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NOTE

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

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

ANNEX D

SOMATIC EFFECTS OF RADIATION

CONTENTS

CONTENTS *(continued)*

I. Physical factors influencing somatic effects

Introduction

1. The present annex summarizes knowledge of the biological effects of ionizing radiations on animals and man; the object is to assess the effect of radiation on the individual.

2. The principal physical factors determining the biological effects of ionizing radiation are the absorbed dose (rad), its distribution in time (instantaneous dose-rate, fractionation, short-term or long-term exposure), its spatial distribution (anatomical region, fraction of total body, organ depth, distribution, etc.) and the quality of radiation (energy: α-, β-, γ-, X-rays, neutrons, etc.) The inhomogeneity of dose in man, particularly after accidental exposure, raises an important practical difficulty in assessing exposure in man: one can ascribe no single meaningful value for the dose delivered.

Definitions

3. To facilitate prospective and retrospective classification and study, definitions used by the United States National Academy of Sciences-National Research Council Sub-committee on Hematologic Effects (1961) [1] are recommended. Some terms cannot be defined precisely. Others, because of ambiguity, e.g. "acute" and "chronic", are best avoided in describing exposure and effects and reserved for use in their usual medical sense.

Short-term exposure

4. Short-term exposure includes: (*a*) total or substantial body exposure to radiation over a short time (e.g. in nuclear warfare from direct exposure to initial radiation from the detonation of nuclear weapons and nuclear reactor or accelerator accidents), and (*b*) exposure of limited yet substantial body areas in which the radiation is given either as a single dose or fractionated over a few days or weeks (e.g., in therapeutic radiation, diagnostic radiology, or tracer or therapeutic use of radio-active isotopes). A dose $\geqq$ 50 rad is defined, for the purposes of the present report, as a high dose, $<$ 50 rad as a low dose.

Long-term exposure

5. Long-term exposure refers to continued or repeated exposure to radiation over months or years. Such exposure is greatest in certain occupations and in persons containing radio-active isotopes with relatively long effective half-lives. X-ray examinations repeated frequently over a long time also constitute long-term exposure, as do exposures to cosmic radiation, naturally-occurring radio-active isotopes, and fall-out.

Cumulative dose

6. Although the *total dose* of radiation is important in long-term exposure, it is sometimes useful and convenient to indicate degree of exposure as dose per unit time, usually cumulative dose per week:

(*a*) Very low weekly dose $<$ 100 mrad.

(*b*) Low weekly dose: 100-1,000 mrad.

(*c*) High weekly dose $>$ 1,000 mrad.

7. The very low weekly dose is less than that implied by the 1960 maximum permissible dose (MPD) recommended for occupational exposure by the International Commission on Radiological Protection (ICRP)[2] and the United States National Committee on Radiation Protection and Measurements (1958).[3] The dividing line between low and high dose corresponds to the first MPD recommendations of these groups in effect between 1936 and 1948.

Consequences of exposure

8. The initial effects produced by radiation may lead to observable alterations expressed promptly or months or years after irradiation. The development of clinical findings depends not only on the nature and extent of the initial radiation injury, but also on the operation of secondary factors, e.g. the influence of hormonal secretions on the development of radiation-induced mammary tumours. A distinction should also be made between those effects that produce only a cytologic abnormality, e.g. binucleate lymphocytes, and those that produce a serious disease, e.g. leukaemia.

9. It is not possible to distinguish sharply between early and late effects since effects observed soon after radiation may persist. Nevertheless, it is convenient to consider as *early*, effects observable within a few weeks after exposure. *Late* effects are those that appear later not obviously related to the early effects. Late effects include cataracts and tumours; they may not appear until many years after exposure.

TYPE OF RADIATION

10. Different kinds of radiation produce essentially similar biological effects at the macroscopic level, though there are possible differences at the microscopic level; but superimposed on this uniformity they may have a different relative biological effectiveness (RBE), e.g. densely ionizing particles (α rays, neutrons) are more efficient in producing most forms of cellular damage than γ- and X-rays giving lower ion densities. The RBE quoted for a particular kind of radiation depends on the specific biological effect observed, the tissue irradiated, dose, and rate at which it is given. Annex B details the concept of RBE; difficulties in its application to internal emitters are described in section VI of the present annex.

TIME DISTRIBUTION OF DOSE

11. A dose which is lethal if given in a short time may, if spread over a long time, produce effects difficult to relate to the exposure or, especially when recovery intervenes, to detect at all. This poses the key question in assessing somatic effects in man: what are the effects of low doses, single or long-term?

EARLY EFFECTS

12. The early effects in man of large doses are fairly clearly known from the therapeutic use of X-rays and of radio-nuclides such as Ra^{226} (used in teletherapy) and I^{131}, from atomic energy workers in nuclear accidents and from clinical studies on atom-bomb survivors. The acute radiation syndrome is detailed in section IV below.

LATE EFFECTS

13. Late effects in man are inferred from knowledge of specific effects produced in animal experiments, from large-scale observations on population, and from occupational and medical exposures in man. Late effects comprise:

(*a*) Many, if not all types of neoplasm, including leukaemia;

(*b*) Local effects on tissues, e.g. skin changes, precancerous lesions, cataract and sterility;

(*c*) Changes in life-span;

(*d*) Effects on growth and development, e.g. irradiation of the foetus can produce abortion, still birth and developmental abnormalities;

(*e*) Effects on subsequent generations, covered in annex C.

In general, the late effects are not unique to radiation; for the most part they are indistinguishable from disease states induced by other causes commonly present in the population.

14. Although the main late effects are known—indeed familiar—the possibility of other effects being produced cannot be excluded, notably in the foetus. Not enough is known about the relationship between dose and incidence of late effects. Accurate measurement of dose and incidence may be very difficult.

ANOXIA

15. Reducing the oxygen concentration inside cells during irradiation with X- or γ-rays diminishes cell sensitivity by a factor of 2-5, as measured in several ways. This effect of anoxia in the active bacterial cell is independent of events later than 0.02 seconds after irradiation.[4] Analysing such phenomena within such time limits is not easy.[5] The effect of oxygen is reviewed in an-

nex B and anoxia is discussed further in section VIII below (Protection and modification of radiation injury) because of circumstantial evidence suggesting that many protective agents act by interfering with oxygenation of the cell.

Temperature

16. Lowering temperature soon after irradiation, thus temporarily slowing metabolism, promotes recovery in microorganisms. In amphibia and mammals, lowering body temperature after irradiation may delay the onset of symptoms, but there is so far no evidence of an increased degree of recovery.

Nature of radiation injury

17. A big bar to understanding the nature of radiation injury arises from the difficulties in discerning the immediate processes in the interaction between radiations and living cells: (*a*) the low concentration of the reaction products between initial interaction and final expression of damage after biologically effective doses of radiation, makes characterization of these reactions difficult by present physico-chemical techniques; (*b*) the very rapid completion of these interactions allows little time for detection of the intervening events.[5,6,7]

Chromosome damage

18. Much evidence points to chromosome damage as the central mechanism of radiation-induced cell injury and death. This and the considerable effort to explain effects biochemically are reviewed in annex B.

II. Lethal and lesser damage in cells, tissues, organs, neoplasms, and organisms

Introduction

19. Knowledge of the comparative radio-sensitivity of different cells and organisms is significant in studying somatic effects. A theory explaining the large differences in radio-sensitivity among different cells and organisms would be decidedly valuable in understanding radiobiology. Differences in the radio-sensitivity of organs are the principal factors defining the organ whose damage by a given radiation dose impairs the body most.

End-points

20. Various end-points are used to determine comparative radio-sensitivities: (*a*) death of cells; (*b*) dose to inhibit mitosis; (*c*) alteration or loss of functions; (*d*) time taken to regenerate; (*e*) time taken to atrophy; (*f*) LD_{50}. In general the morphological end-points hitherto used cannot be regarded as satisfactory and determination of radio-sensitivity is better based on functional criteria, e.g. the concept of radio-resistance of nerve tissue based on morphology has proved incorrect, since functional transient changes in synaptic transmission result from doses of ~ 0.025 r.[8]

21. The apparent radio-sensitivity of a cell or tissue thus depends on the method of observations, e.g. lymphocyte damage may be measured by structural changes in the cell nucleus, by change in DNA content, or by degree of lymphopenia; bone marrow damage may be measured by examination of bone marrow smears, blood counts, haemoglobin and haematocrit estimations in the peripheral blood, by Fe^{59} incorporation in bone marrow and by blood cells, by degree of aplasia, or by the likelihood of leukaemia being induced years after radiation.

Death of cells as end-point

(a) *Law of Bergonie and Tribondeau*

22. In 1906, Bergonie and Tribondeau[9] proposed a "law" of cellular radio-sensitivity which on the whole is valid in radio-therapy: the most radio-sensitive cells are those which (i) have the highest mitotic rate, (ii) retain the capacity of division the longest, (iii) are the least differentiated.

(b) *Radio-sensitivity of cells in the adult mammal*

23. Cells in the adult mammal can be arranged approximately in the order of decreasing sensitivity on the basis of clinical and experimental data with death of cells as end-point: lymphocytes, erythroblasts, myeloblasts, megakaryocytes, spermatogonia, egg cells, cells of jejunal and ileal crypts, epithelial cells of cutaneous appendages, cells of eye lens, cartilage cells, osteoblasts, endothelial cells of blood vessels, glandular epithelium, liver cells, epithelial cells of renal tubuli, glia cells, nerve cells, alveolar lining cells of lungs, muscle cells, connective tissue cells, and osteocytes.[10]

(c) *Radio-sensitivity of tissue in the adult mammal*

24. The body's organs reflect differences in the radiosensitivities of their cells, usually of those in the generative compartment. The radio-sensitivities of different cells, tissues, and organs of mammals are detailed in section III and quantitative relationships between effect and dosage in section VII of the present annex.

Age and radio-sensitivity

25. Man's sensitivity depends on age at the time of exposure. Embryonic neuroblasts are killed by a much smaller dose of radiation than that which kills adult nerve cells. Children are more susceptible than adults in a number of respects. For example, the child's growing bone is more sensitive than the adult bone. These are but a few examples of the relation between age and susceptibility to radiation. The radio-sensitivity of embryos and foetuses is discussed more extensively in section III, and of children in subsequent sections covering effects on man.

Mammalian cell survival curves

26. Puck *et al.*[11-12] plotted the first survival curves for mammalian cells cultivated *in vitro*; they measured the reproductive potential of each individual cell after radiation. They found that human squamous carcinoma (HeLa) cells responded with a two-hit type inactivation curve, and that the logarithmic fraction of surviving cells was linear with increasing dose beyond the initial shoulder of the curve. The D_{37} was only ~ 100 rad in contrast to $\sim 10^5$ rad for virus inactivation. They suggested that the more sensitive mammalian cells may have more unit targets vulnerable to inactivation.

27. Estimates of D_{37} by Puck for various normal and neoplastic cells *in vitro* have been very close to one another. This may reflect the high rate of growth of normal cells in tissue culture; indeed there is strong evidence of malignant transformation in many types of cells *in vitro*.

28. Hewitt and Wilson[13-14] and Till and McCullough[15-16], in ingenious extensions of the Puck technique

to *in vivo* conditions estimated the sensitivity of mouse leukaemia cells and haematopoietic stem cells irradiated *in vivo* in mice. In both experiments survival curves were very similar to those obtained with human tumour (HeLa) cells irradiated *in vitro*. These observations are important for radio-biological theory, but much work remains to be done to determine how far the results apply to cells in their normal *in vivo* environment. The significance of the shapes of the survival curves for the basic mechanisms involved is still obscure. Elkind's work[17] underscores the considerable significance of repair mechanisms in the response to fractionated or protracted exposure.

Radio-sensitivity of malignant tumours[18]

29. Radio-sensitivity of a tumour depends primarily on the radio-sensitivity of the cell of origin. Gross reduction in tumour size depends on the proportion of cells immediately affected by radiation. A lack of immediate visible response does not necessarily indicate radio-resistance. Radio-sensitivity is not synonymous with radio-curability.

30. Therapeutic irradiation of malignant neoplastic tissue may induce almost immediate inhibition of mitosis followed soon after by increased abnormal mitoses and cell death.[19] If new radiation reinduces this effect, complete tumour destruction may be expected; but in many tumours intensive radiation may not induce this response and the tumours keep growing.

31. Cells within a tumour may differ widely in susceptibility to radiation. In tumours of predominantly radio-sensitive cells (lymphosarcoma, myeloma) a small dose of radiation destroys immediately most cells with evident reduction in tumour size, although the growth may recur rapidly. In tumours havings cells in different stages of differentiation (epidermoid carcinoma), even a large dose of radiation may not visibly affect the most differentiated cells: no gross effect may be seen for days or weeks, yet destruction of basal cells eventually causes complete disappearance of the tumour. In tumours of radio-resistant cells (malignant melanoma, rhabdomyosarcoma), a most intense radiation may not cause any immediate or late effect.

32. Misunderstanding of response of tumours to radiation has resulted in semantic confusion about radio-sensitivity (see discussion of this situation by Stewart and Warren[20-21]). The number of mitoses or the proportion of undifferentiated cells may indicate the immediate response of radio-sensitive malignant tumour, but anaplasia and reproductive activity are not *per se* signs of radio-sensitivity in any or all malignant tumours. Marked differentiation in an epidermoid carcinoma may imply a lesser degree of radio-sensitivity, but no epidermoid carcinoma merits the description radio-resistant; nor does a basal-cell carcinoma simply because it fails to disappear as rapidly as others.

33. Clinical observation has established a scale of radio-sensitivities of malignant tumours, in order of decreasing radio-sensitivity: malignant tumours arising from haemopoietic organs (lymphosarcoma, myeloma); Hodgkin's disease; epidermoid tumours of the upper air passages; seminomas and dysgerminomas; Ewing's sarcoma of the bone; basal-cell carcinomas of the skin; epidermoid carcinomas arising by metaplasia from columnar epithelium; epidermoid carcinomas of the mucous membranes, mucocutaneous junctions, and the skin; adenocarcinomas of the endometrium, breast, gastrointestinal system, and endocrine glands; soft tissue sarcomas; chondro sarcomas; neurogenic sarcomas; osteosarcomas; and finally, malignant melanomas. Even among the latter radio-resistant tumours there may be rare instances which show unpredictably a higher degree of radio-sensitivity (fibrosarcoma and melanoma). One variety of liposarcoma is definitely radio-sensitive and is even radio-curable; this is an exception to the experience that radio-sensitivity of malignant tumours depends upon radio-sensitivity of their cell of origin. This list represents only average radio-sensitivity in each group; individual tumours may show more or less radio-sensitivity than their place. Rare tumours of uncertain radio-sensitivity are omitted.[18]

34. Clinically it has been known for a long time that interference with blood supply of a radio-sensitive tissue diminishes its radio-sensitivity[22] and the important effect of anoxia on radio-sensitivity has already been discussed.

Factors influencing radio-sensitivity

35. Factors influencing radio-sensitivity are reviewed in annex B as are the radio-sensitivities of viruses, bacteria, protozoa, and other unicellular organisms.

LD_{50} values for mammals

36. The data on LD_{50} values (table I)[23] permit tentative generalizations. Other references to LD_{50} values are: mouse and rat,[24-28] hamster,[29] monkey,[30-32] dog,[33-35] burro, swine, sheep and cattle.[36] Additional LD_{50} values for guinea pig will be discussed below.

37. There is a clear demarcation of LD_{50} values (expressed as midline absorbed dose) between small and large animals. Air doses do not reveal this relationship. The LD_{50} for large species is ~ 250 rad or less for X-rays with uniform dose distribution in tissues, that for small species is approximately double this value or greater.

38. The tissue-dose LD_{50} values for small animals presently available are all $\sim$ 400-800 rad for X-radiation, and between $\sim$ 550-800 rad if the guinea pig is excluded. The differences might be smaller if different species were irradiated with identical relative dose distributions. The monkey (*Macaca mulatta*) cannot be considered, radio-biologically or haematologically[37] any "closer" to man than any other small species. Man is difficult to simulate quantitatively in total body radiation TBR studies with smaller animals (table I).[38] The dog is not large enough for direct comparison.

39. The data on guinea pigs given by several previous investigators[24,39-41] are often difficult to evaluate owing to dosimetric and statistical difficulties; possible effects of animal strain; possible disease in some animals.[24,42,43]

40. Large animals exposed under similar geometrical conditions have rather uniform LD_{50}'s (again, the higher LD_{50} values for animals given γ-radiations should be corrected for RBE, and dose rate factors before strict comparison with X-ray data), perhaps partly because large animals, unlike small, provide their own constant, maximum scatter.

LD_{50} and age

41. The average or median acute lethal dose (LD_{50} = 30 days) for young adult mammals is within $\sim$ 300-900 rad. While it is customary to give the LD_{50} for a given strain independently of age, age causes variations.

42. In the mouse susceptibility is maximal at 30 days, decreases rapidly to that in young adults, remains constant until advanced age and then increases rapidly. In the rat the LD_{50} at age 3 months is ~ double that at 3 weeks; beyond 3 months it diminishes approximately linearly with age. More study of this relationship is needed, but it is now evident that susceptibility of a whole population cannot be adequately denoted by a single LD_{50}. Published values are usually obtained from young adults and are therefore maximal or nearly so for the strain. This age-dependence must be taken into account in estimating the LD_{50} for man.

LD_{50} in man

43. Several sources of data are relevant to the LD_{50} in man, but each has serious limitations. There are data on large animals, and also on Japanese at Hiroshima and Nagasaki, on Marshallese, and on patients given therapeutic TBR.

44. If the data for large animals apply also to man, the acute LD_{50} for man should be ~ 250 rad for uniform total body radiation, dose expressed as absorbed dose at the midline. This accords with the low value estimated from the Marshallese exposed to fall-out γ-radiation[38,44] and indicates that the true value probably lies well below the 450 rad air dose commonly quoted. From the Marshallese data, the near sub-lethal dose for man could be estimated; this fixes the lower part of the survival curve at ~ 200 rad. In dogs and swine an increase of 100 rad over that received by the Marshallese would be well within the lethal range. If one uses the same slope for man as for dogs, the 90 per cent mortality dose is about 500 rad. By splitting the difference, the LD_{50} for man, in the absence of complicating thermal injury, trauma or therapy, is ~ 360 rad.[45] Recent data on patients treated with TBR also indicate this low value.[44,46,47] 200 r TBR depresses haematopoiesis severely but one must recall that these subjects are already infirm. Blair[48] extrapolating from the same Marshallese data, concludes that the LD_{50} (air dose) for man probably is not below 400 r. Both authors, using the Marshallese findings, extrapolate from data in animals, and emphasize the large uncertainty in the quantities deduced. Conflicting facts of trauma, thermal injury, poor nutrition, high and low neutron component in the Hiroshima and Nagasaki bombs, and incomplete knowledge of the position of individuals and surroundings, complicate calculation of the LD_{50} for man from the Hiroshima and Nagasaki data.

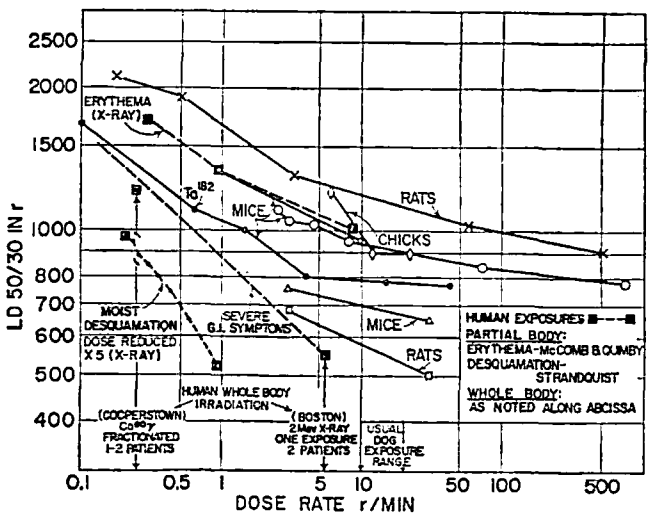


Figure 1. Dependence of $LD_{50}/30$ on dose-rate[56]

$Co^{60}\gamma$ { × Rats (SPRAG-DAW) Logie, Harris *et al*[774]; ◇ Chicks ($LD_{50}/21$) Vogel and Stearner[776]; ○ Mice (CF-1) Vogel, Clark and Jordan[776]; ● Mice (CF-1) Thomson and Tourtellotte[731]

250 kvp X-ray { △ Mice (WR-BAGG) Dacquisto and Blackburn[777]; □ Rats (WR-CF) Dacquisto and Blackburn[777]; ○ Mice (CBA) Neal[497]

45. Recent data on large doses of radiation on man[49,54] do not suffice for accurate estimation of the LD_{50}.[53,55] Difficulties in evaluating complicated dosage situation in reactor accidents have been reviewed elsewhere,[54] and are discussed later in sections IV and VIII on effects in man and on treatment.

LD_{50} and dose-rate

46. Figure 1[56] summarizes data on the relation between LD_{50} and dose-rate. For all species the LD_{50} increases with decreasing dose-rate.

Radio-sensitivity

47. This discussion has dealt with only certain aspects of radio-sensitivity. A survey of the different radio-sensitivities of cells, tissues, organs, neoplasms, and organisms indicates that radio-sensitivity is a complicated concept: theory is incomplete (para. 20) and radio-sensitivities of isolated cells may apparently differ from those of the same cells *in vivo*. Investigators should be aware of these differences and not use radio-resistant organisms in their study of radiation effects from fall-out or for those circumstances in outer space where low dosages are to be expected. Different radio-sensitivities of cells, tissues and organs underlie the hierarchy of deaths in the different lethal dose ranges and also the different patterns of recovery after radiation below this range. This is discussed in section III.

III. Somatic radiation injury and its repair, particularly in mammals

Modes of death with TBR

48. Acute total-body and regional exposure may cause various syndromes or modes of death depending on dose level time after exposure, type of radiation, and species.[57-59] Very high doses (tens of thousands of rad) cause death in mammals in minutes or hours; this syndrome[60-61] depends on irradiation of the brain. The marked symptoms of brain dysfunction suggest that death may be from neurological damage. This type of death can also be produced by radiation of the head only.[62-63]

49. The order of events preceding death are dose-dependent. As dose is reduced, survival time increases until the 3-4 day "gastrointestinal" type of death is seen. This familiar dose-survival time-curve[58] has been examined for X-rays, thermal neutrons, and fission neutrons.[64]

50. In the "bone-marrow" syndrome, in the low-lethal dose ranges, no doubt the sequelae of pancytopenia (infection and haemorrhage) cause death; the precise mechanism of death remains open.[65-66] Sporadic deaths occur in the few weeks after the bone-marrow death period, when the marrow has essentially recovered. The cause of these deaths remains obscure.

Partial body irradiation

51. Quastler *et al.*[67] have reported deaths two weeks after irradiation of the head, jaw or tongue of the mouse with 1,500 r or more. The mechanism remains obscure. Similar deaths have been reported after 1,500 r to the head of rats.[68] Dogs given 1,750 r to the head only survived five months or longer.[69] In the "total head" (brain) studies of Mason *et al* judging from survival time, the effect described by Quastler[67] probably caused death.

52. The gut syndrome is identical if caused by TBR or by local irradiation of a large segment of bowel.[57-59, 71-72] Re-section of irradiated intestine increases survival beyond the time when death from the gut syndrome would otherwise be lethal.[73] Depletion of fluids and electrolytes contributes greatly to the immediate cause of death since massive fluid replacement prolongs survival.[74] Death from this syndrome can be prevented in some animals by shielding only a small portion of the duodenum or ileum, but not by shielding the caecum or stomach;[75] the authors feel that protection operates through protection of some bowel function rather than by repopulation as in spleen or bone-marrow protection.[76]

53. The bone-marrow syndrome and shielding have also been studied by Lamerton *et al.*[77-79] They showed clearly by weight changes two phases of radiation injury, and confirmed that shielding of even a small portion of bone-marrow minimized haematopoietic depression. They also emphasized the importance of anaemia in the acute bone-marrow syndrome in the rat. The remarkable protection given by marrow shielding and the degree to which this may be masked by bowel damage have been shown by Swift *et al.*[80]

54. Maisin *et al.* in Belgium have studied shielding in detail[81-83] and concluded that:

(*a*) There are at least two syndromes after TBR;

(*b*) Shielding of bone-marrow or bowel prolongs survival; and

(*c*) Protection of bowel and bone-marrow by shielding acts synergistically.

These conclusions agree with those of many workers.[57, 58, 75, 84, 85]

Early and late organ effects

Blood and blood-forming organs

55. Haematopoietic tissue is one of the most radiosensitive tissues with cell death as end-point. In general, the sensitivity of bone-marrow of different species increases from rat, rabbit, mouse, chick, man, goat, guinea pig to dog.[86] After an LD_{50} dose the mitotic index falls and erythroblasts decrease within an hour. Within a few hours there are many dead cells and cellular debris. Myeloid elements regress increasingly with cytoplasmic and nuclear disintegration. After 9-10 days, the marrow, filled with a gelatinous, relatively acellular mass containing degenerating cells, has only the relatively radioresistant fibroblasts, blood vessels, and primitive reticular elements. Animals which will survive, regenerate normoblasts and myeloblasts from spared haematopoietic precursors, and eventually the marrow may be completely regenerated. In rats and rabbits, after doses in the lethal range, erythropoiesis regenerates earlier than myelopoiesis;[87-88] in mice both types regenerate at the same time, or myelocytes first.[87-89] The effect of radiation on bone marrow has been reviewed extensively.[88-91]

56. Levels of cells in the peripheral blood reflect changes in number and maturation time of precursors and their own life span and changes in their distribution throughout the body. With some species variation, lymphocytes decrease most rapidly, granulocytes a little more slowly; later, platelets decrease and much later, erythrocytes. Usually an overwhelming bacteremia accompanies profound granulocytopenia; germ-free animals die of anaemia.[92]

57. Leukopenia appears faster and is more severe in irradiated weanling rats and hamsters than in adults, but recovery is more rapid, indicating a more labile homeostasis.[93-94]

58. Extracellular fluid and plasma volume increase after irradiation in dogs,[95] rats,[96] mice,[97] and rabbits[98] at the expense of intracellular fluid. An initial decreased plasma volume of rats accompanies radiation diarrhoea.[99]

59. In rodent spleen, as in marrow, LD_{50} irradiation inhibits mitosis and damage to lymphocytes is evident within an hour. In survivors regeneration begins on days 9-10 but in lymph nodes, destroyed follicles may not be restored for three weeks. As in bone-marrow, injury increases with dose within certain ranges. In different species, a particular dose-level damages lymphatic tissue similarly, regardless of lethality.[99]

60. Cell destruction shrinks lymphoid tissues. The dose-dependency of the weight response of spleen and thymus is discussed in section VII (dose-effect relationships). Weight loss is in part directly due to radiation damage and in part indirectly mediated through the adrenal has a stress effect.[100]

Digestive tract

61. Sensivity of the epithelium of the small intestine is second only to bone-marrow in deciding survival after TBR with X- and gamma rays. After irradiation at high LET, the intestine may be the critical organ determining survival at the LD_{50} in mice.[101] In mice, doses below 1,000 r damage the intestinal mucosa but animals do not generally die from this cause but rather between days 10-14 from bone-marrow damage. From 1,000-10,000 r, mice die 3-4 days after irradiation with complete denudation of intestinal epithelium;[71] death is due to failure of food absorption, dehydration from diarrhoea, and bacterial invasion, and toxaemia.[102, 103]

62. The radio-sensitivity of the various parts of the alimentary system varies greatly: stratified squamous epithelia are of the same sensitivity as the epithelium in the skin;[104] intestinal mucosa is much more sensitive than gastric mucosa; small bowel more than large.[105, 106] "Oral" radiation death has been described in mice.[67] Death does not resemble that from intestinal or bone-marrow damage.

63. The stomach and esophagus are more radio-resistant than the intestine.[107, 108] Two effects may be seen in the stomach: (*a*) functional and degenerative morphological changes with subsequent repair; (*b*) development of gastric ulcers in man several weeks after 1,600 r tissue doses given to the gastric fundus over ten days in divided doses via anterior and posterior fields.[109] Destructive changes seen as early as thirty minutes after moderate doses in rabbits exposed to $LD_{50}/30$ days of X-rays $\sim$ 800 r are most pronounced after eight hours and repaired within four weeks.[110] Similar effects are seen in mice after 350 r, in rats after 400 r, and in chickens after 800 r total body radiation. There is hyperplastic regen-

erative activity with continued degeneration of many cells for the first few days. At twenty-one days all mucosae, possibly with the exception of duodenal crypts, are normal. Damage is greatest in duodenum, least in colon and rectum.

64. Doses of 1,000-1,200 rad given locally[111,112] diminish gastric acidity and gastric ulcers may develop after several weeks.[113-116] Although radiation increases intestine tone and contractions, gastric emptying is delayed.[117-119] In dogs, gastric emptying time is prolonged only after three or four times the LD_{50},[120] but after as little as 25 r in rats.

Reproductive organs

65. Acute doses of radiation causing only marginal changes in the gut or blood-forming tissues may induce permanent sterility and endocrine dysfunction in the female. Males may become temporarily sterile, but the acute doses required to produce permanent sterility in the male are above LD_{100} in all species that have been studied. Understanding the effects of radiation on the reproductive organs is important because those germ cells which survive to form gametes can transmit the genetic changes induced by radiation. Since genetic damage is qualitatively as well as quantitatively dependent on the germ-cell stage in which radiation was received[89,121-124] it is obviously important to know the relative radio-sensitivities of various germ-cell stages over a wide range of doses and dose-rates.

Male animals

66. In the male, the various stages in the development of spermatozoa, from the earliest spermatogonia to the mature spermatozoa, have very different sensitivities to radiation. An understanding of normal spermatogenesis is, therefore a prerequisite in understanding radiation effects on the testis.

67. The spermatogonia of monkeys can be divided into type A_1, A_2, B_1, B_2, B_3.[125] In rodents spermatogonia can be divided into type A (dusty) and type B (crusty) by cell morphology and developmental potentiality; a transitional type between A and B, designated as intermediate spermatogonia, can also be identified in rodents. In mammals, type A spermatogonia are the true stem cells and through stem cell renewal form an unlimited number of spermatocytes while maintaining a constant cell population. This wave of activity leading to new spermatocytes is cyclic. In the monkey, type A spermatogonia undergo mitosis and transform into type A_2 spermatogonia and so on until type B_3 spermatogonia divide to form resting primary spermatocytes. In the mouse and rat type A spermatogonia undergo a series of mitoses, and most of the products of the final division transform into intermediate spermatogonia. The intermediate spermatogonia divide to form type B cells, which in turn divide to form resting primary spermatocytes. Determination of the developmental potentiality of individual spermatogonia takes place before the last division of type A cells, in which certain spermatogonia form the stem cells for the next multiplication cycle.[127,128] This basic process is essentially the same in all mammals studied including the monkey and man,[125,126] variation is associated with differences in the number of identifiable spermatogonial types and duration of spermatogenesis.

68. Because of the similarity in normal gametogenesis, the radiation response of the testis is basically the same for all mammals, but modifications are required in extrapolating from the response of laboratory animals to that of domestic animals and man. Thus species may differ in: (*a*) duration of spermatogenesis (i.e., the time for type A spermatogonia to develop into mature spermatozoa), e.g. spermatogenesis takes 35 days in mice, and according to Arsenyeva and Dubinin ~ 70 days in monkeys.[129] It is probable that duration of spermatogenesis in man is nearer that of the monkey than that of the mouse; (*b*) time for spermatozoa to travel from the testis to the ejaculate; (*c*) regeneration rates, which are a function of (*a*) above; and (*d*) possibly, intrinsic sensitivity.

69. Adult male mice given acute doses of 200 to 1,000 r either to the testes only or to the whole body (high doses, of course, are limited to partial-body exposure), are initially fertile, owing to continued development and utilization of gametes irradiated as mature spermatozoa, spermatids, and possibly spermatocytes. An infertile period follows owing to destruction of spermatogonia. A few type A spermatogonia, however, survive and repopulate the seminiferous epithelium, and almost normal fertility eventually is regained. Doses of 100 r cause temporary sterility in the monkey for ~ 2 to 3 months.[129]

70. Sensitivity of the different stages in spermatogenesis has been most thoroughly investigated in the mouse. Intermediate spermatogonia and early type B spermatogonia have LD_{50}'s in the range of 20-24 r.[128] Type A spermatogonia show a wide range of sensitivities. At doses below 25 r, survival is comparable to that of intermediate spermatogonia; but, at higher doses, survival is relatively much greater.[128] A few type A cells survive doses as high as 1,500 r. Thus the paradox of high sensitivity of spermatogonia, which results in the temporary sterile period coupled with high resistance, which leads to return of fertility, is readily explained.[128] The primary effect leading to depletion of spermatogonia is cell death, mostly in interphase or early prophase, *before* cell division.[130] With doses of 100 r or more, some cells die after cell division, probably because of chromosome imbalance; a few cells appear to divide several times before degenerating, but these effects involve only a very few cells. As a result of extensive necrosis, particularly in interphase and early prophase, it is difficult to estimate the amount of spermatogonial depletion arising from mitotic inhibition; this inhibition is probably comparable with that seen in other germinative tissues.[131] Doses of 100 r caused the death of all B_1, B_2, and B_3 spermatogonia in the monkey.[129]

71. In mice, spermatocytes show no immediate damage even after radiation doses of 1,000 r, but degenerate during meiotic division. From the number of spermatids formed, LD_{50}'s ranging from 205 r for preleptotene to 837 r for diakinesismetaphase I have been obtained.[132] In the monkey, resting spermatocytes are damaged after 100 r.[129] Spermatids formed by irradiated spermatocytes show anisocytosis, indicative of aneuploidy and heteroploidy; this later results in many abnormal spermatozoa in the ejaculate.

72. Spermatids and spermatozoa show no morphological changes after irradiation nor is the rate of spermiogenesis altered. Mature sperms may be motile after 50,000 r.[133] Such sperms, however, have such severe genetic damage that normal development of a resulting zygote is precluded.

73. The efficiency of fractionated *vs.* single doses is influenced by size of the fractions, intervals between

doses, and total dose. In the mouse, fractions given within a 4-day period act as a single dose.[134] Maximum effectiveness of fractionated doses in different species depends on duration of normal spermiogenesis and reproductive potential. Because information is scarce on the dynamics of spermiogenesis in species other than mouse and rat, contradictory assumptions have been made, in planning experiments and in interpreting data. In dogs, a single total body dose of 300-375 r results in only a partial and temporary reduction in spermiogenesis, with return to normal within a year. This contrasts with complete aspermia after 375 r given over twenty-five weeks at 15 r/wk, there being no sign of recovery within a year after irradiation.[45] In the dog, long-term radiation gradually reduces the number, motility and viability of sperm. Such damage is one of the most sensitive indicators of chronic damage seen so far in dogs given 3.0 r/wk, i.e. 30 times the average maximum permissible dose-rate (occupational).

74. With prolonged exposure at low dose rates, an equilibrium is established between the cell death, mitotic inhibition, and regenerative activity of the seminiferous epithelium,[135] this equilibrium being dependent on dose rate rather than total dose. If dose rates are low enough, e.g. 10 r/wk in the mouse or 0.1 r per day[136] in the dog and some other species, fertility remains unaffected even after thirty weeks' exposure. Histologically, however, a decrease in cell populations can be demonstrated after 100 r at this dose rate.[137] At 90 r/wk, cell populations are severely depleted, and if doses of 300 r or more are given, temporary sterility is comparable to that following the same dose of acute irradiation.[138]

75. Testis weight as a biological indicator of radiation damage is discussed later under "Dose-effect relationships" (section VII).

Man

76. A single dose of 400-600 r to the testes may cause permanent sterility.[139] Temporary sterility of twelve-months' duration usually follows 250 r; even 30 r to the human testis may be injurious.[140] In relating studies on laboratory animals to the response in man, it is of primary importance that corrections be made for differences in time-sequence arising from differences in the rates of normal gametogenesis. Such a correction factor would for example explain the slower recovery in man.

Female animals

77. Since there are no cells comparable to type A spermatogonia (stem cells) in the adult mammalian ovary, females of some species are more easily permanently sterilized than are males. The supply of oöcytes if once destroyed is not replaced.

78. The adult female mouse given 300 r acute TBR produces, on the average, 1.4 litters as compared with 14.9 in controls. A dose of 100 r TBR produces complete sterility in twelve weeks, 50 r in twenty-two weeks.[141] Even 30 r, given in three divided doses at weekly intervals, produces sterility in some animals.[142] The mouse ovary tends to develop invaginated tubular downgrowths of germinal epithelium and ovarian tumours. These changes, which are readily increased by relatively low doses of radiation, are, however, not the cause of sterility: sterility results from the killing of oöcytes in developing follicles. Since oögonia are no longer present in the adult, there can be no repopulation of germ cells.

79. In the adult mouse, all oöcytes, except those about to be ovulated, are in dictyate stage. Dictyate oöcytes in early follicles are the most radio-sensitive cells in the adult ovary, and are completely destroyed by 50 r.[143] As the follicles mature, resistance of the contained oöcyte increases, and at least one litter usually is obtained from females given 400 r.[141] A similar increased resistance with development of the follicle has been observed in the rat,[144] but the dose required to sterilize the female rat is higher. Resistance of mature follicles also is shown in women, since there are a few ovulations after 300 r; early follicle stages must be resistant, however, because, after a period of amenorrhea, ovulation begins again.[145]

80. Species comparisons are very difficult in the female, since meiotic prophase stage, relative frequencies of resistant and sensitive oöcytes, rate of follicle growth and number of oöcytes required for normal fertility undoubtedly vary widely. Valid comparisons of intrinsic sensitivities require more information on the cytology and dynamics of normal oögenesis.

81. In mice lowering the dose rate decreases the sterilizing action of a given dose of radiation. The shortening of the breeding period—the characteristic effect of radiation on female fertility—is dependent on dose rate. Fractionation and even more directly, long-term administration of a given total dose postpones the onset of sterility. The greater the fractionation and the more protracted the long-term dose, the longer is the onset of sterility postponed. These results indicate that some radiation damage to oöcytes can be repaired, and that repair is greater at lower dose rates.[141] Conflicting conclusions in the literature[146–148] are due to the use of the first post-irradiation litter, not length of breeding period, as the index of effect.

Sexually immature animals

82. Studies in laboratory mammals show that germ cells may change sharply in radiation-sensitivity as the animal develops. In the female mouse, for example, the late foetus[149–151] and the newborn[152] are relatively more resistant than the adult; but, only two days after birth, a two-week period of extreme sensitivity sets in, during which sterility is much more readily induced than in the adult.[152]

83. The fertility of animals irradiated *in utero* or in early post-natal life can be understood only in terms of the normal development of germ cells and the sexual dimorphism which exists in this respect. During mitotic divisions of the primordial germ cells or their precursors, males and females are about equally sensitive to radiation-induced depression in fertility. In the mouse, both sexes, when irradiated with 200 r as 7½ or 9½ day embryos, show somewhat depressed fertility throughout their lives.[153] In the female, the fertility depression becomes greater following irradiation at a later stage, day 11½ postfertilization, and even greater for day 13½.[153] Similarly, the developmentally corresponding stage in the rat, day 15 is, by histological criteria, the most sensitive of the foetal stages.[154] It should be noted that mitosis of the primordial germ cells in the female is at a maximum at this stage. In the male rat, on the other hand, sensitivity continues to increase and is highest on day 19.[155]

84. With the onset of meiotic prophase, sensitivity is found to decrease, well in accord with the relative radiation-resistance of this stage demonstrated in a wide variety of organisms. In the female mouse and rat, meiotic

prophase begins about four days before birth. In male foetuses of the same age, however, the germ cells present are still in a primordial stage and undergoing mitosis. This sexual dimorphism in development explains the apparent reversal from the adult situation of differential sensitivity of the sexes that has been observed for late foetal stages[149-151] when males are more sensitive than females.

85. Shortly after birth, when the progress of meiotic prophase ceases in the female, and the oöcytes assume the early dictyate phase, a period of extreme sensitivity sets in. This has been demonstrated by fertility studies[152] and histologically[156] in the mouse, and histologically in the rat.[144] In the mouse, an LD_{50} of 8.4 r (95 per cent confidence limits: 7.2 and 9.7 r) has been observed for oöcytes in the smallest follicles of ten-day old females[161] and even long-term irradiation has severe effects on fertility.[152]

86. It may provisionally be assumed that the mouse and rat results here summarized can be extrapolated to equivalent germ-cell stages (rather than equivalent ages in other species. In particular, the existence of periods of extreme sensitivity at certain stages in the development of the human ovary is a possibility of the utmost importance.

87. The effect on foetal cells is discussed further under the section on embryos in this chapter.

Nervous system

88. The brain is more radio-sensitive than generally supposed. Although no morphological change has been seen at LD_{50} doses, transient functional changes have been reported at low doses. Doses of 100,000-200,000 r kill almost instantly, probably by destruction of medullary centres.[157] With lower doses that kill hours after exposure, there is a question how much brain damage is caused directly by radiation and how much is secondary to vascular destruction. The effects of 2,500-10,000 r have been described in rabbits[158-159] and monkeys.[160-162] Doses in the LD_{50} range[163] cause no EEG changes in monkeys but these are induced within 1-2 minutes after γ-radiation at 1,000 r/min.[164] Single exposures of 1,000-1,500 r of X-rays may quickly kill a few oligondendroglia and some neurons.[165] The developing nervous system is much more susceptible to radiation injury. Single doses of a few 100 r kill the most primitive embryonal neural cells, and as little as 20-30 r are damaging in animals.[166] This is discussed later in this section (paras. 170-192).

89. In contrast to the brain, the spinal cord and peripheral nerves are highly resistant. No alteration in structure or function of monkey spinal cord was found after twenty-four hours γ-radiation at 135 r/hour.[167] Damage of the spinal cord blood vessels by doses of 3,000 r and more can induce occlusive disease leading to ischemia of the cord, i.e., radiation myelopathy as a late effect.

90. Radiation can condition the behaviour of rats, mice and cats so that they avoid identifiable stimuli previously associated with radiation exposure.[168-170] Fast neutrons as well as γ- or X-rays can condition such behaviour. A TBR dose of 7.5 rad given animals was sufficient to alter preference for saccharin. Animals learn to avoid a compartment in which they had been irradiated, and this avoidance is more pronounced when taste cues are coupled with radiation exposure. Localized radiation to the abdomen of 54-108 r induced avoidance; similar doses to other areas of the body failed to do so, but such limited exposure was not as effective as TBR. Changes in the conditioned reflexes of dogs have been reported after single TBR and local head irradiation at 5, 10 and 20 r.[171] Work in the USSR on effects of radiation in the central nervous system[172] and on its sensitivity to low-level radiation was recently reviewed.[173] Some effects of low doses, interpreted as effects on the nervous system, are based on the concept that the CNS controls all reactions in the organism. Thus, post-irradiation pancytopenia is considered an effect mediated via the CNS.[172]

Eye

91. The lens of the eye is highly susceptible to irreversible damage by radiation. Sensitivity varies with subjects and with type of radiation. Doses of 15-30 r, X-rays and possibly 1 rad of fast neutrons[174] induce minimal lens opacities in the mouse; the threshold sensitivities of rats, rabbits, dogs and man decrease progressively for X-rays, β-rays and neutrons.

92. The retina is more resistant than the lens. In the monkey, 2,000 r destroys the rods; 30,000 r induces morphological change in all retinal elements.[175-176] Retinal haemorrhages, retinitis, choroiditis, and iridocyclitis developing days to weeks after TBR are due to systemic alterations.[177]

93. Some very low doses—0.5 to 1.0 mr—give the sensation of light in man.[178] In frogs, electroretinograms (ERG) and the discharge of nerve impulses by retinal ganglion cells in response to retinal irradiation have been measured.[179] Less than 11 r caused an immediate temporary rise in the light threshold, and 0.7 r caused an immediate temporary rise in the X-ray threshold 5 × greater than the rise in light threshold caused by a threshold light stimulus. Doses of 5-100 r, after temporary intensification of the electrical response of the retina to light depress it down to complete loss even after the lowest dose.[180] The conclusion that high-energy irradiation of the eye produces effects with doses as low as 0.5 mr needs further study.[179]

Liver

94. Judging by morphology, the liver is radio-resistant as compared with other organs although minor cytological changes have been seen.[181-185] A low (6 per cent) casein diet tends to result in cirrhosis several months after rats are given 500 r.[186-187] Liver regeneration, as measured by weight recovery, is not impaired by 20,000 r.[188] On the other hand, sublethal TBR greatly increases the frequency of abnormal mitoses in regenerating liver of the rat for at least 250 days.[189] Decreased incorporation of P^{32} into DNA of irradiated regenerating liver[190] may, in part, be due to decreased uptake by reticulo-endothelial cells.

95. Changes in liver mitochondria were found in mice 6-8 hours after 500-1,200 r; their structural stability decreased; they became vesiculated, globulated, and fragmented; and were also decreased in number.[191] These alterations are not specific for radiation.

Kidney

96. Because impairment of renal function does not contribute to mortality after TBR, the kidney is considered radio-resistant; this is supported by clinical

radio-therapeutic experience. Only if several times the lethal dose is given the kidney are marginal changes in renal function seen in dogs[192] and rats.[193]

97. Nephrosclerosis developing several months after exposure has been described in mice given 500 r;[194] mice surviving doses of 800 r after treatment with splenic homogenates died probably of renal failure.[195] Similar lesions (radiation nephritis) have been seen in dogs and man after local irradiation of the kidney region with larger doses. Avian kidneys are much more sensitive than mammalian kidneys.[196]

Circulatory system

98. Within a few hours after exposure to single doses of X- or γ-radiation in the LD_{50} range, arterial blood pressure drops. It usually soon returns to normal and remains so until a few hours before death. Although this initial decrease has been reported in every species examined, death from circulatory collapse may be induced by LD_{50} doses in the rabbit, chick, duck and burro.

99. Although only massive doses of radiation induce histological change in the heart, ECG changes have been found in dogs,[197] hamsters,[198] and rats[199] after LD_{50} doses. ECG changes are at least in part due to change in potassium concentration in serum;[200] radiation causes release of potassium from the isolated rabbit heart and from the heart irradiated *in situ*.[199] Doses of 1,000-2,000 r produce slight vasodilation in the perfused isolated rabbit ear; doses of 2,500 r and above bring immediate vasoconstriction;[201-202] after 8,000 r flow is completely inhibited for fifteen to twenty minutes; the blood vessels are damaged at all those doses as indicated by the appearance of increased amounts of protein in perfusion fluid.

Endocrines

100. In general, doses in the LD_{50} range induce few signs of damage in endocrine tissue. The normal adult thyroid gland is fairly radio-resistant: 17,200 r given locally causes negligible changes in rats;[203] 10,000 r may cause histological change in dog thyroid.[204] Local irradiation of the thyroid of young or mature rats with 5,000 r X-rays does not cause morphological change, modified basal oxygen consumption, or loss in body weight.[205] In tadpoles more than 20,000 r are needed to alter the thyrotropic function of the pituitary.[206]

101. Doses of 5,000 r alter the alpha cells of the islets of Langerhans in the pancreas; beta cells show little change below 20,000 r.[207] Adrenals show degenerative changes after heavy local irradiation ($> 5,000$ r) but after 1,000 r only minimal morphological change in cortex and medulla.[208,209]

Skin

102. Degree of skin damage after irradiation depends on the dose received and also on the species of animal. Individual differences in sensitivity are fairly large. Furthermore, the various structures of the skin have large differences in sensitivity.

103. Epithelial changes in the skin of the mouse ear have been described after a dose as low as 35 r.[210] Epidermal mitoses are much reduced. After 600-800 r TBR some inflammatory reactions with slight hyperemia and some oedema are seen.[89,104,211,212] After higher doses the epithelial cells become swollen and vacuolated. Vascular changes presumably play a great role. After severe irradiation the inflammatory changes may be followed by sclerosis with loss of elastic fibres and hyalinization of the collagen. The skin reactions generally are more severe after exposure to less penetrating radiation.

104. From extensive studies on the effects of locally applied radio-isotopes on the skin, it has been found that exposure of the skin to external β-irradiation may induce severe skin lesions.

105. According to Moritz and Henriques[213] β-irradiation of pig skin produced epidermal atrophy, appearing one to two weeks after exposure and lasting for two to three weeks, often with ulcerations and transepidermal necrosis. Healing was slow, and often a chronic radio dermatitis persisted.

106. Presumably the late deleterious changes in irradiated skin are the direct result of radiation damage to epithelial cells and indirectly the result of starvation and anoxia of these cells due to vascular radiation trauma. Radio-sodium clearance measurements have, however, led to the startling observations that the effective blood flow in these densely fibrotic, scarred, and atrophied tissues is functionally unimpaired at any time up to years after irradiation.[214] This indicates that vascular damage plays little role in the deleterious changes after skin irradiation. Some of the changes in the skin after irradiation may be secondary to infection in radiation-induced ulcerations.

107. The skin is more resistant to tumour induction by irradiation than most internal organs. Cutaneous tumours, however, were the first noted in man, owing to the relatively soft X-radiation used earlier and lack of adequate filtration.

108. In animals, tumours of the skin have been induced mainly by β-radiation, and co-carcinogenic or promoting effects have been observed from application of chemical carcinogens[215] or croton oil[216] respectively.

Bone

109. Bone tissue is generally believed to be relatively radio-resistant. Some observations, however, indicate that bone tissue damage may follow even a rather low dose. This is especially so in young individuals. The foetal skeleton is highly radio-sensitive; the system responsible for bone growth may be especially severely damaged by irradiation. The growth of long bones may be inhibited. This is seen in rats after a dose of 600 r.[217] A single dose of 400 r TBR of rats reduced the number of osteoclasts.

110. The retardation in osteogenesis is permanent and irreversible after 2,000 r local irradiation in rats, and 5,000 r to the femurs of guinea pigs caused a complete osteonecrosis.

111. A characteristic feature after irradiation of bone tissue is the absence of any demarcation between normal and irradiated parts. Irradiated bone is more easily infected than normal bone, especially if necrotic spots are present but healing of fractures is not significantly altered after moderate doses.

112. The effects of internal irradiation on bone are described in section VI below.

Late effects

Life-shortening[218]

Introduction

113. In mammals radiation in substantial doses to whole- or part-body shortens life-span. In part-body

exposure, the life-shortening effect is variable depending on the kind and amount of tissue irradiated as well as dose. Radiation may shorten life-span by: (*a*) damaging a specific tissue (e.g., dermatitis followed by skin cancer); (*b*) inducing a specific disease (e.g. leukaemia); (*c*) producing more generalized changes (e.g. lowered immunity, damage of vasculo-connective tissue and premature aging).

114. Data for man are yet inadequate to assess the effect of radiation on life-span. From animal data and the increased incidence of leukaemia in man after total-body or marrow irradiation, some life-shortening is to be expected.

115. Comparisons of mortality rates of United States radiologists with other physicians and the general male population indicate that occupational exposure may have slightly increased mortality rates of radiologists in past decades. The cumulative doses are not known for individuals; the dose-life-shortening relationship cannot therefore be measured. British radiologists showed no clear increase in mortality rates. This subject requires further study.

116. In animals, the survival time for given dose rates is generally shorter the more energy absorbed. Life-shortening is less for a given dose absorbed over a long time than over a short one. Some evidence suggests that radiation-induced life-shortening depends on genetic constitution, age, and clinical status at exposure.

117. Animals irradiated with substantial but sublethal TBR, after recovery from the acute early illness, die prematurely. They develop the diseases of their species earlier than usual and deteriorate sooner than non-irradiated controls, with various physiological and histopathological changes suggestive of senescence. At a first approximation, comparison of mortality curves of survivors of acute radiation mortality and controls suggests that radiation causes premature aging in an actuarial sense.

118. Some premature deaths after radiation are due to the increased incidence of such diseases as malignant neoplasms. This is especially true after localized irradiation from external sources or from locally deposited radio-active materials. After TBR the number and variety of diseases induced are greater than after localized irradiation. At their respective median death times, animals whose lives are shortened by single TBR and controls usually have approximately the same diseases, although not necessarily the same proportions. Irradiation may separately induce each of the diseases of advanced age or cause a general deterioration of body tissues that advances the onset of most diseases to roughly the same extent. Some animal species or strains are unusually susceptible to certain diseases, e.g. ovarian tumours and lymphatic leukaemia in mice, and mammary tumours in rats.

119. In general, irradiation increases the incidence and severity of recognizable diseases at given chronological ages. When these diseases appear rarely or not at all in controls, or are thought to have different pathogeneses from similar diseases in controls, they are regarded as having been induced by radiation. Diseases common to the population which appear earlier in irradiated animals than in controls are regarded as having been *advanced* by radiation. In many experiments both effects may be combined, with induction relatively greater after local radiation and advancement relatively greater after TBR.

120. The life-span of animals often falls short of the potential because infectious diseases kill many well before senescence. In man, the counterparts of these life-limiting diseases have been largely eliminated in countries with adequate medical services; non-infectious diseases associated with senescence are prominent. In animals, diseases of long latency may rarely or never develop spontaneously within the life-span observed. Consequently, it is possible that some, if not all, diseases considered induced by irradiation may be diseases of long latency whose onset has been advanced. When intensive, localized irradiation causes a high incidence of certain diseases, induced or advanced, to the irradiated part, the incidence depends on the latent period of the disease relative to the development of other terminal diseases to which the animals are susceptible. This, in turn, depends on the age of the animals.

121. These considerations on the effects of irradiation on life-span, mortality curves, cause of death, and time of onset of disease, together with available information on clinical, physiological and histopathological effects of irradiation, indicate a resemblance between the pathological events underlying radiological life-shortening and premature aging processes. Whether the two processes are similar is not clear, and whether they are identical cannot be decided until the causes of radiological life-shortening and physiological aging are better understood.

Life-shortening by single doses in animals[218]

122. Recent data demonstrating life-shortening of mice and rats by single TBR with X- or γ-rays have been given.[219-231] Data on rodents indicate that the life-shortening effectiveness of single TBR with X- or γ-rays increases as dose increases. The life-shortening can be expressed either as an absolute time interval or as a percentage reduction of life span. The use of the latter definition in the following paragraphs does not imply that a value obtained for one strain or species will necessarily hold for another of different life-span. For doses up to 300 rad, the reduction per 100 rad is constant or slowly increases with dose, but increases rapidly for doses approaching the LD_{50}. Other data are not inconsistent with a linear relationship.[232] At doses from 200-500 rad (γ), the reduction is 2-4 per cent per 100 rad depending on dose. As one approaches the LD_{50} (600-800 rad) etc., reduction of life-span is accelerated about 25-50 per cent (5-10 per cent per 100 rad).

123. Doses < 200 rad do not usually significantly shorten life in the numbers of rodents tested to date. On the assumption that effect remains proportional to dose down to the smallest doses, extrapolation from present data gives an upper limit of $\sim$ 1-5 per cent per 100 rad to the life-shortening effect of single doses below 200 rad. It is possible that effectiveness falls below this value for 10 rad or less.

124. Female mice show more life-shortening than males at all dose levels, presumably due to endocrine disturbance after radiation damage to the ovary. The extraordinary radiation sensitivity of mouse ovary has no known parallel in other species, nor is there evidence of disproportionate life-shortening in female rats or guinea pigs. There is no basis for expecting a large sex differential in life-shortening in man.

125. The RBE of fast neutrons for shortening life is compared to X- or gamma-radiation $\sim$ 2-3 at the LD_{50} level. The RBE for life-shortening is thus about the same as that for acute lethality. Although survival data

after a wide range of neutron doses are not yet available, accumulating evidence suggests that life-shortening is nearly proportional to dose, rather than an accelerated function as after X- and gamma-rays. Consequently, the neutron RBE for life-shortening increases as dose decreases. If the X- and gamma-ray effectiveness becomes proportional to dose, at sufficiently small doses the RBE for life-shortening by fast neutrons may approach a limiting value. The highest value so far experimentally seen is ~ 10.

126. Several studies are in progress[220,233,234] on life-shortening after a wide range of dosages; data from Operation Greenhouse[194] remain the most extensive. The conclusion[235] that life-shortening is a non-linear function of dose, with an accelerating rate of loss of life with increasing dose, has been challenged.[236] The data of Gowen and Stadler[231] covering a wide dose range indicate a curvilinear relationship; and the data of Storer and Sanders[226] compatible with a linear relationship, do not permit a choice between the alternatives. No studies to date provide direct evidence for or against a threshold dose below which radiation is ineffective.

Life-shortening by multiple doses or protracted irradiation in animals[218]

127. Small animals given comparatively small daily doses of X- or γ-radiation for several months or more have about 11 per cent life-shortening per 1,000 rad. The effect is proportional to dose, or nearly so, for accumulated doses of 500-2,000 rad or more. This factor is consistent with the rough estimate given for life-shortening by small single doses.

128. The dose-effect curve for exposures over days and weeks falls between those for single doses and those for highly fractionated exposure; the slope of the curve diminishes as exposure time lengthens. But, there is no sharply defined point on one side of which response is similar to that with a single dose and on the other response is similar to that for continuous exposure. Effects intermediate between single and continuous exposure have been shown.[235] At present, data are insufficient for formulation of empirical relations to predict responses for all conceivable fractionation schedules. One difficulty is the variable response of different strains of mice. Appropriately timed fractionated exposures are clearly more leukaemogenic than single exposures[237,238] for certain strains with a high susceptibility to radiation-induced lymphatic leukaemia. In such mice if leukaemia is a major cause of death, fractionated exposures may be more potent in life-shortening than single exposures[238] even though the incidence of degenerative diseases, such as nephrosclerosis, decreases with increasing fractionation. Such data can be corrected for the high incidence of leukaemia, or other strain or sex specific tumours to evaluate life-shortening from other causes.[224] Corrected data, unfortunately, are not usually reported. Data on life-shortening effect of a long-term protracted radiation with fast neutron compared to X- or gamma-radiation suggest an RBE of around 10.

Age effects[218]

129. Kohn and Guttman[229] studied the important problem of the effect of age at time of radiation on life-shortening in mice. Mice given single X-ray exposures at ages 160, 435 or 535 days had less life-shortening than mice irradiated at later ages. Total gross tumour incidence was also decreased. In another study, Kohn[239] found that exposure of mice 730 days old did not reduce life-span. An explanation for this decrease in effect with age is perhaps found in experiments[240] in which mice 435 days old exposed to 500 r of TBR had an increased death rate over controls twenty-four weeks later in male mice and sixteen weeks later in females. Thus the damage which induces premature death evolves slowly and since twenty-four weeks are an appreciable fraction of normal life-span, irradiation of animals late in life does not allow sufficient time for damage to express itself.

Partial-body exposures

130. Partial-body exposure of mice and rats is far less effective in shortening life-span than TBR.[228,230,240-243] The extent of life-shortening depends on area irradiated, size of field, and total dose. Maisin *et al.*[242] found that in rats survival curves had different shapes depending on body part exposed. They concluded that the TBR survival curve is a composite of partial-body curves and that injury to various body regions summates to produce the total-body effects. Lamson *et al.*[240] reported that life-shortening was roughly proportional to the percentage of body radiated. But no clear-cut relationship allows direct extrapolation of TBR information to partial-body exposure.

Role of genetic constitution and physical status[218]

131. Information on the influence of genetic constitution on long-term survival after radiation is meagre but permits preliminary discussion. Most work on genetic constitution in radiation-sensitivity of mammals examines differences in response of genetically homogeneous (inbred) mouse strains and their hybrids. Susceptibility to early, acute death differs by somewhat less than a factor of 2 between the most sensitive and the most resistant strains. Resistance to acute death is apparently correlated with general vigour; most radiation-resistant strains are longer-lived and less susceptible to spontaneous infectious disease. A short life-span, if due to high susceptibility to leukaemia does not appear to influence susceptibility to acute death.

132. Lifetime follow-up of several inbred strains and their hybrids after radiation indicates that the number of days lost varies less between strains than does acute sensitivity. Most strain differences in life-shortening is due to strain difference in susceptibility to radiation-induced leukaemia; when leukaemia mortality is excluded, life-shortening due to all other causes varies comparatively little between strains and is independent of normal life expectancy. Thus, in the mouse, a major component of life-shortening is independent of genetic make-up, aside from the variable susceptibility to leukaemia and ovarian tumour. The contribution of these strain-specific diseases to total mortality is greater in the mouse than in other species for which data are available; nevertheless, the range of variation in over-all life-shortening between strains is less than a factor of 2.

133. These results only partially answer the role of genetic constitution on life-shortening even in the mouse. Inbred mouse strains are highly selected genetic material from which many genes that could alter viability may have been eliminated. These genes are maintained in wild populations by various mechanisms, some of which could make an additional contribution to life-shortening by radiations. Furthermore, several of the most widely used mouse strains are genetically related, and are therefore unrepresentative of the genetic potentialities of the species.

134. Human populations are genetically heterogeneous. There is as yet no way to determine the influence of this heterogeneity on radio-sensitivity from individual to individual. Ethnic differences in spontaneous leukaemia incidence suggest that, in man, as in the mouse, genetic constitution plays a role in susceptibility to radiation-induced leukaemia.

135. A fraction of the human population may have hereditary traits giving extraordinary susceptibility to radiation-induced malignancies. Existence of such a trait can only be established from data on familial tendency towards such susceptibility or from a demonstrated correlation between such malignancy and some other genetically determined trait. Large numbers of presumptive radiation-induced cases would be required; may they never become available.

136. Vigour or fitness probably correlate with acute radiation-sensitivity in man—as in experimental animals. Study of the influence of nutrition, exercise, disease, and other environmental and physiological variables on radiation effects has only begun; present judgements must therefore be based on incidental clinical and experimental observations.

137. Stresses may activate chronic or latent diseases. Radiation may so act in certain disease; e.g. *inactive* tuberculosis in monkeys and man and diseases caused by *Bartonella* or *Salmonella* in rats. The nature of activation is unknown, but is probably due to impairment of immunological response.

138. In contrast, a therapeutic or prophylactic effect of irradiation on certain infectious diseases can mask the life-shortening effect in experimental animals. The observed life-span of animals is sometimes greater with daily doses of 1 rad or so throughout adult life than that of their controls.

Life-lengthening

139. Data on rodents exposed to small accumulated doses (about 100 to 400 rad per lifetime) at low dose rates were puzzling because such animals frequently survived longer than controls.[244,245] Although sampling errors and bias in experimental conditions may have contributed, some recent findings suggest this effect may be real.[246] In many experiments showing increased survival, there was considerable intercurrent mortality early in life in control animals, presumably from infectious disease, whereas irradiated animals had less mortality in the same period. There is no evidence the maximal life-span is extended in this situation, or that the incidence of cancer or degenerative disease is decreased. Since the cause of the prolonged survival is unknown, the significance for man is unknown.

Nature of the lesion in life-shortening

140. The primary lesions responsible for non-specific life-shortening in irradiated animals have not been identified. Casarett and co-workers[247,248] view arteriolo-capillary fibrosis as the major radiation effect. If they are correct, it should be possible to show deficits in circulation in various organs and decide whether these deficits go with normal aging. Such findings would not prove a cause-and-effect relationship, but would at least show an association. Various hypotheses and models to explain aging and life-shortening by radiation have not helped as guides for histological or physiological studies. Information theory and somatic mutation[249–255] do not indicate experimental approaches going beyond the presently recognized genetic apparatus. Statistical theories based on fluctuations in mean physiologic state[234,256] point to whatever the investigator is familiar with as potential areas for study. Theories based on irreparable levels of injury[257,258] point out methods for measuring the level without achieving its identification and similarly the hypothesis of progressive loss of ability to repair damage[259] does not tell anything about the repair function itself. Life-shortening probably summates so many insults that one must be careful not to single out any particular lesion as of primary importance —at least not without overwhelming new evidence. The only clear candidate as an especially vulnerable site of radiation damage is the replication of DNA as noted earlier.

Radiation carcinogenesis

141. Data from irradiated animals and man indicate that enough radiation to almost any part of the body increases the incidence of malignant neoplasia.[89]

142. Radiation-induced tumours often take long to develop, not beginning necessarily immediately after obvious changes in the cells. Obvious tissue disorder need not exist at the site of origin of the cancer: radiation can induce malignant disease through physiological mechanisms as with e.g., ovarian, thymic and pituitary tumours in mice which are clearly indirect (i.e., where irradiation of the cells of origin of the neoplasm is not the critical factor).

143. Most animal experiments, usually with relatively homogeneous populations, have shown that there are dose levels that induce no detectable increase in incidence of certain neoplasms. Some investigators construe such data to mean that there is a threshold dose of radiation below which certain neoplasms cannot be induced or their age-specific incidence increased. It must be recognized that no dose-incidence experiment can prove the existence of a true threshold dose since, however large the number of animals used, the tumour incidence at a given dose may be too small to be demonstrated. On the other hand, a linear dose-effect relationship extrapolating back to zero dose would strongly suggest the absence of a threshold dose. This has been demonstrated in a few experiments for certain types of tumour.

144. A major difficulty in short-lived laboratory animals is that at low doses the latent period for tumour induction may exceed the life-span and hence no effect may be seen.

Relation to rate of mitosis[260]

145. Although neoplasia arises most commonly in proliferating tissues, in the long-term effects of Operation Greenhouse (mice exposed to atomic bomb radiation—table II) tumours of lung, liver, mammary gland stroma, and anterior hypophysis—sites of relatively slow cell turnover—were more frequent than those of skin, bone marrow, and intestinal mucosa—sites of more rapid cell turnover.

Relation to age

146. In the same study[260] the incidence of all tumours increased with time after irradiation, with one exception. This was lymphoma of thymus, which reached a maximum early in life in heavily irradiated populations. Tumours arose earlier in irradiated mice and then advancement in onset corresponded to reduction in mean age at death of the entire population. As regards the influence of age at the time of irradiation, diverse effects

have been seen. Osteogenic sarcomas and tumours of the gastro intestinal tract have shown a higher incidence in animals irradiated when young, whereas the reverse occurs with leukaemias and tumours of the mammary gland.[261]

Relation to radiation dose

147. The relation between tumour incidence and dose varied from one neoplasm to another. The incidence of some increased with increasing amounts of irradiation (e.g., thymic lymphoma), the incidence of others was maximal at intermediate dose-levels (e.g., hepatoma, ovarian tumour, pituitary adenoma), and some usually common, decreased in frequency with increasing dose (e.g., non-thymic lymphoma, sarcoma of breast, adenoma of lung).[260] In no instance did tumour incidence vary as a simple linear function of dose, and extrapolation, therefore from the high doses in this experiment to doses near those from natural environmental radiation is not possible, and the question of whether or not very low doses of radiation cause some slight increase in the over-all risk of malignancy (so-called threshold) remains unsettled. As a general rule, single-dose irradiation is more effective in producing cancer than greatly protracted exposure with the same dose.

Mechanisms of carcinogenesis

148. Of the various neoplasms induced by radiation some may be caused indirectly without irradiation of the tumour-forming cells themselves. Thus in certain strains of mice, presence of the thymus is necessary for induction of lymphomas[262] although the thymus itself need not be irradiated. Strong evidence that induction is indirect is given by the neoplasm arising in a normal thymus transplanted to an irradiated host.[263] In other strains, thymectomy shifts the site of origin of the tumour to other lymphoid tissue.[264] Repeated radiation in proper sequence causes a higher incidence of lymphoma in mice than do single exposures to the same total dose.[237,264,265] Inoculations of normal bone marrow or spleen,[195] partial shielding[265,267,268] and certain radiation-protective agents,[70] decrease incidence. There is dose-rate dependence in response[269,271] that, together with the incidence after various radiation dosages[255] suggests a curvilinear relationship between dose and response.

149. Indirect carcinogenesis also appears responsible for the development of thyrotrophic pituitary tumours in mice thyroidectomized by I^{131}.[272] Such tumours may possibly be more readily induced if the pituitary is also irradiated.[273,274] Other pituitary tumours are as readily induced by local radiation of the pituitary as by TBR, suggesting that their pathogenesis is direct.[274] For these as for many other types of radiation-induced tumours, the relative importance of direct and indirect causes is not yet understood. In certain instances, both causes seem to operate; e.g., the induction of ovarian tumours depends on destruction of ovogonia and ovocytes by direct irradiation and on gonadotrophic stimulation of remaining ovarian stroma by pituitary hormones.[275]

150. Studies on radiation-induced mammary gland neoplasia in the rat[276,280] have shown that a single sublethal dose of X- or γ-irradiation in young male or female rats results in an increased incidence of mammary gland neoplasia. The dose-effect relationship appears linear over 25–400 r, and the curve within limits of error, extrapolates to zero. No data are obtained below 25 r; above 400 r, etc., the curve was either flattened or declined, since the greatly increased incidence at 400 r depends on intact ovarian function and direct radiation injury to the breast is necessary for an increased incidence of radiation-induced neoplasia. These results indicate that primary radiation damage to the breast tissue is necessary, but this primary damage can be dormant and not result in neoplasia unless an additional mechanism is operative.

Somatic mutation theory

151. Under a broad definition of mutation, generally used by geneticists, as including all sudden heritable changes in a cell line, the somatic mutation theory of carcinogenesis can embrace almost all currently proposed mechanisms (e.g., gene mutation, chromosome breakage or loss, mutation or loss of cytoplasmic particles, or even virus infection). Under such circumstances the theory is reduced to a truism and merely serves to describe well-known characteristics of malignant disease. As a special case of this, simple gene mutations or other single-hit changes have often been invoked as a single basis for radiation-induced neoplasia, and incidentally as a basis for predicting effects under conditions that preclude direct observation. The simple point mutation hypothesis remains to be substantiated, as does the theory that naturally occurring point mutations cause "spontaneous" cancer.[281,282] A widely held view has been that, if a single hit on a gene or other cellular structure were the basis for radiation-induced neoplasia, then the dose-effect relationship might well be linear with no-threshold. The rat mammary tumour data and others indicate both a primary and secondary mechanism in this type of radiation-induced neoplasia. The neoplasms themselves were seen only when both mechanisms were operative. The secondary mechanism in the present situation (normal ovarian function) could not reflect a somatic mutation. Even if the primary event were a somatic gene mutation (or a single-hit chromosome break), the dose-effect curve[278] would not have been linear with no-threshold unless the secondary mechanism were operative. It follows therefore that lack of linearity and of an apparent threshold does not rule out somatic mutation as the primary event. Lack of such a response might simply indicate a non-operative necessary secondary mechanism.

152. Furth[339] concludes from the findings of several authors that radiation-induced rat mammary gland neoplasia "are best interpreted by supposing that radiation causes a subtle, irreversible change in the mammary gland which remains latent until the organ is subjected to proliferative stimuli".

153. The demonstration of a two-stage mechanism in the induction of some neoplasms throws doubt on the use of dose-response curves as arguments for or against the point mutation theory (or any simple one-hit theory). No "one" experiment even if the animals are numerous can settle this question for all types of malignancy and all circumstances. If the dose-effect curve is not linear, nothing would have been necessarily proved about the primary mechanism. If a linear no-threshold response obtained down to the lowest doses, the somatic mutation interpretation, if it could be made under these circumstances, would apply only for the particular neoplasm in the particular strain and species. Extrapolation would not be valid.

Chromosomal changes and carcinogenesis

154. The role of chromosomal changes as an intermediate cause in carcinogenesis has been widely de-

bated.[284,285] Malignant tumours often have aberrant (usually aneuploid) chromosome numbers and a high degree of instability in chromosomal constitution.[286] It by no means follows that the chromosomal changes are the cause of the malignancy; inaccuracy in the transmission of genetic information may be merely the price of proliferation at unrestricted speed. Association of chromosomal variation with tumours therefore does not of necessity imply any cause-effect relationship.

155. Chromosomal aberrations can be induced in normal human and monkey cells cultured *in vitro* by X-ray in doses as low as 25 r[287,288] and such aberrations (presumably of mixed 1-hit and 2-hit origins) in *in vivo* monkey bone marrow cells show a rough proportionality with doses from 50-100 r. Blood cells cultured from two patients given radiation for ankylosing spondylitis showed numerous chromosome structural abnormalities but these rapidly declined in number.[289] Similar changes have been seen in patients with chronic myeloid leukaemia after X-ray treatment.

156. The persistence of chromosome aberrations in peripheral blood leukocytes $\sim 2\frac{1}{2}$ years after accidental whole-body irradiation of eight men by mixed gamma and fission neutrons has recently been reported.[781] Five men received doses > 230 rad; three others, <70 rad. The frequency of cells with chromosome counts differing from 46 ranged from 4-23 per cent in the irradiated compared to 2 per cent in controls. In the five cases with high doses, there were grossly altered chromosomes such as rings, dicentrics, and minutes; these were often in cells with abnormal count with a frequency of 2-20 per cent. No polyploidy was seen. A detailed karyotype analysis of some normal-looking cells from irradiated individuals revealed the presence of pericentric inversions, translocations, and deletions. A comparison of the frequency of induced chromosome breaks in tissue culture preparations suggests that the frequency of aberrations diminishes with time, and that polyploid cells are eliminated more quickly.

157. There is increasing evidence of an association of specific types of leukaemia with chromosomal anomalies. In many cases of chronic myeloid leukaemia there is a specific abnormality (possibly a deletion) in one of the chromosomes of pair-21 or pair-22 (the Philadelphia chromosome). Variations in the proportion of cells with this Philadelphia chromosome in blood-cell cultures from different patients with myeloid leukaemia and its absence in skin cultures from the same patients strongly suggest the presence of a somatic chromosomal anomaly in these patients' leukaemic cells. Moreover, the incidence of acute leukaemia is greatly increased in mongolism, a disease[291] now known to be associated with trisomy-21. These observations suggest that either a deficiency or excess of genetic material of chromosome pair-21 may result in different types of leukaemia. For other types of leukaemia, no such consistent associations have been established as yet.[290,782,783,784]

158. These chromosomal aberrations and especially the possibility of a specific chromosome abnormality in myeloid leukaemia and the hereditary nature of the neoplastic change in subsequent cell generations suggest that cancer reflects a genetic change in the cell. But the course of evolution of malignancy in certain tumours argues against a one-stage cause, such as single point mutation or chromosomal aberration.[285,292,293] Moreover, induction of neoplasia by indirect effects on the host cannot be due to the mutagenic action of radiation on the cancer-forming cells, since the cells themselves are not irradiated. Here radiation probably merely favours selection of spontaneous carcinogenic mutants, possibly by excessive growth stimulation during recovery.

Radiation leukaemogenesis

159. Studies of radiation leukaemogenesis use the mouse because of ease of leukaemia induction and the availability of different leukaemias associated with various inbred strains. Mouse leukaemia is not a single disease; much confusion arises because precise classification is often lacking.[294,295] The most studied mouse leukaemia is lymphatic arising in the thymus, classified variously as thymic leukaemia, thymic lymphosarcoma, malignant lymphoma, and "mouse leukaemia". In the mouse, the thymus normally atrophies in early adult life instead of in early childhood as in man. Extensive studies by Upton *et al.*[264] show that factors inducing this neoplasm differ from those inducing myeloid or granulocytic leukaemia. Since most radiation-induced leukaemias in man are granulocytic, thymic leukaemia of mice have little relevance to man.[294] Myeloid leukaemia in mice, possibly more analogous to human radiation-induced leukaemia, has been studied less.

160. In spite of these reservations about the comparability of human and murine leukaemias, the leukaemia responses of the two species share certain features.[296] Both species show an increased incidence of leukaemia after TBR. In mice, the leukaemia incidence in irradiated groups returns to or near control levels 18-20 months after exposure.[223,297] The Hiroshima and Nagasaki survivors[298] had still some excess leukaemia mortality over their unirradiated controls by 1959. By adjusting time scales, human and murine experiences can be superimposed; for comparable radiation exposures, the factor of increase in age-specific leukaemia mortality over control is nearly identical for the two species.[296]

161. Data of Kaplan *et al.*[263] indicate that lymphomata in thymectomized irradiated mice can appear at the site of transplantation when the thymus from non-exposed mice is transplanted into the irradiated animal. The origin of the neoplastic tissue has been studied[263,299,301] and although in some instances the cells may be derived from the donor cells, in others they are derived definitely from recipient cells.

162. Radiation-induced myeloid leukaemias of the mouse are uninfluenced by the thymus but are reduced by splenectomy.[264] They are more effectively induced by relatively lower radiation dosages than is the thymic form and their induction is apparently not similarly enhanced by fractionation of the exposure.[264] Partial shielding reduces incidence[264] as does prophylactic administration of mercaptoethyl guanidine,[302] a radioprotective agent. The incidence reaches plateau at radiation doses above 150 r.[264] The shape of the dose-response curve is not definitely known, but data after doses of 16 and 32 r[72] and after 128 or more[264,303] suggest curvilinearity in the low-dose range. In rats and mice injected with strontium-90, more differentiated forms of leucosis predominate when the accumulated dose to the bone marrow is small and less-differentiated forms when the dose is large, i.e., of the order of 6,000 rep or above.[304]

163. Variables besides radiation dose affect the probability of an animal developing leukaemia, e.g., strain, age at time of irradiation, sex, and endocrine status. Leukaemia incidence can be modified by endocrine status and genetic inheritance (by selection, hybridization, etc.), or by removal or implantation of tissues.[294,305-311]

Virus theory

164. Evidence that viral agents cause various types of cancer in mice[312-315] stimulated the search for filtrable leukaemogenic agents in mice with radiation-induced leukaemias.[316-318] Results as yet are not conclusive, but they suggest viruses as possible etiologic agents in radiation-induced leukaemia.[293] Depression of host immunity by radiation may promote infection by an exogeneous carcinogenic virus or radiation may activate a latent carcinogenic virus infection analogous to the induction of lysogenicity in bacteria. To these hypothetical mechanisms must be added the possibility of viral transduction of carcinogenic substances from one cell to another.[312,319]

Risk of carcinogenesis from low doses

165. Carcinogenesis is the most important late effect of radiation. Knowledge of the mechanism of radiation carcinogenesis is a prerequisite for the accurate assessment of risk at low doses. Since the mechanisms of carcinogenesis are unknown, any such assessment of risk must be purely speculative, although possibly of some value in estimating upper limits.

RECOVERY AND THE CONCEPT OF IRREPARABLE INJURY[320]

166. Radiation injury, like other injury, immediately sets off the classical reactions of homeostasis and repair; to some extent, radiation affects the repair processes themselves.

167. In the weeks after a single sub-lethal dose, damage gradually is repaired. Many, if not all, cells destroyed by radiation are replaced by regeneration from surviving cells. Irradiated organisms may resume a normal or near-normal appearance. With time there is recovery of resistance to lethality from further radiation. Most radiation injury from X- and γ-rays is thus frequently reparable. Animals, therefore, survive a prolonged dose several-fold larger than a single dose.

168. Despite apparent recovery residual damage (e.g., incomplete regeneration or residual defects in cells and tissues) and late effects seen after maximal recovery show that some injury is irreparable. Certain specific injuries associated with the formation of bone tumours caused by radiation are reparable. Recovery is more likely with injuries which are caused by β- than by α-radiation.[261,304,321]

169. Life-shortening by radiation implies that an irreparable component of injury is detectable. This component is detectable as premature aging in an actuarial sense. But how closely this process parallels and contributes to that cumulative injury called natural aging is unclear in the quantitative sense. Likewise, it is not known whether the irreparable component represents abrupt aging at the time of injury or initiation of gradual aging. Limited observations in rodents, dogs, and swine indicate that irreparable injury is measurable, after an interval of presumed complete repair, as a reduction in acute lethal dose. This suggests that irreparable injury is at least partially sustained at the time of radiation and is potentially observable as a persisting tissue change; the distinction between reparable and irreparable injury has not yet been related to morphology.

EARLY AND LATE EFFECTS ON EMBRYOS AND FOETUSES

170. Ionizing radiations profoundly disturb developing embryos. Their susceptibility while very high may be no higher than that of certain actively dividing and differentiating adult tissues. Irradiation of an embryo with 5-25 r causes evident changes; similar exposure of adult haemopoietic or epithelial tissues is likewise followed by morphological and functional disturbances. The difference between embryonic and adult response to low doses of radiation is that an over-all effect in embryos is even more extensive than in the adult probably because a minor irreversible injury in embryo, particularly after the blastomeres have lost totipotency, is amplified in development: morphogenetic relations are upset through death of cells in various precursor fields, and this leads to faults in the formation of adult structures.

171. Radiation effects in embryos may reflect two mechanisms: developmental alterations through cell destruction in the embryo and physiological disturbances in the mother.

The mammalian embryo

172. Mammalian pre-natal development can be divided into three periods with respect to radiation effects: (*a*) pre-implantation when early deaths are induced but survivors are mostly normal; (*b*) major organogenesis, yielding neonatal deaths and abnormalities; (*c*) the foetal period when sensitivity to death and gross malformations decreases. The general pattern in mice is given in figure 2.

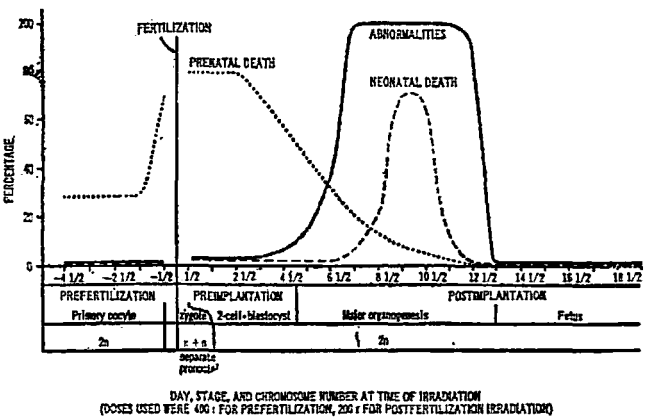
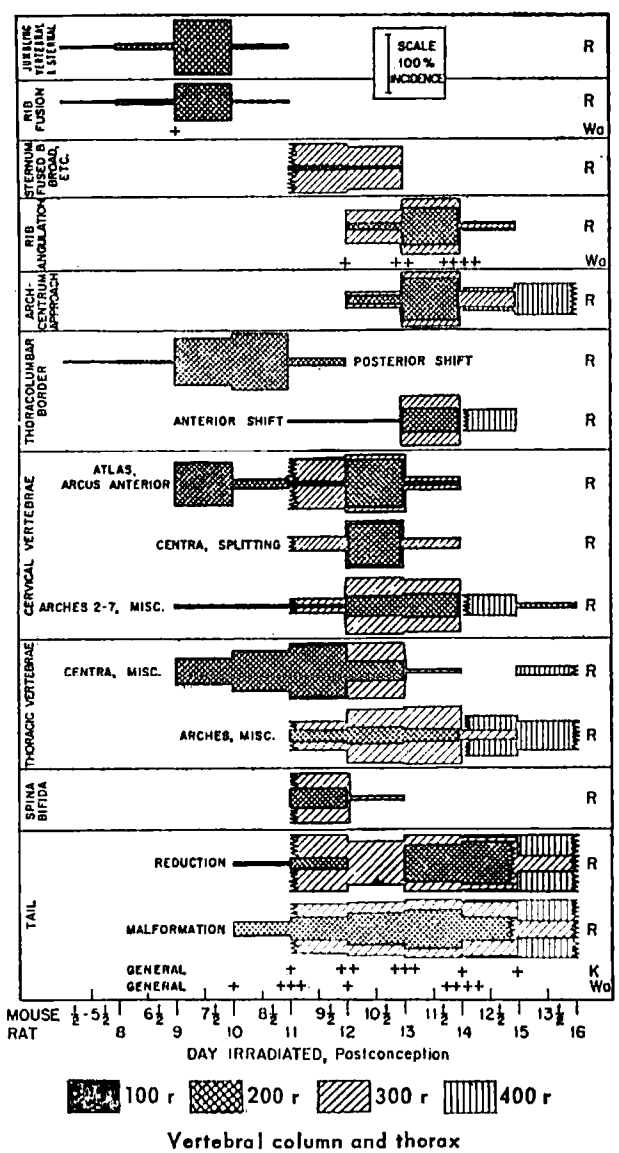


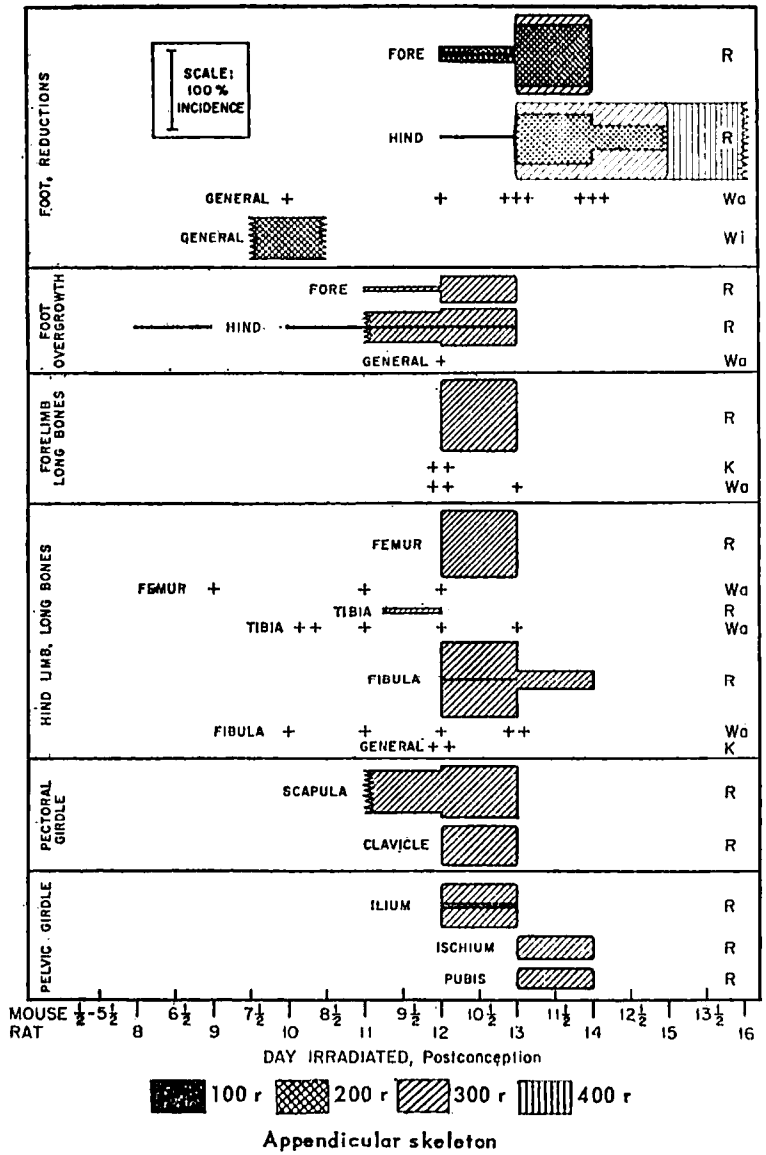
Figure 2. Incidence of pre- and neo-natal death and of abnormal individuals at term after irradiation at various intervals (separated by 24 hours) pre- and post-fertilization. Abnormal individuals may have more than one abnormality[324]

173. When females are irradiated after fertilization but before implantation, high and rapid mortality of the fertilized ovum is the main effect. Studies by the Russells[322,323] indicate that deaths are maximal for radiation given during the first two post-copulation days, and that one-third of total deaths are in the pre-implantation period. Most deaths, especially among embryos irradiated later after fertilization and closer to the expected implantation time, ensue shortly after implantation. No deaths in excess of controls occurred after day 10½.

174. Survivors of irradiation in the pre-implantation period were free of obvious defects[322] had normal birth- and post-weaning heights, exhibited normal fertility and showed no evidence of decreased survival throughout life.[153] The all-or-none response to irradiation during cleavage stages which has also been observed in rats and guinea pigs[323] has led Russell to suggest that mammalian blastomeres are totipotent.[323,324] On the other hand, Rugh and Grupp[325] showed that a dose as low as 50 r to a pre-



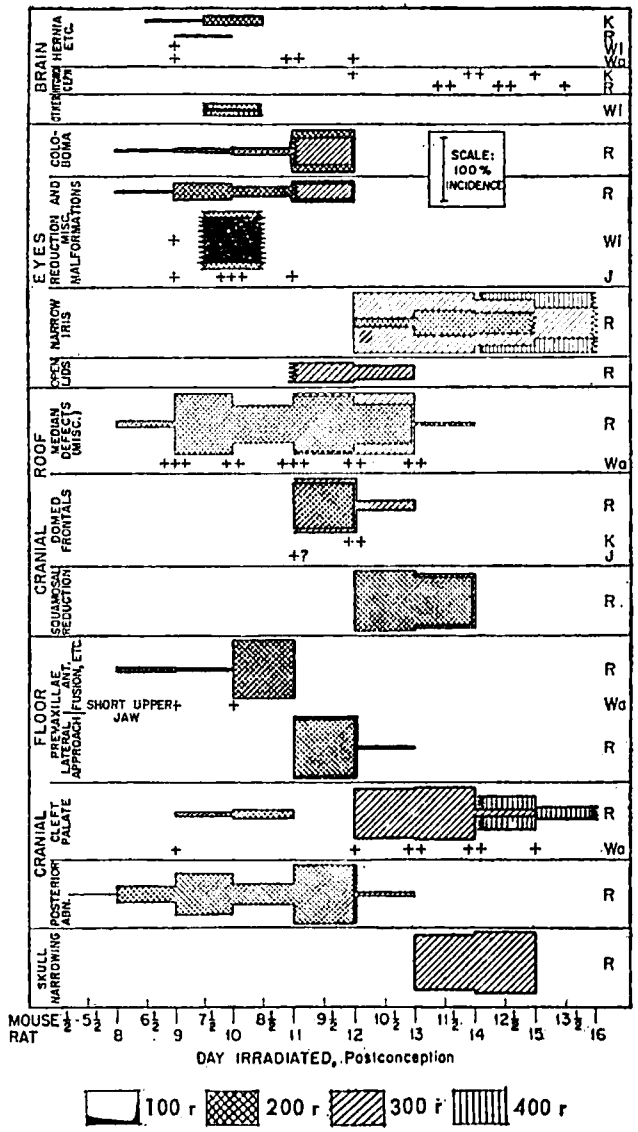
Vertebral column and thorax



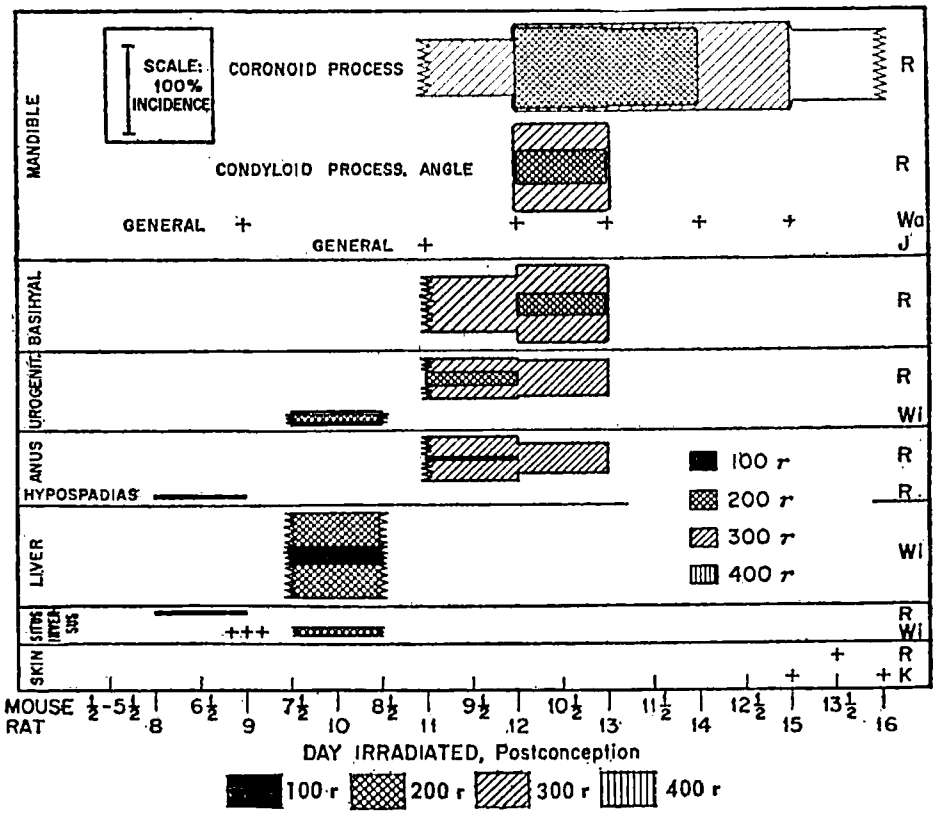
Appendicular skeleton

Figure 3. Critical periods in radiation-induced abnormalities in mammals.[323]

Wherever sufficient data are given in the original publication, representation here is by (*a*) percentage incidence of abnormality and (*b*) magnitude of dose required to produce abnormality. Thus, the wider and more heavily shaded a band, the greater the sensitivity. Absence of a band at a particular stage indicates that the abnormality did not occur in the irradiated group, except where the serrated end of a band indicates that the dose series was not continued to the stage in question. For cases where the exact incidence for a given stage and dose cannot be calculated from the original data, representation is only roughly quantitative. In general, + = 1.49%, > 200 r; + + = 1-49%, 1-200 r; + + + = 50-100%, > 200 r; + + + + = 50-100%, 1-200 r



Central nervous system, eyes, skull



Visceral skeleton, viscera, and miscellaneous

Figure 3 (continued)

implantation embryo might induce cerebral abnomalies. This result has not yet been confirmed by other investigators.

175. The pre-implantation mouse embryo is highly radio-sensitive. Earlier studies indicated that 200 r prevented about 80 per cent of all embryos from reaching the tenth day of gestation. It was recently shown that 25 r killed 38 per cent of embryos exposed before first cleavage. A dose of 5 r increased resorption.[325] However, the degree of radio-susceptibility of an embryo may be species specific: the rat embryo before implantation can withstand a dose of 300 r.[123]

176. Mouse embryos given 200 r or more between gestation days 6.5-13.5 developed but had a high incidence of abnormalities. A certain proportion of the abnormal foetuses died at birth. The proportion of prenatal deaths was much lower than in animals exposed in the pre-implantation period. The LD_{50} for neo-natal death was > 200 r for irradiation in the pre-implantation period and through day 8.5; decreased to between 100-200 r for days 9.5 and 10.5 and then increased to 200-300 r for day 11.5 and finally to > 300 r for later periods in development.[323, 324] With 200 r the incidence of grossly abnormal new-borns is 100 per cent for irradiation of most stages during major organogenesis. Doses as low as 25 r have been shown to be effective in causing morphological changes.[326]

177. Neo-natal mortality is greatest in embryos irradiated between gestation day 8½ to day 12. Exposure in the same period decreased the weight of new-born mice[124, 323, 324] comparable quantitative studies have not been made in other mammals but there are frequent reports of marked decrease of size among rats and rabbits irradiated during development.

178. Several investigators have tried to decide whether specific developmental abnormalities depend on the stage of development at which radiation is given. Early work by Kosaka[327] indicated that the brain and spinal cord are the most sensitive tissues at the beginning of major organogenesis, while at later stages thymus and, to a lesser degree, liver and spleen, become the most sensitive. A more detailed description of "critical periods" has been given by Job *et al.*[328] The peak incidence of abnormalities was reached with embryos irradiated between gestation days 8-11. Hydrocephalus was easily induced in embryos irradiated at day 9, eye defects at day 10, jaw defects at day 11. According to Kaven[329] the structure of the tail was most affected in embryos exposed on day 11, brain hernias on day 8, and skin defects on days 13-14. The results of Russell[124, 330] and others on critical periods are given in figure 3. Maximum susceptibility to defects was between days 7-13, the beginning coinciding with the appearance of many differentiating centres. Irradiation at day 9 caused anencephaly, at day 10 eye defects, at day 11 hydrocephalus and spinal anomalies, and at day 12 anomalies in the fore-brain.

179. Embryonic neuro-blasts are particularly susceptible to radiation. Within two hours after 100 r, there are scattered areas of necrosis, and necrotization of individual neuro-blasts after doses as low as 40 r. With increasing exposures, more areas of developing neural tissues are affected. Intermitotic neuro-blasts are more susceptible to radiation than those in mitosis.[331] Cells during active differentiation may well be more sensitive than completely differentiated cells. Further studies are needed, and the radio-sensitivity of erythro-blasts, myelo-blasts, and spongio-blasts should be compared with corresponding mature cells.

180. The existence of "critical periods" in development has thus been demonstrated, but the use of the term must be properly qualified.[324] For some anomalies, the critical period is greatly extended, e.g. exencephaly can be induced by radiation at any time before neural differentiation.[332] Sometimes induction of a specific anomaly does not coincide with an apparent period of increased developmental activity, e.g. induction of polydactyly.[124] Also, the limits of periods of sensitivity seem to depend on the dose[323, 324] and how it is fractionated;[153] however, stage of maximum sensitivity is usually revealed by the use of low-dose single exposure.

The human embryo

181. The first harmful effects of ionizing radiation on human embryos were recorded in 1901-1904. Soon afterwards, reports drew attention to serious hazards in irradiating pregnant women. Earlier clinical literature has been reviewed extensively.[332–336] Table III summarizes observed malformations. Malformations specifically reported for human embryos are marked with an asterisk. The most frequent abnormalities are in the central nervous system, then eye defects and skeletal malformations.

182. Malformations among children irradiated *in utero* have been reported. In a 1929 survey of 75 children born of 106 irradiated women, 38 were abnormal, and in 28 of those the likeliest cause of malformation was radiation.[337] The dose was estimated to be 30-250 r.

183. The frequency of malformations in man, as in other animals, depends upon developmental stage.

184. The marked qualitative similarities between radiation-induced abnormalities in man and other mammals make extrapolation of experimental studies to man apropos. For that purpose, a graph correlating development of mouse and human embryos constructed by Otis and Brent is useful[338] (figure 4). The correlation between the appearance of some morphological features in the mouse and in the human embryo is given in table IV. Since mouse experiments have shown that

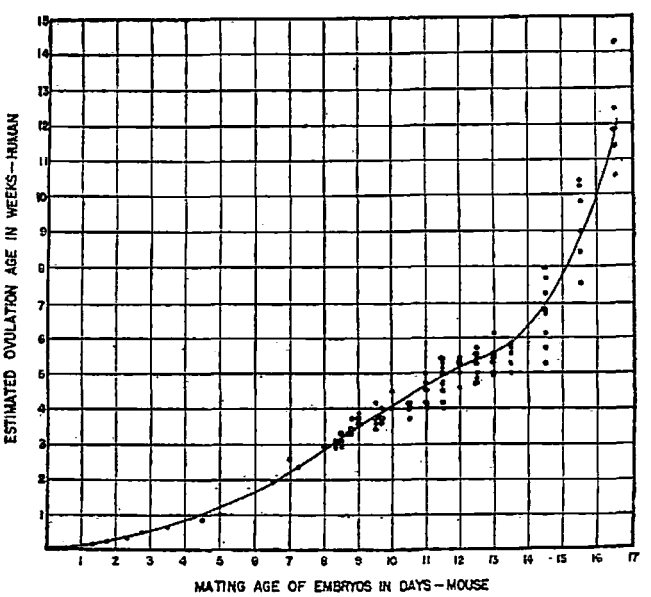


Figure 4. Graph of the time of appearance of structures in mouse and human embryos[338]

irradiation during the period of major organogenesis is potentially most hazardous and since part of that period occurs at a time when pregnancy may still be unsuspected Russell and Russell have suggested that whenever possible pelvic irradiation of women of child-bearing age be restricted to the two weeks following the menses.[339, 340]

185. Besides abnormalities in embryos, foetuses, and in early childhood, several effects of irradiation during gestation have been reported, appearing at a later age in children. Stewart and collaborators[341] concluded that there was an increased incidence of leukaemia and cancer among children irradiated *in utero*, and also an increased incidence of mongolism.[342] Children of Japanese mothers exposed, during gestation, to atom bomb radiation tended to show stunting[343] and some mental retardation, especially among boys,[344] but neither observation has been supported by other studies.[345, 346] Among children who, while *in utero*, had received an average of 3-5 rad during maternal diagnostic X-ray, 15 of 1,101 had phenotypic changes involving colour sectors in the iris of the eye. The incidence was only 11 in approximately 7,092 non-irradiated control siblings and parents. The difference is highly significant. This somatic effect is only seen in the children of women irradiated at 6 to 6½ months of pregnancy. It is not yet known whether the effect is due to genic chromosomal or other changes. These studies are discussed further in section V under the heading "Late effects".

Recovery and protection in irradiated germ cells and embryos

186. In the sea-urchin egg, as time elapses between irradiation and fertilization, there is the increased proportion of cleavages pointing the possibility of recovery.[347] The effect was described by Miwa[348] for *Pseudocentrolus depressus* irradiated with α- or γ-rays. This does not imply recovery to pre-irradiation stage.[349] The delay between irradiation and fertilization counteracts the delaying effect of irradiation upon cleavage, but does not increase the number of embryos capable of normal development. In frogs Rollason[350] found no evidence for this kind of recovery.

187. Recovery was seen when an organ from an irradiated embryo was transferred to a normal one. The irradiated organ, e.g. of a frog[351] or chick embryo[352] developed further and survived longer than it would have in its original environment. This does not necessarily denote recovery; it is perhaps better explained by assuming that the transfer of the organ removes it from the noxious environment of a dying embryo.

188. Recovery in embryonic tissues has been postulated by several authors from the observation that irradiation of embryos at an early stage brings early death, but survivors develop normally. Recent experiments[325] have shown that exposure to radiation, even almost immediately after fertilization, caused marked abnormalities (brain hernia); survivors that developed without big abnormalities nevertheless showed stunting and some impairment of the ability to learn.[353]

189. After radiation-injury the embryo as a whole may show a certain recovery in that survivors of radiation continue to develop despite morphological damage.[354] This does not imply that the injured tissues have recovered; the survivors are usually stunted and there is some topographical reorganization of undamaged tissues, which might indicate that the maintenance of viability and shape is due to some of the cells from surrounding areas invading the lesion.[332] Recovery of an embryo is more the outcome of a regenerative process, aided by the remarkable powers of reorganization of embryonic tissues and scavenging activities of macrophages, than recovery of the cells actually damaged.

190. Expected radiation injury may be prevented to some extent by several factors; hypoxia, lowered temperature, and various thio compounds. Lowering the ambient temperature protects against immediate radiation effect in frogs, an effect lasting only as long as a low temperature is maintained;[355] in salamander larvae, protection appears to persist.[356] Also in chick embryos Goffinet[357] protected against radiation by lowering temperature.

191. The effects of hypoxia were studied by Russell and collaborators:[324,358] mouse embryos exposed to doses 100-400 r had a lower percentage of abnormalities if irradiated in 5 per cent oxygen in helium. Allen, Schjeide and Piccirillo[359] showed that the proportion of cells injured by radiation was reduced if irradiated cells were maintained afterwards in mildly anoxic conditions; anoxia reduces cell division.

192. Cysteamine as well as several other compounds protects to some extent against radiation if given before irradiation. The survival of chick embryo was improved after giving cysteamine, cystamine, and methylamine; the efficacy of these compounds was highest when the circulatory system began to function.[357, 360] It has been observed that mercaptoethylamine can protect the rat foetus if irradiated on days 15-18,[361] and that cysteamine and similar compounds permit mouse foetuses to maintain a higher growth rate and lower mortality than irradiated untreated controls.[362, 363]

IV. Acute radiation injury in man

Acute radiation syndrome

193. The acute radiation syndrome differs from ordinary injuries since there are integrating patterns of symptoms after higher doses, or a latent period at lower doses during which hidden histological changes are taking place from the time of exposure until the recrudescence of symptoms and frank danger of death. Recovery from the initial symptoms does not signify real recovery. Review of reactor accidents (see below) emphasizes the problem of inhomogeneous irradiation of the body in man and the influence of the part irradiated upon the symptoms that follow. Effects of localized irradiation on individual organs are discussed in earlier sections of the present annex.

Sources of information

194. There are four sources of information on acute radiation effects in man: (*a*) the largest, but studied under obvious difficulties, is the experience of the Japanese at Hiroshima and Nagasaki; (*b*) the less serious and smaller experience of the Marshallese, American servicemen, and Japanese fishermen to fall-out radiation during atomic tests in 1954; (*c*) exposure of a few people to reactor and radiation accidents in the United States, the USSR and Yugoslavia; (*d*) exposure of patients to therapeutic radiation. Some shortcomings of such information have been discussed earlier in paragraphs 43-45 above. Information on atomic bomb, fall-out, reactor accident, and whole-body radiation injuries has been summarized.[50, 364, 372, 373, 388, 393, 702]

Total body response[365]

195. The total body response in man to radiation in sufficient doses includes: (*a*) radiation sickness beginning during or very soon after acute exposure, and overlapping with other responses; (*b*) degeneration and repair of proliferative tissues; (*c*) local and generalized toxaemia; (*d*) changes in homeostasis; (*e*) deterioration in physical and mental fitness.

Radiation sickness

196. After a single dose of radiation of 50 rad and above given to whole-body, symptoms have appeared in 1-2 hours. The onset, duration and severity of all symptoms varies depending largely on dose and partly on susceptibility.[366] Symptoms may include:[367] (*a*) general: headaches, vertigo, debility and abnormal sensations of taste or smell; (*b*) gastro-intestinal: anorexia, nausea, vomiting, diarrhoea; (*c*) cardiovascular: tachycardia, arrhythmia, fall of blood pressure and shortness of breath; (*d*) haematological: leukopenia, thrombopenia, and increased sedimentation rate; and (*e*) psychological: increased irritability, insomnia, and fear.

197. The incidence of radiation sickness is affected by the part of body irradiated.[368, 369] Exposure over the whole trunk and partly over the upper abdomen causes more radition sickness than does exposure of comparable tissue volumes in the extremities. Explanations for radiation sickness include: (*a*) release of toxic substances from disintegrating cells;[370] (*b*) disturbance of pituitary-adrenal cortical function;[371] (*c*) tissue destruction giving rise to histamine and mildly toxic histamine-like products.

General clinical picture

198. Although the different organs have widely different radio-sensitivities for the acute radiation syndrome in man, three are important:[53, 372, 373] the central nervous system (CNS), small intestine, and bone marrow, together with lymphoid tissue (table V). The acute radiation syndrome may therefore take three primary forms—cerebral, gastro-intestinal, and haematopoietic, depending on the dose. To induce acute effects in the central nervous system requires several thousand r; damage is seen within minutes to hours. The dose for the acute small intestine form is 300-500 r, with a latent period of $\sim$ 5 days. For severe haematopoietic changes, the dose is $>$ 200 r and the effect takes $\sim$ 3 weeks to develop.

CNS form

199. The clinical picture of the CNS form must be extrapolated from animals and a few accidents in man. The onset is prompt and death may occur in minutes to hours. After the initial phase of radiation sickness, there is swift progression from listlessness, drowsiness, and languor to severe apathy, prostration, and lethargy probably caused by small non-bacterial inflammatory foci appearing throughout the brain in 1-2 hours; this development of vasculitis or encephalitis gives rise to cerebral oedema. After $>$ 5,000 r, one deals with seizures ranging from generalized muscle tremor to epileptoid convulsions similar to grand mal. This convulsive phase lasts a few hours and is followed by ataxia from vestibulocerebellar disturbance. Convulsions and ataxia probably result from the degenerative pyknosis in the granule layer of the cerebellum within two hours after exposure, concomitant with brain oedema. TBR causing the CNS syndrome is fatal.

Gastro-intestinal form[53, 69]

200. The gastro-intestinal form predominates with lower doses (500-2,000 r). The prodromal nausea and vomiting begin promptly and do not subside. For some people these symptoms develop within 0.5 hours after exposure; in others not for several hours. Gastro-intestinal symptoms may continue (anorexia, nausea, vomiting, and diarrhoea). Sometimes these symptoms disappear after 2-3 days and recur $\sim$ day 5 just when the patient's condition seemed to have improved, owing to injury of intestinal epithelium, leaving bare villi. Rather abruptly, malaise, anorexia, nausea and vomiting prevent normal food and fluid intake, leading to serious electrolyte imbalance. Simultaneously high fever and persistent diarrhoea—rapidly progressing from loose to watery to bloody stools—appear. The abdomen is distended and peristalsis is absent. Rapid deterioration leads to severe paralytic ileus. Exhaustion, fever and perhaps delirium follow; dehydration and haemoconcentration develop; the circulation fails, and the patient becomes comatose and dies a week or so after exposure from circulatory collapse.

201. After doses where regeneration is possible, fluid replacement during days 4-6 keeps dogs alive.[74] The epithelium regenerates and vomiting and diarrhoea subside. This is only a temporary respite as evidence of marrow aplasia and panctyopenia begin within 2-3 weeks. After doses that cause this severe intestinal damage, marrow regeneration is unlikely, so that even if there is spontanous recovery or successful treatment, individuals have yet to experience the effects on haematopoiesis.

Haematopoietic form

202. In the haematopoietic form, after lower doses of radiation, e.g., $<$ 500 r, the haematopoietic symptoms are due to different origins and appear in two successive phases. Leucopenia, thrombocytopenia and haemostatic abnormalities are a direct consequence of lesions of the haematopoietic organs. Symptoms such as haemorrhage and anaemia may be secondary to the visceral lesions and associated with ulceration of mucous membranes. Anorexia, apathy, nausea, and vomiting, and some diarrhoea are maximum 6-12 hours after exposure. The symptoms may subside so that by 24-36 hours individuals feel well, but their bone marrow, spleen, and lymph nodes are atrophying. The patient enjoys apparently normal health until $\sim$ days 19-20 (many Japanese soldiers returned to work only to die later in the pancytopenic phase), when the patient has chills, malaise, and fever, headache, fatigue, anorexia and dyspnoea on exertion, and at this time partial or complete loss of hair is likely. Within a few days the general condition worsens, hospitalization is needed. The patient then develops sore throat and pharyngitis, accompanied by swelling of gingiva and tonsils and petechiae in the skin with a tendency to bruise easily, followed by bleeding from gums and ulcerations on gingiva and tonsils. Similar ulceration in the intestines causes a renewal of diarrhoea. The patient has high fever with complete anorexia. Weeks 5-6, with agranulocytosis, anaemia, and infection, are critical. The increased susceptibility to infection is caused by the dose dependent decrease in circulating granulocytes and lymphocytes, impairment of antibody production, impairment of granulocyte and RES function, lessened resistance to diffusion in subcutaneous tissues, and haemorrhagic ulceration permitting entrance of bacteria. Thereafter, if the patient recovers, fever, petechiae and

ecchymoses subside; ulcerations heal and convalescence begins about the end of the second month after exposure. These symptoms tend to merge into one another.

Prognosis

203. Early symptomatology in the diagnosis of radiation injury is a useful guide to management.[44, 375, 376] Subjects with intractable nausea, vomiting, and diarrhoea will generally die—the *survival-improbable* group. Those in whom nausea and vomiting is brief, 1-2 days, followed by well-being, have a good chance to survive.

204. After initial symptoms, the effects of haematopoietic damage predominate. The *survival-possible* group are in the lethal dose range. The *survival-probable* group includes those with no initial symptoms or only mild and fleeting ones disappearing within a few hours. Practical experience on the Marshallese, Los Alamos, Argonne, Y-12, Vinca and Lockport accidents demonstrate that physical measurements to compute probable doses take more time than do several haematological procedures. The dose must be judged on the basis of symptoms. This is especially important in determining management and prognosis when physical measurements are not available, or when radiation exposure has been non-uniform.

(a) *Nausea and vomiting*

In general, if nausea and vomiting are absent, it may be assumed that the dose was relatively low. Nausea and vomiting warrant hospital admission for observation. The rapidity of onset of nausea and vomiting provides some notion as to the severity of the exposure: usually, the earlier the onset and more protracted the vomiting, the higher the dose.

(b) *Erythema*

Much depends on the type of radiation as to whether erythema will result. It is difficult to make judgements of the dose on the basis of erythema but its presence is evidence of a serious exposure.

(c) *Haematopoietic and bone-marrow picture*

Where casualties are few it is simple to carry out all haematological procedures and other studies that might be of value. In a radiation disaster, extensive studies would be impossible, although many leukocyte counts would be practical with modern electronic counting devices:

(i) Lymphocytes are valuable as an early criterion for judging radiation injury. In normal individuals, a fall in lymphocytes is seen within the first 24-48 hours. If at 48 hours the lymphocyte count is 1,200 or above, it is unlikely that the individual has received a fatal exposure; if the lymphocyte count is in the 300-1,200 range, a dose in the lethal range may be suspected; counts below 300 indicate an extremely serious exposure;

(ii) Early bone marrow examination is advisable for determining whether the patient was haematologically normal at the time of exposure and might give some insight to the extent of damage. Some workers consider that multiple bone marrow examinations would be no more helpful than peripheral blood examinations and have the disadvantage of being potential sources of infection. Cronkite and Bond have proposed a determination of the mitotic index in bone marrows on day 4 as a measure of dose exposure—a mitotic index of zero indicates an exposure of 200 rad or more.

(iii) The total white-cell count is of particular value for following the patient throughout the course. In general, the drop in neutrophils will reflect the degree of exposure; a fall in white count beginning within the first week denotes a rather high exposure whereas late falls, such as observed in Marshallese, indicate a less serious exposure;

(iv) The platelet count, while being of some prognostic value, is of more importance in the general management of the patient. In general, the fall in platelet count would parallel the change in neutrophils, although occurring somewhat later, and the neutrophil count is more readily available, particularly in accidents away from hospital centres;

(v) The reticulocyte count would serve as a guide as to the extent of erythropoietic damage. Fe^{59} turn-over studies would be of little value; to be meaningful, they would have to be done serially and even then would add little information beyond that derived from the reticulocytes.

(d) *Recovery potential*

The type and extent of injury following radiation represents a spectrum and it is not possible to divide injury into clear-cut syndromes. In general, however, at higher doses, the predominant injury would be cerebral and the outcome uniformly fatal. With doses lower than this, the major injury would be to the gastro-intestinal and haematopoietic systems. Judicious use of fluid, electrolytes, and treatment of the haematopoietic injury as outlined below provide hope for recovery. In the so-called lethal dose ranges with X- and γ-radiation, the injury is primarily to the haematopoietic system. At doses of approximately 50-100 rad, symptomatology is mild, and below 50 rad, symptoms are virtually absent even though there is some injury, particularly to haematopoietic tissues.

Prognostic value of the leukocyte count

205. At Operation Crossroads depression in leukocyte count correlated with distance from the bomb.[377] At Operation Greenhouse[378] there were four groups of dogs with mortalities of 100 per cent, 100 per cent, 80 per cent, and 10 per cent. In the group given 800 rad, the total leukocyte count fell to zero; all the animals were dead by day 10. Group 2, given about 500 rad, had a smaller fall in leukocycte count. Group 3, with 80 per cent mortality, received $\sim$ 400 rad, and group 4, given 200 rad with 10 per cent mortality, had a smaller decrease in leukocyte count.

206. Extrapolation to man directly is difficult, because the rate of change in leukocytes in man as shown in the Marshallese and various clinical experiences is much slower.[44, 372, 373] Jacobs, *et al.*,[379] re-analysed the leukocyte counts done in Hiroshima and Nagasaki after the explosion; despite the limitations of the data depression in total leukocyte count at different times correlates well with survival. The treatment of the acute radiation syndrome in man is discussed in section VIII.

ANALYSIS OF PAST ACCIDENTS

207. There have been at least eight major radiation accidents:

Los Alamos I	21 Aug. 1945	Criticality (experimental assembly)
Los Alamos II	21 May 1946	Criticality (experimental assembly)
Argonne	2 June 1952	Criticality (reactor)
USSR	?	Criticality (reactor)
Oak Ridge	16 June 1958	Criticality (processing)
Yugoslavia	15 Oct. 1958	Criticality (reactor)
Los Alamos III	30 Dec. 1958	Criticality (processing)
Lockport, New York	8 Mar. 1960	Radar X-radiation

The Idaho SL-1 reactor accident on 3 January 1961 is not discussed because the three fatalities were caused by blast from the nuclear excursion. The immediate dose calculations in the above accidents were of necessity very uncertain and probably not too meaningful. In the study of reconstituted accidents more accurate dosimetry has been obtained particularly from the point of view of non-uniformity of the exposure. Even here, there are important practical difficulties in assessing exposure when with the neutron component significant dosimetry is further complicated by considerations of distribution and RBE. In the present state of knowledge the doses presented should be considered as approximate orders of magnitude rather than exact measurements.

First and Second Los Alamos accidents

208. The first nuclear accident occurred at Los Alamos on 21 August 1945 and the second on 21 May 1946.[380, 381] The accidents occurred during experiments with critical assemblies of a fissile core surrounded by neutron reflector material. In the first accident the reflector was tungsten carbide; in the second beryllium. In both accidents the man doing the experiment was touching the reflector at the time of the reaction. Exposure of these two fatally injured operators was non-uniform; hands and arms received the largest dose, abdomen and chest somewhat less, and head and legs the smallest. All others were presumed uniformly exposed, except for case 4, whose body from mid-chest down was partly shielded at the time of the second accident. The head, upper chest, and left arm of this patient received the highest dose.

209. Dose calculations are uncertain and probably not particularly meaningful; e.g., if 5 per cent of neutrons had an energy exceeding 5 mev the dose would have been increased by 45 per cent; the choice of RBE was critical. With these reservations, five cases received an estimated dose of less than 100 rem of soft radiation and less than 10 r of penetrating radiation. Case 6 (dose unavailable) had no symptoms of any kind after exposure. The only laboratory findings of significance were an initial rise in granulocyte count and a lymphopenia of less than 1,000 cells/mm³ from day 40. The lymphocyte count remained low for two years. In 1959 the patient retired, aged 68, with no signs of injury and a normal blood count.

210. Case 1, received an estimated average body dose of 840 rem of soft radiation and almost 500 r of γ-rays. His hands and arms, especially the right, received many thousand r. His hands and arms were tensely swollen 30 minutes after the accident, and soon thereafter he began to vomit and retch almost continuously for ~ 24 hours. His temperature rose gradually reaching 41.7° C rectally on the day of death 24 days after exposure. His pulse increased abruptly on day 6 and remained high with an episode of acute paroxysmal tachycardia on day 15 following a blood transfusion. Cardiac symptoms, abnormal electro-cardiograms, low blood pressure, enlargement of heart with friction rub were related at the time to his known congenital defect (Wolfe-Parkinson-White syndrome). The patient had extreme necrosis of the tissues of hands and arms, and extensive third-degree burns of the body extending to the precardial region. The underlying heart undoubtedly received a high dose. At autopsy, the heart showed extreme fibrinous pericarditis with no microscopic evidence of damage to cardiac muscle. At the time this response was related to his known cardiac defect but in retrospect this probably represented radiation injury to the heart. Several isolated cases of pericardial effusion and constrictive pericarditis have been reported in patients given radiation therapy to the chest.[380-382]

211. The second fatality received an estimated average dose to his torso of about 2,000 r of soft and 150 r of penetrating radiation, with considerably greater exposure of his hands. The patient vomited on his way to the hospital. Both hands were swollen within an hour after the accident. His temperature, pulse, and respiration rose abruptly on day 6 and increased until death on day 9. His hospital course was characterized by severe intestinal symptoms, with almost complete paralytic ileus and extreme abdominal distention. Continuous gastric suction was required. He had no diarrhoea. Both arms, packed in ice, were in effect amputated. The most striking features of the patient's blood count were the initial high white count, the complete disappearance of all lymphocytes from the peripheral blood by day 2, and the abrupt fall of the total white count on day 6. These findings are similar to those in the first case. At autopsy, among other findings, there was severe damage to intestines.

212. Case 4, a 34-year-old man, received an average estimated dose to the entire body of 400 r of soft and 40 r of penetrating radiation. His head and upper chest are believed to have received a larger dose than the rest of his body. On day 5 he developed fever, along with lethargy and somnolence for no clear cause at the time. The fever may possibly have been associated with damage to the CNS like that in the Lockport accident. His lymphocyte count fell to below 1,000 cells/mm³ by the sixth hour after exposure.

213. This patient had severe fatigue 15 days after exposure on discharge from hospital, and at first had 16 hours bed rest per day, improved gradually and was back to normal in 10 weeks. Although completely aspermic for several years after exposure, he recovered completely, lived an active normal life, and became the father of an additional two normal children. The patient had mild hypertension at the time of exposure. In the next several years his blood pressure rose but was treated successfully with reserpine. In 1955, aged 43, the patient had a severe posterio-lateral cardiac infarction. (It is difficult to relate this to his radiation exposure. The patient's coronary vessel probably received a relatively small dose. Patient's father died of a heart attack in his early 40's.) Within a year after the heart attack a diagnosis of acute myxedema was made. From clinical findings and laboratory tests this condition had undoubtedly been present for several years, and contributed to the coronary thrombosis. Whether radiation exposure to the neck was responsible for the thyroid damage is uncertain.

Argonne accident

214. A reactor criticality accident occurred at Argonne Laboratory on 2 June 1952. Four persons were exposed to a mixed field of radiation, γ-neutron dose ratio ~ 10 : 1. Clinical and dosage details were reported.[374, 385] There were no deaths. The calculated doses range from 10.8-159 rad.

USSR accident

215. One reactor accident has been reported in the USSR causing "short general external exposure" of two people to neutrons and γ-rays.[386] Doses of 300 r and 450 r were assigned but no γ-neutron ratio was given. Since fuller data are not available these dosages are uncertain.

Oak Ridge accident

216. A criticality accident occurred on 16 June 1958 in the Y-12 plant at Oak Ridge. Enriched uranium component was drained inadvertently into a waste drum[387] causing a chain reaction. Eight persons received significant TBR; five were exposed to 236-365 rad including a neutron component of slightly more than one quarter. There was no associated trauma, the whole body was fairly uniformly exposed, and the radiation dose was rather accurately determined. Three persons received between 20-70 rad. In the five higher-dose patients the haematological values emphasized that TBR in man causes clearly defined symptoms. Blood and bone-marrow changes appeared over several weeks in well-defined stages: early and persistent lymphopenia and variable transient leukocytosis; mild leukopenia during the first ten days; abortive rise in white cells, and some increased erythropoeisis at about two weeks; severe depression of neutrophiles and platelets greatest at weeks 4-6; rapid recovery of platelets and neutrophiles; and anaemia maximal at week 7, with recovery accompanied by reticulocytosis. This sequence is uniform in different persons and similar after radiation over a wide range of dose. The patients showed the greatest depression of leukocytes and platelets between days 24-37. All five patients recovered from the early post-radiation effects and have now no visible damage.[388-390]

Yugoslavian accident

217. On 15 October 1958, the zero-energy reactor at the Boris Kidrich Nuclear Science Institute, Vinca, Yugoslavia, became super-critical, injuring eight people. The reactor was constructed with natural uranium rods suspended in a large tank that could be filled to various depths with heavy water. Six received significant doses of neutrons and γ-rays.[391-393] Following a brief hospitalization in Belgrade, the six patients were transferred to the Fondation Curie in Paris under the care of Dr. H. Jammet. The early dose estimates described by Jammet, *et al.*,[391] on the basis of local information from Vinca were 1,000-1,200 rem for the highest exposure and 300-500 rem for the lowest, placing five of the six in a range considered to be above the LD_{50}. All six had the acute TBR syndrome: nausea, vomiting, anorexia, asthenia beginning after the first hour and lasting 2-3 days; thereafter their general condition was relatively good, in contrast with the progressive evolution of haematological and cutaneous changes: fall in lymphocytes, then granulocytes, thrombocytes, and erythrocytes. Towards the end of the fourth week and during the following weeks there was a worsening in general condition with fever and clinical evidence of haemorrhagic disease. The individual originally believed to have received the highest dose was given foetal bone-marrow on 11 November, and the four patients having the next highest exposure were given homologous bone-marrow from adult donors at various times between 11 and 20 November. The man who received the foetal bone-marrow died as a result of radiation with no immunological reaction. Extensive clinical studies have been detailed.[391, 394]

218. Comparison of the haematological and other clinical effects of the four Yugoslavian accident victims who survived after bone-marrow infusion with the five men exposed to 236-365 rad at the Y-12 plant, leads to the following conclusions:[395] (*a*) the effects of injury suggest a somewhat higher dose in the Yugoslavian than in the Y-12 accident; (*b*) haematological patterns in the two groups of patients are remarkably similar, the Yugoslavs showing generally more severe injury; (*c*) haematological recovery occurred at about the same time after exposure in the two groups of patients; this and the fact that the bone-marrow was given just at this time to the Yugoslavs, makes evaluation of its therapeutic effect difficult.

219. An international group under the auspices of the International Atomic Energy Agency studied the dosimetry of the Vinca accident in a reconstitution of the accident.[396] The recalculated doses, still under discussion, were between $\sim$ 320 to 440 rad in the five treated.

220. In the follow-up[397] on the Yugoslavs the patients continued to have slight reticulocytosis, 0.5-1.7 per cent, for several months. Electro-encephalograms showed slight abnormalities characterized by low voltage and instability; the tracings lacked the usual individuality of patterns expected in five patients and all looked remarkably alike. At 2 years, basal metabolic rates are normal. Lens opacities developed, decreased, and are no longer present. The female patient has had persistent menstrual difficulties with excessive bleeding. In the male patients sperm counts are still very much depressed 2 years later. The peripheral blood shows light lymphopenia. The patients complain of fatigue and neuro-circulatory instability—evaluation of both symptoms is difficult.

Third Los Alamos accident

221. A third radiation accident at Los Alamos on 30 December 1958 of a critical excursion, during a routine plutonium salvage operation caused massive overexposure of one man.[398, 399] The average TBR exceeded 3,000 rad; the dose to the anterior chest was $\sim$ 12,000 rad, that to the front of the head $\sim$ 10,000 rad. The victim went into a state of profound shock within minutes. The outstanding finding was right-sided heart failure with resulting renal ischemia and nitrogen retention. The patient died 35 hours after injury.

222. Less than 30 seconds after the accident the patient was ataxic and disoriented, needing support to remain erect. He complained of "burning up" and appeared flushed at this early time. Within 5 minutes he was virtually unconscious and was admitted to hospital 25 minutes after the accident. At this time, he was semi-conscious but disoriented and clearly in general shock with depression of blood pressure. Vigorous efforts to return the patient's blood pressure to a satisfactory level and to maintain it were made by giving pressor amines in heroic doses. Five hours after the accident the patient appeared to be in a satisfactory condition, he was relatively comfortable and mainly at ease. By this time it was obvious from dosimetric studies that his radiation exposure had been supra-lethal. His leukocyte count rose steadily to a peak of 28,000/mm^3 but lymphocytes had virtually disappeared from the circulating blood in < 6 hours. He had marked oliguria, voiding a total of < 600 ml of urine over 22 hours with a total fluid intake of 14 litres in the same period. More than 30 hours after the accident the patient abruptly became worse, developed increasing abdominal cramps, became more cyanotic, and despite oxygen, lapsed into coma. His heart, that had received nearly 12,000 rad, stopped 34¾ hours after the accident.

223. At autopsy, the picture was that of acute right heart failure caused by right-side myocarditis complicated by excessive fluid intake. The most striking histological findings were in heart muscle: severe oedema and beginning degeneration of muscle fibre with cellular

exudate between fibres showing the presence of true interstitial myocarditis. In short, this could be termed a cardiac death. It should not be regarded as representative of all kinds of radiation injury to the heart, as in a slightly different position he could have received most of his exposure to the left side of the heart. In other accidents, other parts of the body might receive the greatest dose and other mechanisms of quick radiation death are possible.

Lockport accident

224. On 8 March 1960 nine technicians were exposed to pulsed X-radiation from an unshielded klystron tube at Lockport, New York.[400] Two of the exposed were seriously injured, five others less seriously damaged, while two remained asymptomatic during observation. Shielding of greater or lesser areas of the body in men working closest to the tube was critically important in determining the outcome. To date, satisfactory integrated dose estimates of the entire body in any of the men are not available. Clinical exposure appeared to have been greatest over the right side of the head, right arm, and axilla of A, the man most seriously injured. Exposures of the nine varied with their individual activities. The best present estimates are that doses to A could have been as high as 1,200-1,500 r over certain parts of the body. Since even a few inches back and forth would result in major changes in exposure there is considerable uncertainty. B's exposure is slightly less than A's due to his smaller stature and slightly different position. C's position on the floor limited his exposure largely to head and upper chest. The next four, D, E, F, and G, were exposed over greater portions of their bodies for 60-120 minutes at 6 inches at 4-6 feet, and H and J were minimally exposed for ~ 120 minutes at 8 feet. Nevertheless, because of the pulsed nature of the radiation, the actual exposure time was only 7.2 seconds/hr.

225. A was exposed from head down to mid-thigh, B from head to pubic symphysis. C was exposed largely above the shoulder level. Throughout exposure the men were unaware that they were being irradiated. Nevertheless, symptoms appeared during exposure, severe enough to make B and C seek medical aid on their way home. Headache was the first complaint, beginning during exposure and described as severe, deep within the centre of the head, and unlike any headache ever experienced before; even walking around caused intolerable pain. The headache persisted for several hours after exposure. Nausea and vomiting began in the most seriously injured shortly after the beginning of the headaches. Vomiting persisted throughout the first day; nausea subsided very slowly. The most seriously injured man continued to have morning nausea for a week after exposure and sporadically for several weeks. Of all the symptoms, nausea and fatigue were the most persistent. With the exception of F all the exposed developed conjunctival reddening. In A conjunctivitis and acute eye pain was followed by the development of haemorrhage and exudates in both eyes, with severe interference of vision in the right eye due to macular involvement. His eye difficulty has continued to be present and has changed only in that the acute symptoms have subsided. Vision in the right eye did not improve and that in the left eye remained stationary. Parotid swelling was the most severe in A. Both A and B had temporomandibular tenseness and pain on moving the jaw. Treatment was conservative throughout the patients' hospital course. In A an initial wave of erythema was present during the first 7 days after exposure, a second wave between days 13-19, and a third wave, also seen in B, D and C, between days 24-29. These waves are shown in figure 5 that also

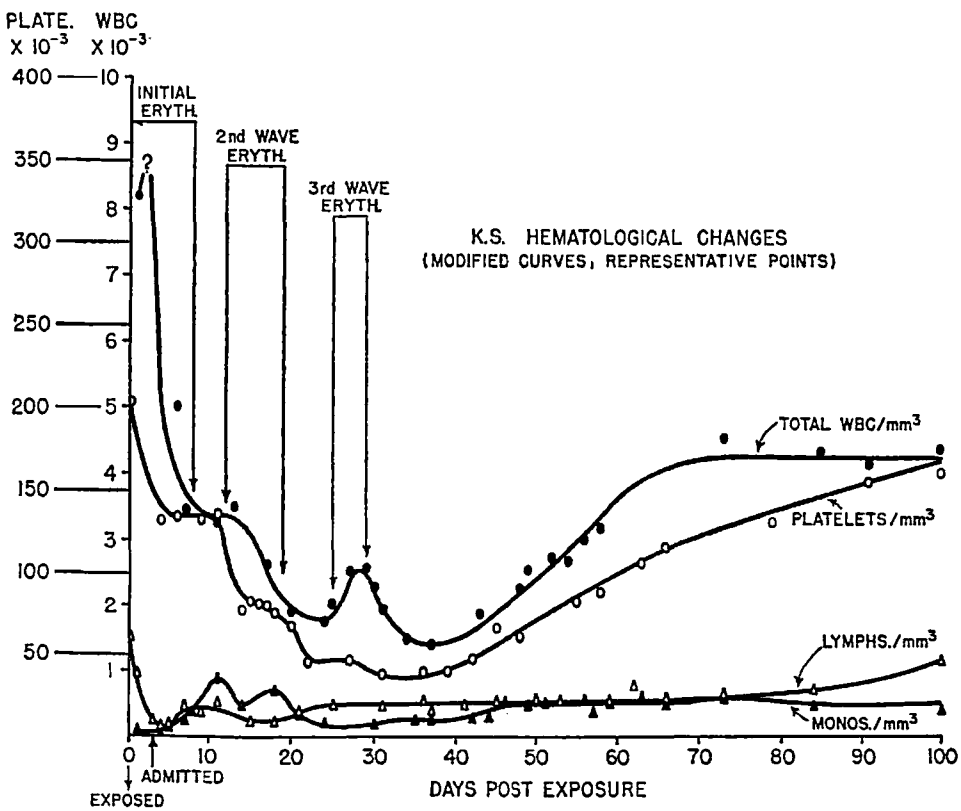


Figure 5. Graph showing the periods of erythema and levels of leucocytes, platelets, lymphocytes, and monocytes in K. S. (A) injured in the Lockport accident[400]

shows changes in the total white count, platelets, lymphocytes, and monocytes.

226. A's total leukocyte count fell from the time of admission until approximately the sixth post-exposure week. At that time minimal counts of ~ 1,400/mm³ were seen. Monocytosis was a prominent feature of the peripheral blood during acute stomatitis present days 7-15. Lymphopenia was severe in this patient and was an important indication that A had sustained major radiation injury. Platelets reached minimal level of 35,000-40,000/mm³ duing the fifth post-exposure week. There was no evidence of abnormal bleeding, with the exception of a few petechiae on the palate and one foot during the fourth post-exposure week.

227. At day 38, A became febrile, somnolent and mentally depressed; these symptoms increased, so that at day 44 he was moderately ataxic with transient paresthesias of the right arm and left hand, and mild transient reflex changes. These neurological symptoms varied over 12 days. Electro-encephalograms showed multiple, large and small focal abnormalities. The records improved gradually, until a normal record was first obtained on 12 September 1960. Mild fatigue with improvement in over-all symptoms continued at day 210.

228. In A there was complete aspermia by the sixth month, with complete return to better than normal values at the end of one year. Sperm samples of the others showed at most only the minimal depression during the acute phase.

229. Follow-up examinations on A, B and D at one year showed all observations on B were normal, progressive deafness in D—apparently traumatic—but no other significant findings, continuation of the eye symptoms in A, complete correction of aspermia, secondary loss of hair over the right temple and eyebrow, and mild asthenia.

Assessment of injury

230. At present, the severity of illness following radiation damage can only be assessed by comparing the response of the patient with that of others previously exposed under similar conditions, who have survived or have been fatally injured. For this reason, detailed information concerning radiation dose, exposure conditions, and the clinical course of each patient injured by radiation should be available to all likely to be concerned with these conditions. There is need for further biological indicators of radiation damage, other than the existing methods, of which the early rate of fall and ultimate depression of lymphocytes appears the most sensitive. A number of patients from reactor accidents showed a high urine level of amino acids[380,401] and it was hoped that this might serve as an index of tissue breakdown.[381] The metabolism and re-utilization of amino acids by the body is so rapid that their release from proteins being quickly broken down after irradiation can be shown only by the use of special research techniques[402,403] not yet applicable to clinical diagnosis.

231. Creatine excretion in the urine is a good indicator of muscle break-down. Patients with muscular dystrophy excrete large amounts of creatine. It is possible that the weakness of irradiated patients might also be reflected in excretion of excess creatine. Radiation-induced creatinuria has been studied.[404–408] There is a correlation between large integral doses of radiation to muscle and creatinuria. Since creatine estimations are simple and accurate this would appear to be a promising line for further study. Similarly the excretion of beta amino isobutyric acid is an index of the break-down of cell nuclei but the analytical method is less simple.

V. Late effects of irradiation in man, including carcinogenesis

Life-shortening

Effect of long-term radiation on life-span in man

232. The problem of extrapolation of animal life-shortening data to man is difficult because of the lack of data on life-shortening for large animals with life-spans intermediate between man and rodents. TBR of rodents shortens life-span; this effect has not been shown unequivocally in man. Three studies have compared mortality of radiologists with other physicians or with the general male population.

233. Dublin and Spiegelman[409] investigated 2,046 deaths of United States medical specialists age 35-74, 1938-1942. Mortality in all specialist groups was less than that for all physicians, but mortality of radiologists and dermatologists was 16 per cent and 25 per cent respectively above that of all specialists combined. From their data, the mortality of radiologists and dermatologists, combined or separated, differs from that of specialists not using radiation routinely by an amount bordering on statistical significance. Dublin and Spiegelman did not calculate occupational risk in differences in life expectation, but estimated from their data and life tables for physicians that the difference between radiologists and dermatologists and other specialists is 1-3 years.

234. Warren[410] used 82,441 obituaries of physicians reported 1930-1954 in *Journal of the American Medical Association* to compare the mean age at death of United States radiologists (60.5 years) to that of other physicians not exposed occupationally to radiations (65.7 years); he concluded that radiologists died 5.2 years earlier.

235. Court Brown and Doll[411,412] compared the mortality of British radiologists 1897-1957 with those of all physicians and of men of equivalent social class (defined by the Registrar-General). Correcting for age distribution and various biases in vital statistics, they concluded that British radiologists show no evidence of life-shortening. They attribute this to early adoption of effective safety measures.

236. These studies suffer from uncertainties and limitations that bedevil evaluations in man. Dublin and Spiegelman did not intend an analysis to apply to mortality in radiologists specifically. For this purpose their work suffers from small sample size. Warren's data were not corrected for age distribution of groups at risk. Seltzer and Sartwell[413] found "the difference between radiologists and other physicians as to average age at death can be accounted for simply by differences in age composition between the two groups". The differences found by Dublin and Spiegelman included consideration of age distributions. These data were analysed in annex G of the 1958 report.[414]

237. Warren has compared the survival of radiologists averaged over five-year periods with survival of the general population.[415] The latest report giving survival of the general population and radiologists (Warren, personal communication) suggests that the slope of the

radiologists group is approaching that of the general population, i.e., the survival of radiologists has increased from 1930 to 1957 at a more rapid rate than that of the general population. This suggests in retrospect that the evidence of life-shortening in American radiologists should not be dismissed out of hand. The fact that no life-shortening was found among radiologists in the United Kingdom probably reflects not only differences in safety procedures, but also in practice. In the United Kingdom, most radiology is done in hospitals, and therefore many examinations are made by radiographers rather than radiologists themselves. In the United States the private practice of radiology is much more extensive, and the radiologist tends to do this himself. Fluoroscopy is much more extensively practised in the United States than in the United Kingdom and probably the number of X-ray films used in radiographic examinations is likewise greater.

238. A lower limit can be set for life-shortening of United States radiologists by considering leukaemia incidence only. A statistically significant excess of leukaemia among those radiologists has persisted for years, decreasing recently.[416–419] This is equivalent to a life-shortening of 3-12 months, depending on assumptions.

239. In conclusion, occupational exposure of United States radiologists increased mortality in past decades, but the radiation doses and distribution are unknown. The exposures must have been heterogeneous with hands, arms, and upper body receiving the most. A life-shortening effect in man after substantial TBR is to be expected from animal data. Despite uncertainties, data on radiologists and other medical specialists represent one of the best available means for studying late effects of radiation in man.

Carcinogenesis in man

240. It was early known that skin cancers were common in radiologists and dermatology patients. Later, radiation-induced tumours were seen in haematopoietic tissue, bone and thyroid. Increased leukaemia has been reported in United States radiologists, in Japanese atomic bomb survivors, in children irradiated in infancy for benign conditions (usually thymic enlargement) and in ankylosing spondylitis patients. Some retrospective studies have reported that a greater proportion of children with leukaemia and other malignancies were exposed to X-ray *in utero* than selected controls without malignant disease.

Leukaemogenesis

Situations in which a relationship between radiation and leukaemia has been established

241. Single doses of external radiation to whole body at ~ 100 rad or more and irradiation of an appreciable portion of the bone marrow with ~ 500 rad or more, slightly increase the incidence of leukaemia in man. There is no evidence of an increase in the first fifteen months after exposure. In the Hiroshima data, limited to 2 km from hypocentre, the incidence increased to a maximum between years 4-7, declined thereafter but was still above the expected incidence in 1959. The Japanese data[420–426] shows that with short-term exposures to doses greater than ~ 100 rad, the incidence of leukaemia integrated over fifteen years increases with dose. The exact quantitative relationship between dose and incidence of leukaemia is unknown. Assuming proportionality, the increase over the natural incidence, averaged over the fifteen-year period, is about 100 cases per 10^6 persons per 100 rad for each year at risk. This estimate is probably too low in children and too high in adults. Additional data are needed for selected age groups.

242. Large amounts of external radiation, protracted over a long time given to the entire body or a large segment of bone marrow, are leukaemogenic in man. Nevertheless, present uncertainties about the influence of dose rate, fractionation and total dose make it impossible to estimate the probability of leukaemia other than under short-term exposures to high doses. Moreover, long-term exposure is probably less leukaemogenic than short-term exposure for the same total dose.

243. I^{131} given in high doses, e.g., therapy of carcinoma of the thyroid has in some cases caused leukaemia.[455]

244. Cases of leukaemia in which a relationship to radiation exposure was shown[427,426] indicate that with few exceptions the leukaemia was either acute or chronic granulocytic. In the United States and United Kingdom, the commonest chronic leukaemia is lymphocytic; its increasing incidence has not been correlated with irradiation.

Situations in which a relationship between radiation and leukaemia has been suspected but not established

245. It is not known whether short-term exposure to doses of less than ~ 100 rad given to the entire body or a portion is leukaemogenic. In particular there is a question about an increased incidence of leukaemia among children exposed *in utero,* during diagnostic pelvimetry of the mother.[428–437]

246. There are no documented cases of leukaemia as a late effect of radio-isotopes such as $Sr^{89,90}$ and radium at any body burden. With thorium while there are nine recorded cases, the relationship between thorium and leukaemia is hard to gauge because of scarce clinical and dosimetric information.

247. Since leukaemia has been seen after irradiation in Japanese, British and sporadically in other nationalities, there is no reason to believe there is any outstanding racial sensitivity to radiogenic leukaemia.

Leukaemia in the Japanese survivors of the atom bomb

248. The increased leukaemia incidence in Japanese, exposed to nuclear explosions in Hiroshima and Nagasaki, is inversely related to the distance from the hypocentre. Dose-estimates are uncertain even after the results of recent tests which simulated an actual nuclear explosion with extensive shielding. Heyssel *et al.*,[425] summarizes studies by the Atomic Bomb Casualty Commission since 1951 on the increased leukaemia in the Hiroshima survivors and relate incidence to calculated dose from γ-rays and neutrons combined in the open air at various distances from the hypocentre. In these calculations, they used an RBE of 1 for neutrons. They estimated that 60 per cent were indoors at the time of the explosion, reducing the air dose by 30-70 per cent. With leukaemia cases diagnosed up to 1957 they postulated a linear relationship between incidence and calculated open-air dose of 177 rad or more. The point, representing the leukaemia incidence of 3,605 persons receiving a mean estimated air dose of 77 rad, falls almost on the line drawn through points at higher doses. No cases of leukaemia were seen in 3,512 and 1,305 persons receiving an average estimated air dose of 34 and 19 rad respectively.

249. These authors also show that the latent period between exposure and development of leukaemia depends on dose. They report that nearly all cases in the exposed and non-exposed persons were acute leukaemia or chronic granulocytic leukaemia. Among the Japanese, chronic lymphocytic leukaemia is very rare; a very few cases were found in exposed and unexposed groups and their significance, if any, is hard to evaluate. Heyssel *et al.*, estimate that radiation increased the incidence of leukaemia rather than accelerated the appearance of spontaneous cases.

250. For several reasons, individual dose values can be appreciably in error. At least 200 survived where the mean open-air dose was calculated to be 2,620 rad.[438] Allowing for shielding and assuming that they were at the edge of zone, the doses received, by these calculations, must have been > 100 per cent lethal. In the low-dose region, the accuracy of the calculated doses may be seriously questioned since many victims in the 2,000-2,499 metre zone, where the calculated average dose was less than 10 rad, had symptoms (epilation, oropharyngeal lesions, and purpura)[427] suggestive of severe radiation dosage. The calculated dose is far below that producing radiation sickness after TBR and it may be that the quoted doses are a serious underestimate because of the contribution of induced radio-activity. On the other hand, since victims even farther away were also said to have similar symptoms it is the consensus of opinion of the observers[438] who interviewed these patients that their symptoms were complicated by malnutrition and factors other than radiation exposure.

251. These studies by Heyssel *et al.*,[425] suggest a straight-line relationship between doses above ~ 100 rad and the incidence of leukaemia among bombed Japanese. Considering the large variation inherent in incidence and dose estimations, the data could also have been represented by a straight line with a different slope, or by a curved line.[428] Although the data are not enough to say whether the relationship is linear over the entire dose range, they do allow a conservative estimate of the probable incidence of leukaemia in a population of all ages over the first 10-15 years after a single exposure to high doses. A reasonable estimate might be an average of 100 additional cases per 10^6 persons per 100 rad for each year at risk during that period.

252. It is not possible to demonstrate an age-incidence relationship because of the small number of cases of leukaemia in Japan although there is some indication of a higher rate among bombed children than bombed adults. Hence, prediction of incidence in selected age groups or calculation of the probability of leukaemia among the individuals exposed may be speculative.

253. There are some data which suggest an increase in leukaemia incidence in Hiroshima among persons who were not directly exposed to the atomic explosion but who entered the area very soon afterwards. These data should not be overlooked, although there is great difficulty, at the present time, in making any accurate calculation of the dose received from the induced radio-activity.[439]

Leukaemia in ankylosing spondylitis

254. Court Brown and Doll[412,440] in the United Kingdom reviewed 13,352 patients, presumed to have ankylosing spondylitis given X-ray treatment to their spines, from 1 January 1953 to 13 December 1954. They reviewed death certificates and clinical and pathological data of all suspected of dying of leukaemia or aplastic anaemia; they calculated from dose records mean dose to spinal marrow and whole-body integral dose of a large sample. There were thirty-two proved and five probable cases of leukaemia and four cases of aplastic anaemia; the number expected from national vital statistics was 2.9 for leukaemia and 0.3 for aplastic anaemia, a significant increase in mortality from these causes.

255. They estimated the annual incidence of leukaemia for the general male population not therapeutically irradiated to be $50/10^6$. The annual incidence in man given a mean dose of over 1,750 rad to only spinal marrow was 1,600-1,700/10^6. For all patients regardless of site of exposure, the annual incidence was 7,200/10^6, with a mean spinal marrow dose of over 2,250 rad.

256. Classifying cases by mean spinal marrow and integral dose shows a correlation between dose and leukaemia incidence. The shape of the incidence-*vs*-dose curve depends upon whether mean spinal marrow or integral dose is used, and whether the cases given extra-spinal radiation are excluded. However, whatever the method of analysis, the relatively small number of cases of leukaemia and the dose parameter used make it impossible to decide whether the dose response relationship is or is not linear (figure 6).

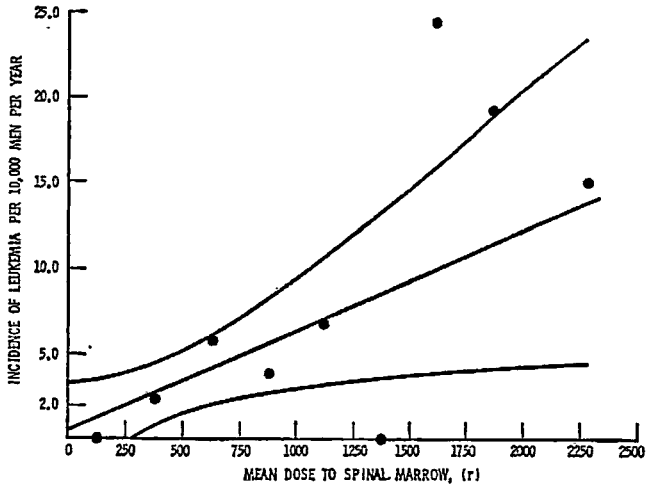


Figure 6. Incidence of leukaemia in relation to mean spinal marrow dose of therapeutic irradiation. The regression line was obtained after weighting the rates according to their reliability and is given by $Y = 0.00586X + 0.380$; the 95 per cent probability limits of the value of Y for each value of X are shown by the curved lines. Redrawn from Court Brown and Doll[786]

257. The single point below 500 rad is based on two cases of lymphatic leukaemia, one chronic that developed after a mean marrow dose of 471 rad, and the other in which the spine received 113 rad but extra spinal regions received additional larger doses.

258. There were ten cases of leukaemia within five years after a single course of therapy. Of the thirty-seven leukaemias, including those with multiple courses over years and those with a single course in a month, the diagnosis was made in thirty-five within five years of the last treatment. Of the fifty leukaemias in spondylitic patients after X-rays, including those reported by Court Brown and Doll, thirty-eight were acute and only eight were chronic—with only one of the latter being chronic lymphatic leukaemia. Data in the remainder were insufficient to establish clinical type.

259. Some leukaemia patients showed a sequence of pathological changes: a persistent damaged or aplastic marrow was a precursor rather than a consequence of leukaemia; other cases of aplastic anaemia were seen after the same dose range.

260. In attempting to extrapolate the incidence data to low doses, use of the incidence of spontaneous leukaemia in the general population as a control is questionable since there appears to be a strong hereditary factor in ankylosing spondylitis.[441] This is underscored by the report of Abbott and Lea[442] showing an association between untreated rheumatism and leukaemia. The only available control group of 399 untreated spondylitic patients is too small to be useful.

261. Because of limited data in the lower dose range and lack of an adequate control group, this study does not provide evidence on leukaemia incidence after doses below 500 rad.

262. Leukaemia is a rare disease; cases after radiation represent only a small portion of its incidence. Nevertheless, in a single case where the onset of leukaemia associated with radiation exposure occurs within an appropriate interval after a known single exposure to over 100 rad, the probability that the disease is due to radiation is high. It is possible to estimate this probability by considering the normal incidence in the population and the probable increase in the incidence of leukaemia after a single high dose.[443,444] This probability will increase to a maximum around the fourth-seventh year after exposure and thereafter decrease perhaps ultimately diminishing to the level of the incidence expected in the general population.

Leukaemia in children (table VI)

263. Some investigators found an increased incidence of leukaemia in children given radiation to the thymus; others have not. There is no satisfactory control group for a conclusive statistical evaluation. Simpson, Hempelmann, and Fuller,[445] Simpson and Hempelmann[446] and Simpson[447] found in 2,393 such cases in upstate New York—87 per cent traced[438]—twenty-one cases of malignancy instead of 3.6 expected, and nine confirmed and one unconfirmed leukaemia deaths instead of one expected. Most other malignancies were thyroid carcinomas. There was no significant difference between expected and observed incidence of cancer or leukaemia in 2,722 untreated siblings of children in this study.

264. Exposures measured in air were known or calculated from radiation factors for all but 299 children. Four of the known leukaemias were in 1,050 children with a cumulative exposure of less than 200 r, 5 were in 1,025 children given 200-600 r. All other malignant neoplasias were among children given 200 r or more. Average survival between irradiation and death from leukaemia was 5.3 years.

265. Since the state of the thymus gland in the sibling group is unknown and is, in general, normal in children of the general population, this study does not differentiate between the association of leukaemia and (*a*) X-ray exposure, or (*b*) thymic enlargement. Because it is impractical if not impossible to get an accurate control group, (i.e., children with thymic enlargement at birth not treated with X-rays), children irradiated for other reasons must be studied.

266. Conti *et al.*[448,449] studied in 1948 1,564 children treated with X-rays in Pittsburgh—96 per cent had thymus glands of normal size at birth. The radiation factors were uniform; 88 per cent were given 75-300 r (usually 150 r) to the manubrium; the remainder were restudied 11-18 years after therapy. Four cases of malignant disease, including one of leukaemia, were expected in this group; none was found. There was no significant difference between the number of expected and observed cases of cancer and leukaemia in untreated siblings.

267. The failure to find the four expected cases of neoplasia is not significant, since one-tenth of the group was not located. One can conclude, nevertheless, that there was no evidence of an increased cancer rate in treated children or of a greatly increased leukaemia frequency.

268. To avoid variables due to considering children given X-ray therapy to the mediastimal region only, a study was made of 6,473 children in Rochester, New York, treated with X-rays for various benign conditions in the past twenty-five years.[434] The difference between the eight leukaemia cases observed and the two expected is significant. There were five leukaemia deaths in 2,750 children treated for thymic enlargement; two were in seventy-five children treated for pertussis and one in 1,073 children given X-rays to the head and neck region, mainly for lymphoid hyperplasia of the nasopharynx. There were no leukaemia deaths in 2,460 children treated with superficial X-rays for benign skin lesions.

269. Similar surveys of children treated for thymic enlargement and other benign lesions are now being made in the United States. Latourette and Hodges[450] reported the incidence of neoplasia in 861 children treated for thymic enlargement, 1932 to 1951. Most children were treated with 200 r or less, through a large 10 x 10 cm port. The two cases of lymphoma (one being leukaemia) were more than expected, but not significantly so. One child had a carcinoma of the thyroid and others had various benign tumours. Snegireft[451] found two thyroid tumours in 148 children followed out of 1,131 children treated for thymic enlargement; Moloney, in a discussion of Simpson's work[447] mentions seven cases of thyroid neoplasias including two malignancies in 125 of 700 children so treated.

270. Saenger *et al*[452] reported on 1,644 out of 2,230 children treated for various benign conditions. Of 675 given treatments exclusively to the chest, mainly for thymic enlargement, only 124 received more than 200 r. Eighteen cases of thyroid neoplasia (eleven diagnosed as malignant) and one case of leukaemia were found in the entire group. They also report a striking incidence of morbidity of all types of non-fatal illnesses in these children, indicative of the selected nature of the group.

271. From these studies it is clear that an association between radiation exposure and subsequent leukaemia has been established only in one group of children treated with X-rays for thymic enlargement. Further epidemiological studies are needed to establish the true incidence of leukaemia in children given thymic irradiation, and especially the relation of incidence to dose, port size, and part of body treated.

272. Numerous studies of children given radiation to the thymic region showed an increased incidence of thyroid neoplasia; in contrast, an increased leukaemia incidence was found only in one study.

273. Long-term exposure to radiation will increase slightly the incidence of leukaemia in man. This opinion is based mainly on the reported increased incidence of

leukaemia in United States radiologists and the appearance of sporadic cases following long-term exposure from diverse sources.[428] Since information on dose and other data are poorly documented, this evidence is not as good as that for short-term radiation. Data are inadequate to allow even a guess as to relationship between dose and induction of leukaemia after long-term exposure. Experiments in animals indicate that the leukaemogenic effects of cumulative doses are less in long-term than in short-term exposure.[269] Whatever the dose rate in long-term radiation, it is likely that the cumulative dose exceeds ~ 100 rad in those cases where leukaemia is believed to have been induced by radiation.

Leukaemia in radiologists

274. Among United States physicians the ratio of leukaemia deaths to total deaths between radiologists and non-radiologists was 10.3:1, 1929-1943,[416] 6.7:1, 1944 to 1948[417] and 3.6:1, 1952-1955.[418] The downward trend probably reflects better precautions by radiologists and possibly an increase of leukaemia among non-radiologists. From 1938 to 1952, there were seventeen leukaemic deaths in United States radiologists (35-74 years of age) —an average annual rate, after correction for age distribution, of $610/10^6$ compared with the population average, $121/10^6$.[419] The ratios vary, depending upon time and corrections for age distribution.

275. Braestrup[453] estimates that radiologists working with old-type X-ray equipment and few protective measures received as much as 100 rad per year; that exposure before 1930 was considerably higher; and that at present it averages considerably less than 5 rad per year. His estimates of accumulated total exposure of a radiologist using old-type X-ray machines was about 2,000 rad during forty years of practice. Lewis[419] assumes the average exposure of all radiologists to be 30 rad per year or 1,200 rad in forty years. However, these estimates and assumptions of dose must be treated with great reserve in view of the uncertainty involved in their derivation, and it also has to be recognized that the distribution of radiation dose throughout the body was far from uniform.

276. In contrast, British radiologists who began practice after 1921 have had no increase in leukaemia; the only two known cases were among those in practice before this time,[452] probably for reasons previously discussed in the differences in life-shortening.

Pelvic irradiation and leukaemia in children (table VII)

277. In an extensive retrospective survey, Stewart, Webb and Hewitt[430] interviewed mothers of: (*a*) 677 of 792 children under ten certified as having died of leukaemia in England and Wales, 1953 to 1955; and (*b*) 739 of 902 children under ten certified as dying in the same period from other cancer. They also interviewed a control group of mothers whose children were still alive and who were matched with the study children for age, sex, and locality. They found a higher frequency (13.7 per cent) of diagnostic X-ray pelvimetry in mothers of children dying from cancer than in mothers of control children (7.2 per cent). There was some correlation between size of the ratio between numbers exposed to abdominal irradiation and number of X-ray films reported to have been taken. The ratio was highest for mothers exposed during the first few months of pregnancy.

278. Four similar retrospective studies were made in different parts of the United States. Ford *et al.*[431] compared seventy-eight leukaemic children and seventy-four children having other malignancies with 306 dead controls matched for colour, age and place of death in New Orleans. Their findings are in line with observations of Stewart *et al.*[430] 26.9 and 28.4 per cent of the children with leukaemia and other forms of malignancy were irradiated *in utero*, compared with only 18.3 per cent of control children.

279. The three other studies, using other methods for selecting controls, do not show the same excess of foetal irradiation in leukaemic children. Polhemus and Koch[433] found no significant difference in the history of pre-natal irradiation in 251 diagnosed leukaemic cases in the Children's Hospital of Los Angeles, compared with the same number of matched control children with non-orthopaedic diseases on the surgical service of the same hospital. In a current study of childhood leukaemia in California, Kaplan and Moses[432] found that the number of children with leukaemia having a history of pre-natal irradiation exceeded that of the group of siblings used as controls; such an excess was not seen, however, when the leukaemic children were compared with healthy playmates. Murray *et al.*[434] found no significant difference in the history of pre-natal exposure of sixty-five children with leukaemia, sixty-five matched dead controls, and the 175 living siblings of both groups.

280. In these retrospective studies, the choice of the control group is crucial. The studies as presented do not differentiate clearly between the association of leukaemia and (*a*) the effect of the medical condition which prompted the diagnostic examination, or (*b*) the effect of X-rays.

281. In an extensive prospective study on the incidence of leukaemia after exposure to diagnostic radiation *in utero*, Court Brown, Doll and Bradford Hill[435,436] followed up 39,166 live-born children whose mothers had been subjected to abdominal or pelvic radiation during pregnancy, 1945 to 1956. Among their children nine were found to have died of leukaemia before the end of 1958, instead of the normally expected number, 10.5.

282. It is clear, therefore, that existing data on sequels to irradiation *in utero* have led to conflicting conclusions. Stewart's data are very important for evaluating somatic effects in man as they are the only data pointing to low doses of radiation being carcinogenic. Because of their serious implications, the circumstances surrounding these data must be understood. If these data are not misleading for reasons yet unknown, one would have expected double the incidence of leukaemia in the Court Brown, Doll, Bradford Hill study just cited, i.e., twenty cases instead of the nine actually found. The data of Court Brown *et al.* thus put into doubt the conclusions of Stewart *et al.* On the other hand, if the ratio from Stewart *et al.*'s[429] earlier report is used, 1.7:1 instead of 2:1, the difference between the expected figure of 17 ± 4 and 9 ± 3 is not such that a definite conclusion can be drawn.

283. The conclusion of Stewart *et al.*[430] also implies that foetal haematopoietic tissue is much more susceptible to the leukaemogenic effect of irradiation than adult tissue. As previously stated, it is not known whether short-term exposure to doses less than ~ 100 rad to the entire body or a portion is leukaemogenic. Nevertheless to answer the question raised by the data about the incidence of leukaemia among children exposed to diagnostic pelvimetry *in utero* certain theoretical estimates can be made. Such estimates for the adult suggest that 1 rad to bone-marrow produces one case of leukaemia per million

persons per year for perhaps ten years of risk. Since the normal annual incidence of leukaemia in England and Wales under age ten is ~ 37 per million and the amount of radiation received by the foetus from irradiation of the mother's abdomen is estimated to be ~ 1 rad, it follows that if this dose were to double the incidence of leukaemia in children it would have to be ~ 40 times more leukaemogenic than the same dose in the adult.

284. Although foetal tissue appears more radiosensitive than adult tissue, e.g., foetal nervous and thyroid tissues are more radio-sensitive than their corresponding adult tissues, there is no evidence that this holds for haematopoietic tissue. In fact, adult haematopoietic tissue appears to be the one adult tissue that is as radio-sensitive as embryonic tissue. From their study of patients irradiated for ankylosing spondylitis, Court Brown and Doll[412] estimated the dose to marrow that doubles the expected incidence of leukaemia to be 30-50 r. Assuming that the leukaemogenic effect of radiation is the same in foetus and adult and that 40 r is the doubling dose, and that radiation to the foetus *in utero* is as high as 4 r, one would not expect to find more than a 10 per cent increase in leukaemia in children irradiated *in utero*, i.e., in the Court Brown, Doll and Bradford Hill study the increase to be expected over the estimated 10.5 would be one case.

285. Doubts about the controls in Stewart *et al.*'s study have been discussed.[435] A probable bias is underreporting of radiation exposures by the control mothers since it is reasonable to suppose that mothers of dead children would recall the events of pregnancy more completely than mothers of children who are alive and well. In the light of the study of Court Brown *et al.*[435] the question of the effect on the foetus remains open. Clearly a further study of this problem is needed.

286. It has not been established whether internal emitters selectively deposited in bone (bone-seekers) but not delivering a uniform dose to the marrow are leukaemogenic in man. The apparent increase in leukaemia among patients with polycythemia vera treated with P^{32} is suggestive but not conclusive in the absence of an adequate control population. Leukaemia has followed giving I^{131} in high and repeated doses in patients treated for carcinoma of the thyroid. Leukaemia has also been reported after treatment of hyperthyroidism with relatively small doses of I^{131}. In the latter instance, since the number of cases is small and there are metabolic and other complicating factors in these patients, it is not possible to decide whether or not radiation alone at this dosage level is leukaemogenic in man. A recent extensive survey by Pochin[455] gives no indication that this treatment induces leukaemia. Mouse leukaemia has been induced with bone-seekers;[456] however, it is questionable whether this disease, or the conditions or irradiation and tissues irradiated, are comparable to those for man. An estimate of the probable incidence of leukaemia from deposition of Sr^{90} has been computed.[419] No confidence can be placed in such estimates because of lack of meaningful estimates of dosage to the marrow. Data obtained from external exposure studies[420–426, 440, 441] are not directly applicable in the case of non-uniformly deposited isotopes.

Malignant neoplasms in the Japanese survivors of atomic bomb

287. Harada and Ishida[457] have recently reported on the incidence of neoplasms among survivors at Hiroshima during May 1957-December 1958. These are tumour registry figures and the data, not based on a closed sample, are subject to the factors of selection that might enter into the admission of cases to this series. With this important reservation the incidence increased in inverse proportion to hypocentre distance. If the background incidence of all malignant neoplasms, i.e., 280 per 100,000 among the non-irradiated population is subtracted from the incidence of malignant neoplasms the curve is linear and parallels the incidence of leukaemia (figure 7). The incidence correlated to site was higher in all age groups (figure 8). Table VIII shows a significant difference between observed and expected cases of cancer of stomach and lung at the 1 per cent confidence level, while differences in cancer of the cervix and ovary are significant at the 5 per cent level, though the numbers are still small. These preliminary observations need extension in numbers and time so that the increased incidence of carcinoma developing only after many years of latency after irradiation can be correlated with dose and temporal occurrence.

288. Despite the numerical weakness of the data,[455] the degree of initial leucocyte count depression in the first fourteen weeks after exposure correlated with the occurrence of late effects. The data indicate that the more severe the initial exposure as indicated by clinical signs and early laboratory work, the oftener late effects appear (figure 9).

Local effects

Radiation cataract

289. Exposure of the optic lens to X-rays, γ-rays, β-particles and neutrons causes cataracts in man.

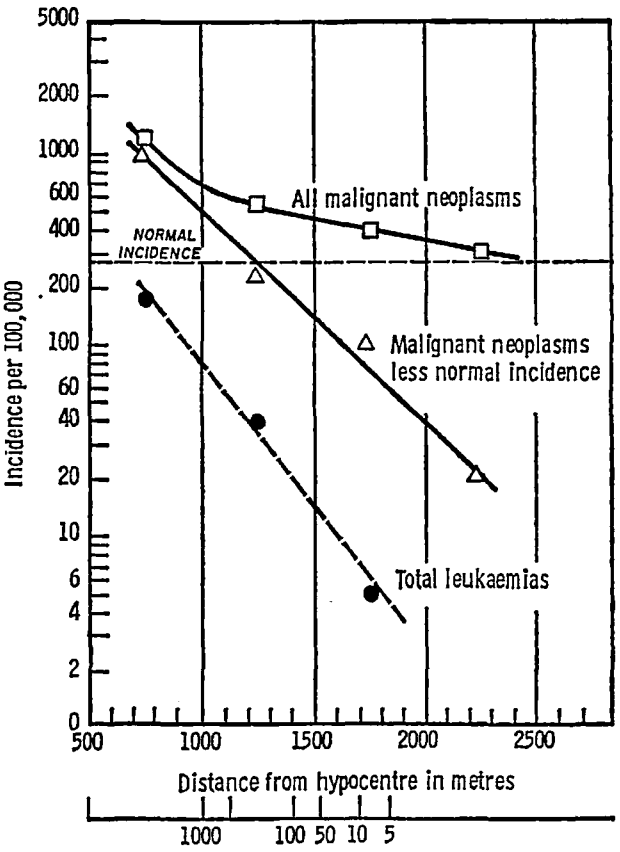


Figure 7. All malignant neoplasms (including leukaemia) among atom bomb survivors, May 1957-December 1958, and total leukaemias, 1950-1957, by distance from hypocentre per 100,000 population per year. Modified from Harada and Ishida[457]

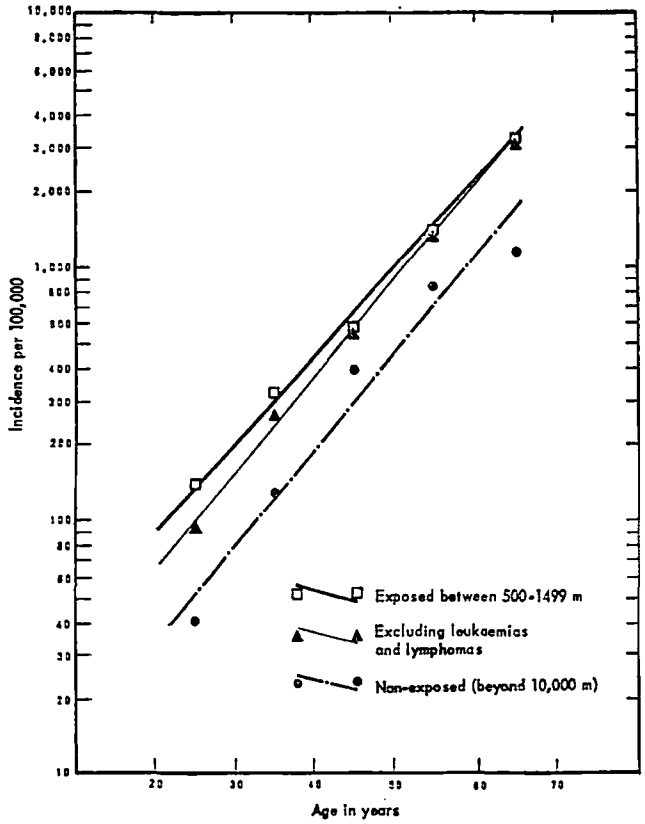


Figure 8. Malignant neoplasms (excluding lymphoma and leukaemia) per 100,000 per year by age and exposure status, May 1957-December 1958. Modified from Harada and Ishida[457]

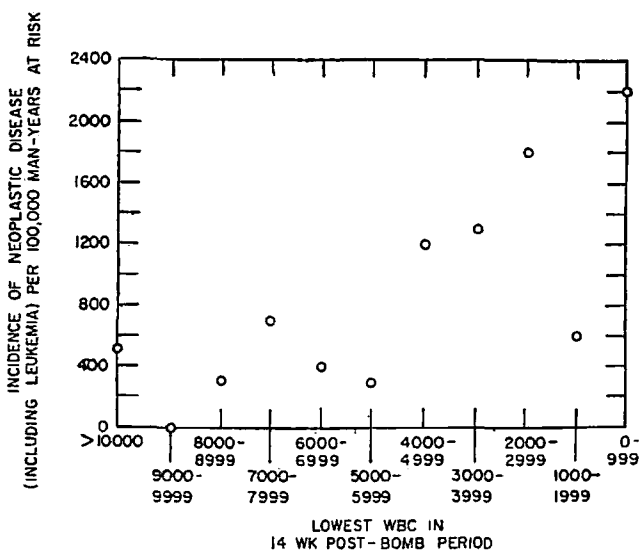


Figure 9. Incidence of late effects among Hiroshima atom bomb survivors, plotted against the lowest leukocyte count in the first 14 weeks after exposure[458]

Although changes in the optic lens have been detected after doses as low as 200 r, the minimal effective X-ray dose (200 kv) for the production of clinically significant cataract is 600-1,000 rad; this dose may be lower for infants or children and is highly dose-rate dependent. Neutrons are 5-10 × more effective in causing cataracts than X-rays.

290. The characteristics of radiation cataract in early states of development are: an initial dot-like opacity, usually at the posterior pole of the lens, around which small granules and vacuoles develop as it enlarges. The central opacity develops a relatively clear centre, giving it a doughnut appearance by the time the opacity is 3-4 mm in diameter. At this time, granular opacities and vacuoles may develop in the anterior sub-capsular region of the lens, usually in the pupillary area. The opacity may remain stationary at any stage. Often it shows a slow progression for a long time to the point described before it remains stationary. If the opacity progresses, it takes on a non-specific appearance and cannot be differentiated from cataracts from other causes.

291. X- or γ-radiation have caused ~ 200 cases of radiation cataracts in man.[459,467] Most had latent periods but in many these were not related to radiation variables such as quality, dose, or duration of treatment. The dose and factors that might permit its calculation were not reported in many cases.

292. The problems of minimal cataractogenic dose—effect of dose and mode of exposure on incidence of stationary or progressive cataracts, influence of dose fractionation and dose or duration of exposure on the latent period, effect of radiation quality, and age on lens sensitivity—are still unsolved for man.

293. From animal studies, radiation cataract results from radiation destruction of the anterior epithelium, which supplies cells that differentiate into fibres of the lens. Young animals exposed pre- or early post-natally have greater lenticular radiation-sensitivity than older animals.

294. Merriam and Focht[464] studied in man 100 cases of radiation cataract and seventy-three cases of irradiation to the head without subsequent cataract. Duplicating the radiation factors, they measured X- or γ-ray dose to the lens in a phantom. Any clinically recognizable characteristic opacity was regarded as a radiation cataract regardless of whether vision was affected. Numerous uncontrollable variables in this study made it impossible to determine the threshold dose.

295. The minimal effective doses were the least radiation producing some lenticular opacity. It was impossible to classify cases by dose and degree of lens opacity; they were classified by whether opacities were stationary or progressive and this was then related to dose.

296. Ninety-seven of the radiation cataract cases and seventy without radiation cataract were classified by timing of treatment: single, fractionation over three weeks, to three months, and fractionation > 3 months. The minimal doses for production of lenticular opacity in cases for each group were 200 r, 400 r, and 500 r respectively. These figures suggest that the threshold dose increases with duration of treatment.

297. Of thirty-seven cases irradiated in a single treatment (with radium plaques), all twenty with doses from 200-1,150 r developed lenticular opacities. The other seventeen received doses from 40-175 r to the lens without developing lens changes. There were only two cases of stationary lens opacities of minimal degree at an estimated dose of 200 r, first seen nineteen and twenty-two years after treatment. Because of the small number of cases (four) with doses from 200-350 r, the fact that there were none without cataracts does not prove that the lens cannot tolerate higher single doses. Further information on the effects at these dose levels is necessary to determine the upper limits of tolerance. The maximal non-cataractogenic dose in this treatment group was 175 r in a patient followed for 8½ years.

298. Of eighty-seven cases given multiple treatments for three weeks to three months, forty-nine developed lenticular opacities with X- or γ-ray doses of 400-6,100 r to the lens. Lens opacity after 400 r (one case) was first seen 2½ years after treatment and was stationary. The maximal non-cataractogenic dose in this group was 1,000 r with a treatment time of 2½ months and a follow-up period of 13½ years. The following table gives the incidences and types of lenticular opacities in patients after irradiation in various dose ranges for a three-week –three-month over-all time.

Dose range (r)	*Cataract incidence*	*Cataract type*		
		Stationary	*Progressive*	*Indeterminate*
40–350	0 of 18 patients	—	—	—
351–550	4 of 9 patients	3	0	1
551–750	6 of 10 patients	5	1	0
751–950	16 of 26 patients	7	6	3
951–1,150	2 of 3 patients	1	1	0
1,151–1,399	No cases	—	—	—
1,400–6,100	21 of 21 patients	2	18	1

299. Of forty-three cases irradiated over a period longer than three months, twenty-eight developed lenticular opacities after X- or γ-ray doses of 550-6,900 r to the lens. There were two cases of cataract after 550 r, one progressive and one stationary, first seen forty-four months and four years after treatment respectively. The maximal non-cataractogenic dose in this group was 1,100 r, with a treatment time of 1½ years and a follow-up period of twenty-two years.

300. The 100 per cent incidence level of lenticular opacities occurred at the lowest-dose level for the single treatment group (200 r) and at any greater dose. In the multiple treatment cases, the longer the duration of treatment, the lower the incidence at a given dose range below 1,150 r; the higher the dose for a given treatment, the shorter the time of appearance of the lens changes and the higher the incidence of progressive opacities with resulting decrease of vision. In general, fractionation of dose delays the time of onset of cataracts and decreases the incidence of severe opacities.

301. The lenses of children under one year of age seem to be more sensitive to radiation than those of older children and adults.

302. Cataract production by fast neutrons compared with X-rays increases significantly with protracted exposure; i.e., the RBE is about 2-4 for high-intensity and 9 or greater for low-intensity radiation, only because the dose of the "standard" radiation changes, not that for neutrons.

303. By December 1948, at least ten nuclear physicists of mean age thirty-one had incipient cataracts after cyclotron exposure.[468] Three cases were severe with definitely impaired vision. Four were moderately severe, and three were minimal. It was estimated that over periods of 10 to 250 weeks, these men had received total doses of fast neutrons to the lens of 10 n-135 n with a median dose of 50.* At the time the cataractogenic exposures were received, periodic blood counts done on most showed no change in blood picture warning of over-exposure to radiation.

304. After the finding of radiation cataracts in the physicists, Cogan *et al.*[469,470] found 10 heavily irradiated Japanese atom bomb survivors with radiation cataracts. In studies by Kimura in 1949, described by Fillmore.[471] 98 cases of lenticular opacity were reported, 85 among the 922 survivors in the high-dose region 1,000 metres or less from the hypocentre. The severity of the lesions was not reported, but it is inferred that they were generally mild.

305. In 1955, Sinskey[472] reported an intensive investigation of 3,700 exposed and non-exposed Hiroshima Japanese from May 1951-December 1953: there were 154 survivors with posterior sub-capsular plaques in the lens large enough to be visible with the opthalmoscope. Opacities not so visible in the greater percentage of survivors were not considered because they did not decrease visual acuity in standard tests. Because of the relatively negligible effect of the atom bomb on visual loss seven years after the bombing, the term cataract, associated with severe loss of vision or blindness, was avoided in this survey.

306. Sinskey found that of 425 survivors in Nagasaki between 400-1,800 metres from ground, 47 per cent had lens changes detected by slit-lamp examination, with or without history of epilation and shielding. Although most opacities were so insignificant as to be invisible with the opthalmoscope, statistically significant lens changes were present in survivors with no other known early or late evidences of radiation damage.

307. Among ~ 8,000 exposed survivors of Hiroshima and Nakasaki examined by 1956 (eleven years after the atomic bomb explosions), ten cases of severe cataract were found. The relationship between these cases and radiation alone is not clear.

Radiation effects on fertility

308. The late pathological effects in gonads are chiefly a hastening in involutional changes associated with advancing age. In animals, there is little evidence of radiation-induced testicular tumours, but ovarian tumours are increased by radiation.

309. Histological sterility is complete absence of gametes and even gametogenic elements. It is difficult to predict its permanency by biopsy or from necropsy sections. Permanent and complete histological sterility requires large doses to the gonads; such doses would be lethal given in a short time to the whole body or a substantial part.

310. *Functional* sterility can be induced by smaller doses; this may be temporary or permanent depending upon size and intensity of dose. In the male, the rate of sperm production need only be reduced to where there are insufficient sperm in semen to be effective. An increase in abnormal sperm after irradiation also reduces the number of effective sperm. Since the number of nor-

* 1 *n* is equal to ~ 2 rad.

mal sperms per ejaculate necessary for reproduction is large, sub-fertility may be associated with considerable but subnormal spermatogenesis. These conditions can be induced by doses to the gonads sub-lethal if given as TBR.

Sterility doses for men and women

311. The long-term pathological effects of radiation on gonads have had little study with accurate dose estimates. From fragmentary data certain estimates are attempted.

312. Gonadal doses affecting fertility are probably similar for men and women: a single dose of ~ 150 rad to gonads may induce brief, temporary sub-fertility in many men and women; a single dose of ~ 250 rad may induce temporary sterility for 1-2 years, and 500-600 rad permanent sterility in many, especially in people with borderline fertility, with temporary sterility in others for several years; single doses of 800 rad or more would probably cause permanent sterility in all but a few most resistant men and women.

313. Gonadal doses causing only temporary alterations in fertility in fertile people are sub-lethal if given as TBR. Gonadal doses that permanently sterilize most fertile people are likely to equal the TBR lethal dose.

314. Limited experience with the Marshallese, exposed Japanese, and certain accident cases suggest that substantial fractions of the mid-lethal dose for man (400-600 rad) do not have a serious, permanent effect on fertility, but gonadal doses are not known with certainty; few people have been studied for this purpose for a long time after exposure.

315. Men may be sterilized permanently without prominent changes in interstitial sex cells, hormone balance or libido. Women sterilized by radiation undergo greater physiological changes since ovarian production of sex hormones is intimately related to development and discharge of ova. Radiation termination of production of ovarian follicles induces an artificial menopause in women similar to natural menopause, with amenorrhea, "hot flushes", diminished libido, and occasionally psychic depression. From experimental data, long-term radiation may seriously impair fertility in animals such as man with relatively poor gonadal regenerative ability.

Degenerative diseases and histopathological changes

316. Injuries of the skin, atrophy, dermatitis, epilation, and epidermal neoplasia were among the first recognized late radiation effects. In human skin, 500-700 rad may induce permanent epilation. Smaller doses cause temporary epilation, may decrease pigmentation or gray the new growth of hair in irradiated areas. This effect has not been reported in Japanese. Doses in the erythema range or higher may also increase pigmentation of skin, epidermal atrophy, and decrease sebaceous and sweat glands in irradiated regions. Hyperkeratotic areas in skin, and vascular sclerosis are also late effects of skin radiation. Surface doses of ~ 1,600 rad may cause considerable permanent dilation of capillaries (telangiectasia) in irradiated areas. In the past late changes were seen more commonly than today in the skin of hands and faces of persons occupationally exposed to radiation; radiation dermatitis and ulcers were often followed by epidermoid carcinomas.

317. Nephrosclerosis is long known as a complication of over-exposure of the kidneys in radio-therapy. Renal hypertension may be induced in man within months or a few years by single localized X-ray doses of ~ 3,000-5,000 rad or by fractionated doses of lesser size (e.g., a total dose of 2,300 rad to both kidneys in 35 daily doses).[473] These conditions have been induced in experimental animals in a short time by local radition of the kidneys with large doses. More recently, nephrosclerosis with renal hypertension and associated generalized arteriosclerosis were induced in rats and mice as late effects of TBR with much lower doses (sub-lethal or LD_{50} range). Although the pathogenesis of nephrosclerosis as a late effect is not clear, histopathological data indicate that changes in fine vasculature are important in early and late initiation and development.

318. Nephrosclerosis and related hypertension may appear as a late radiation effect in animals in which it has rarely or never been seen within the average lifespan (later periods are not well studied) or its onset may be advanced in animals in which the disease has appeared spontaneously. Renal hypertension, once established and progressive, increases vascular sclerosis throughout the body; progressive arteriosclerotic changes often induce progressive atrophy of parenchymatous organs. Consequently, when irradiation has induced or advanced nephrosclerosis with related hypertension in animals or man, the incidence of death from related causes (e.g., renal and cardiac failure, and cerebral haemorrhage) increases with corresponding reduction in death from other unrelated causes or from diseases having longer induction times. Irradiation of human brain or spinal cord with several thousand rad, given singly or in large fractions over a few weeks, may injure blood vessels, cause ischemic damage of tissues, and progressive sclerosis of blood vessels, with subsequent secondary degeneration of brain or spinal cord. Blood vessels may rupture one to several years after exposure.

319. Atrophic and fibrotic changes, often with arteriosclerosis, have been seen in human haemopoietic organs long after local radiation. Secondary anaemia has been associated with myelofibrosis after long-term radiation of bone marrow and also as a late complication of radiation therapy. Radiation *osteitis* is a late degenerative effect of intensive irradiation (a few thousand rad) of bone. The degenerative and destructive processes develop slowly, and after many years lead to necrosis, pathologic fracture, and osteogenic sarcoma.

320. The gastro-intestinal tract has shown some permanent and late effects after fractionated doses of several thousand rad; atrophic and fibrotic changes and sometimes late ulceration in mucosa, and permanently reduced secretion of acid and pepsin by the stomach.

321. Intensive irradiation of the lungs in radiation therapy causes slowly developing progressive fibrosis, with vascular damage and arteriosclerotic changes. Radiation fibrosis[474] usually develops slowly, but there have been fatalities eight weeks after therapy. Lungs show fibrosis with thickening of alveolar walls and vascular system. The alveolar walls may be lined by cuboidal epithelium and the remaining alveolar sacs may be filled with cells. Cough and dyspnea are the principal symptoms. Roentgenographs are similar to those of pulmonary fibrosis from other causes. There is considerable unexplained individual variation in post-irradiation fibrosis but in general the incidence depends on dose. The degree of disability depends also on the amount of lung tissue irradiated; thus, treatment of intrathoracic neoplasms where a large part of pulmonary tissue is

exposed is apt to be more serious than treatment of carcinoma of the breast, where usually only part of one lung is exposed.[475] Malignant neoplasms of the lung have been seen in miners who inhaled radio-active substances, and have been induced in animals by intra-tracheal injection and implantation of radio-active substances.

322. Substantial doses of radiation to actively proliferating mammalian tissues reduce their regenerative capacity. Failure of such tissues to regenerate parenchymal cells to normal numbers is often associated with increased connective tissue and vascular changes. In general, incomplete regeneration varies directly with size of the single dose or with dose rate in long-term radiation; in some tissues such as testis, fractionation may increase dose efficiency in damaging regenerative capacity. It is not clear to what extent the permanence of this effect is due to the direct effect of radiation on stem cells, or to damage of supporting tissue. Nor is it clear to what extent in each tissue incomplete regeneration is due to: (*a*) decreased reproductive capacity of existing stem cells, (*b*) decreased stem cells surviving, (*c*) asynchrony in regeneration of histological elements with increase in connective tissue, or (*d*) damage of fine vasculature, although any or all factors may be implicated depending upon dose. Little is known quantitatively about the reproductive capacity of individual stem cells or the numbers of primitive stem cells surviving in the post-recovery period after irradiation. Fibrosis of small blood vessels with general reduction in vascularity is often associated with subsequent reduction in number of parenchymatous cells and increase in connective tissue.

323. Changes in vascular and lymphatic systems, with destruction of radiation-sensitive parenchymatous cells, are important in the pathogenesis of many late radiation effects. Many late effects may come from metabolic and nutritional disturbances due to impaired blood supply that reduce function and reparative capacity, and increase susceptibility to traumatic damage, infection and disease in general.

Effects on growth and development

324. The regenerative processes of the body are fairly sensitive to radiation; their inhibition may be prolonged especially if vascular integrity is impaired. More quantitative study is needed after local and TBR.

325. Some quantitative studies in rats indicate that repeated TBR at 24 rad/wk inhibits growth. A significant decrease in growth can be caused by repeated TBR without decrease in haemoglobin or absolute neutrophils levels.

326. Localized irradiation of the epiphysis inhibits bone growth and shortens bones in man and animals, the effects being greatest in youngest animals. Localized irradiation of the jaws decreases tooth growth.

327. Studies in Japanese children after the atomic bomb indicate a statistically significant if slight retardation of growth and maturation. However, the effect of non-radiation factors has not yet been adequately evaluated. Extensive measurements on 4,800 children at 6, 7 and 8 years after exposure in Hiroshima showed generally that growth was retarded and maturation delayed.[476,477] In another study of several hundred children in Hiroshima and Nagasaki, in years 2, 4 and 5 after irradiation, physical growth and development were affected adversely, and retardation of height, weight, and skeletal development was still evident at the end of 1950.[478] The investigators believed that factors other than radiation—e.g. malnutrition—may have contributed to these effects.

VI. Special features of internal and external contamination

PHYSICAL CONSIDERATION[479]

328. The hazards of exposure to radio-nuclides depend greatly on their physical and chemical properties; these determine their entry into the body and retention in various organs. The duration of radiation depends also on physical half-life and in some instances on complicated decay chains causing a shift of the emitter from one place to another as the isotope undergoes transmutation.

329. The nature of the emitted radiations may determine the range of exposure and hence the pattern of injury e.g., an energetic α-ray will penetrate no further than 0.07 mm. in tissue; β-rays deposit their energy largely locally; γ-ray energy will be absorbed in larger volumes or an appreciable portion of the energy will escape the body altogether.

330. The degree of damage depends to some extent on the concentration of ions along the path of ionization. For an equal energy, this is greatest with the shortest range emissions i.e., α-rays. For most types of response the effects are greater where ionization is dense.

331. In recent years, attention has centred on the long-term hazards of radio-nuclides of long half-life, e.g., Sr^{90} and Cs^{137}. But, intermediate and short-lived isotopes may be important, depending on circumstances. Possible accidental discharge of radio-active material from reactors, as nuclear detonations, may contaminate local areas with various fission and activation products. Even in global fall-out from the thermo-nuclear tests, fission products of intermediate half-life are a source of γ-radiation which, for a few months after detonation at high altitudes, has exceeded that from Cs^{137}.[480] Among the short-lived isotopes the most interesting, especially in nuclear accidents is I^{131}.

332. The important isotopes of intermediate half-life include Ba^{140}, Ru^{103}, Ru^{106}, Co^{60}, Ce^{141}, Ce^{144}, Y^{91}, Zr^{95}, and Sr^{89}. Some are so poorly absorbed that for practical purposes they may be considered as external γ-ray sources; Ba^{140} and Sr^{89} are absorbed and must be considered with Sr^{90} as contributing dose to the skeleton.[481]

333. In past weapon tests, studies of fall-out patterns have shown that the geographical distribution of isotopes depends on many factors, including the altitude of explosion and the nature and amount of surrounding material. Particle size and their solubility vary with distance as with other factors.[482] Any nuclear accident is likely to produce a unique pattern of variables, e.g., due to the features of the accidental discharge from the Windscale reactor in Great Britain the contaminating fission mixture had a lower content of radio-strontium relative to radio-iodine than might have been anticipated.

SPECIAL PROBLEMS ASSOCIATED WITH INTERNAL EMITTERS

Localization of radiation

334. Theoretical and experimental considerations suggest that the effects in tissues from uniformly applied radiation may differ from the effects of radio-active

particles aggregated into a "point source".[483] In the latter, dose-rates close to the point source differ from those near the end of the range of the particles. Dose-rate near the origin is extremely high; these high rates may be important, if the relationship between injury and dose-rate is non-linear. Dose-rates are unimportant if the effects of radiation are related to dose in a linear non-threshold way. Then, the effect may reflect a single-event so that only total dose is important; dose-rate and spatial distribution are inconsequential. When the radio-element is diffusely deposited, the probability of the distribution of injury is the same for all cells in the tissue, whereas in discrete deposition, the probability of injury of cells close to the aggregate is increased but that of injury to the cells far away is reduced.

335. If the relation between dose and degree or probability of injury is not linear then spatial distribution is important. Also, different biological effects may show different relationships with dose. Present data are not adequate to define differences in hazard between focal and diffuse radiation.

Concept of RBE

336. Even with uniform irradiation the concept of RBE is by no means simple, as is discussed in other parts of the report, since the relative effectiveness of radiations of different quality may depened on many factors other than LET, including dose, dose-rate, biological end-point, and other factors. With many internal emitters and particularly with the bone-seeking isotopes, there is the additional problem of a very non-uniform distribution of radiation dose, which introduces further severe problems into the use of RBE factors, which have not yet been solved.

337. Because of the many difficulties, the concept of RBE can be applied only in a very general way, especially to internal emitters, and care must be taken when using it to establish standards of radiation safety for various types of ionizing radiations. In particular, it must be emphasized that an RBE established for one biological effect is not necessarily valid for another.

Modes of entry of radio-isotopes into animals and man

338. Among the fission products only few are of significance with regard to internal contamination. The uptake and metabolism in the organism depends on the nature of the materials and their chemical and physical properties. The routes of environmental contamination into the body are ingestion, inhalation, and skin absorption.

Ingestion

339. Gastro-intestinal absorption is the most important route of uptake of Sr^{90} and Cs^{137} from nuclear weapons tests. The levels of these isotopes in animals and man correlate with their levels in the diet; they are readily absorbed.

340. Ingestion is an important mode of entry only for soluble isotopes. The solubility of interest is solubility in body fluids rather than solubility in water. Many soluble compounds may be converted to relatively insoluble hydroxides at the pH of body fluids. Also, relatively insoluble compounds may be converted to soluble compounds in body fluids. Only those having intermediate or long half-lives can be absorbed by man in proportion to fall-out levels except where rainwater is used for drinking and cooking because of the relatively long times in the ecological pathway.

341. Another factor is whether the isotope is a radio-nuclide of an element required by the body or of one chemically similar to a required element. The actinide and lanthanide rare earth series of elements have no chemically similar counterparts among required body constituents and are usually poorly absorbed by plants and animals. For these radio-nuclides, inhalation may be relatively more important than ingestion.

342. Although some generalizations are possible from the similarities of elements with families of the periodic table and from similarities to required body constituents, each radio-nuclide has its own metabolic properties. There is a continuing need, therefore, for data on gastro-intestinal absorption of all radio-nuclides that are potential contaminants of the environment.

Inhalation

343. In industry, inhalation has been found to be the most important route of entry of potentially hazardous materials. Inhalation of radio-active isotopes creates three potential hazards: absorption into the systemic circulation and subsequent deposition in a critical tissue or organ; irradiation of the lungs themselves from materials deposited on respiratory surfaces and picked up by bronchial lymph nodes; ingestion. Inhalation is generally the most important route of entry of short-lived radio-nuclides and of insoluble radio-active materials.

(a) *Size of inhaled particles*[484]

344. The relationship between size of radio-active particles and their deposition in the respiratory tract is complex, since retention and movement vary with particle size. In general, very small particles may be deposited throughout, freely entering the lower portions of the lung. As particle size increases, deposition throughout the respiratory tract decreases, and reaches a minimum at a particle size of $\sim 0.4\ \mu$. With further increasing particle size, up to $\sim 10\ \mu$, the fraction deposited in the total respiratory tract increases. Particles $> 10\ \mu$ will not penetrate the passages to the alveoli, and are deposited mainly in the upper respiratory tract, where there is rapid clearance. As particle size increases further, the point of deposition is further up the respiratory tract, until the probability of inhalation of large particles becomes low because of the filtering action in the nostrils.

(b) *Radio-activity of inhaled particles*

345. Suspended radio-active materials may be very heterogeneous in particle size and in other physical and chemical properties. Compounds of several radio-elements can be attached to a particle of inert material, or a single radio-active compound can be the entire particle. Usually radio-nuclides become associated with inert materials during information or after subsequent agglomeration.

(c) *Solubility of inhaled particles*

346. Once a radio-active substance is deposited in the body, its fate—translocation and excretion—is partly determined by its solubility in body fluids. Solubility depends principally on chemical composition, but physical properties such as size, shape, and surface area are also important, especially of heterogenous particles in which radio-active substances are adsorbed on the surfaces of inert nuclei.

Skin absorption

347. Absorption of radio-isotopes through the skin has not been sufficiently studied. The skin is not usually considered an actively absorbing organ, especially for inorganic substances. Animal experiments have been limited because anatomical and physiological dissimilarities between human skin and that of the more common laboratory animals lead to problems of interpretation. The skin does not appear to be an important route of entry of nuclides contaminating the general environment. However, skin absorption of radio-active materials should not be ignored, especially when large quantities may come in contact with the skin surface in industrial accidents. A specific example is tritium as tritium water (H^3_2O). The amount of atmospheric tritium water that exchanges with moisture on the skin surface and enters the circulation is about equal to that entering via inhalation of the same tritum-containing atmosphere.[485,486] Absorption of a few other radio-nuclides through human skin has been studied.[487] When the skin is broken, e.g. in wounds, absorption of radio-nuclides is greatly accelerated and increased.

Effects of radio-isotopes after absorption

348. The effects of radiation from materials within the body are similar to those of external radiation. Important differences arise because (*a*) radio-isotopes are not distributed uniformly within the body; and (*b*) they serve as more or less continuous sources of radiation.

Early effects

349. In animal experiments, haematopoietic symptoms of acute radiation disease appear 7-10 days after lethal amounts of radio-isotopes given intravenously or parenterally[488,490] Sub-acute effects, frequently seen 1-5 months later, may include haematopoietic symptoms as well as malfunction of those organs within which the radio-isotope is deposited most heavily, e.g., polonium leads to kidney damage, plutonium and the rare earths to liver damage, radio-iodine to thyroid damage, and radio-strontium to bone damage.[489,492] A recent paper on the accidental exposure of 103 luminous-dial painters to Sr^{90} gives data on its urinary excretion in man and gives some information on possible early haematological effects.[493] A more complete account on urinary excretion of Sr^{90} in man is given in a report on a case of accidental inhalation.[494]

350. It is unlikely that many human cases of acute or sub-acute poisoning due to internal emitters will ever occur. In nuclear war or a reactor accident, the chance of serious damage from external radiation greatly overshadows that from radio-nuclides which might enter the body. On the other hand, the long-term effects of small amounts might become a serious problem.

Late effects

351. Experience with the long-term effects of internal emitters in man is essentially limited to radium, used therapeutically and in the dial-painting industry, to thorium used as a contrast medium for roentgenographic diagnosis, and to elements in the decay chains of radium and uranium to which miners have been exposed. Cancer has appeared in these groups.[495–499] More recently, radio-phosphorus, radio-iodine, and other new nuclides have been used in treatment and diagnosis; scanty reports of tumour induction require verification.

Effects of internal emitters on the lung, including cancer of the lung

352. In 1939, Rajewsky reported a technician in a radium plant who died with pulmonary fibrosis similar clinically and anatomically to that after external irradiation.[500] The technician was twenty-four years old and had worked three years in the plant. At death, his lungs contained $\sim 6.2 \times 10^{-2}$ μc of radium which would give a mean dose rate of ~ 0.2 rad per week. Most radium previously deposited had almost certainly been cleared from the lung at the time of death; therefore earlier dose rates must have been much higher. The lung cancers in the miners of Joachimsthal and Schneeberg, in Czechoslovakia, are familiar. The mines were first opened in 1410 for copper and iron; in 1470 silver and arsenic were discovered and mined, and later bismuth, nickel and uranium. Other metals found were tin, zinc, cobalt, manganese, magnesium and lead. At the beginning of the twentieth century, uranium was the principal element mined for the dye industry. Three surveys were made to establish the incidence and determine the cause of cancer of the lung among the miners.[501–503] The concentration of radon in the air of the mines[504,505] varied considerably in different shafts ($0.36 \times 10^{-6} - 47 \times 10^{-6}$) and averaged 2.9×10^{-6} μc/cc.

353. Although the exact role of radium in the etiology of the lung cancers is unknown, there seems little doubt that their incidence among the Schneeberg and Joachimsthal miners is at least 50 per cent higher than that in the general population. The cancers of the lung are morphologically similar to those in other groups of the population, with the possible exception of the absence of adenocarcinoma. The average latent period for the induction of lung cancer in these miners was $\sim$ 17 years, and calculations have suggested that assuming uniform distribution the dose to the lung would have been $\sim$ 1,000 r during this time.[506]

Long-term effects of internal emitters in animals

354. In animals, effects are generally measured in terms of tumour induction and life shortening. Tumours may appear in those tissues in which the isotope is located and also in adjacent tissues within the range of the radiation. Thus radio-strontium, which localizes in bone, induces in mice osteosarcomas and rarely epidermoid carcinomas of the oral and nasal mucosa.[491] In man radium has caused, in addition to the usual sequela of bone malignancy, epithelial tumours arising in the mastoid cavity and the accessory nasal sinuses.[499] Other instances in which tumourgenesis is associated with the direct action of ionizing radiation on tissues include tumours of the liver, gastro-intestinal tract, lungs and skin. In the case of thorium, for example, hepatic carcinomas and hemangio-endotheliosarcomas have been noted abnormally often in patients given thorotrast intravenously for angiography.[507] The incidence of these tumours increases with the quantity of incorporated radio-isotope, the dose up to a given point and may also depend on the dose-rate within the critical organ.[304]

355. In other instances, however, irradiation by radio-isotopes may lead to abscopal (other than local) effects. Neoplasia of endocrine glands and of sex organs (typified by the hypophysis and ovaries) are induced by various radio-isotopes irrespective of their organ distribution. Their incidence is not clearly related to dose or dose-rate, and may depend strongly upon such factors as strain and sex. Hormonal dysfunction induced by radiation plays an important role in their etiology.[304]

An intermediate position is occupied by mammary tumours and lymphomas, where the incidence is dependent on dose, but which are unaffected by the pattern of isotope distribution. In mice, lymphocytic neoplasms may arise where the primary target is bone, perhaps resulting from the TBR occurring while the isotope is circulating.[491]

Effects of internal emitters on the lung in animals

356. More striking effects were seen after deposition of radio-active gases and particles in the lungs, e.g. high incidence of pulmonary tumours in mice inhaling radon.[508] They were exposed continuously to air containing radon at 1.2×10^{-6} μc/cc, and lived 161-453 days. Ten or twelve animals had lung adenomas, and one an adenocarcinoma arising in a small bronchus. There was one adenoma in the controls. Tracheal administration of 50 mg of quartz and three-hour exposure to air containing 8×10^{-6} curies radon per litre retarded weight increase and changed the peripheral blood composition.[509] Radon affected the silicotic process significantly inducing metaplasia of bronchial and alveolar epithelia, and in some cases, malignant tumours and bone tissue in the lung parenchyma and in blood vessel walls. Proliferation of bronchial epithelial cells along with atrophy and proliferation of the tubular epithelium of the kidney were seen in mice five months after an eighteen-hour exposure to 2.4×10^{-4} curie of radon per litre of air.[510] The carcinogenic action of radon is due to its distintegration products.[511, 512] Pneumoconiosis does not play a decisive part in the pathogenesis of lung tumours due to the effect of radon.[513]

357. Changes in pulmonary histology have been seen after various α- and β-emitting elements, Ru^{106}, Rh^{106}, Sr^{90}, Ce^{144}, Pu^{239}, Po^{210} and Co^{60}, were given to rodents, mostly by intratracheal injection.

358. Strontium-90 was given by transthoracic injection of glass beads[514] and in one study Ru^{106} was plated on a platinum cylinder introduced into a bronchus.[515] In most studies, squamous metaplasia of the bronchial epithelium was seen in many of the animals; fibrosis and pneumonitis were common. Because of the high frequency of lung pathology in rodents, it is unsafe to ascribe all changes to the radio-active elements. The tumours thought to be bronchogenic were unencapsulated and invasive. In studies with implants many of the tumours surrounded the implants.

359. Cember intra-tracheally injected up to 4.5 millicuries of S^{35} as $BaSO_4$, in rats, and found no effects definitely attributable to the radio-active particles.[516] In another study after 375 microcuries of $BaS^{35}O_4$ given intra-tracheally to twenty-four rats once a week for ten weeks, two of sixteen rats surviving showed severe squamous metaplasia in the lung, and two had bronchogenic squamous cell carcinomas. The estimated average dose to the lung during ten weeks was 12,000-20,000 rad.[517]

360. Cember also reported bronchogenic squamous cell carcinoma after pulmonary implantation of Sr^{90} glass beads.[514] Four squamous cell carcinomas, two lymphosarcomas, and one lymphoma were seen in rats carrying the Sr^{90} beads. Six tumours were intimately associated with the beads. The total dose given the lung ranged from 5×10^4 rad to $> 2 \times 10^5$ rad.

361. Warren and Gates[518] induced epidermoid carcinoma of the bronchus in mice with Sr^{90} glass beads and with Co^{60} implants. For Co^{60} the radiation doses were high, up to 400,000 rad in 200 days, to the nearest viable bronchial epithelium, or 12,000 rad to epithelium one cm. from the source. They were unable to produce carcinoma in mice at doses $> 70{,}000$ rad to bronchial epithelium. For Sr^{90} the dose given bronchial epithelium to within five mm from the source was 13,000 rad after 200 days. Not all mice developed epidermoid carcinoma.

362. Other experiments with relatively insoluble particles retained in the lung for long times have shown an increase in malignant tumour incidence. Intratracheal $Pu^{239}O_2$, 0.06 to 0.16 microcurie, caused fibrosis, sterile pneumonitis, and benign papillary cystadenomas in 60-80 per cent of mice within 100 days.[519] Similar results were seen after intra-tracheal $Ru^{106}O_2$. Malignant lung tumours were seen in these mice. For various tumours a dose has been calculated assuming uniform distribution of radio-isotope in lung tissue and exponential loss from lung.[520] The authors original estimate of dose to lung was used where reported (table IX).[484] The smallest lung doses mean values associated with malignant tumours were 115 rad after 0.003 μc $Pu^{239}O_2$ and 300 rad after 0.15 μc $Ru^{106}O_2$.[521] However, the etiology of these tumours is uncertain because autoradiograms failed to show radio-activity in the area of the tumour.

363. In other studies, at least 2,000 rad was the estimated dose to lungs that developed tumours. The estimated dose is questionable in many cases because of the non-uniformity of the distributed radio-active materials. Autoradiograms showed that inhaled particulates were localized in discrete areas of the lung.[519] In these cases, dose to microvolumes of tissue could be considerably greater than that estimated by assuming uniform distribution. Therefore, from the dose estimates given in table IX one should not conclude that the dose required to induce lung cancer is necessarily as low as 2,000 rad; it may, indeed, be much greater. Lung carcinogenesis after inhalation of radio-active particles has not been very common; only a few studies have been completed. Lisco[522] has described epidermoid carcinoma, adenocarcinoma, and hemangio-endothelioma in 50-100 per cent of rats inhaling about 0.2 to 1 μc PuO_2 smoke. Recently, Temple *et al.*,[523] in preliminary work, found a bronchiolar carcinoma in a mouse killed 500 days after deposition of 0.01 μc of $Pu^{239}O_2$ by inhalation. In most reports summarized in table IX, the authors also found significant metaplastic changes, some at doses lower than those given in the table. Other effects causing death of mice were seen after inhalation of $Pu^{239}O_2$.[524] Ninety per cent mortality occurred within ten months after deposition of 0.34μc. No increased mortality occurred after deposition of smaller quantities, although some lung pathology was present. Cember reported no increase in non-specific mortality after implantation of sufficient Sr^{90} in glass beads to produce bronchogenic carcinoma.[514]

364. Although radio-isotopes accumulate in pulmonary or tracheobronchial lymph nodes, little is known of their effects. A tracheobronchial lymph node from a dog two years after 20 μc of intratracheal $Pu^{239}O_2$ showed characteristic radiation damage. The architecture of the node was destroyed and there was only limited regeneration of lymphatic tissue. In other dogs, possible histologic changes were seen within a year after inhalation of 2 μc $Pu^{239}O_2$.[525]

Effects of internal emitters on bone[526]

(a) *Histological damage in bone*

365. Whatever the source of radiation, external or from internally deposited isotopes, the general patterns of histological change are remarkably similar in different

species. Histological damage includes: (i) empty lacunae, (ii) vessel injury, (iii) irregular abnormal new bone, and (iv) varying degrees of fibrosis; in addition, in rats and mice where endochondral ossification continues in adult animals and in young rabbits there may be (v) unresorbed cartilage, (vi) abnormalities of cartilage in the epiphyseal plate, and (vii) severing of old and abnormal resorption of new spongiosa.

366. Bone damage takes two forms. First, bone may be injured probably by indirect destruction through vascular injury and by direct action on the osteocytes. The presence of osteotropic isotopes especially Sr^{90} during a chronic phase of injury (after 180-200 days and later) induces a sharp deterioration in the blood supply, as a result of the emptying of considerable sections of the vascular bed of blood forming and bone tissues with the disruption of vascular innervation.[527,528] The damage to osteocytes and vessels can be seen within a few days in animals given a large short-term radiation; but it is best seen as a late change in bones of patients with radium poisoning, as well as in experimental animals. Secondly, radiation having damaged osteoblasts and osteoclasts, can initiate abnormal activity in osteogenic connective tissue. Short-range α-emitters, radium, mesothorium, radio-thorium and plutonium affect the osteogenic connective tissue lining endosteal surfaces and resorption cavities of bone trabeculae, inducing marked terminal fibrosis, especially when the dose injected is high. The longer-range β-emitters, Sr^{90} and P^{32}, and external irradiation affect loose connective tissue in the bone marrow spaces between bony trabeculae as well as on the surface of the trabeculae. They induce variable degrees of active cellular fibrosis often characterized by proliferation of pleomorphic spindle cells with conspicuous numbers of mitotic figures and abnormal giant cells.

367. At higher dose levels most changes are seen in different species. Their severity decreases considerably with time, especially with an isotope of relatively short half-life, e.g., P^{32}, where irradiation is short compared with that of longer-lived isotopes. With decrease in dose or end of radiation, these changes become less severe, and at sufficiently low doses, the initial damage is repaired so that no histological evidence of damage remains; bone has a considerable capacity for repair.

(b) *Histogenesis of bone tumours*

368. Gross damage causing dead bone and repair may occur without malignant change. Tumours do not necessarily arise at the site of maximum damage. In fact, it is possible that, in very heavily irradiated bone, the tumour incidence decreases, since the capacity of the tissue to proliferate will be greatly influenced. There is no obvious correlation between incidence of sarcoma and degree of radiation damage. Thus external irradiation of the knee joint and adjacent ends of the femur and tibia of rats damages and induces tumours in the epiphysis and metaphysis of both long bones; but not in the patella, where energy absorption is lower. In the long bones of rats given P^{32} and of rabbits given Sr^{90}, the earliest microscopic tumours appear as small foci of proliferating cells amongst spindle cells of osteogenic connective tissue that show fibrosis in rats. In rabbits fibrosis is less evident. This does not mean that the tumour arises from cells responsible for fibrosis—only that it arises in the same region of bone. To have a reasonable chance of seeing microscopic tumours when animals are killed, one must use a radiation dose large enough to give high tumour incidence. The types of cells giving rise to tumours cannot be defined morphologically because of the extremely abnormal environment in damaged tissue. The histological characteristics of tumours seen in various species show that the cells at risk are the "osteogenic" connective tissue cells. There is no precise evidence as to whether all these cells are equally susceptible to irradiation, though it appears unlikely that the osteocyte is. The cell may be an undifferentiated "reticulum cell"; if so, it is surprising that there is no evidence of myeloid leukaemia unless there are at least two different types of undifferentiated "reticulum cell". The increased leukaemia in mice after Sr^{90} was always lymphatic.

369. The sequence of bone tissue changes in rats from the moment of introduction of the radio-isotope (Sr^{90}, Sr^{89}, Ce^{144}) to the appearance of the primary tumour nodule, postulated by Kraevsky and Litvinov[321] is:

(i) 1st to 20th day: initial unspecific response of the bone in the form of development of endosteal tissue and intensified remodelling of bone;

(ii) 20th to 80th day: inhibition of bone modelling. Slowing down of osteogenesis. Abrupt dystrophic changes in the osteogenic tissue. Reduction in the number of osteoblasts and vessels. Coarsening of the basic material. Onset of atypical bone formation—the background for subsequent tissue malignancy;

(iii) 80th to 120th day (first pre-tumour phase): onset of redundant and degenerate bone formation. Intensified formation of pathological bone structure in a radically changed environment;

(iv) 120th to 150th day (second pre-tumour phase): growth of polymorphous osteogenic tissue among pathological bone structures. Appearance of accumulation of atypical, free, intensively-dividing, osteogenic cells;

(v) 150th to 180th day (third pre-tumour phase): proliferation of atypical osteogenic and immature bone tissue;

(vi) 180th day and later: tumour-appearance of primary tumour nodules and their subsequent growth.

370. Whether antecedent histological bone damage is always found in a bone having a radiation-induced tumour must be left undecided at present.

(c) *Relationship between the pattern of radiation dose in space and time, histological bone damage, and bone tumour induction*

371. The radiation dose, i.e., the absorbed energy expressed in rad, is important in relation to histological damage. Some investigators have considered only the dose given or retained in μc without attempting to calculate rad, since there are many difficulties in calculating a meaningful dose in rad. Calculations in rad should be encouraged since it is only in this way that a quantitative relationship between radiation and biological effect can be obtained. The relationship between dose, dose-rate and the formation of bone tumours has been studied in experiments with Sr^{90}, Ce^{144}, Pu^{229}, Pm^{147}, Y^{91},[504,529,530] Within certain limits the incidence of osteosarcomas increases with dose and dose-rate.

372. Most difficulty in interpreting the response of bone to bone-seeking isotope arises from the considerable spatial and temporal non-uniformity of dose, and from the changing spatial relationship between cells and radiation source, especially in young growing animals. The difficulty is knowing which of the many variables predominates in inducing histological changes. Two variables are: (i) accumulated dose and (ii) dose-rate to the site. The incidence of osteosarcomas increases with dose

and dose-rate. Accumulated dose and dose-rate are interrelated: a great problem with accumulated dose is the time over which it should be integrated. The dose accumulated up to the time of tumour induction is useful, but a proportion of radiation given in the later stages may be "wasted" for tumour induction. Attempts have been made to relate accumulated dose and dose-rate to damage and tumour production in studies in space and time with Sr^{90} and P^{32} in rats and rabbits. Information on dose and bone damage with other isotopes is far less detailed.

(d) *Accumulated radiation dose to the site*

373. With isotopes that emit long-range β-rays, e.g., Sr^{90}, Y^{90} and P^{32}, maximum dose-rates in different parts of the skeleton of rats and rabbits varies considerably from one bone to another, mainly because of variation in bone size. In a small bone, contribution to dose-rate from cross-fire in neighbouring deposits is less than in a larger bone. This causes variation in the maximum accumulated dose in different bones. When maximum accumulated dose is compared with distribution of osteogenic sarcomas in the skeleton with Sr^{90}, sites of maximum accumulated dose correlate with sites of osteogenic sarcomas. However, other factors must also be important: sites of maximum accumulated dose (usually the ends of the long bones in young animals) are also the areas of maximum growth and therefore of actively proliferating tissues; they are also the largest volume of irradiated bone.

374. Where damage was compared with dose-rate in time and accumulated dose in the upper half of the tibia of young rabbits, given Sr^{90} (i) as a single intravenous injection or (ii) as daily pellets by mouth, the bone volume given maximum dose-rate and accumulated dose correlated with the sites of tumour origin. In animals given a single injection, maximum dose-rate and accumulated dose and site of tumour origin were confined to a small length, $\sim$ 5 or 6 mm., of bone. In fed animals, maximum dose-rate and accumulated dose were along a 3-cm length of bone along which abnormal bone tissue appearing to be the tumour origin was wide-spread.

375. The injection of P^{32} at different time intervals (fractionated doses) shows that the rate at which tumours appear can be altered for a given total injected dose. The maximum accumulated dose was approximately the same in groups of rats injected at different intervals; this indicates that factors other than maximum accumulated dose also influence the induction of bone tumours.

376. From a comparison of the dosages in mice given Ca^{45} and Sr^{90} causing the same incidence of bone tumours, the conclusion was that cells on the surface of the bone and bone trabecules (osteoblasts and connective tissue cells) were the cells at risk and not osteocytes. This conclusion is not necessarily unique. In this comparison, two difficulties are: (i) at the dose levels compared there were fewer tumours in long bones with Ca^{45} than with Sr^{90}; and (ii) dosimetry of Ca^{45} is subject to error. These data suggest that after Ca^{45} and Ra^{226} "hot spots" might soon become buried in bone and hence unimportant in giving significant radiation to bone surfaces. The "diffuse component" with these isotopes, may be the more important in giving the effective dose.

377. Several workers have reported complete histological recovery in bones of young animals of all species with maximum accumulated dose (to time of sacrifice) 2,000 rad. However, since this dose still induces a significant incidence of tumours, a more detailed histological search or a new indicator might reveal persisting damage. Pre-tumour proliferations of immature osteogenic tissue can be resorbed if the dose-rate (Sr^{89}, Y^{90}), is reduced, thus demonstrating that repair of "carcinogenic" injuries is possible.[321]

(e) *Radiation dose-rate to the site*

378. A range of dose-rates from 50 rad/min. for X-rays, 0.2 rad/min. for P^{32} and 0.05 rad/min. for Sr^{90} induced similar tumour incidence, i.e., 30-60 per cent for maximum accumulated doses of 3,000-8,000 rad. In a small group of rabbits a maximum dose of $\sim$ 20,000 rad over 6-8 months gave 100 per cent tumour incidence. Over this relatively high range, the dose-rate may not be important in carcinogenesis.

379. At the relatively high radiation dose levels maximum accumulated radiation dose correlates with bone damage and tumour incidence with Sr^{90} in rabbits; this relationship is less clear with P^{32} in rats. Data are not yet available from which to plot the relationship of radiation dose to damage with short-range β-emitters or α-emitters.

380. Many other variables, such as volume and oxygen supply of tissue, proliferative activity, and irradiated movement of cells at risk must be important in determining the effect of dose-rate and accumulated dose; their relative importance is unknown.

Dose and dose-rate in carcinogenesis by internal emitters

381. The relationship between tumour induction and absorbed dose of radiation is obscured by a series of problems. The basic difficulty is that internal irradiation, unlike external irradiation, continues indefinitely, but at an ever-changing intensity. Consequently, questions such as the relative importance of dose-rate and total dose in time and space are difficult to attack experimentally.

382. Several lines of evidence indicate that dose-rate is a major factor in the induction of osteosarcomas by bone-localizing isotopes. In mice, tumour incidence has increased as the second or third power of the dose expressed in terms of amount of radio-activity given, and tumour incidence has varied with the time pattern of administration.

Internal emitters and leukaemia

383. An increased incidence of leukaemia after internal emitters have been seen in mice but it is overshadowed by far greater induction of bone tumours.[581] An increased incidence of leukaemia induced by incorporated isotopes was obtained in rats with Sr^{90}, Cerium-144, Niobium-95, Caesium-137 and other isotopes and in dogs with Sr^{90}.[532,533] The disease has been reported in radium patients, but only in those exposed occupationally also to much external γ-irradiation.[534] In studies of tumour induction by radium in dogs, no leukaemias or allied conditions have been seen under conditions that induce a high incidence of bone sarcoma.[535]

Internal emitters and life-shortening

384. Reduction in life expectancy is an important consequence of radiation from internal emitters: this response has been seen in mice irradiated at low levels that failed to show an increased incidence of neoplasms. At such levels of radiation it has not been possible to attribute reduction in life span to any specific degenerative or infectious disease. The animals die with the same pathological conditions seen in control populations.

METABOLIC CHARACTERISTICS OF PARTICULAR ISOTOPES[479]

Alkaline earths (calcium, strontium, barium, radium)

385. These nuclides are metabolized qualitatively like calcium: they are rapidly and almost exclusively deposited in the skeleton, where they are retained very tenaciously. Unless the physical half-life of the isotope is short, the significant residence time of these bone-seeking radio-elements may cover the life span of man. Like calcium, they are readily absorbed from the intestine, provided they are in soluble form.

Radium-226

386. Radium-226 is of special significance since its toxicity in man is well established. It has, therefore, been used for estimating the potential toxicity of other bone-seeking radio-elements. The value for maximum permissible burden was established without reference to the time of exposure. The symptoms of radium poisoning and body burdens alluded to earlier were found in people $\sim$ 20-30 years after their exposure to radium. During the early part of the post-exposure period, the amount of radium in the body was certainly considerably higher than that finally measured. The best estimates are that an individual retaining 0.1 μg Ra^{226} 30 years after a single exposure must have initially absorbed about 10 μg.[536]

387. Many dial painters, who provided much of the information on Ra^{226} toxicity, were also exposed to other emitting elements, specifically Ra^{228} and Th^{228}. Thus they received a much greater radiation dose than is estimated from Ra^{226} burdens alone. Such a single exposure, or exposures of reasonably short duration, produce heterogeneous deposition patterns in bone. Continued exposure, as shown for Sr^{90}, causes a much more uniform pattern. This further complicates definition of the effective dose. There has been no work showing how the effects of Ra^{226} in the adult may differ in children.

Strontium-90

388. The general qualitative similarities in the distribution and metabolism of the alkaline earths have been shown from single-dose studies after strontium, radium and calcium in several species, although their rates of transfer are not identical. Thus knowledge of the metabolism of the other alkaline earths assists in understanding the fate of Sr^{90} in the human body. This information, combined with tracer experiments with strontium and studies of stable strontium, enables reliable estimates to be made of the body burden after a given intake of Sr^{90}, but some uncertainties remain in estimates made on newborn and young children.

389. Sr^{90} is found universally in the biosphere, and its primary source in man is from calcium-rich foods, especially milk. It follows calcium qualitatively in the biosphere and its absorption into plants varies somewhat with availability of calcium. This may be partly true also in animal uptake of Sr^{90}; however, there is evidence that the absorption of Sr^{90} from the intestine proceeds independently of calcium to some extent. Growing animals retain Sr^{90} more efficiently than adults, reflecting the more active calcium deposition in young animals.[537]

390. The metabolic patterns of the alkaline earths differ quantitatively, e.g., preferential absorption of calcium over strontium from the gastro-intestinal tract and greater renal excretion of strontium.

391. Recent work with Sr^{85} retention in normal adults shows results similar to those in animals.[538] The retention of the alkaline earths, including Sr^{90}, can be described by a power function of the form

$$R_t = At^{-b}$$

where R_t is retention at time t, in days after injection, A is equal to R_t at one day, and b is the slope of the log-log line. The slope, b, for strontium in man is about half that estimated for Ra^{226} in man, i.e., the rate of excretion of Sr^{90} at time t is considerably less than that rate of excretion of Ra^{226} at the same time after exposure. However, experiments with rats and dogs indicated qualitatively the opposite; this further complicates direct comparisons between Ra^{226} and Sr^{90}.

Lanthanide and actinide rare earths (including yttrium)

392. The lanthanide rare earths are produced in high yields in fission reactions: the parent materials in such reactions are members of the actinide rare earth series. These elements behave similarly in their chemical and biochemical reactions. However, differences in chemical behaviour within these groups (particularly the lanthanides) are reflected in changes in their biological behaviour.[539]

393. Members of both classes are distributed over the earth from nuclear devices; they have not as yet been identified in appreciable quantity in mammals and man. This is undoubtedly because of their extremely low solubility and correspondingly low absorption from the intestine. In animals, less than 0.01 per cent of an ingested dose is absorbed. Very young animals may be exceptional since suckling mice absorbed 2-3 per cent of plutonium given orally in milk or as citrate.[540] Distribution studies suggest concentration of plutonium in bone, liver and ovary. In the latter organ, auto-radiography has shown a selective uptake in certain follicles.[541]

394. These materials, put directly into the blood stream, behave like colloids and are rapidly taken up in the reticulo-endothelial system and in the more superficial parts of the skeleton. In the skeleton retention is very tenacious, but movement from the reticulo-endothelial system is appreciable over a few months.[542]

395. Locally injected solutions of the uncomplexed ions tend to remain at the site of injection. The complexed ions are removed from the site fairly rapidly and follow the pattern of the intravenously injected material.

396. Attempts to damage the intestinal mucosa by repeated high doses of the rare earths (yttrium and plutonium) have shown that the susceptibility of rats to such an exposure is low. Considerable energy is absorbed within the contents of the large intestine, while passage through the small intestine is quite rapid.

Caesium-137

397. Caesium-137 is present in the biosphere. Early spectrographic studies failed to detect radio-caesium in any animal. More recently, it has been found in mammalian and other vertebrate species. In man, the concentration of stable caesium is about 1×10^{-10} g/g wet tissue. Cs^{137} from nuclear debris has now been measured in food and man.[543]

398. The amount of Cs^{137} in the body reflects the quantity of isotope in the diet in turn affected by the degree of radio-active contamination. As a result of the relatively short residence time of Cs^{137} in man (the bio-

logical half-time is about 140 days)[544] attention is being focused on this isotope as a means of studying fall-out rates and mechanisms.

399. The major portion of the Cs^{137} burden of the United States population is probably derived from milk, and meat products are the second most important source.[545] The 1959 mean Cs^{137} burden of a United States resident is estimated at 0.01 μc.[546] This burden contributes a dose of $\sim$ 1 mr/yr., i.e., $\sim$ 2 per cent of natural radiation background.

400. Because of the chemical similarity of caesium, potassium and rubidium, their metabolism is similar. Caesium, like potassium, occurs chiefly intracellularly, with low concentrations in body fluids and bone. Tissue distribution studies have shown that muscle mass contains the largest part (perhaps 60 per cent) of body caesium, with visceral organs, brain, blood, bones and teeth following in that order.[547] Radio-autographic studies in mice have confirmed the high accumulation in muscles and also indicated a rapid and high uptake of Cs^{137} in cartilage.[548]

401. Caesium salts are quite soluble, and are quickly and completely absorbed, more or less independently of route of administration. The ion is excreted through the kidney, except in ruminants where a considerable portion is excreted by way of the gut. Tracer studies in the cow show that about 13 per cent of a single dose will find its way into the milk within 30 days.[549]

Iodine-131

402. I^{131} is produced abundantly in fission and being volatile is readily liberated. Therefore, under special conditions, I^{131} may constitute a problem. Whenever such a situation arises, the concentration of iodine in the small volume of the thyroid gland is the primary hazard.

403. The Windscale reactor incident in England in 1957[550] is an example of this. An accident during reactor operation released fission products from the reactor stack. The fission products escaping through the filters were predominantly I^{131}. Significant downwind contamination covered an area of 518 square kilometres. The only major vector for human intake of I^{131} was milk. The adult thyroid tolerates at least 4,000 rad with no demonstrable ill effects. However, evidence from young children given 200 r of X-rays to the neck suggests that this dose may produce carcinoma of the thyroid in $\sim$ 3 per cent.[449] This comparison of the carcinogenic effects at high levels (thousands of rad) of irradiation with I^{131} in the adult thyroid and effects of lower levels (hundreds of rad) of external radiation with X-rays should not be taken to mean that the child thyroid is more susceptible than the adult to the carcinogenic effect of radiation. Evidence of a carcinogenic effect of external X-irradiation on the adult thyroid is still most scanty, but very limited data suggest that irradiation of the neck of young adults treated for tuberculous adenitis has induced thyroid cancer.[551] Moreover, the very low incidence of thyroid carcinoma in patients with hyperthyroidism[552] and the well-documented experimental evidence that carcinogenic dose response curves eventually reach a maximum and decline at high levels with many types of neoplasm, and particularly in the induction of thyroid tumours by I^{131} in rats, (figure 10),[553] presumably due to complete thyroid destruction at higher dose levels, casts considerable doubt on the significance of the apparent resistance of the adult, and usually hyperthyroid thyroid, to the carcinogenic effect of large doses of I^{131}. In the child's thyroid weighing $\sim$ 5 gm, 1 μc of I^{131} per gramme of thyroid was estimated to yield an integrated dose of about 130 rad. After the Windscale incident, milk samples from nearby farms contained more than 1 μc/litre. To limit radiation to the thyroids of children to 20 rad, it was necessary to prohibit consumption of milk containing more than 0.1 μc of I^{131}/1 of milk. This meant discarding much milk for six weeks.

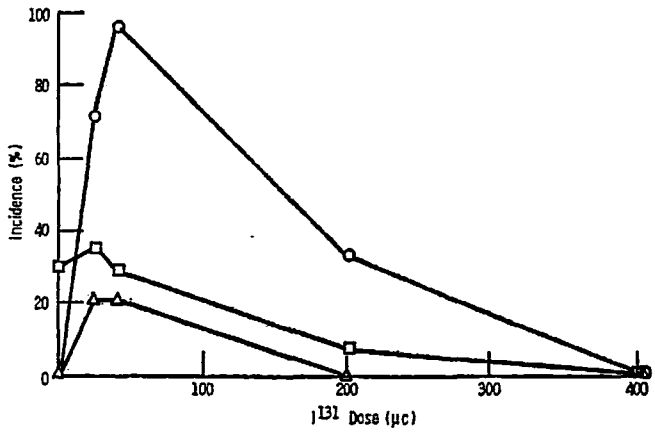


Figure 10. Incidence of thyroid tumours in male Long-Evans rats given injections of various doses of I^{131} [779,780]

o Follicular adenoma
□ Alveolar carcinoma
△ Papillary and follicular carcinoma

404. Two problems in radio-isotope metabolism are of special concern: (*a*) estimation of body content from excretion data; (*b*) acceleration of excretion of a deposited radio-isotope by therapeutic measures. Where total body counting methods are inapplicable, due to the radiation characteristics of the isotope, measurement of radio-isotope levels in excreta offers the only method for estimating body content. The relationship between body content and excreta levels as a function of time after exposure and route of exposure is therefore an important study in large animals and in man after exposures giving rise to detectable radio-isotope excretion. Efforts to promote the excretion of deposited radio-isotopes are discussed in paragraph 525 below.

VII. Dose-effect relationships

EARLY EFFECTS

Immediate

405. At very high doses, usually > 10,000 r, mammals die in minutes or hours probably due to brain injury. Typical central nervous symptoms develop soon after irradiation (acute ataxic phase), similar to irradiation of the head only.[62] An experimental exponential relationship has been established for mice[64] between dose and survival time: log (median survival time, hrs) = a — b dose (figure 11).

Early death

406. Between 1,200-10,000 r, the survival time of animals is $\sim$ 2-6 days. Death is caused by "intestinal syndrome". No dependence of survival time on dose within this range was found (according to Cronkite[375] the range is even broader, up to 30,000 r), but this may be fortuitous: injury to intestines might be decreasing

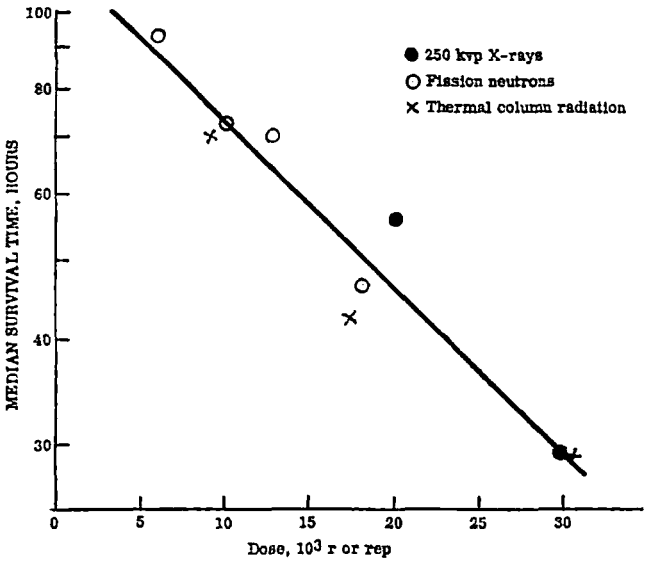


Figure 11. Relationship between high dose and survival time in irradiated mice[64]

with decreasing dose, and the effects of the "bone marrow" or other injury might become more pronounced. Autopsies of animals always show changes in many organs.

407. From 1,000 r down to 50 per cent of the LD_{50} dose survival time is increased. Death after weeks is due to bone marrow injury accompanied by secondary infection. Survival *vs.* dose follows the familiar sigmoid curve, often seen with delayed toxicity. From such curves, conveniently after probit transformation, the mean lethal dose can be calculated. The mean lethal dose, LD_{50} for mammals, is ~ 200-900 rad (table I).

Body weight loss and organ atrophy

408. Irradiated animals lose body weight; this loss is dose dependent, and represents atrophy of different organs and a general deterioration of nutrition of many tissues. Damaged metabolism and lowered food intake contribute to weight loss.

409. Voluntary food and water intake by an irradiated animal can be used for plotting dose-effect curves; no doubt other indices would serve also.

410. Unfortunately assessment of atrophy has usually been limited to weighing the organ. Some components of tissues decline rapidly after radiation; biochemical descriptions are lacking. In mouse spleen after TBR, concomitant atrophy of some elements and hyperplasia of others result in a complex dose relationship.[554]

External irradiation

411. Smith and Tyree[555] irradiated rats with 250 kvp X-rays and showed that three responses to radiation increase with dose—weight loss, time required to regain pre-irradiation weight and limitation of food and water intake. The linear relationship was obtained (24 hours after radiation) for percentage of weight lost or percentage of food intake against log of dose over 25-1,000 r.[117] (figure 12). Weight loss of rats increased linearly with dose over 100-1,200 rad.[556] When weight loss of irradiated rats was compared with that of starved and dehydrated rats, no linear relationship was found within 50-1,400 rad for X-rays and thermal column radiation.[117]

Internally-deposited radio-isotopes

412. Pregnant rats were injected with P^{32} and embryos weighed days 6-10 after fertilization to measure weight loss due to internally-deposited radio-isotopes. Weight loss of 6-day-old embryos correlated linearly with dose but was curvilinear for older embryos.[557]

Intestinal atrophy

413. The weight of intestines decreases sharply after irradiation; correlation between dose and effect is linear.

414. The weight of intestines (expressed as percentage of control) of rats given 250 kvp X-rays and thermal column irradiation depended linearly on dose

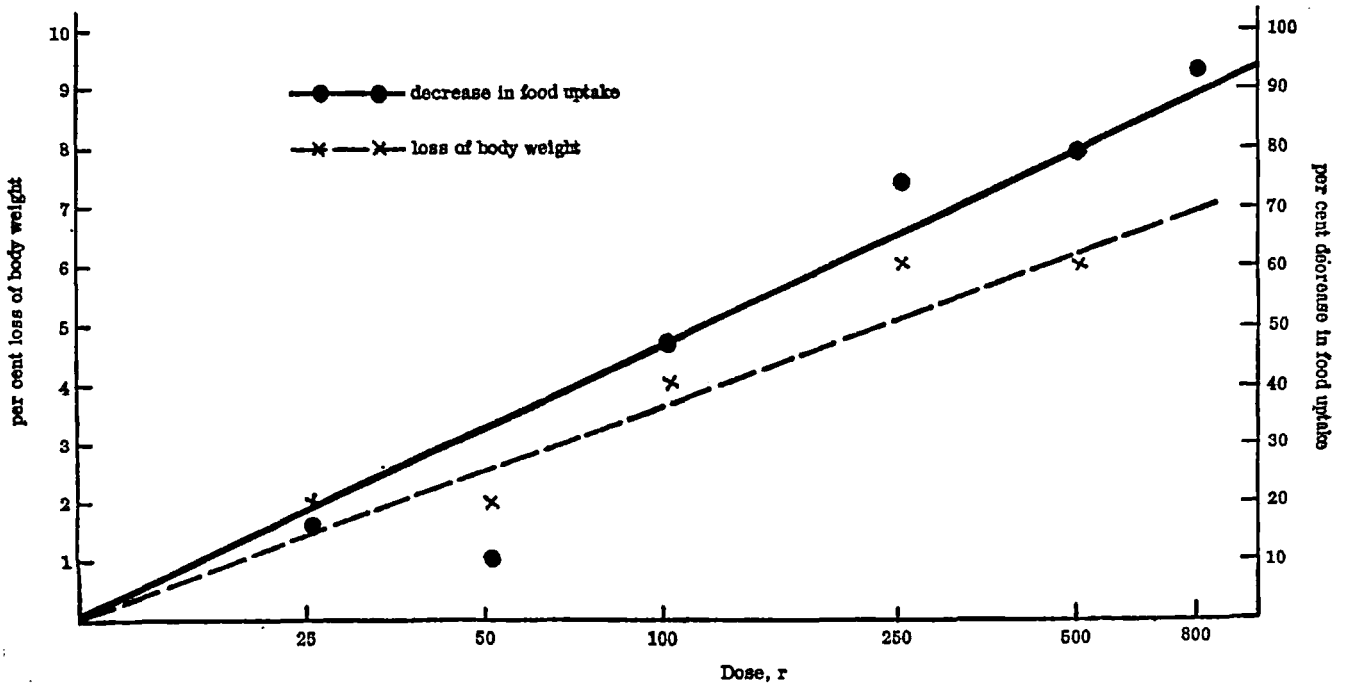


Figure 12. Relationship between body weight lost or decrease in food intake in rats plotted against dose[117]

over 100-400 rad.[556] The equation of the regression line was: intestinal weight (per cent of control) = 102.1 − 0.075 dose (rad).

415. The method, although simple and rapid, is not convenient for studying dose-effect relationships because the change is small: even at high dose (about 400 rad) no more than 30 per cent weight reduction of intestines was found. This is because the radio-sensitive component of intestines, the epithelium, forms only a part of the total weight, the rest being radio-resistant muscle.

416. DNA content as an index for measuring radiation atrophy of intestines was recently suggested by Mole and Temple[558] but detailed studies have not yet been published.

The atrophy of spleen and thymus

417. Thymus and spleen weight decrease in irradiated animals. This effect has been used to correlate dose and effect, and to estimate the RBE of various radiations.

External irradiation

418. Weight loss of spleen and thymus in mice exposed to various radiations was related linearly to the log of dose. With 250 kvp X-rays, organ weight decreased 10 per cent after 50 rad; no experiments with other radiations have been done at doses < 100-150 rad, at which a 20-30 per cent weight loss was found with Co^{60} γ-radiation, 4MeV γ-radiation, thermal, 14 MeV, and fission neutrons.[556]

Internally deposited radio-isotopes

419. The dependence of organ atrophy on dose from internal sources of radiation suffers from uncertainties in dose estimation and chemical toxicity. In mice given tritium-water the rapid equilibration of water enables dose to be calculated on the assumption of an even distribution of tritium. The percentage reduction in spleen and thymus weight was linear with log of dose over 150-600 rad; the corresponding weight loss was 30-70 per cent.

420. Correlation between organ atrophy and radiation from internally deposited fission products (plutonium plus products of neutron irradiation of plutonium deposited in tissues) showed a linear relationship between reduction of spleen weight and log of the concentration of radio-active isotopes in tissue. The dose-range was ~ 400-1,600 rad. The thymus did not incorporate any isotope and could not be used as an index.

421. Thymus is useful for correlating dose and atrophy because of its relatively simple cellular composition. However, there are two competing processes in thymus atrophy: (*a*) decrease of mass, predominating in the lower-dose range, and (*b*) weight gain predominating at higher doses especially > 1,000 r.[559] Perhaps measurement of ribonucleic acid (RNA) would be a more useful index of radiation injury to thymus. Concentration of RNA[560] (per wet weight of tissue) correlated linearly with dose; RNA decreased 10-80 per cent within 100-600 r. Activity of nucleodepolimerases in thymus was also dose-dependent, varying from 40-60 per cent with 40-160 r.[561]

Testicular atrophy

422. Testes weight (expressed as log of percentage control) of mice, rats and hamsters irradiated with 250-kvp X-rays varied with dose, but with important species differences.[562] The dose-effect curve in mice indicated at least two components; in hamsters and rats only one. The first component was highly radio-sensitive: after 75 r, testes weight was ~ 75 per cent of control. The over-all equation of the dose-effect curve, over 0-1,500 r, was:

$$W = Ae^{-k_a D} + Be^{-k_b D}$$

in which W = weight, D = dose.

423. In mice irradiated with 250-kvp X-rays, Co^{60} γ-rays, thermal-column neutron, and α-particles together with Li^7 recoil nuclei dose dependence was entirely different. The relationship was exponential, over 50-300 rad with 20 per cent weight loss at the lowest dose and 55 per cent at the highest. The computed equation was: W = a-b log D. This discrepancy cannot be resolved at present.

424. The exponential equation of Kohn and Kallman[562] suggests that a single event inactivates one biological unit in testes; the effect appears independent of dose-rate.

425. However, this interpretation is questionable in the testis containing various cells, ranging from diploid to haploid, with numerous intermediates. One type of spermatogonia is extremely radio-sensitive; their number is significantly reduced after 20 r. Testes atrophy is due to loss of mature cellular components, along with inhibition of differentiation of earlier stages.

Lymphatic tissue

426. Recently in rabbits given 35 r-1,000 r with 220 kvp X-rays sensitivity of lymphatic tissue was measured by the volume of the appendix *in vivo* and *in vitro*.[563] The appendix volume decreased 55-75 per cent. The percentage decrease of appendix *vs.* dose has two components; from 35-100 r linear and > 100 r exponential (figure 13).

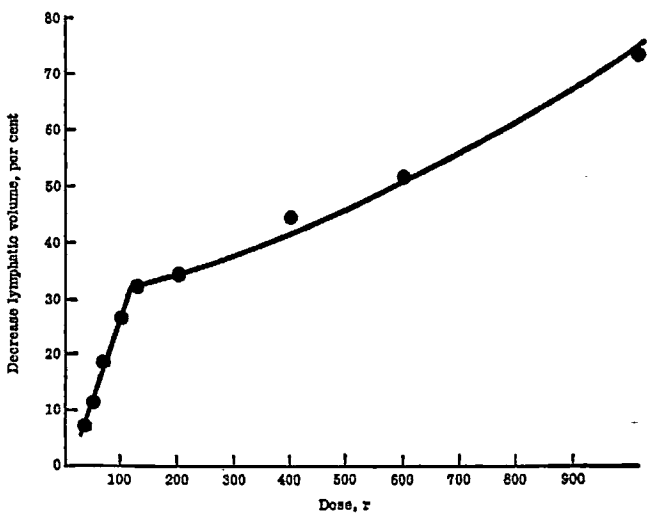


Figure 13. Decrease in volume of appendix irradiated *in vivo* in rabbits plotted against dose[563]

Depression of mitotic activity

427. Suppression of mitotic activity is a prominent effect of ionizing radiation.

428. With isolated single cells, e.g. grasshopper neuroblast, mitosis and the influence of radiation may be followed directly. Radiation given in late prophase

shortly before dissolution of the nuclear membrane is more efficient in inhibiting mitosis (in grasshopper neuroblast) than if given later.[564]

429. The numerous mitoses in irradiated animal tissues make quantitative evaluation more difficult; results depend not only upon irradiation but also upon the stage of mitosis at the time of irradiation. The general picture from many studies is that irradiation decreases the number of prometaphases, metaphases, anaphases and telophases. This is probably because cells irradiated in one of these phases complete mitosis regularly while cells in interphase are prevented from entering mitosis. The decrease in prometaphase-through-telophase cells correlates with dose. If the dose is sufficient to reduce mitotic cells to zero, the time of their reappearance also directly relates to dose.[565] (figure 14).

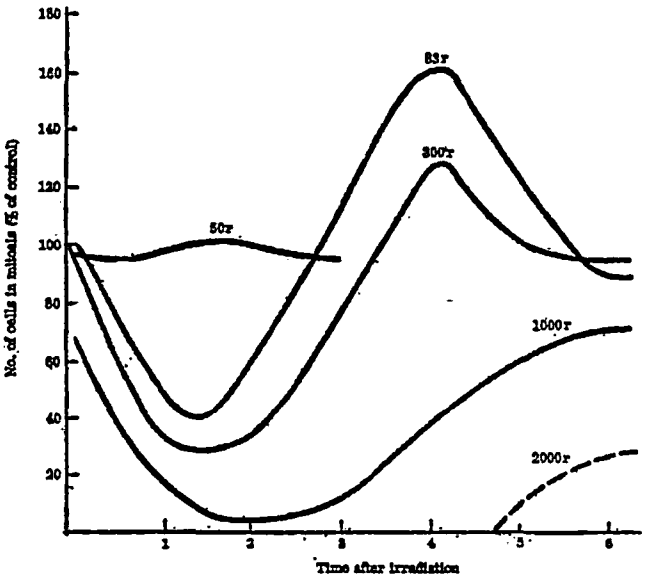


Figure 14. Relationship of dose to time of reappearance of mitosis[565]

430. The effect of radiation upon mitotic activity of animal somatic cells has been studied quantitatively on chick fibroblasts, rat retina cells, grasshopper neuroblast and epidermal and lymphatic cells of mice.

431. The doses of X-rays in chicken fibroblasts were 80-450 r; the smallest depression of mitotic index was ~ 60 per cent.[566] The relationship between dose and percentage of normal mitotic index was curvilinear, but lack of data at lower doses precludes extrapolation of the curve. A similar curve was obtained with rat retina cells;[567] their radio-sensitivity was higher than chicken fibroblasts: ~ 30 r reduced the mitotic index ~ 70 per cent, and doses of 180 r decreased the mitotic index to zero. Grasshopper neuroblast was still more sensitive; the dose-effect curve was similar (figure 15).

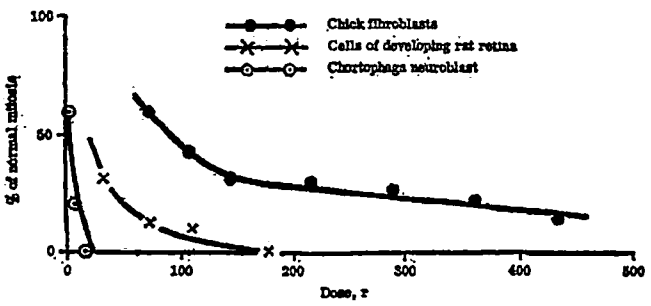


Figure 15. Relationship between dose and percentage of normal mitosis in chicken fibroblasts,[566] cells of developing rat retina,[567] and grasshopper's neuroblast

432. Doses as low as 5 r of X-rays depressed by 50 per cent the mitotic activity of the adrenal glands, jejunum, lymph node and epidermis of mice (figure 16).[568] Log of dose *vs.* percentage reduction of mitosis was approximately linear. Some curves showed a threshold effect; others did not.

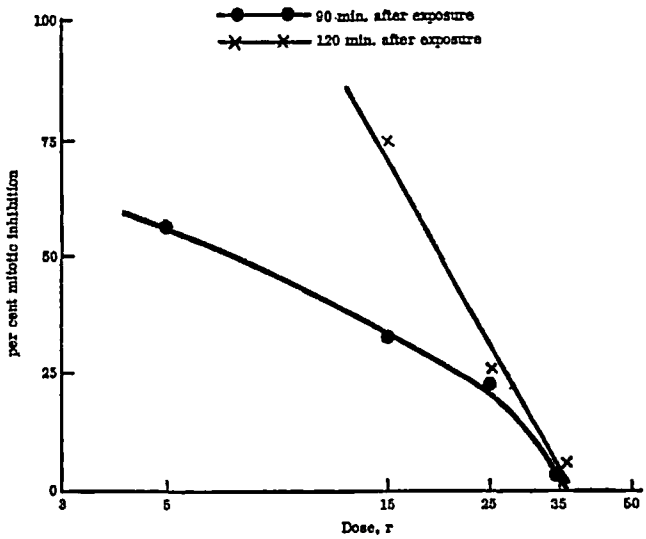


Figure 16. Relationship between dose and mitotic activity of the adrenal glands, jejunum, lymph node and epidermis of mice[568]

433. Probably a more useful method of following dose-effect relations is by measuring the time for the mitotic index to return to normal. This method used to study the mitotic index of mouse ear epidermis cells irradiated with thermal neutron or X-rays over 5-55 rad showed a linear relationship between log of duration of depression of mitotic activity and dose.[565]

Depression of iron uptake by erythrocytes and erythocyte-forming tissues

434. The functional state of erythrocyte-forming tissue is usually gauged from incorporation of Fe^{59}. More extensive studies usually measure Fe^{59} in erythrocytes simultaneously with isotope content in isolated bone-marrow cells and various other tissue compartments, e.g., spleen, liver and plasma. Irradiation depresses iron incorporation.[569]

Quantitative studies

435. Iron incorporation by bone-marrow of animals (mice) irradiated with X-rays (250 kvp), γ-rays (4 MeV Co^{60}), neutrons (14 MeV fission and thermal column), and tritium β particles over 40-300 rad[556] was depressed 10-80 per cent. Correlation between dose and effect followed the exponential equation; effect = a − b log dose.

436. A different dose-effect was found in rats irradiated with Co^{60} gamma-rays and with thermal neutron (with RBE equal about 1) over 40-500 rad (figure 17);[570] iron-uptake decreased steeply with increasing dosage; it was significantly lowered at 60 rad and reached about 30 per cent of control value at 150 rad; further increase in dose had less effect on iron uptake. The two-

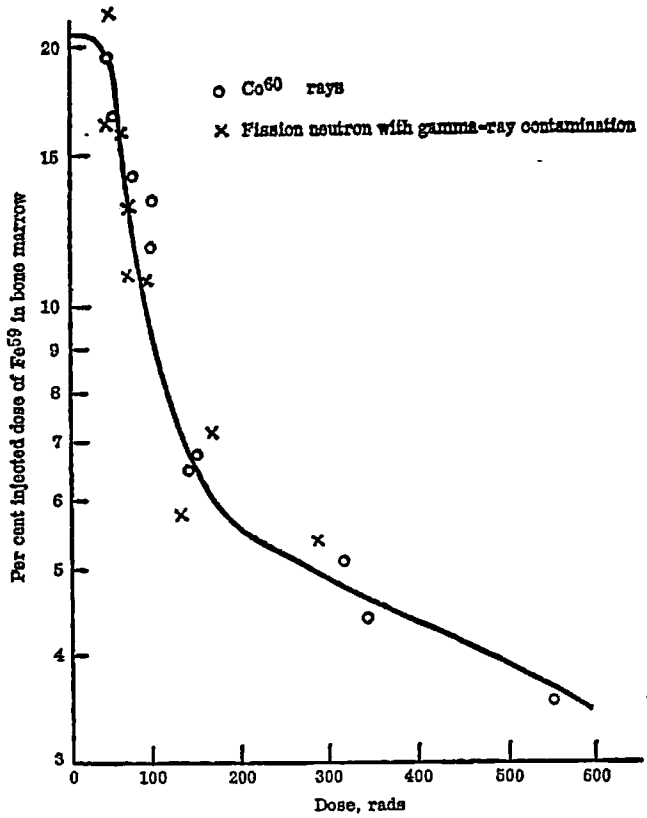


Figure 17. Depression of Fe^{59}-uptake in bone-marrow of rats irradiated with Co^{60} γ-rays and thermal neutrons[570]

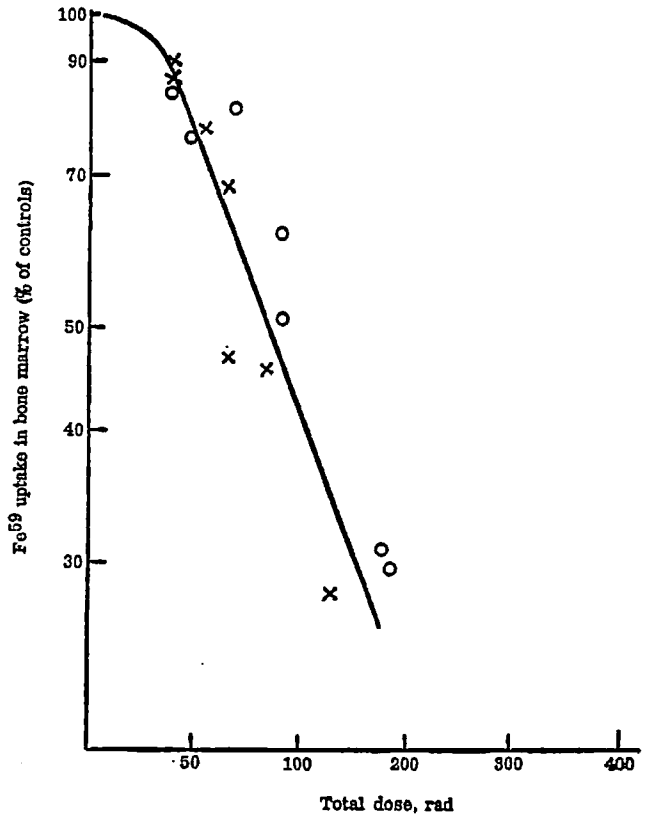


Figure 18. Effect of dose on Fe^{59}-uptake in bone-marrow of rats after 40-150 rad[570]

component character of the curve corresponds probably to two main systems of iron incorporation in blood marrow (*a*) in dividing and differentiating cells of normoblast series, (*b*) in surviving, less sensitive cells (e.g. reticulocytes), and perhaps the iron-protein storage complexes in bone-marrow.

437. A plot of log percentage iron uptake *vs.* dose over 40-150 rad gave a straight line. The graph shows that doses below about 40 rad have very little if any influence on iron uptake by bone-marrow. The equation derived is log-effect = a − b dose (figure 18).

438. Results obtained by various authors disagree, possibly due to differences in experimental methods. Storer's and Rambach's studies show a threshold dose for iron incorporation at 30-40 rad while others found an impairment of bone-marrow erythropoietic function at 5 rad. A still more pronounced difference is apparent between dose-effect function of the two groups of investigators: in Storer's results effect varies proportionately to log-dose; in Rambach's data, log of effect varied with dose. Experimental differences were considerable; the incorporation time for iron in one group was 6 hours, in the other, 72 hours; the amount of radioactive iron given controls was five times larger in Rambach's work than in Storer's.

439. The high sensitivity of erythropoietic tissue and the ease and precision with which its functional status can be followed make it one of the most suitable for work on the sensitivity of mammalian cells. It is doubtful whether single dose experiments will solve the problem, as fast division leading to numerous cell types at each moment in bone marrow implies a mixed population of presumably different radio-sensitivities. Long-term irradiation, preferably at very low levels, might be more useful in evaluating the effects of radiation on erythrocyte-forming cells. Unfortunately no satisfactory experiments have been done. In some reported so far, long-term irradiation has been given as repeated single irradiation and this, obviously, might permit recovery between irradiations; also, the time between the last irradiation and the assay of the iron uptake was in some experiments 10-11 days—ample to make injury negligible by repair. Some injury persists as shown by experiments of Baum and Alpen[571] who computed the exponential correlation between number of exposures and decrease of Fe incorporation into erythrocytes. In long-term exposure, this irreversible or very slowly reversible injury might accumulate and become a noticeable injury.

Suppression of immunological mechanism

440. TBR damages the immune response of the body: production of antibodies is suppressed, susceptibility to infection increased and transplanted heterologous tissues survive in the host for a long time. Neither antibody production nor susceptibility to infection is a convenient index of the effect of radiation. However, the incidence of successful tissue transplants has been used to study the dose-effect relationships.

Leukaemia transplantation

441. The incidence of successful transplants of mouse leukaemia into another strain increases with dose over 100-500 r. A straight line can be plotted of probit of percentage of leukaemia *vs.* log of dose.

442. In mice irradiated with X-rays or neutrons 100-600 r or rep-log of dose was linearly related to percentage of successful leukaemia transplants (after probit transformation).[572] Different strains of mice showed marked

differences. The mean dose producing 50 per cent leukaemia deaths ranged from 327 ± 20 r-470 ± 41 r for X-rays, and from 258-363 rep for thermal column irradiation. The slope of the probit percentage incidence *vs.* log dose line varied 5-10 for various strains.

Late effects

Induction of lens opacity

443. Cataract formation is not understood; but opacity of the lens is due to radiation damage of lens epithelium that has a relatively high mitotic activity. The mitotic index decreases to ~ 0 after ~ 1,500 r, followed after a time (dose-dependent) by recovery with a typical overshoot in mitotic index. Abnormal cells are formed: some showing increased size, decreased transparency and multiple nuclei. Similar abnormal cells can also be seen in many other tissues of high mitotic activity, but they cannot be shed from the lens as they can from bone-marrow. They remain inside the lens structure (probably because of the restricting tough capsule surrounding the lens) and form centres of opacity. Recent data indicate that slight recovery of the lens is possible.[573]

444. Cellular homogeneity along with inability to slough the injured cells make the lens useful for studies on dose-effect correlation, only limited by the methods for assaying the injury and by difficulties in estimating the dose.

Methods

445. The degree of injury (i.e. the degree of opacity) is estimated by an ophthalmoscope or slit lamp; this necessarily subjective method has a rather high threshold of resolution. Comparison of the effect of radiation in various animals is more difficult because of variation in susceptibility among species and dependence on age. Lastly, estimation of the dose to the lens has a large margin of uncertainty, especially with neutron-irradiation.

446. Reduced glutathione decreases in an irradiated lens, as does the activity of the enzymes of glutathione metabolism.[574] Irradiation also decreases the weight and RNA content of the lens, even when no opacity is seen.[575]

Human studies

447. The lowest dose for lens opacities formation has been estimated from experimental as well as human accident studies. The slow formation of cataract makes the outcome difficult to interpret.

448. Notwithstanding these reservations, a number of estimations of the critical dose for cataract formation have been made. Among Japanese survivors up to 1950, 100 people with radiation cataract have been found among those who received an estimated dose of 5-15 rep in neutrons and about 600 r of γ-rays.

449. In 10 cases of nuclear accidents, August 1945-September 1946, cataract formation was seen in only one person who received whole body dose of 15 rep neutrons and 26 r of γ-rays; the calculated dose to the eye was 45 rep. The critical dose for cataract formation apears to be ~ 20-45 rep.

450. The data on radiation-induced cataract in man are hard to analyse quantitatively. Dosage is often very uncertain and the follow-up time of patients not long enough. A report of Cogan and Dreisler[460] shows that one out of three patients given 600 r of 200-kvp X-rays developed a cataract; with increased exposures the time for appearance of opacity was shortened. A survey of 100 cases of radiation cataract and 73 cases of patients given radiation to the head was made by Merriam and Focht.[464]

451. The patients were grouped according to the time-schedule of irradiation. For the cases given a single dose, the minimum cataractogenic dose was 200 r, for the cases given doses spread over 3-12 weeks the cataractogenic dose was 400 r, while for those whose treatment spread over more than three months the dose was 550 r. The greater the dose the less the time for the appearance of cataract. In figure 19, incidence of cataract is shown as a function of dose among patients irradiated with doses given over more than three weeks.

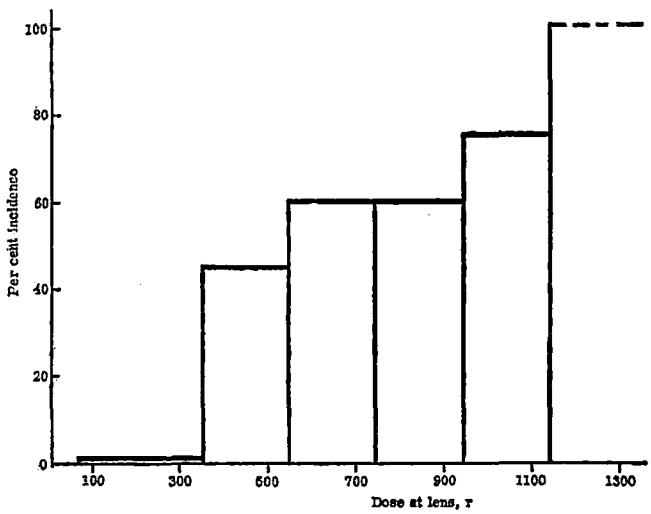


Figure 19. Relationship of cataract incidence to dose given over more than three weeks[464]

Experimental studies

452. A number of experimental studies permit rough estimation of the lowest dose for cataract formation. Storer[576] found that any doses of 250-kvp X-rays, 12.5 r and up increased the incidence of cataract in mice (lower doses were not tested); this agrees well with the increased incidence of lens opacities after 15 r of X-rays.[174,577] The lowest dose for rabbits for hard X-rays (1,200 kvp) was ~ 250 r.

RBE

453. Neutrons have a higher efficiency in inducing cataract: their RBE for purposes of human protection has generally been taken as 10 by ICRP (A). Some earlier studies on neutron-induced cataracts employed cyclotron-produced beams, i.e. neutrons together with hard γ-rays: Evans[578] found that 80 rep of fast neutrons produced lens opacity in 100 per cent of mice. Storer[576] found the RBE of neutrons was 15 relative to 250 kvp X-rays; 2.9 rep of fast neutrons produced lens opacities in 50 per cent of exposed mice.

454. During Operation Greenhouse, mice receiving 1-10 rep of fast neutrons (together with about 1 r of hard gamma-rays) all showed cataracts. In rabbits, Cogan *et al.*[579] estimated the threshold dose of 14 MeV neutron for cataract induction to be ~ 10 rep (RBE of neutrons ~ 220).

Dose-effect correlation

455. Cataract formation is dose and dose-rate dependent: the RBE of different radiations is perhaps more diverse than with other radiation injuries and does not permit setting up an equation for dose *vs.* effect. The dose dependence of cataract formation for neutrons[580] and for γ-rays[174] shows a clear correlation between dose, energy of neutrons, and degree of opacity (figures 20-21). Constants cannot be derived.

Shortening of life-span

456. Continuous exposure to low doses of radiation does not cause the dramatic effects seen at high doses. The symptoms are not specific to radiation. The effects of long-term exposure necessitate study of life-span and comparison of causes of death between exposed and non-exposed populations. Observations have to continue until the death of irradiated subjects. Experiments are limited, therefore, to short-lived animals. Exclusion of multiple intercurrent factors, e.g. infections which in long-term experiments might affect any group is essential. Moreover, for adequate study of the cause of death, large numbers of animals are needed, especially when the main interest lies in a rare effect, e.g., as in studying the incidence of tumours. Strains with higher incidence of this effect may be selected but this may restrict the validity of the results. Usable results are therefore still rather meagre.

457. The life of animals exposed to continuous irradiation is usually shortened. Survival plotted against time gives sigmoid curves; the median survival time is shortened with exposure. Different strains of mice differ in sensitivity to radiation as measured by LD_{50}'s[28] and in different life-span shortenings linearly related to their life expectancy.[224]

458. If shortening of life-span is plotted against dose-rates, the relationship is linear for γ-rays and fast neu-

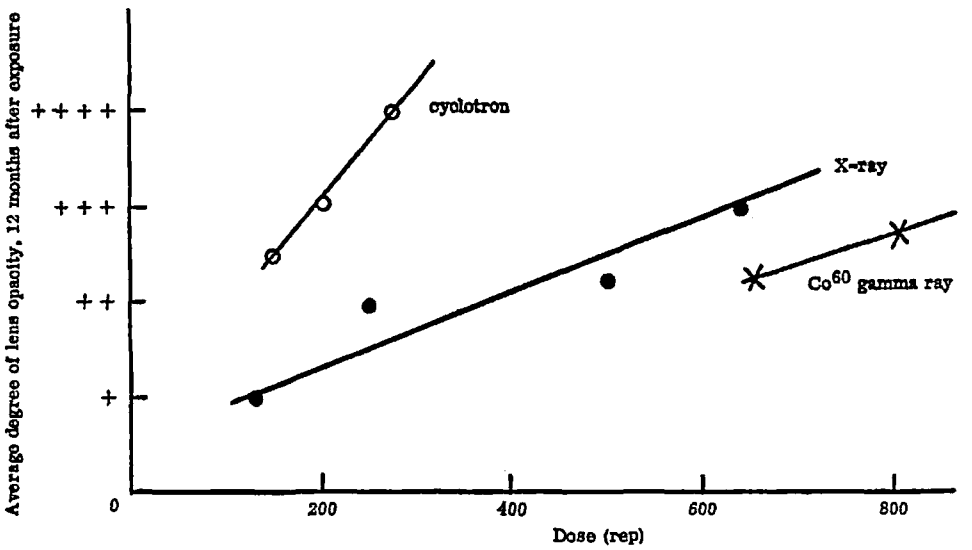


Figure 20. Relationship between dose and degree of opacity[174]

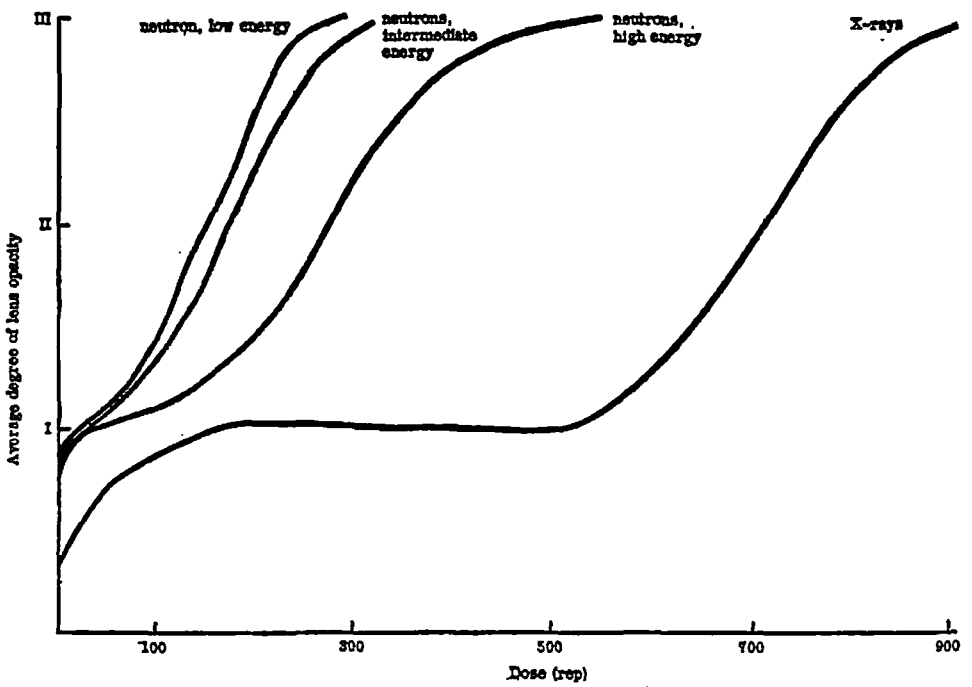


Figure 21. Relationship between dose and degree of opacity[580]

trons within the range of dose rates shown in figure 22.[581]

459. When irradiated animals are given a second course of irradiation, the LD_{50} depends on the time between the first and second exposure, and increases asymptotically with time.[582]

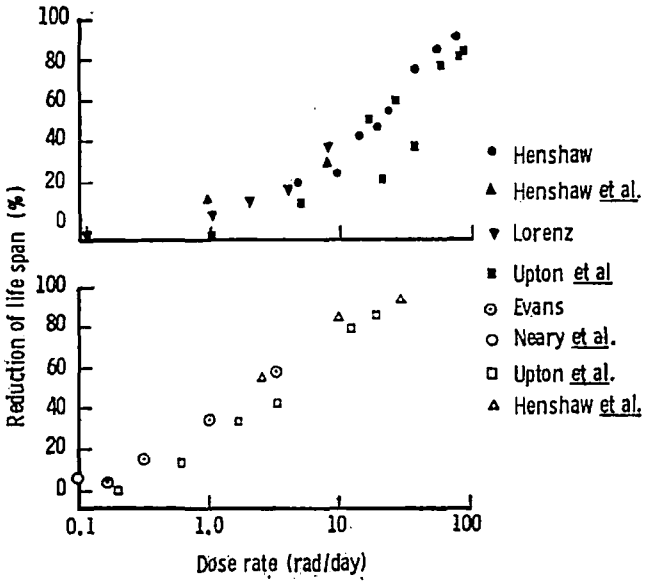


Figure 22. Reduction of mean or median survival time in mice exposed daily for the duration of life (solid symbols, X- and γ-rays; open symbols, fast neutrons). Redrawn from Upton[553]

460. From these data, Blair formulated a theory on the shortening of life-span by irradiation:[257]

(*a*) The total injury caused by radiation is proportional to the dose;

(*b*) The injury is partly reparable;

(*c*) Recovery from reparable injury is exponential;

(*d*) Irreparable injury accumulates in proportion to total dose;

(*e*) Reparable and irreparable injury are additive and death occurs when their sum reaches a level inversely related to the age of exposed animals.

461. Blair's theory has stimulated design of experiments and many results fit its predictions.[48] Blair's postulates have been challenged. Radiation damage is made up of many individual injuries,[583] mostly unidentified, and the pattern varies from strain to strain.[224] Accordingly any simple recovery mechanism is over-simplification. Recovery also differs according to kind and manner of irradiation.[66] That the lethal threshold is inversely related to life expectancy is doubtful, since the LD_{50} varies with age but less simply than as proposed by Blair.[584-586]

462. Demographers have long known that the log of age-specific death rate of a population ("the force of mortality") plotted against age at death, is roughly linear beyond early childhood. This relationship, Gompertz' law, applies to irradiated populations. Force-of-mortality curves for exposed animals parallel control curves at a distance directly related to dose for single exposure, whereas for constant long-term irradiation, the slope of the curve increases by a factor depending on dose rate.[235]

463. These observations have encouraged analogies between chronic irradiation injury and aging. Aging, while familiar to everyone, is difficult to define. What is observed statistically is not aging but mortality—something related to it and which measures it. The analogy is supported by the pathology of irradiated animals, showing histological damage resembling lesions of senescence.

464. Sacher[231, 256] has stated that the physiological state of an individual fluctuates around some central value and any individual leaves the population when his state reaches a limit called the lethal boundary. It is assumed that such a limit is a fixed one, common to all individuals of the population. The physiological state of the individual decays with time, approaching asymptotically the lethal boundary. From mathematical argument Sacher asserted that log rate of mortality follows linearly the mean physiological state of a homogeneous population. If it is assumed that the physiological state decays linearly with age, as seems the case for many physiological characters, the force of mortality will also be linearly related to age. This is indeed observed for most animal populations. A corollary of Sacher's theory is that impairment of the physiological state brings it closer to the lethal boundary, so that the probability of transgressing it through random fluctuations increases. Irradiation would shift the physiological state so that the force-of-mortality curve of the exposed population would coincide with the curve for some later age.

465. Sacher's brinkmanship theory is closely related to the information approach to lethality and radiation damage. Although cloaked in different language and using different mathematical conventions, this theory as expounded by Quastler[252] and by Yockey[587] leads to a parallel with Gompertz' law.

466. In their present state these theories are so all-inclusive that they are not concerned with the nature of the radiation injuries or with the recovery processes; physiological state (or degree of orderliness according to Yockey) is largely undefined, as is the death to which the theories refer. Accidental deaths are not considered by them; it is less clear whether the only relevant deaths are not those ascribable to senility—the observed causes of death are dependent on diagnostic accuracy. Radiation studies have been confined mostly to recording the overall mortality, thus lumping specific and "senile" causes of death; but as the experiments are expanding, consideration of the causes of death becomes unavoidable.

467. Differences among strains disappear for males when deaths from leukaemia are excluded. On the other hand, when animals dying from leukaemia or females carrying ovarian tumours are excluded, even differences between sexes disappear.[224] Larger numbers of animals might well have brought out further differences ascribable to the differential incidence of other conditions. Something of the kind is seen in human populations where Gompertz' law holds, but only approximately and over a limited age range. However, on plotting the force of mortality for individual causes against age, linearity of most of the resulting graphs is strikingly improved and can be carried down to a much earlier age.

468. Although nothing is known about the lesions shortening life-span in multi-cellular organisms, knowledge that irradiation is powerfully mutagenic has incited speculation about the role of somatic mutation.

469. Somatic mutation has been invoked by Szilard[588] as the cause of aging. He thinks a cell dies when both homologous genes of a pair responsible for an essential cell function are impaired by mutation. Mutation can be inherited, when it is called a fault, or be spontaneous, and

called an aging hit. The number of faults carried by an individual is fixed at birth, whereas the aging hits accumulate randomly with time, so that at any moment the number of surviving cells carried by an individual depends on his hereditary load and on his age. Death occurs when the number of surviving cells carried by the individual approaches a critical limit. Szilard calculated the average number of faults carried by the individual in human populations, and predicted the shortening of life-span by radiation in man. His results cannot be checked in our present state of ignorance about the life-shortening effect of radiation in our species. The theory in its present state does not predict the expected parent-offspring correlation in life-span; if it did it would prompt a not too difficult test on human populations.

470. Besides Szilard, Failla[255] also interpreted aging as a mutational effect, and showed that Gompertz' law can be derived by assuming that the change in mortality rates with time is a one-hit process. It is none the less premature to attribute such a complex phenomenon as aging to somatic mutation which in vertebrates has been studied mainly in cell cultures. There is little knowledge about possible repair and recovery mechanisms of mutational effects. Even in unicellular organisms, radiation damage is not confined to the genome and it would be surprising if this were not true for the cells of higher organisms. Attempts to shorten life-span by giving chemical mutagens were unsuccessful,[589] but more recent work in two laboratories has confirmed the radiomimetic effects of chemical mutagens for life-shortening.[219, 590]

Induction of tumours

471. In man the induction of leukaemia at present provides a basis for inferences about the dependence of incidence on dose, and data being accumulated as to the induction of bone tumours by radium is adding valuable information to this.[591] Animal data prove that ionizing radiation induce benign and malignant tumours. If tumour incidence increases with dose, taking into account the statements made later on threshold, studies on dose-effect relationships are by their nature inconclusive about what the mechanism is.

472. Knowledge on tumour growth is limited and experimental difficulties abound. The long latent period in the appearance of tumours impedes work at higher doses, since other radiation-induced pathological disturbances may cause death before tumours appear. At low level of irradiation animals have to be kept a very long time; intervening infections often vitiate experiments. Moreover, the incidence of tumours is low; low-level irradition studies require unwieldy numbers of animals.

473. As a further complication, radiation is not necessarily the direct cause of tumours: lymphoma in mice and mouse ovarian and pituitary tumours are an indirect effect of irradiation.

474. The role of co-carcinogens is almost completely unknown in radiation carcinogenesis. In chemical carcinogenesis, with a co-carcinogen, the amount of carcinogenic agent was related linearly to tumour incidence; carcinogen alone has a threshold.[592] Croton oil after radiation increased the incidence of benign tumours in skin.[593]

475. Combined radiation and methylcholanthrene were synergistic in inducing leukaemia, P^{32} and methylcholanthrene[594] in inducing skin tumours, and mechanical irritation and X-rays in inducing sarcomas.[595]

476. Change in susceptibility with age of animals is still another complication in studies on tumour-induction.[596] This and the long latent period for tumour-induction make correlation of injury with accumulated dose difficult in animals exposed to long-term low-level irradiation.

Quantitative studies

477. The rate of tumour development and amount of strontium-89 injected into mice were related linearly, after a latent period which increased with diminishing dose.[597] However, the plot of the number of tumours at any time after treatment becomes curvilinear and appears as a higher power of the dose.[285]

478. Dose-response curves for mouse lymphomas,[297] ovarian tumours and myeloid leukaemia were non-linear.[303] Bone tumour induction in mice by strontium-90 is not proportional to incorporated radio-isotope and may be described as proportional to the square or cube of the dose.[598]

479. Data on the influence of dose-rate in the induction of neoplasm by ionizing radiations are as yet fragmentary. In most instances a given dose is substantially less carcinogenic absorbed over a long period at low dose-rates than it is absorbed in a single short exposure.[553, 599] Blum,[600] from skin-cancer induction in mice by ultraviolet light, suggests that the time for the appearance of tumours is inversely proportional to the square root of the dose-rate; the dose-effect curve would have a rising inflection with increasing dose-rate, and a threshold, if any below limits of observability.

Radiation-induced leukaemia in man

480. Radiation-leukaemia surveys may examine a population of exposed and non-exposed people and observe directly the incidence of leukaemia in the two groups. In retrospective studies, groups of leukaemic and non-leukaemic populations are selected, the frequency of irradiated and non-irradiated individuals calculated, and the risk of leukaemia estimated.

481. Retrospective studies, beginning with people selected without prior knowledge of their radiation history, are likely, in the present state of radiation records, to misestimate exposure; the reliability of information about past radiations depends largely on memory.

482. Three major prospective studies are the Hiroshima and Nagasaki atom bomb survivors,[420–426] children treated with X-rays for thymus enlargement,[438, 445] and adults treated with X-rays for ankylosing spondylitis.[412, 440]

The Hiroshima and Nagasaki surveys[420–426]

483. The Hiroshima and Nagasaki explosions offer a unique and most important opportunity to study the radiation-leukaemia problem. They should answer the question about the long-term effects in child and adult. The irradiation dose was large and the population exposed substantial: $\sim$ 1,000 survivors received an LD_{50} dose, and 10,000 a dose over the greater part of the body of $\sim$ 100 rad or more. Important effects could hardly be missed. Overlooked effects could only be those produced from prolonged exposure to smaller doses or those requiring intense radiation to a restricted part of the body. Such effects would be observed most readily among people occupationally exposed and among patients given large doses of therapeutic radiation.

484. Data from the Hiroshima and Nagasaki populations will be less clear about dose-effect relationships. The irradiation was instantaneous; the results cannot tell what is likely to happen where the dose is spread out in time or intermittent. Great efforts are being expended to make exposure history as accurate as possible; nevertheless, how people were shielded is, in many instances, uncertain and hence there will always be some uncertainty about the exact irradiation received. Therefore, information about dose-effect relationships must also be sought elsewhere. Here data from hospital patients or persons occupationally exposed should prove useful. The dose-effect relationship is discussed in paragraphs 248-253.

Children irradiated for thymus enlargement[436, 438, 445]

485. The data are too scanty to warrant conclusions about the relationship between dose and incidence of leukaemia or thyroid cancer among children given radiation to the thymus (see paras. 263-272).

X-ray treated ankylosing spondylitis[412, 440]

486. An extensive survey on irradiated ankylosing spondylitis in England by Court Brown and Doll gave special attention to dosage expressed as maximal bone-marrow dose, mean bone-marrow dose, and whole-body integral dose for every leukaemic, and for every patient belonging to a random sample of the whole exposed population. The results are familiar. As there were only two leukaemic female patients, the quantitative study was limited to males. Age distribution ranged from fourteen years onwards.

487. The clinical treatment of ankylosing spondylitis consists usually in irradiating the affected bones with a dose of $\sim$ 1,000 r. If the symptoms recur, re-treatment is often given. This is the explanation in this study of the positive correlation between cumulative mean bone-marrow dose, and the time between the first treatment and death of the patient. One possible explanation of the findings not excluded by the data could be that patients with ankylosing spondylitis, irrespective of the method of irradiation, are more likely to develop leukaemia than healthy people.

488. With these limitations in mind, the incidence of leukaemias was plotted against maximal bone-marrow dose, mean bone-marrow dose, mean bone-marrow dose among patients whose spine and sacroiliac regions only were exposed, and whole body integral dose. The incidence in all depends on dose and the dose-response curve bends upward. This suggests a non-linear relationship between exposure and incidence.

489. Owing to the fewness of cases on which it is based, the ankylosing spondylitis survey only proves that there is a dependency of incidence on dose but gives little information as to quantitative relationship. Further details on the dose-effect relationship are given in paragraphs 254-262.

Concept of threshold

490. Thresholds have been observed for many somatic effects, but it is a question whether radiation and leukaemia incidence are related below a certain dose. Whatever the dose-response curve, a critical exposure level might be required before irradiation brings about the cellular derangements responsible for inducing leukaemia and other tumours. Experimental and clinical data on tumours and leukaemia considered as demonstrating the linear character of the dose-effect curve are all obtained in the higher dose-range, 100 rad and above. The nature of this relationship has not been studied for lower dose levels. Kamb and Pauling[601] have expressed the view that the existence of a very low threshold or its absence cannot be feasibly determined by studies in animals. A. V. Lebedinsky's[602] conception may prove to be correct: he believes that for initial changes in any structures of an organism at the molecular level there is no threshold dose at which the various types of ionizing radiation begin to have an effect, whereas a threshold does exist at the level of the cell, the tissue, the organs and the organism due to compensatory responses and regenerative processes. The ankylosing spondylitis and the Hiroshima surveys hint that at the lowest doses no difference can be shown between the observed incidence of leukaemia and the incidence expected in the general population. In such circumstances a search for a threshold is futile. It cannot be taken as axiomatic that if at moderate or large doses an effect is proportional to dose it is justifiable to extrapolate the same relationship to lower doses. Recent evidence neither proves nor disproves the existence of a threshold for radiation effects in inducing tumours in man. To avoid the danger of under-estimating the probability of radiation-induced leukaemia and other malignancies, it seems reasonable to assume that the observed cases of malignancy will not exceed the number predicted, if the relationship between incidence of malignancy and dose were considered linear (no threshold) for all doses.

VIII. Protection and modification of radiation injury

Introduction

491. This chapter discusses the physiological, biochemical and biological methods that have been developed to protect against and modify the injury of living organisms by radiation. Although to date work on radiation protection and recovery has found few practical applications to the survival of higher organisms, this is a rapidly developing field and more recent ways of promoting recovery by transplanting blood-forming cells may develop practical significance.

Protective agents

Anoxia

492. That anoxia reduces radiation mortality was first shown by Lacassagne[603] in newborn mice. Also, rats exposed to 800 r in 5 per cent O_2 + 95 per cent N_2 were alive 30 days after exposure; all controls died.[604] At 1,200-1,400 r, 50 per cent of treated animals survived 30 days. Results with mice in 7 per cent O_2 + 93 per cent N_2 were less impressive; $\sim$ 80 per cent of the treated animals survived 800 r, lethal to all controls. Similar results were obtained in chicks,[605] rats,[606-607] and mice.[608, 609] Some symptoms, e.g., desquamation, can be alleviated by hypoxia.[610] Lamson *et al.*[611, 612] studied long-term effects, such as life-shortening, tumour incidence, hypertension, and nephrosclerosis, in rats surviving 1,000 r of hypoxic TBR. Carbon monoxide also reduced the radio-sensitivity of mice,[613, 614] guinea pigs, rabbits, and rats.[615] CO_2 was ineffective.[616] Correlation of anoxia with various responses has been reviewed[617] and the mechanism discussed.[618-620] Cyanide-induced anoxia was particularly effective in mice;[621] other workers have had difficulty in getting similar re-

sults.[95,96,622,623] Nitrate also reduced radiation mortality somewhat.[624,625] P-aminopropiophenene, a methaemoglobinaemia-producer, gave 72 per cent survival in mice given an LD_{100} radiation exposure.[626,627] Another way of lowering O_2 tension, hypothermia, increases survival rate in newborn mice[628] as confirmed in mice and rats.[629,630] On the whole, this approach, while illuminating the mechanism of protection, offers few practical possibilities.

493. Radiation response may be modified in two ways: (*a*) preventing injury to vital parts of the organisms; (*b*) aiding recovery of the affected system. Injury can be prevented by supplying cells with chemicals interfering with or limiting formation of free radicals or making the cell constituent less susceptible to interaction with the radical; the protective chemical might even reverse actual damage, e.g., oxidized thiol groups. A pharmacological drawback of preventive chemicals is that they must be given immediately before irradiation so as to be at the target site during irradiation. Biological entities—cells or tissues—introduced after radiation can replace affected cells and tissues and thus permit recovery. Modifying factors in irradiated organisms may be transient or permanent.

Protective chemicals

494. Serious study of protective chemicals began after Barron's demonstration that sulfhydryl compounds protect many enzyme systems *in vitro*.[631] Patt[632] first used a sulfhydryl compound for protection of animals, and was soon followed by others.[633]

495. Table X[634] lists many varied compounds tested for protective effects.

496. The way in which protective compounds work is controversial. Table X shows how widely different chemical entities offer varying degrees of protection. Presumably, no single theory encompasses all substances.

497. Protective chemicals may act in the following ways:

(*a*) Inactivation of radiation-induced free radicals;

(*b*) Minimizing free radicals formed by induction of hypoxia;

(*c*) Induction of metabolic changes;

(*d*) Reversion of injury in the primary target.

498. Inactivation of free radicals formed in water by radiation is the most widely accepted theory of chemical protection.

499. Thiol compounds are known to react rapidly with free radicals[635] thereby scavenging intra-cellular free radicals. Some sulfur-containing compounds are protective *in vivo* through the formation of a thiol, e.g., alkyliso-thioureas rearrange into mercaptoalkylguanidines.[636,637]

500. The radical-scavenging hypothesis does not account for several facts in radiation protection. Marked differences in protection are given by structurally closely related compounds (e.g., N-diethylcysteamine and N-methylphenylcysteamine);[638] reaction products of thiols with free radicals in irradiated serum are a minute fraction of the total free radicals formed;[639] also, it does not explain protection against the direct action of ionizing radiation which is probably responsible for most damage.[640]

501. Differences in activity of closely related compounds might reflect inability of some to enter the cell. Protection against the direct action of radiation might be explained by assuming that thiol compounds restore enzymes to the —SH condition needed for their function —an hypothesis suggested by Pihl and Eldjarn.[634] Proteins form mixed disulfides easily, e.g., insulin fragments.

502. Compounds containing the labile —SH group protect molecular structures against direct and free radical-mediated-action of radiation. Undoubtedly, an additional action is lowering intracellular O_2 tension and reducing number of free radicals;[641] thiols share the latter property with several other chemicals e.g. choline derivatives.[642] Several thiols protect animals against O_2 poisoning; this supports the belief that lowering of O_2 tension is important in the action of protective chemicals.[643]

503. These theories of the action of protective chemicals cannot account for the protection given by certain pharmacologically active substances, e.g., reserpine[644] which can protect rats if given as early as 24 hours before irradiation; its action correlates with obvious changes in tissue metabolism. Similarly, the effects of parathyroid hormone and EDTA could be related to the effects of calcium on cell permeability that prevent the loss of intracellular constituents due to the radiation-induced increase in permeability.[645,646]

Modifying treatments

504. Death of an animal exposed to the lower range of lethal doses is mainly due to bone-marrow injury. This suggested treatment with viable bone-marrow cells that might permanently or temporarily take on the function of the destroyed cells. The feasibilty of repairing radiation-induced damage by biological means was suggested from the prevention of thrombopenia in X-irradiated guinea pigs by shielding of bones in the early experiments of Fabricius-Moller[647] and by the shielding experiments of Jacobson *et al.*[648] The success of bone-marrow therapy depended on genetic similarity between irradiated host and donor animals. Isologous marrow gave many more survivors than homologous marrow, and heterologous grafts were even less effective.[649-651] Proof of cellular colonization was given by Lindsley, Odell and Tausch in 1955,[652] using as index antigenic differences between cells of host and donor. Ford *et al.*,[70] distinguished host and donor cells by means of marker chromosomes.

505. The survival of transplanted bone-marrow is determined by the compatibility of its antigenic pattern with that of the recipient. As a rule, only bone-marrow from a uniovular twin or from another individual of the same highly inbred strain (isograft), persists; transplants from another individual from the same outbred species (homograft) or from another species (heterograft) are rejected. If the immunological mechanism of the host is suppressed, the graft may take. One way of suppressing the immunological mechanism is irradiation; this is why animals exposed to much radiation accept marrow transplants. However, if the suppression of immunological mechanisms in the recipient is transient, as may happen if the dose of radiation is not high enough, the graft will eventually be rejected. If the dose is high enough, the graft will take, but owing to the immunological competence of the transplanted marrow, a reverse immunological reaction will take place, i.e. reaction of

the grafted tissue against the host. This reaction, called "secondary disease", is a wasting syndrome characterized by atrophy of the host's lymphatic tissues, which frequently results in death.

506. The antigenic pattern of tissues is determined by isoantigens. Two broad groups of isoantigens are distinguished: (*a*) the so-called H-antigens evoke production of humoral antibodies; (*b*) the other type, T-antigens, produces tissue immunity by accelerated rejection of grafts, but does not elicit the appearance of antibodies in blood plasma and body fluids.

507. The chemistry of H-antigens is understood, mainly from studies by Morgan and Kabat.[653] H-antigens are polysaccharides in which an amino-acid or lipide moiety is firmly bound but does not contribute to immunological specificity. Immunological specificity is determined by a small segment of the polysaccharide molecule. Several more-or-less distinct molecules of the same immunological specificity may be found in the same individual: blood-group substances in erythrocytes are lipopolysaccharides, while blood-group substances in tissue fluids are polysaccharide-amino-acid complexes; the latter show broad polydispersity.

508. The chemistry of T-antigens is largely unknown. The relatively insensitive and imprecise tests available for assessing their activity, along with the inherent difficulty in isolating them from living mammalian cells, made it appear that "T-antigenicity" is the property of living cells only. However, R. B. Billingham, L. Brent and P. B. Medawar[654] isolated an antigenically active substance in a DNA-containing fraction of disintegrated lymphoid cells. Activity was destroyed by DNA-ase treatment, by periodate oxidation, and by digestion with crude enzyme preparation known to be mucolytic and capable of destroying the activity of blood-group substances. Current information shows that T-antigen may again be mucopolysaccharide,[655] and therefore not unlike H-antigens.

509. Even though repeated skin-grafts do not cause the appearance of precipitating or cytotoxic antibodies in the blood of recipient animals,[656] several studies indicate an association between tissue transplantation and the appearance of cytotoxic, haemaglutinating or other antibodies;[657-659] H-antigens and T-antigens may be different complex molecules but with the same haptenic-groups in their structure.[660] The antigenic potency as well as chemical stability depend on molecular components not directly determining immunological specificity. Morgan[661] has shown that purified somatic hapten of *Sh. shigae* may acquire full antigenic potency if coupled with protein derived from the same or other bacterial species; human blood-group substance A from erythrocytes (lipopolysaccharide) is resistant to hot alkali, while blood-group A substance from body fluids (an amino-acid-polysaccharide) is easily hydrolyzed by the same treatment.[662] If the T-antigens were lipopolysaccharide, then their lesser potency compared with H-antigens in eliciting the production of humoral antibodies, and their liability to lyophilization and other procedures, would be explicable. The T-antigens and the H-antigens might well be a diverse group of substances upon which the histo-incompatibility genes have imprinted specific antigenic configuration, probably in their polysaccharide components.

510. The ability of transplanted bone-marrow cells to persist in irradiated animals has been variously demonstrated. Erythrocytes and platelets were identified by specific agglutination.[663-665] Identification of donor's granulocytes was carried out by demonstrating alkaline phosphatase in the circulating cells, alkaline phosphatase being present only in the rat's (donor) granulocytes and not in the mouse's (recipient) granulocytes.[665-667] The repopulation by rat's lymphoid cells in irradiated mice has been shown by finding rat's chromosome number and structure in dividing lymph node cells of the recipient[76] and by employing cytotoxic sera with cell-culture technique.[663]

511. When animals, irradiated with doses sufficient to cause acute death due to bone-marrow syndrome, are injected with living erythropoietic cells, they survive. The 30 days' median lethal dose is roughly doubled if bone-marrow transplantation is used to protect mice; with other types of irradiation the results are less consistent, but at certain dose levels of γ-rays and 14-MeV neutrons marked protection has been shown.[669]

512. Many authors confirmed the protective action of bone-marrow transplantation in acute radiation syndrome in various species. Homologous bone-marrow protected rats,[670] hamsters,[671] rabbits,[672] dogs,[673] and guinea pigs.[651]

513. The feasibility of bone-marrow transplantation in man has been studied to a limited extent. An exchange of bone-marrow cells can occur between non-identical twins before birth.[674-676] The phenomenon can be explained as acquired immunological tolerance, due to transplantation of immunologically immature cells, as seen by Owen.[677]

514. In studies on man, suppression of immunological defence of the host has been achieved by "acquired tolerance". Attempts at homo-transplantation of bone-marrow into donors whose immunological mechanism has been suppressed by radiation or by radiomimetic drugs have met with little success, and indeed contra-indications seem clearer. The studies may be divided into two groups: (*a*) patients accidentally exposed to high doses of radiation; (*b*) patients deliberately irradiated to replace diseased with normal marrow. Thomas *et al.*[678] have shown that transplanted marrow functioned temporarily in leukaemic patients given TBR: the donor cells in some cases persisted for two months in the recipient though they disappeared completely after ~ 3 months. In another study,[679] 9 patients with acute leukaemia irradiated with 300-500 r were given marrow (obtained from excised human bones) containing about 5×10^9 viable cells without evidence of a successful transplant. Bone-marrow given to patients with bone-marrow aplasia, without irradiation, gave similar results. There is evidence of a temporary acceptance of bone-marrow in irradiated leukaemic patients.[680-682] In most studies, the percentage of donor's type blood cells in the recipient's circulation was low at the beginning and steadily decreased; a notable exception is a patient with bone-marrow failure due to chemotherapy of Hodgkin's disease[682] given bone-marrow taken from her sister. The difference in blood groups between donor and recipient was marked, and skin grafts were rejected. Nevertheless, bone-marrow transplantation was successful, the donor's blood cells, low at first, began to increase in the recipient's circulation at about the sixth month after transplantation and were still present after nine months. The success in this case is probably due not only to pre-treatment with radio-mimetic drugs but also to Hodgkin's disease: a patient with Hodgkin's disease[683] may tolerate a skin graft for a prolonged period. Hodgkin's disease is accompanied by a production of abnormal

γ-globulins and a marked decrease of immunological reactivity; proliferation of abnormal and immunologically incompetent cells may be taking place at the expense of normal lymphoid cells.

515. Bone-marrow was given five men accidently irradiated in Yugoslavia on 15 October 1958. Of six exposed, the five who received the higher doses were given marrow. The man in most serious condition was injected at first with foetal bone-marrow (4×10^9 cells), and then with adult bone-marrow. There was no evidence of improvement after foetal marrow; after adult marrow the number of blood cells, mainly platelets and granulocytes, increased sharply. Neverthless, the patient eventually died with symptoms of delayed intestinal damage and haemorrhages from the respiratory tract. The remaining four patients were given bone-marrow a month after the accident from donors of a similar blood-group pattern; about 10^{10} marrow cells were injected. Soon after transplantation of marrow, the number of circulating blood cells increased. However the initial number of donor's cells, ~ 20 per cent of the total, dropped to negligible values in 3-4 months.[394] It appears that for a short time the transplanted bone-marrow assumed normal haemopoietic activity, although the evidence supporting this has been challenged by Fliedner[785] and it was certainly ultimately rejected. The relatively low percentage of the donor's type blood cells, and their rapid disappearance demonstrates that the recipient's bone-marrow maintained its activity although diminished throughout the period of acute radiation sickness. Furthermore, as discussed earlier in paragraphs 217-220, the haematological recovery patterns were similar to those of patients recovering spontaneously from lesser amounts of radiation.

516. The transplantation of foreign bone-marrow in experimental animals prevents acute death; the same is presumably true for man. Survivors usually die later, the mortality beginning usually in the fifth week post-irradiation, but sometimes earlier. Death of animals is preceded by diarrhoea, loss of weight and dermatitis; at autopsy a generalized atrophy of lymphoid tissue is visible. The syndrome is usually called *secondary* disease, but sometimes also homologous disease or foreign bone-marrow disease. The main cause of secondary disease is reaction of grafted tissue against the host, the latter having been rendered immunologically incompetent by irradiation. Minor factors influencing both time of onset of secondary disease and its final outcome include late radiation effects in the host and decreased resistance to infection.[684]

517. Evidence for the immunological pathogenesis of secondary disease is based mainly on genetical studies, F_1-hybrids do not usually react against grafted tissues of either parental strain but may in certain circumstances react immunologically against inbred parental strain tissue. However, when irradiated hybrids received parental tissue, fatal secondary disease ensued. In the reverse case, i.e. irradiated parental strain grafted with hybrid tissues, the survival was almost complete. In the first case, parental tissue encounters foreign antigens in the host, derived from the other parent and produces antibodies to histo-incompatibility antigens; in the other case, the specificity of transplanted tissue is broader than that of the host and no antibody production is possible.[685, 686]

518. Secondary disease can be potentiated if transplantation of bone marrow is accompanied by even a small amount of the donor's lymph-node cells.[684]

519. These two lines of evidence indicate that the immunological reaction of grafted tissues against the host form the basic pathogenetical factor in secondary disease; several other factors enter. Delayed radiation effects in the host is one[687, 688] and the delayed reaction of the hosts' recovering immunological system against grafted tissue is another.[684] Transient decrease in resistance to infection, at a time when the host lymphoid system has not yet recovered and the grafted bone-marrow is not potent enough, contributes considerably to the mortality due to secondary disease.

520. The indications for transplantation of bone-marrow in cases of radiation damage are limited. It may be useful when the patient's bone-marrow remains viable even though seriously affected: the implanted tissue may in this case help the organism through the most dangerous period of haemopoietic failure; eventually the foreign tissue will be rejected and the danger of fatal secondary disease will disappear. In serious cases, grafting bone-marrow, substituting for the patient's haemopoietic cells, may eventually cause death by secondary disease.[689] The dangers in bone-marrow treatment of acute radiation disease influenced the decision not to use it in the Y-12 accident in June 1958.[388]

521. There are at least three possibilities of increasing the usefulness of bone-marrow treatment: (*a*) pretreatment of the recipient with "enhancing antibody"; (*b*) use of foetal marrow; and (*c*) antigenic adaptation of transplanted marrow to the hosts' antigenic pattern.

522. Enhancement might be useful when the host's immunological reaction is not completely abolished and is sufficient to cause speedy rejection of the graft before it might exert supportive action. Enhancement supports the growth of transplanted tissues by inducing the immunity status in the host, before transplantation. It can be effected by injection of the lyophilized tissue to be implanted[690] or by passive immunization with a serum containing anti-implant tissue antibodies.[688] The latter but not the former method might be useful clinically.

523. The persistence of grafted bone-marrow could be improved if its antigenic pattern was made compatible with the antigenic pattern of the host. Very little work has been done in this direction. From the studies on the transplantation of neoplastic tissues, it is known that tumours after passage through F_1-hybrids (strains of tumour origin and some others) have more takes when tested in backcrosses with the same two strains.[691] This finding is open to more than one interpretation: Klein[692] showed that the increased frequency of takes in backcrosses is due to antigenic adaptation of tumour tissues and not to selection of more resistant cellular clones during the passage. The phenomenon resembles the changes by paramecia of their antigenic pattern to suit unfavourable environments containing specific antibodies, in which the newly-acquired character is inherited cytoplasmically.[693, 694] In tissue transplantation, some preliminary experiments aimed at inducing antigenic compatibility have been carried out:[695] parathyroid embryonic tissue was cultured in media containing increasing concentration of recipient sera before implantation. The evidence for the successful grafting was clinical improvement. No analogous experiments have been done on marrow cells, but with modern techniques of marrow cultivation, it should be possible to assess the probability of increasing takes and survival time in donors.

524. On the basis of the immune tolerance theory, foetal marrow, theoretically, might lead to the creation

of a permanent chimera where there has been total destruction of lymphoid tissues. The grafted marrow cells would not be rejected and in time should acquire tolerance to the host's antigens. If foetal cells are used, as has been shown, immunological interaction between donor and recipient is reduced.[696-698] Similar experiments in man are limited and very preliminary. Mathé *et al.* injected foetal marrow in one of the victims of the Yugoslav reactor accident but found no evidence of haemopoietic activity of implanted tissue: the patient, however, was apparently in the preterminal stage with intestinal symptoms.[394] In toxic bone-marrow failure, injection of foetal liver cell suspensions produced circulating blood cells characteristic of the donor's for about three weeks.[699]

Internal decontamination

525. Recent efforts to promote the excretion of deposited radio-isotopes, such as plutonium, thorium, yttrium and the rare earths, have been encouraging. For these elements, the chelating agent, diethylenetriaminepentaacetate (DTPA) has proved much superior to the earlier studied ethylenediaminetetraacetate (EDTA) and should be a practically useful agent for the prompt treatment of accidental exposure to these radio-isotopes.[700] Prolonged treatment with DTPA is effective in removing substantial fractions of firmly deposited plutonium from bone.[701] The removal of strontium or radium appears less hopeful; no practically useful treatment can be recommended for radio-isotopes of these elements. Increasing the level of dietary calcium deserves to be studied further as a possible means of delaying the uptake of strontium-90. However, the benefits to be obtained therefrom must be large enough to justify any risks entailed in greatly increasing the intake of calcium,

Treatment of acute radiation syndrome[702, 703]

526. The management of radiation injury is governed by the same considerations that influence the management of any other clinical problems, namely the history, clinical picture, laboratory data, and estimated magnitude of exposure to the injurious agent. In most instances, it is not possible to estimate dose accurately. Even if it were possible, knowledge of the dose would be of limited value in governing the management of the patient since there is individual variation in the response to a given dose as well as great uncertainty about the dose-effect relationship in man. Experience with the Japanese atom bomb casualties, the Marshallese exposed to fall-out radiation, reactor and critical assembly accidents, and other accidental exposures to radiation, have shown that some estimate of biological effects can be made from careful clinical and haematological data. Such continuing scrutiny should determine therapy.

527. The conservative medical management of the acute radiation syndrome is recommended,[44, 388, 704] reserving for desperate situations those therapeutic measures that carry a high intrinsic risk to the patient.

Summary

528. Biological effects depend not only on total dose (energy absorbed) but also on type of radiation; distribution of dose in time and space and on the physical state of the organism and species. Determination of biological effects of small dose irradiation should now be based primarily on an analysis of functional changes and not only on morphological changes as in the past.

529. While the mechanisms of radio-sensitivity have not yet been clarified, the radio-sensitivities of cells, tissues, and organs can be arranged in order, and show a remarkable similarity in all mammalian species.

530. The clinical course of the acute radiation syndrome in man is well known through observation on Japanese and Marshallese exposures, criticality accidents, and radio-therapeutic experience. However, largely because of uncertainties as to the physical factors, the exact relation between dose and effect is not well understood. The best estimate of the median lethal dose for man is 300-500 rad, short-time TBR.

531. At low doses, functional changes appreciably outweigh permanent somatic damage. Among the more sensitive of these are transient changes in gametogenesis, neural function, and haematological responses, especially in the lymphocytes. However, evidence of permanent damage becomes apparent only with larger doses approaching the lethal range.

532. Life-shortening in animals has been well established as a consequence of long-term and of short-term irradiation. Life-shortening in man is probable, however, results are still inconclusive.

533. The development of neoplasia may follow short-term or long-term exposures of both animals and man. Apparently, leukaemia is the earliest neoplastic change that has been observed in man. Leukaemia induced in the Japanese and in other groups of exposed human beings has usually been of the chronic myeloid type or of the acute type, and the incidence has increased roughly with dose.

534. There is some evidence of an increased incidence of some malignant tumours other than leukaemia in Japanese survivors, but the evidence so far is inadequate to permit reasonable inferences as to dose-effect relationships.

535. There is no satisfactory evidence as to the concentration-effect relationships in man as regards carcinogenesis from internal emitters. No tumours have thus far appeared with residual radium of less than 0.7 μg.

536. Consideration of possible mechanisms of radiation carcinogenesis, including a number involving the genetic apparatus of somatic cells, indicates a wide divergence in possible dose-effect relationships as a consequence, and indicates further that the question of these mechanisms may be amenable to experimental testing. Further analysis of carcinogenic action of radiation will require careful study of the dependence of such action on the type of radiation (alpha, beta, etc.) and its physical properties (quantities of energy, ionization density, etc.) and, in particular, a study of the role of dose-rate. These data will provide the key to an understanding of the relevant mechanisms. However, elucidation of this problem will require an equally careful study of the processes of regeneration, particularly in relation to dose rate and the temporary characteristics of irradiation. An analysis must be made of the types of mutation which result in the formation of tumours, and their probable character. Lastly, there must be a stage-by-stage analysis of data to establish a scale of effects related to the conditions of irradiation.

537. The embryo, at least in certain stages, is more susceptible to radiation than the adult.

538. Radiation protection can be achieved in animals by a variety of chemical and physical procedures, none of which has yet been established as of value in man except possibly in instances of localized therapeutic irradiation.

539. Many investigations are under way to determine the value of general supportive and specialized therapy for the treatment of acute radiation injury in man and for decontamination.

TABLE I.[85] LD_{50} VALUES FOR MAMMALS*

Species	Radiation used	Radiation factors	LD_{50} value: Air dose (r)	LD_{50} value: Absorbed dose (rad)	Ref. No.
Mouse	250 kvp X-ray	0.5 mm. Cu, 1 mm. Al HVL 1.6 mm. Cu	362+ to 443+	521+ to 638+	(705)
	200 kvp X-ray	0.25 mm. Cu, 1 mm. Al HVL 0.8 mm. Cu	405	558+	(706)
	Bomb gamma	High energy and dose rate	759	666+	(707)
Rat	200 kvp X-ray	0.45 mm. Cu, 1 mm. Al HVL 1 mm. Cu	665	815+	(708)
	200 kvp X-ray	0.5 mm. Cu, 1 mm. Al HVL 1.05 mm. Cu	640	796+	(709)
Ground squirrel	250 kvp X-ray	0.25 mm. Cu, 1 mm. Al HVL 0.9 mm. Cu	700	>700+	(710)
Hamster	2,000 kvp X-ray	HVL 5 mm. Pb	800	>800+	(711)
	250 kvp X-ray	0.5 mm. Cu, 1 mm. Al HVL 1.6 mm. Cu	460+	586+	(712)
	200 kvp X-ray	0.25 mm. Cu, 0.5 mm. Al HVL 1.5 mm. Cu	700	>700+	(671)
Guinea pig	200 kvp X-ray	0.25 mm. Cu, 1.0 mm. Al HVL 0.8 mm. Cu	337	400+	(42)
	186 kvp X-ray	0.25 mm. Cu, 1.0 mm. Al HVL 0.8 mm. Cu (crossfire exposure)	400	380+	(649)
	Co^{60} gamma	Multiple sources	500	490+	(43)
	1.10 Mev (50%) 1.33 Mev (50%)	Dose rate 70 r/min (4π exposure)			
Rabbit	200 kvp X-ray	0.5 mm. Cu, 1.0 mm. Al HVL 0.98 mm. Cu (bilateral exposure)	800	735+	(24)
	250 kvp X-ray	3.25 mm. Cu HVL 3.4 mm. Cu (multiport exposure)	805	751+	(713)
	250 kvp X-ray	Parabolic filter HVL 2.0 mm. Cu (crossfire exposure)	700+	680+	(714)
	Co^{60} gamma		1,094	911+	(715)
	1.10 Mev (50%) 1.33 Mev (50%)	HVL 5.1 cm. Al Dose rate 50 r/hr (multiple sources)			
Monkey	250 kvp X-ray	HVL 1.6 mm. Cu Dose rate 3 r/min. (bilateral exposure)	760+	546+	(65)
	250 kvp X-ray	0.5 mm. Cu, 1.0 mm. Al HVL 1.0 mm. Cu (animals rotated)	550	522+	(716)

TABLE I.[85] LD_{50} VALUES FOR MAMMANS* (*continued*)

Species	Radiation used	Radiation factors	LD_{50} value: Air dose (r)	LD_{50} value: Absorbed dose (rad)	Ref. No.
Dog	250 kvp X-ray	0.5 mm. Cu, 1.0 mm. Al HVL 1.5 mm. Cu (bilateral exposure)	281	244+	(717)
	1,000 kvp X-ray	HVL 2.0 mm. Pb (bilateral exposure)	304	250+	(38)
	2,000 kvp X-ray	HVL 4.3 mm. Pb (bilateral exposure)	312	260+	(37)
	Co^{60} gamma 1.17 Mev (50%) 1.33 Mev (50%)	HVL 5.1 cm. Al (bilateral exposure)	465+	303+	(718)
	250 kvp X-ray	14.2 mm. Al Parabolic filter, 0.5 mm. Cu HVL 2.15 mm. Cu (unilateral exposure)	450	322+	(38)
	Bomb gamma	High energy and dose rate	271	250+	(378)
Swine	1,000 kvp X-ray	HVL 2.0 mm. Pb (bilateral exposure)	510	247+	(38)
	2,000 kvp X-ray	HVL 4.3 mm. Pb (bilateral exposure)	388	237+	(719)
	2,000 kvp X-ray	HVL 4.3 mm. Pb (unilateral exposure)	500	305+	(719)
	Bomb gamma	High energy and dose rate	225	187+	(720)
	Co^{60} gamma 1.17 Mev (50%) 1.33 Mev (50%)	HVL 5.1 cm. Al Dose rate 50 r/hr (multiple sources)	618	242+	(721)
Sheep	Nb^{95} and Zr^{95} gammas 0.73 Mev (93%) 0.23 Mev (7%)	HVL 3.9 cm. Al Dose rate 20 r/hr (multiple sources)	524	205+	(722)
Goat	200 kvp X-ray	0.5 mm. Cu, HVL 0.98 mm. Cu (bilateral exposure)	350	237+	(723)
Burro	Co^{60} gamma 1.17 Mev (50%) 1.33 Mev (50%)	HVL 5.1 cm. Al Dose rate 50 r/hr (multiple sources)	784	306+	(721)
	Ta^{182} gamma 1.22 Mev (57%) 1.13 Mev (37%) 0.2 Mev (6%)	HVL 4.3 cm. Al Dose rate 20 r/hr (multiple sources)	651	256+	(724)
	Nb^{95}-Zr^{95} gamma 0.73 Mev (93%) 0.23 Mev (7%)	HVL 3.9 cm. Al Dose rate 20 r/hr (multiple sources)	585	229+	(722)
Man	Fall-out gamma 1.5 Mev (19%) 0.75 Mev (57%) 0.1 Mev (24%)	Dose rate variable (plane field)	350 (?)	300 (?)	(53)

* See text for additional explanatory material relating to the table.

+ Value not given in work cited. Calculated or estimated from data given.

All dose-rates used were of the order of 5 to 60 r/min., and all exposures were unilateral unless otherwise noted. The LD_{50} values in rad represent the absorbed dose in soft tissue at the centre (midline) of the animal. The dose in rad was estimated as follows: the tissue dose in r was first estimated, if not given, from the air dose by estimating all scattered radiations and taking into account the geometry of the exposure conditions used.[38] Scatter can be approximated from standard depth-dose data.[38, 706, 725, 728] The present authors duplicated as nearly as possible many of the experimental conditions and used the air/tissue dose ratio thus obtained. The tissue dose obtained represents the dose a dosimeter would indicate if it were embedded in tissue (or phantom material). The tissue dose in r was converted to absorb dose in rad, using the appropriate soft-tissue conversion factor.[727, 729] The conversion from air to tissue dose is an approximation made in many cases from incomplete physical data, and the conversion factors from tissue dose to rad are still open to question (see above). Additional details of the conversion used for any of the situations will be furnished on request. Total scatter varied with essentially full scatter, from less than 5 per cent of the air dose with Co^{60} gammas to approximately 45 per cent with 250 kvp or lower energy X-rays.[38, 728, 730] Ellinger quotes the LD_{50}/14-day value for guinea pigs, which is not significantly different from his LD_{50}/30-day value. Depth-dose measurements under the unusual geometrical conditions of the Oak Ridge multicurie γ-ray exposure field were made by the present authors in collaboration with Col. Bernard Trum. The large ratios, air dose-midline absorbed dose, obtained for burros, sheep, and swine result principally from geometrical factors.[38] In most positions, occupied by the exposed large animals, over 50 per cent of the dose is received from a target to skin distance of less than 1.5 m.; thus inverse square fall off is appreciable. Large animals standing in the field receive much of the dose at the midpoint in the animal from the anterior or posterior directions, as opposed to the transverse (shorter) axis with bilateral irradiation in the laboratory (this would not apply to an upright man). All midline doses probably are maximal for an acute LD_{50} value, since if the data for the effect of dose rate on LD_{50} in the rat[731] apply to the larger species, the values should be further reduced by a factor of approximately 0.8 to allow comparison with radiation delivered in the course of minutes. The values should be also reduced further for comparison with X-ray LD_{50} values because of the apparently reduced effectiveness of γ-radiation relative to X-radiation.[67] The LD_{50} value for man can be considered only a rough approximation, since the dose is poorly known and there was no mortality in the exposed group (see below).

TABLE II. DISEASES OF MAJOR FREQUENCY IN γ-IRRADIATED MICE (OPERATION GREENHOUSE)[260]

Disease	Percentage observed incidence in mice receiving indicated γ-ray dose									
	Control		223 rad		368 rad		578 rad		697 rad	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
None	4.25	0.97	1.90	0.94	3.16	0	1.96	1.68	4.07	2.63
Pneumonia	9.48	12.01	6.19	3.77	7.91	6.21	5.23	4.36	5.56	3.76
Nephrosclerosis, mild	1.31	2.60	2.38	2.36	2.85	3.79	3.59	6.71	3.70	4.51
Nephrosclerosis, moderately severe	0.33	0.33	0	0.47	0.63	1.38	1.63	3.02	3.33	7.14
Nephrosclerosis, severe	0	0.65	0.48	0.47	1.58	3.45	10.13	18.79	21.48	37.22
Nephrosclerosis, severity unspecified	0.33	1.95	3.81	2.36	7.59	4.48	24.51	17.79	28.52	15.79
Enteritis and colitis	4.58	2.27	3.33	2.36	1.90	2.41	4.90	3.36	1.85	1.88
Dermatitis	10.78	1.95	10.48	2.36	8.86	0.69	4.90	0.67	3.70	0.38
Emaciation	0.65	1.62	0	0	1.27	1.03	0.65	1.68	5.56	3.38
Cyst, liver	2.61	1.30	1.90	2.83	0.95	2.07	1.96	4.36	1.11	1.88
Cyst, kidney	0.65	0	1.43	0	0.95	0	2.94	1.01	1.48	0.75
Cyst, ovary		1.30		1.42		1.72		1.34		1.50
Cyst, all sites	3.60	3.25	3.33	4.25	2.53	4.83	4.90	9.06	2.96	4.89
Atrophy, bone marrow	0	0.32	0.48	0.47	0.32	0.69	0	1.68	1.48	0.75
Atrophy, testis	0.65		1.90		0.95		0.95		1.11	
Atrophy, adrenal cortex	0.33	8.12	1.43	8.96	1.27	7.93	1.63	8.72	2.96	10.53
Dental defects	8.83	1.63	7.15	1.42	8.86	2.07	6.86	1.68	1.48	1.13
Volvulus	0.98	0.65	3.33	0.47	0.63	1.03	0.65	0.34	1.11	1.50
Abscess, all sites	7.52	2.92	8.10	1.42	3.48	1.72	1.31	1.34	1.11	0.75
Hyperplasia, endometrium		1.95		1.89		1.38		0.67		0.38
Hyperplasia, adrenal cortex	0	0.97	2.86	3.77	2.12	3.45	3.92	3.36	5.18	6.01
Hyperplasia, Harderian gland	0.98	0	0.95	0	2.85	2.07	1.31	1.01	0.74	0.75
Hyperplasia (myeloid), bone marrow	0.33	0	0	0.94	1.27	0.34	4.58	2.35	4.44	3.01
Hyperplasia (myeloid), spleen	0.33	1.30	1.43	3.37	1.90	4.48	6.21	6.38	7.41	15.41
Hyperplasia (lymphoid), spleen, lymph nodes	0	0.32	0	0.47	1.27	1.03	1.63	1.01	2.59	2.26
Haemorrhage, testis	0		0		0.63		2.29		1.11	
Haemorrhage, brain	0	0	0	0	0.63	0.34	0.33	1.68	1.85	1.13
Haematoma, testis	0.65		0.95		0.95		1.31		1.85	
Haematoma, ovary		13.31		10.38		12.76		13.42		7.52
Haematoma, adrenal	0	0	0	0	0	0	0	2.01	0.37	2.63
Thrombosis, auricle	0.65	1.62	1.90	0.47	2.85	2.41	1.96	2.35	0.37	1.13
Infarct, all sites	0.65	0	1.43	0.47	1.58	0.69	2.94	2.01	1.48	2.63
Angiitis, all sites	0.65	0	0.95	0.47	1.03	2.98	6.71	5.04	7.04	13.91
Hepatoma	7.84	3.25	7.62	10.38	11.71	14.83	8.82	8.05	4.44	1.79
Luteoma		1.30		16.51		19.66		17.11		15.41
Granulosa-cell tumour, ovary		0.32		3.30		4.14		4.36		2.26
Tubular adenoma, ovary		0.32		5.19		4.48		2.68		1.50
Mixed tumour, ovary		0.32		10.85		10.69		7.05		5.64
Supcapsular cyst, ovary		19.16		2.36		2.41		1.68		0.38
Cystadenoma, ovary		0		2.83		2.76		0.67		2.26
Adenoma, pituitary	0.98	3.57	1.43	4.25	0.95	7.59	1.96	12.42	0.74	3.38
Adenoma, lung	9.48	9.42	9.05	8.49	11.08	7.59	7.19	6.04	2.96	2.26
Adenoma, kidney	1.96	0	1.43	0	1.90	1.72	1.63	1.01	1.11	0.38
Adenoma, adrenal	0	0.97	2.86	0	2.22	3.10	3.27	3.69	1.48	1.88
Cytadenoma, lung	2.29	3.25	3.33	1.89	4.75	4.48	3.59	2.01	1.48	1.13
Cystadenoma, Harderian gland	0	0.32	0.95	1.42	1.27	1.38	0.33	2.01	0.37	0
Squamous-cell carcinoma, stomach	0.98	0.65	2.38	1.42	1.58	1.38	0.65	0.34	0	0
Squamous-cell carcinoma, skin	0.33	0	0	0.94	0.32	0	0.98	0.67	0	0.38
Adenocarcinoma, lung	2.94	0.97	0.48	2.36	1.27	1.38	0	1.01	0.74	0
Adenocarcinoma, breast	0	0.97	0	3.77	0.32	3.79	0	3.02	0	1.88
Adenocarcinoma, Harderian gland	0	0	0	1.42	1.58	1.38	0.33	0.34	0.74	0
Sarcoma, voluntary muscle	0	0	0.48	0.47	0.63	0.69	0.33	0.67	0.37	0
Sarcoma, breast	0	6.82	0	3.77	0	4.14	0.65	2.01	0	0.38
Sarcoma, bone	0	0.65	0	0	0	0	0.33	2.01	0	0.75
Lymphoma, thymus	1.64	3.24	2.86	5.66	2.85	4.13	6.86	11.08	13.07	10.15
Lymphoma, abdomen	7.52	20.22	12.38	14.62	13.30	8.64	3.92	6.72	2.60	3.63
Lymphoma, other	10.14	18.52	7.21	10.85	12.34	16.21	9.14	9.06	4.81	4.89
Myeloid leukemia, all sites	0.33	0.65	0.48	1.42	0.95	1.03	1.31	0.34	1.11	0.38
Number of neoplasms per mouse										
Neoplasms, all sites	1.08	1.15	1.37	2.21	1.46	2.26	1.11	1.73	0.66	1.07

TABLE III.[732] MAJOR ABNORMALITIES INDUCED IN MAMMALS BY FOETAL IRRADIATION

Brain

- Anencephaly
- Porencephaly
- Microcephaly*
- Encephalocoele (brain hernia)
- Mongolism*
- Reduced medulla
- Cerebral atrophy
- Mental retardation*
- Idiocy*
- Neuroblastoma
- Deformities
  - Narrow aqueduct
  - Hydrocephalus*
  - Rosettes in neural tissue
  - Dilation of 3rd and 1st ventricles
  - Spinal cord anomalies*
  - Reduction or absence of some cranial nerves

Skeleton

- General stunting
- Reduced skull dimensions
- Skull deformities*
- Head ossification defects*
- Vaulted cranium
- Narrow head
- Cranial blisters
- Cleft palate*
- Funnel chest
- Congenital dislocation of hips
- Spina bifida
- Reduced and deformed tail
- Overgrown and deformed feet
- Club feet*
- Digital reductions
- Calcaneo valgus
- Abnormal limbs*
- Syndactyly*
- Brachydactyly*
- Odontogenesis imperfecta*
- Exostosis on proximal tibia
  - Metaphysis
  - Amelogenesis*
- Scleratomal necrosis

Eyes

- Anophthalmia
- Microphthalmia*
- Microcornia*
- Coloboma*
- Deformed iris
- Absence of lens and/or retina
- Open eyelids
- Strabismus*
- Nystagmus*
- Retinoblastoma
- Hypermetropia
- Congenital glaucoma
- Partial albinism
- Cataract*
- Blindness
- Chorioretinitis*
- Ankyloblepharon

Miscellaneous

- Situs inversus
- Hydronephrosis
- Hydroureter
- Hydrocoele
- Absence of kidney
- Degenerate gonad*
- Abnormalities in skin pigmentation
- Motorial disturbance of extremities
- Increased probability of leukaemia
- Congenital heart disease
- Deformed ear*
- Facial deformities
- Pituitary disturbances
- Dermatomal and myotomal necrosis

* These anomalies have been found in humans exposed *in utero* to radiation and are attributed to the action of radiation.

TABLE IV.[732] CORRELATIONS IN DEVELOPMENT: MOUSE AND MAN DEVELOPMENTAL STAGE IN HUMAN: ORGAN PRIMORDIA

Age in days		*Embryo*	
Mouse	*Man*	*mm*	
5	6		Implantation
	14	0.15	Germ layers, extra emb. membranes
	16	0.40	Primitive streak
8	20.5	1.5	Neural groove, blood islands, notochord
9	25.5	2.4	Cephalization, extensive vascularization, neural folds meet, primordia of sense organs, thyroid, limbs, muscles, pronephros, branch, arches, somites
10.5	28.5	4.2	Prim. brain w. vesicles, complete circulation, GI tract and derivatives, mesometanephros, vertebrae, 31 somites, yolk haemopoiesis
11.5	33.5	7.0	Genital ridge, heart, liver, mesonephros protuberant, limb and lung buds, 5 brain vesicles, all sense organs, cardiac septs and 38 somites
12.5	36.5	9.0	Heart chambered, nerves and ganglia differentiating thyroid anlagen bilobed
13.5	38.0	12.0	Sexless gonad primordia, liver haemopoiesis, brain flexures, limbs, thymus, GI tract actively differentiating
14.5	47.0	17.0	Cerebral hemispheres, corpora striatum, thalamus, blood vessels all actively differentiating, endocrine glands, peripheral and sympathetic nerves, eyes well formed
15.5	65.0	40.0	Cerebral cortex, intest, villi, thyroid follicles, first ossifications, sex differentiation with sex cords and germinal epithelium

TABLE V.[783] EFFECTS OF IONIZING RADIATION ON MAN—SCHEMATIC SURVEY

	Acute radiation syndrome, form		
	Cerebral	*Gastro-intestinal*	*Haematopoietic*
Determining organ.....	Central nervous system	Small intestine	Bone-marrow
Threshold dose, r.....	2,000	500	100
Latent period.....	½–3 hr.	3–5 days	3 weeks
Characteristic signs and symptoms	Lethargy, convulsions, ataxia	Diarrhoea, fever, disturbance of electrolyte balance	Leukopenia, purpura, infection
Underlying pathology.....	Inflammatory reactions in central nervous system, brain oedema	Denudation of gastro-intestinal mucosa	Atrophy of bone-marrow
Time of death (if occurring)...	Within 2 days	Within 2 weeks	Within 2 months
Cause of death.....	Respiratory arrest	Circulatory collapse	Haemorrhage, generalized infection
Prognosis.....	Hopeless	Poor	Good
Source of information	Animal experiments	Animal experiments, bomb casualties, nuclear accidents	Bomb casualties, nuclear accidents, radio-therapy

TABLE VI. EPIDEMIOLOGICAL STUDIES OF THYROID NEOPLASIA AND LEUKAEMIA IN CHILDREN TREATED IN INFANCY ON THYMIC REGION: SUMMARY OF PUBLISHED DATA

Reference	*Reason for irradiation*	*Dose range in r*	*Number of irradiated children*	*Control*	*Thyroid carcinoma*	*Leukaemia*	*Expected number*
Conti *et al.* [448] Pittsburgh	Prophylactic thymus irradiation	75–300	1,564	2,923	0	0	3 cases of malignancy 1 leukaemia
Simpson-Hempelmann-Fuller [445]	Thymic enlargement	(1) 200	2,393 (80% traced)	2,722	21	9	3.6 cases of malignancy
Simpson-Hempelmann [446]		(2) 200–600					1 leukaemia
Simpson [447]							
Latourette and Hodges [450]	Thymic enlargement	Average 200	861		1	1 lymphoma 1 leukaemia	0.1 carcinoma 1 lymphoma and leukaemia
Murray *et al.* [434]	Various benign diseases (45% chest)	Average 400	6,473			8	2 leukaemia
Snegireff [451]	Thymic enlargement	Average 400	148	162	0	0	
Cronkite-Moloney-Bond [428]	Thymic enlargement		125		2 (out of 7 neoplasias)	0	
Saenger [452]	Chest—mainly for thymic enlargement	50–1,200 r	1,644	3,777	11	1	0.12 carcinoma
Stasek *et al.* [734]	Cervical lymphadenitis	100–300 r	52		1		

TABLE VII.[435] FREQUENCY OF ABDOMINAL IRRADIATION DURING PREGNANCY OF MOTHERS OF CANCER CHILDREN AND MOTHERS OF CONTROL CHILDREN: SUMMARY OF PUBLISHED DATA

Reference	Cancer children		Control children	
	Description of group	Proportion of mothers who received abdominal irradiation during pregnancy	Description of group	Proportion of mothers who received abdominal irradiation during pregnancy
Kjeldsberg [430]	Children with leukaemia seen at Riks-hospitalet, Oslo, 1946–56	5/55 (9.1%)	Healthy children	8/55 (14.5%)
Kaplan [433]	Children dying of acute leukaemia in California, 1955-56	37/150 (24.7%) 34/125 (27.2%)	(*a*) Closest Sib (*b*) Most habitual playmate	24/150 (16.0%) 27/125 (21.6%)
Polhemus and Koch [433]	Children with leukaemia seen at the Children's Hospital, Los Angeles, 1950–57	72/251 (28.7%)	Children attending the Children's Hospital, Los Angeles, 1950–57 with other selected conditions	58/251 (23.1%)
Ford *et al.* [431]	Children dying of leukaemia under 10 years of age in Louisiana, 1951–55:		Children dying of causes other than cancer under 10 years of age in Louisiana, 1951–55:	
	(*a*) White	20/70 (28.6%)	(*a*) White	48/247 (19.4%)
	(*b*) Coloured	1/8	(*b*) Coloured	8/59
MacMahon [736]	Children dying of cancer under 10 years of age in New York City, and born in a specified maternity hospital, 1947–57	8/114 (7.3%)	1% sample of children born in one of 11 specified maternity hospitals, 1947–57, residents of New York City only	173/2,520 (7.3%)

TABLE VIII.[457] COMPARISON OF OBSERVED AND EXPECTED INCIDENCE OF MALIGNANT NEOPLASMS IN SELECTED SITES AMONG SURVIVORS IN HIROSHIMA EXPOSED WITHIN 1,500 METRES FROM THE HYPOCENTRE, APRIL 1957-DECEMBER 1958

	Observed	Expected	Ratio	Test result
Cancer of stomach, sexes combined	24	12.41	1.93	*
Cancer of lung, sexes combined	10	2.32	4.31	*
Cancer of breast	5	2.49	2.00	N.S.
Cancer of cervix uteri	8	3.67	2.18	**
Cancer of ovary	4	1.01	3.96	**

N.S. Not significant.
* Significant at the confidence level of 1%.
** Significant at the confidence level of 5%.

TABLE IX.[479] OBSERVED TUMOURS AND CALCULATED DOSE FROM RADIO-ACTIVE MATERIALS DEPOSITED IN THE LUNG

Material and radiation[a]	*Species*	*Results*	*No.*	*Calculated dose (rad)*[b]	*Remarks*	*References*
Po^{210} (alpha)	Rat	Squamous cell carcinoma	2/15	2,500	5 and 15 months after 5 μc/Kg	510
$Pu^{239}O_2$ (alpha)	Mice	Fibrosarcoma[c]	1/21	115	500 days after 0.003 μc	521
		Squamous cell carcinoma	2/17	2,300	400 days after 0.06 μc	
	Mice (inhalation)	Bronchiolar carcinoma	1	600	500 days after 0.1 μc	523
	Rats (inhalation)	Epidermoid carcinoma	—	—	Between 50 and 100 per cent surviving 250 days after deposition of 0.2 to 1 μc developed malignant tumours	522
	Mice	Bronchiolar carcinoma	1/41	4,000	100 days after 0.16 μc	523
$BaS^{35}O_4$ (beta)	Rat	Squamous cell carcinoma	2/16	12,000 to 20,000	300 days after 375 μc/week for 10 weeks	517
$Ru^{106}O_2$ (beta)	Mice	Lymphosarcoma[c]	1/23	300	340 days after 0.15 μc	521
		Alveolar cell carcinoma	1/10	4,000	422 days after 2 μc	
		Non-differentiated tumour	1/11	9,000	350 days after 4.5 μc	
Ru^{106} (metal cylinder) (beta)	Rat	Bronchogenic carcinoma	5/26	$2–9 \times 10^5$	224 to 337 days after implantation of 2.1 to 14 μc (dose calculated at 100 microns from source)	515
Sr^{90} (glass beads) (beta)	Rat	Lymphosarcoma	4/23	50,000	131 to 375 days after implantation of 1.1 to 59 μc	514
		Carcinoma		70,000		
$Ce^{144}F_3$ (gamma)	Rat	Carcinoma	1/27	2,200	127 days after 5 μc	736
			1/23	5,500	48 days after 15 μc	
			7/28	8,900	93 days after 25 μc	
			4/15	15,000	83 days after 50 μc	
Co^{60} (gamma) (wire)	Mice	Epidermoid carcinoma of bronchus	—	12,000 to 400,000	200 days after implantation	518

[a] All materials administered intratracheally or otherwise as indicated.

[b] Assuming uniform distribution and exponential loss unless otherwise indicated.

[c] Classed as incidental by author because autoradiograms showed no radio-activity in area of tumour.

TABLE X.[737] CHEMICALS USED FOR PROTECTIVE EFFECTS

Thiols related to cysteine and cysteamine

Compound	*Animal*	*Dose mg/kg*	*Protective effect*[a]	*References*
N-Alkyl and N-aryl derivatives of cysteine and cysteamine				
Cysteine	Mice, rats	950–1,200 i.p.	3	738, 739, 632
Cysteine	Rats	1,900 per os	2	740
Cysteamine	Mice, rats	75–250 i.p.	3	741, 738, 742, 363, 743
Cystine	Mice, rats	240–280 i.p.	0	744, 745
Cystamine	Mice	150–300 i.p.	3	744, 746, 747, 363
Cystamine	Mice, rats	400–600 per os	2	748, 749, 750, 751
N-Monomethylcysteamine	Mice	60–120 i.p.	2	638
N-Dimethylcysteamine	Mice, rats	40–70 i.p.	2	752, 638
N, N'-Tetramethylcystamine	Rats	60 i.p.	2	638
N-Diethylcysteamine	Mice	50–60 i.p.	2	752, 638
N-Piperidylcysteamine	Mice	25 i.p.	0	638
N-Methylphenylcysteamine	Mice	250 i.p.	0	638
N-Phenylcysteamine	Rats	150 i.p.	0	638
S,2-Aminoethylisothiruonium bromide HBr (AET)	Mice	240–480 i.p.	3	753, 636
S,2-Aminoethylisothiuronium bromide HBr	Mongrel dogs	100 i.p.	0	754
S,2-Aminoethylisothiuronium bromide HBr	Macaca mulatta monkeys	200–250 i.p.	3	755
S,2-Aminoethyl-N-methylisothiuronium chloride HCl	Mice	150 i.p.	2	637
N-Acyl derivatives of cysteine and cysteamine				
Glutathione	Mice, rats	800–1,000 i.p.	3	744, 756, 757, 745
Glutathione	Rats	2,000 per os	0	745
N-Acetylcysteamine	Mice, rats	120–250 i.p.	2	752, 638, 747
N-Acetoacetylcysteamine	Mice	240 i.p.	0	637
Aletheine	Mice	250–300 i.p.	1	752, 738
Pantetheine	Mice	350–550 i.p.	0	746, 752, 738
N-Acetylmethylcysteamine	Mice	150 i.p.	0	638

TABLE X.[737] CHEMICALS USED FOR PROTECTIVE EFFECTS (*continued*)

Compound	*Animal*	*Dose mg/kg*	*Protective effect**	*References*
Compounds with covered sulfur function				
α-Homocysteine thiolactone	Mice	—	+	758
N,S-Diacetylcysteamine	Mice	280–320 i.p.	0–1	339, 636, 752, 738
S-Methylcysteamine	Mice	850 i.p.	0	744
S-Benzylcysteamine	Mice	160 i.p.	0	738
Methionine	Mice	500–1,500 i.p.	0	738
S,2-Dimethylaminoethylisothiuroniumchloride HCl	Mice	350 i.p.	0	637
S,2-(1-Morpholyl) ethylisothiuronium bromide HBr	Mice	150 i.p.	0	637
Di(ethylaminoethyl)sulfide	Mice	140 i.p.	0	752
Compounds with branched or prolonged carbon chain				
3-Mercaptopropylamine	Mice	90 i.p.	3	752
3-Mercaptopropylguanidine	Mice	125–250 i.p.	3	637
Homocysteine	Mice	450 i.p.	2	738
1-Mercapto-5-diethylamino pentane	Mice	35 i.p.	0	638
1-Mercapto-7-aminoheptane	Mice	40 i.p.	0	638
α-Methylcysteine	Rats	100 i.p.	0	638
Thiols with alcoholic or carboxylic acid groups				
Thioglycolic acid	Mice	180 i.p.	0	744, 738
Mercaptosuccinic acid	Mice	350 i.p.	0	744
2,3-Dithiopropanol (BAL)	Mice, rats	150–200 i.p. and s.c.	0–1	82, 752, 737
Dithiopentaerythrit	Mice	75 i.p.	0	759
Thiophenols				
2-Mercaptothiazoline	Mice	100 i.p.	0	637
1(-)-2-Thiolhistidine	Mice	420 i.p.	0	759
Ergothioneine	Mice	500 i.p.	0	744
4,6-Dimethyl-2-mercapto pyrimidine	Mice	270 i.p.	0	759
o-Aminothiophenol	Mice	50 i.p.	0	759
Miscellaneous sulfur-containing substances				
Ammoniumdithiocarbonate	Mice	500 i.p.	3	760
Diethyldithiocarbamate	Mice	600 i.p.	3	760, 761
Thiourea	Mice	2,500 i.p.	2	762, 763, 738, 760, 764
Thiocyanide	Mice	200 i.p.	0	744
Thicacetamide	Mice	150 i.p.	0	744, 759
Sodium tetrathionate	Mice	150 i.p.	0	750
Sodium sulfide	Rats	5 i.v.	0	745
Compounds with pronounced pharmacological and toxicological activity				
Histamine	Mice	220–350 i.p.	2	744, 746
		500 i.p.	0	765
Tryptamine	Mice	75–95 i.p.	3	744, 746, 765
Serotonin	Mice	95 i.p.	3	746
		25 i.v.	3	766
DOPA	Mice	95 i.p.	2	746
Tyramine	Mice	80–275 i.p.	3	744, 746
		80 i.p.	0	765
Hydroxytyramine	Mice	50 i.p.	0	765
		75–300 i.p.	3	744, 746
Arterenol	Mice	3–5.5 i.p.	2	746
		2.75 i.p.	0	765
Epinephrine	Mice	0.7–1.4 i.p.	1	767, 768
	Chickens	5 i.m.	1	605
Amphetamine	Mice	1 i.p.	1	766
Ephedrine	Mice	78 i.p.	0	746
		6 i.p.	0	766
Oxytocine	Rats, mice	23–40 units/kp i.p.	3	767, 769
Reserpine	Mice	4 s.c.	3	644
Sodium cyanide	Mice	5 i.p.	2	744
Malononitrile	Mice	6.5 i.p.	3	744
p-Aminopropiophenone	Rats	15–30 i.p.	3	770
Apresoline	Mice	10 i.p.	2	771
		10 s.c.	2	771
Amine oxides	Mice	250 or.	2	772

TABLE X.[737] CHEMICALS USED FOR PROTECTIVE EFFECTS (*continued*)

Compound	*Animal*	*Dose mg/kg*	*Protective effect**	*References*
Various metabolites and "inert" compounds				
Fructose	Mice	13,500 i.p.	2	744
		5,000 i.v.	0	608, 773
Glucose	Mice	13,500 i.p.	1	744
		5,000 i.v.	0	773
Propylene glycol	Mice	3,000 i.p.	3	744
Glycerol	Mice	185 i.p.	0	744
Formic acid	Mice	92 i.p.	2	744
Pyruvic acid	Mice	700 i.p.	1	744
		250 i.v.	2	608, 773
Lactic acid	Mice	180 i.p.	0	744
		250 i.v.	0	608, 773
β-Ketobutyric acid	Mice	250 i.v.	1	773
Caprylic acid	Mice	290 i.p.	2	744
Salicylic acid	Mice	275 i.p.	2	744
Succinic acid	Mice	950 i.p.	1	744
α-Ketoglutaric acid	Mice	250 i.v.	1	773
Ethylenediaminetetraacetic acid	Mice	580 i.p.	2	744

* *Protective effect.* The grading of the optimal protective effect has been carried out according to the following arbitrary scale: 0 = no protective effect; 1 = slight or dubious protective effect (e.g., α—ketoglutaric acid); 2 = moderate protective effect (e.g., formic acid); 3 = strong protective effect (e.g., cysteamine, AET). i.p = intraperitoneally; i.v. = intravenously; i.m. = intramuscularly; s.c. = sub-cutaneously; or. = orally.

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