of follow-up.

[d] Mt = mortality; Mb = morbidity.

[e] A = adults; C = children; F = fœtuses.

[f] NE = no excess or no statistically significant excess.

[g] No neutron RBE applied to calculate dose.

[h] Based on the over-all excess among those exposed to known doses > 10 rad (average 113 rad).

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