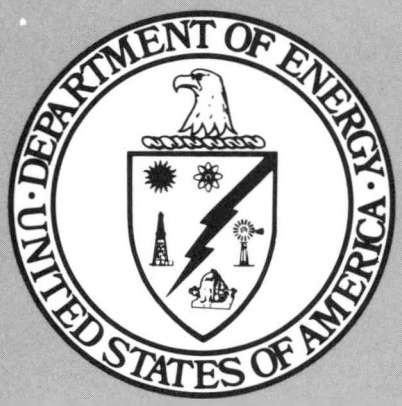

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RADIATION CARCINOGENESIS IN MAN: A CRITICAL REVIEW

By
Helen Quincy Woodard

August 1980

Memorial Sloan-Kettering Cancer Center
New York, New York

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FOREWORD

This review has developed from a series of intramural seminars which I gave from time to time for the benefit of thos of my colleagues in other fields who wished to keep abreast of major advances in radiobiology. There are several recent reviews which were prepared by broadly based committees and are much more comprehensive and detailed than this one. They are, however, directed at specialists and often are intended to assist regulatory agencies in setting standards. They are not very helpful to scientists in other disciplines who wish to know more about the nature and magnitude of the risks of radiation carcinogenesis, and there appears to be no concise manual to which they can turn. It is for the information of such readers that I have prepared this critical review of information presently available and of my own assessment of needs for future studies.

I am greatly indebted to many of my associates who have supplied me with information in fields which are not closely related to the radiobiology of bone in which much of my personal experience lies. In particular I thank Dr. Klaus Mayer of Memorial Hospital and Dr. David Becker of New York Hospital who criticized the chapters on leukemia and thyroid cancer respectively. Dr. John Harley, Director, Environmental Measurements Laboratory, not only encouraged me to undertake the review but has been of essential help in criticizing the chapter on lung cancer and in preparing the manuscript.

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RADIATION CARCINOGENESIS IN MAN
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CHAPTER I - - INTRODUCTION

CHAPTER I --INTRODUCTION

I.1 Cancer induced by ionizing radiation is a disease new to human history. It did not become an important problem until opportunities for human exposure were increased greatly by techniques based on the discovery of X-rays in 1895 and of radioactivity in 1896. It thus is primarily a disease of the 20th Century. The first significant exposures occurred considerably earlier than this, however. The mines in Joachimstal and Schneeberg in central Europe began to be worked about 1400 A.D., first for copper and iron, then for several other metals, and finally for uranium. A lung disease peculiar to workers in these mines was described as early as 1500 A.D., but it was not recognized as cancer until 1879, and the etiological role of radon was not suspected until 1932, and not generally accepted until the 1960's (Pir 32, Hol 69). It is possible that workers in ancient mines may have been similarly exposed but, if so, I am not aware of any descriptions of syndromes in miners that might have been due to radiogenic lung cancer.

I.2 Mortality was very high among these uranium miners, but the numbers at risk were only a few tens or hundreds at any one time, and were all in two small areas. Such small foci of disease, however lethal, are not comparable with the great epidemics and pandemics in mankind's past. Malaria limited the utilization of large regions in the tropics and scurvy prevented the full development of the cereal economics of northern Europe. Bubonic plague altered the political history of whole continents. The growth of population centers was impeded by the prevalence of enteric organisms. It is only recently that most of these major health hazards have been controlled but it is already well recognized that the resulting economic, social and political changes are profound. Except in the event of nuclear war it seems unlikely that radiogenic cancer will have an impact on future society comparable to that of the great sicknesses of the past. Nevertheless, the hazard is real and its cause is known. Its future magnitude is difficult to assess, since it can not be determined experimentally in humans, and extrapolation from results of animal experiments is uncertain. It is likewise difficult to estimate the extent of the radiation carcinogenesis which has already resulted from human exposure in the past 80 years because

the available information is incomplete and often controversial. Such evaluation is not impossible, however.

I.3 It is my purpose in the present review to examine such reports as are available in which there is reasonable evidence that human cancer has been caused by ionizing radiation. I shall not attempt a truly comprehensive review, but shall make a critical appraisal of the studies that seem most definitive. I shall then attempt to correlate the reported incidence of cancer of each type with such factors as seem pertinent and for which data have been recorded. Some of these are listed in Table II.1. Many factors are interrelated and can not be considered separately, but I shall give major emphasis to radiation quantity. This will include both a consideration of the dose-response relation where there is good evidence that cancer has been caused by radiation and a consideration of situations where the evidence for carcinogenesis by very small radiation doses is doubtful. I shall quote freely from results of experiments in animals, but only insofar as they may clarify observations in man. I shall not attempt to forecast future incidences of radiogenic cancer in humans.

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CHAPTER II - - PHYSICAL FACTORS INFLUENCING RADIATION CARCINOGENESIS

CHAPTER II -- PHYSICAL FACTORS INFLUENCING RADIATION CARCINOGENESIS

II.1 It seems obvious that the first requirement of any study of radiation carcinogenesis should be the assurance that the lesion under study actually is cancer. In a surprising number of published reports this requirement is not met. In some experimental work adequate distinction is not made between the benign adenomas which are common in the lungs of rats and mice of certain strains and malignant lung tumors which may have been induced by irradiation of these animals. In clinical studies there may be a similar confusion between benign and malignant nodules in the human thyroid. A related problem arises when a tumor which is undoubtedly malignant is found in a tissue in which it did not originate. This is especially troublesome when data on bone tumors are obtained from death certificates. Here tumors of soft part origin metastatic to bone may be classified as bone tumors. Since metastases in bone are much more common than primary tumors of bone, conclusions from such statistics may be highly misleading. In the reverse situation, I have seen a well documented radiation-induced osteogenic sarcoma arising in the bones of the skull listed in the death certificate as a brain tumor because it had invaded the cerebrum.

II. 2 Another requirement which is not always met is that, in order to be considered to be radiation induced, a tumor must have originated in irradiated tissue. A report that a patient "received a nominal midline dose of N rads" can not be accepted in evaluating the etiology of a subsequent cancer. Nor can a well documented radiation exposure of one part of the body be considered to be the cause of a solid tumor developing in a region 30 cm distant from a well collimated radiation field. It is only in the leukemias and related conditions in which progenitor cells are exchanged freely throughout the body and the exact site of origin is not known that the use of some sort of average value for the radiation dose may be justified. This difficulty obviously does not arise when the exposure has been to the whole body, whether in the atomic bomb survivors or in persons who have had chronic low level occupational exposure to high energy photons. Very complicated problems in dosimetry occur when cancer appears to have been induced by an internally deposited radionuclide which is metabolized very selectively by different tissues.

II.3 Once there is a reasonable probability that a cancer is radiation-induced it is important to estimate the qualitative and quantitative factors which have influenced this development. The most important of these are listed in Table II.1. I shall consider only the general implications of these factors here but will examine some of them in more detail later in connection with special types of carcinogenesis.

TABLE II.1

Factors Influencing Radiation Carcinogenesis

Physical Factors

- Radiation Quantity
  - Dose-response Curve
  - Threshold Dose
- Radiation Quality
- Radiation Dose Rate
- Metabolism of Radionuclides

Biological Factors

- Species
- Age at Irradiation
  - Prenatal
  - Juvenile
  - Mature
- Latent Period
- Death Rate from other Causes
- Natural Incidence of Cancer

II.4 There can be little doubt that the quantity of energy absorbed from a field of ionizing radiation by an exposed tissue is the most important factor in determining whether some of the cells in that tissue will undergo malignant transformation. As discussed above, in actual examples it is sometimes difficult to determine whether, or how heavily, a tissue has been exposed. Even when the exposure dose is not in doubt there may be both practical and theoretical problems in calculating the absorbed dose. There is usually little difficulty in the dosimetry of photons of the energies most commonly encountered in medicine or industry, although even here the dose to

cells within, or adjacent to, bone mineral is still somewhat uncertain. More difficult is the dosimetry of photons with energies of only a few tens of kilovolts such as are used in mammography. Here the absorption of energy is influenced strongly by the mean atomic number of the exposed tissue. This is often known only approximately. For particulate radiations of high linear energy transfer (LET), where the range is not more than a few cell diameters, the dosimetry is seldom satisfactory. If the particulate radiation arises from internally deposited radionuclides the difficulty may be more biological than physical in that the geometrical distribution of the transforming particles relative to cell structure is poorly understood.

II.5 In addition to the problems associated with the determination of the dose absorbed from a known exposure, serious difficulties arise from the need to estimate the probable results from an exposure at one quantitative level from the known results of exposure at a different level. These difficulties are important both in evaluating experimental and epidemiological data and in setting standards for permissible exposures. For the latter purpose it is often assumed that the response is linear and without threshold. This is considered to be conservative, tending to overestimate, rather than underestimate, the hazard from small doses, and thus to require more protection than is needed rather than less. It is well known that the dose-response curves for many biological effects do not have this form. Linear, exponential, or power functions of dose have been shown in different biological systems or in the same system for different radiation qualities or dose rates. There is an extensive literature on the subject, some of which is reviewed and analyzed by Brown (Bro 76,77). The next UNSCEAR report will be devoted largely to this subject (UNS 79). I shall not discuss the problem in depth but I give a hypothetical example to illustrate the nature of the uncertainties involved.

II.6 In Figure II.1, which is re-drawn and amplified from (Bro 76), it is assumed that the solid line represents a true, but unknown, curve of some biological response vs. radiation dose. In A the observed points between dose levels Y and Z are derived from results of heavy exposures in animal experiments or human accidents, and it is desired to know whether dose level X is permissible for occupational exposure. A least squares fit through the three experimental points and the origin results in the

dotted line. This greatly overestimates the effects of doses at level X, and thus can be considered to be conservative. In B the open circles represent available points such as might be obtained from epidemiological studies and show a barely significant effect at dose level X. It is desired to know whether dose level Z can be permitted for emergency or rescue operations. The linear fit suggests that such a dose might not entail severe hazard, but here such a fit is obviously not conservative, but grossly underestimates the risk at high doses. It is also obvious that, if the only experimental points available were those shown by the solid circles in B, a linear fit would imply a substantial threshold between levels X and Y. For purposes of illustration the theoretical curve has been so drawn as to exaggerate the sigmoid form and to deviate from the linear by a factor of 5 at dose levels X and Z. In actual practice deviations are often considerably less, but even so may result in two-fold errors in extrapolated values.

II.7 Sigmoid dose-response curves such as the hypothetical one shown here are common in experimental radiobiology, while linear curves with or without threshold are well established in other systems. Many explanations for these different forms have been advanced, but none is entirely satisfactory because of the inadequacy of the data on the actual mechanisms of radiation damage at the molecular level. Probable factors are the number, one or more, of events needed to produce the biological effect under study, and whether one or all of the effects can be repaired and how fast, whether the dose rate and/or LET of the radiation are high enough to cause the accumulation of the requisite number of events in a critical volume before they can be repaired. Since relative and absolute values of these parameters are seldom known well, predictions of results at widely different dose levels are uncertain. It is likely that the fall-off of the curve at very high doses is due to overkill. Dead cells do not show biological activity, cancerous or otherwise.

II.8 Threshold - The question of the existence of a true threshold dose below which cancer will not be induced is closely related to the uncertainties in the shape of the dose-response curve. This is evident in Figure II.1.B, and is of great practical importance. The existence of a true threshold is not susceptible to strict

proof, since a negative can not be proved in finite systems. There is, however a high probability that there is a practical threshold dose below which cancer will not be induced in some biological systems during the natural life span of the species. This is especially true of bone cancer, and will be considered later.

II.9 Radiation quality - The term "radiation quality" is used to describe the property of radiation which determines the rate at which it transfers energy to matter along a linear path. The linear energy transfer (LET) of photons of the qualities commonly used in medicine and industry (100 keV to 10 MeV) is quite low. In living tissue in the path of such photons ionization is so sparse that many cells or sensitive areas of cells are missed entirely. Two or mor events seldom occur close enough together to interact at critical sites except at very high doses and dose rates. In contrast, alpha particles and neutrons may have such high LET values that they cause multiple events in single cells. The LET of electrons varies widely but is usually intermediate between that of alpha particles and photons. It has long been known that the relative biological effectiveness (RBE) of radiations tended to vary with their LET's. This has led to various theoretical treatments of the mechanisms involved, some of the most thorough being those in references Bon 66, 78a, 78b, Kel 71, Mars 77 and Ros 77. Highly reliable physical measurements of the energy absorbed from a great variety of radiation sources in various substances including simulated animal tissue are now available. They are, however, made in dimensions of centimeters, millimeters, or, at the least, hundreds of micrometers. The theoretical work just cited carries the analysis of dose distribution down to the subcellular dimensions in which the biological results of ionizing events presumably take place. At present there is only a little direct experimental confirmation of these theories (Bir 79, Col 79, Ros 79), and Marshall (Mars 77) gives a good correspondence between theory and clinical observations. If further confirmation can be obtained, the results should be of great importance in understanding the roles of radiation quality and dose rate in carcinogenesis.

II.10 Radiation dose rate - There is an extensive literature, which will not be reviewed here, on the effect of dose rate on various biological parameters. The indications of radiation injury most frequently studied have been loss of cloning ability in cells in

culture and time of survival in mammals, usually mice, during whole-body irradiation. At exceedingly high dose rates (rads/μ sec) the results are determined by the rates of diffusion and recombination of primary radiogenic species relative to cellular dimensions rather than to biological repair mechanisms. In ranges of rads/sec. down to rads/day, survival rate tends to vary inversely with dose rate. This is generally interpreted as meaning that, at slower dose rates, more time is available for repair of damage from early events in cells before second lesions can be caused. Many experiments have been so designed as to identify the nature of the damage and the mechanisms of repair. Damage is most frequently shown by defects in the synthesis of protein or of nucleic acids during replication of the cell. Repair may involve several processes in sequence, as when a damaged portion of a DNA strand is deleted by one set of enzymes and replaced by other enzymes. It is postulated that errors may occur in such sequences and result in a cell which is abnormal but still capable of replication. If the abnormality is in the mechanism which controls replication the result may be a cancer cell. In the higher intact animals it is probably that complex metabolic sequences are involved.

II.11 If the hypothesis is correct that radiation-induced cancer is due to replicable defects caused by faulty repair of damaged DNA, it seems to me that a total dose given at a slow rate should allow the persistence of more errors in repair, and hence more cancer, than the same dose given at a rate high enough to result in the accumulation of a lethal number of defects. At present the studies of cancers in the human which have followed exposures at different dose rates do not provide clear-cut evidence for or against this mechanism. It is evident, however, that cancer in humans has been observed following radiations delivered at very different dose rates. This is illustrated in Table II.2.

TABLE II.2

Approximate Dose Rates of Radiations that have Caused Cancer in Man

Radiation	Dose Rate	
	Crude	rads/sec
Atomic Bomb Photons & Neutrons	1000 rads/sec	10^3
X-ray Therapy Photons	100 rads/min.	1.7×10^0
Radium-226 (Eva 74) Mostly Alphas	10^4 rads/40 yrs.	7.9×10^{-6}

Since cancers have been observed in man after radiation exposures delivered at dose rates varying over more than eight orders of magnitude, it seems clear that dose rate is not a critical factor in this process although some effect, especially at low rates, is not excluded.

II.12 Metabolism of Radionuclides - Exposure to external photons or electrons may affect amounts of tissue varying from a few grams to the entire body but the dose absorbed by different tissues depends primarily on the physical properties of the radiations. The properties of the tissues themselves influence the dose only in so far as the different mean atomic numbers of bone, fat, etc., determine the amount of energy absorbed. The effects of internally deposited radionuclides, on the other hand, may depend critically on the chemical form and biochemical properties of the elements themselves. A few examples will be given here; details will be considered later.

II.13 Radium is a chemical homologue of calcium and the isotopes of radium are metabolized in a manner very similar to that of calcium. Yet the lifetime dose to bone cells from Ra-224 is about 10 times that from an equal number of microcuries of Ra-226. The reason is that the initial site of deposition of both isotopes is on mineral surfaces adjacent to the major portion of the bone cells. Radium-224, with its short half life of 3.7 days, delivers most of its radiation in this location before there is time for the slow transport mechanism to carry it to deeper sites in the bone. Radium-226, with a half-life 20 times the human life span, is translocated during

months or years to regions where cell populations are sparse and much of the high LET alpha radiation is absorbed harmlessly by bone mineral.

II.14 The metabolism of calcium is well understood, the understanding having, in fact, been aided greatly by studies of the fate of Ra-226 in humans. The metabolism of some other radionuclides of biological importance is understood poorly or not at all. This may be because of the scarcity in nature of the stable isotopes (e.g. the lanthanide rare earth metals) or because the elements are almost wholly man-made and thus new to biology (e.g. the trans-uranium actinides). Plutonium is the only one of this group whose biochemistry has been studied thoroughly. A physicochemical property of plutonium which has a marked biochemical effect is its tendency to form stable colloidal micelles. An extensive series of experiments has shown that, when plutonium in monomeric form as the citrate is injected intravenously into animals of several species, it is taken up selectively and held tenaciously on bone surfaces where it induces osteogenic sarcoma in the adjacent cells. If, on the other hand, polymeric plutonium is injected intravenously, it is taken up by the reticuloendothelial cells in the liver and causes carcinoma of the liver instead of sarcoma of bone. Inhaled plutonium is known to be retained to some degree in the lung, while redistributed material divides about equally between bone and liver. The effects of chemical form and particle size have not been studied fully. Plutonium is also a chemical poison, as are many other heavy metals, but its radiological hazard far overshadows its chemical toxicity.

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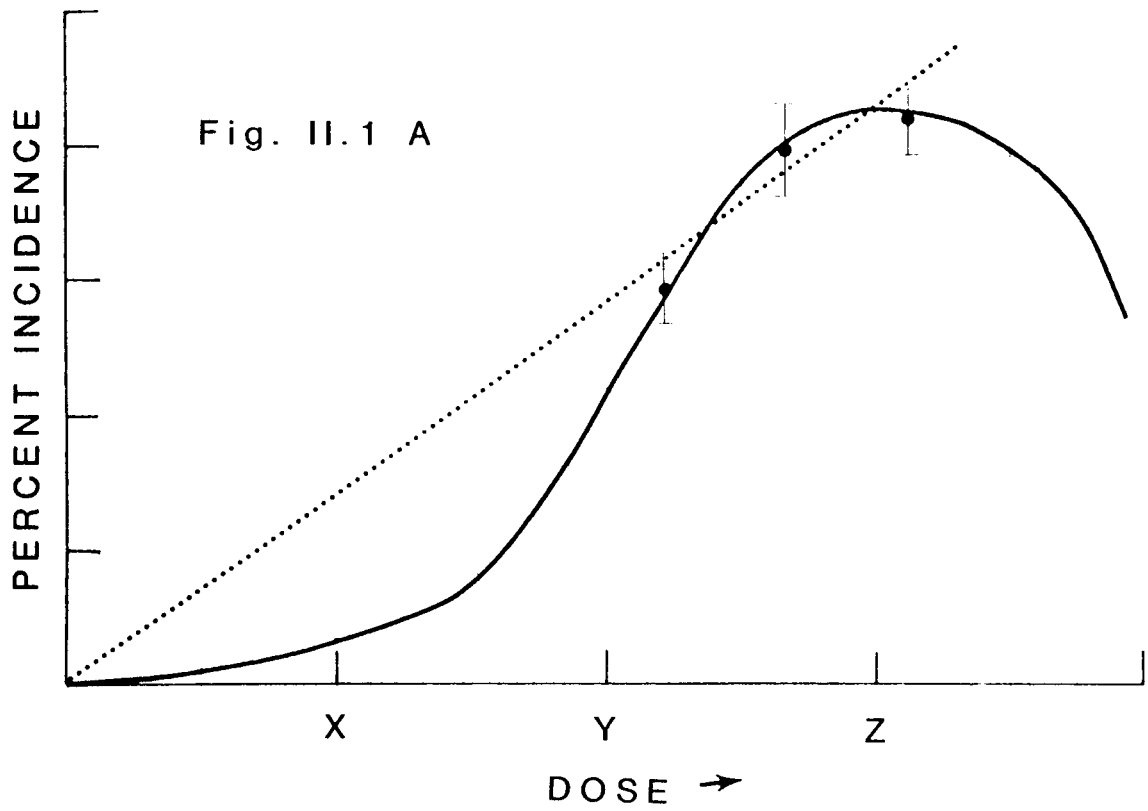

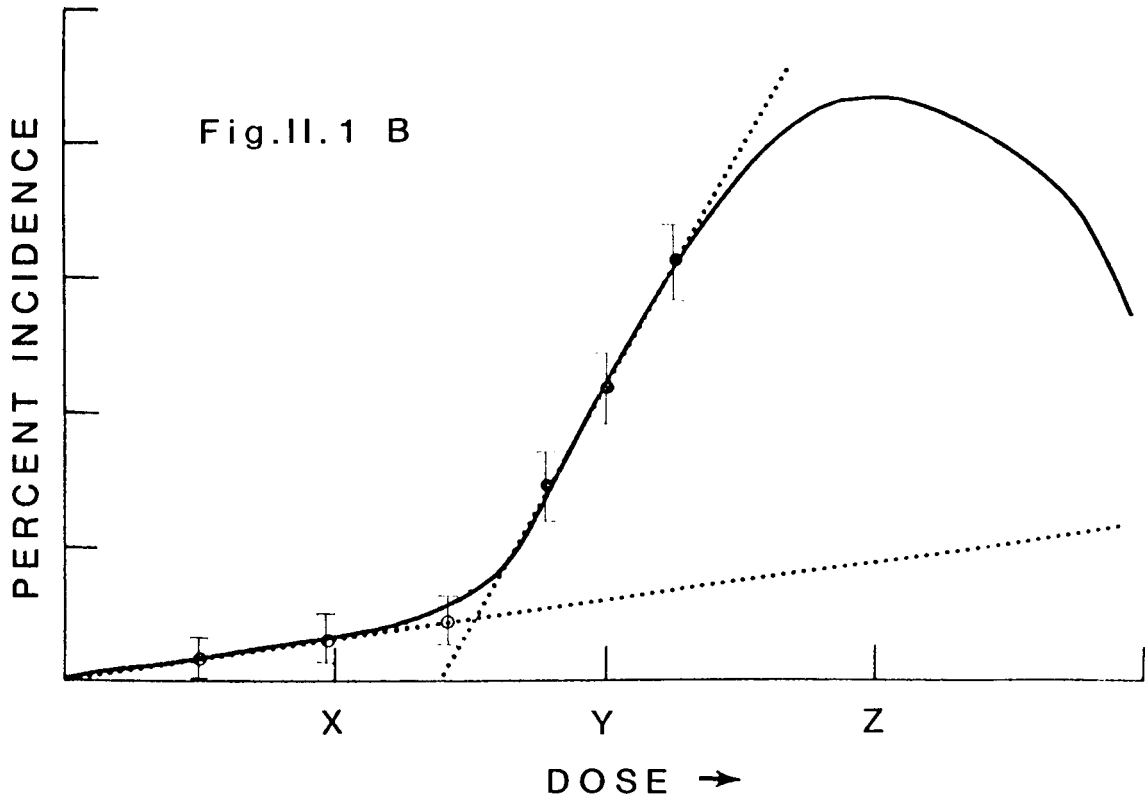

Figure II.1 -- Dose-Response Curves. Solid line is true dose-response curve; circles or dots represent available data points and dotted lines are best linear fits of observations (Redrawn from Brown, Health Physics 31:234 (1976)

RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER III -- BIOLOGICAL FACTORS INFLUENCING RADIATION CARCINOGENESIS

CHAPTER III -- BIOLOGICAL FACTORS INFLUENCING RADIATION CARDINOGENESIS

III.1 While the quantity of ionizing energy absorbed by a biological system is of major importance in determining the probability that such an event as carcinogenesis will take place, the readiness with which the irradiated organism undergoes the metabolic changes leading to cancer is critical in the determination of the final result. It has been recognized since the pioneer work of Zirkle (Zir 53) that the nucleus was the site at which the radiation injuries most important for subsequent cell activities took place, but the mechanisms of changes leading to the development of cancer still remain poorly understood. Some possibilities have already been discussed in Chapter II, 10, 11. Although the exact mechanisms remain in doubt it is generally agreed that tissues in which a large proportion of cells are replicating at any one time are more likely to undergo malignant change when irradiated than are tissues in which cells seldom replicate or are in a resting phase when exposed. This generalization applies to a variety of tissues in animals of several species and of different ages. In the human the most conspicuous examples are the susceptibility of the rapidly replicating cells of the bone marrow to the induction of radiogenic leukemia, contrasted with the resistance to malignant change of the cells of the skeletal muscle which do not replicate in adult life except during repair of injury.

A conspicuous exception is the mucosa of the small intestine. Throughout the life of the individual, the cells of the intestinal crypts replicate with a cycle of only a few hours, and they are even more susceptible to lethal radiation injury than are the cells of the bone marrow. This susceptibility to lethal injury is not reflected in susceptibility to carcinogenesis, however, both spontaneous and radiation induced cancers of the small intestine being among the rarest of human neoplasms (Berg 69). Some of the many other factors involved will now be considered.

III. 2 Species - Different living organisms show very large quantitative differences and somewhat smaller qualitative differences in their responses to exposure to ionizing radiation. For example, it is well known that adult insects can survive 2

orders of magnitude more whole body radiation than would be lethal to most mammals. This radioresistance arises from the fact that the somatic cells of insects do not replicate in adult life and so never show the type of damage which is apparent only at cell division. The insect genetic cells do replicate, however, and are killed readily by radiation doses that have little effect on the soma, this being the basis of the sterile male method of insect control. There are other marked differences between phyla in susceptibility to death from whole-body radiation within times not more than a few percent of the natural life spans. Differences between more closely related animals are smaller. Thus, the mammalian species for which the mean dose of whole-body radiation which will cause death of one-half of those exposed within 30 days (LD-50(30) has been determined seldom differ by more than factors of 2 or 3 in this parameter.

III.3 The species difference with which we are concerned here is not prompt death but susceptibility to late carcinogenesis. The two do not necessarily run parallel. Not only are there differences in susceptibility to radiogenic cancer between species but there may be profound differences between strains of the same species. A recent paper by Maisen et al. (Mai 78) brings this out strikingly in two inbred strains of mice. In the BALB/c strain a whole body dose of 650 rads appeared to protect against the natural high incidence of deaths in old animals from carcinoma of the lung, but this apparent protection was due to removal of a large fraction of the initial population by early deaths due to enhanced incidence of thymic lymphoma and leukemia. In the C57Bl strain, irradiation caused an increased incidence of early deaths from leukemia and of late deaths from non-malignant radiation changes, but only minor changes in the natural low incidence of carcinoma. In view of these and other instances of marked differences between inbred strains of the same species it seems evident that extrapolation to humans of results obtained from experiments in animals should be made with caution. Even in the highly heterozygous human species there are differences such as those between the spontaneous incidences of breast cancer in Japanese and North American women which make the choice of control groups for epidemiological studies very difficult.

III. 4 Age at irradiation - It is often assumed that, in mammals at least, radiosensitivity varies inversely with age. To some extent this is true. It might be expected to be so on statistical grounds alone since, in the growing organism, a larger fraction of the entire cell population is in mitosis than in the adult. There are many exceptions, however, and the metabolic state of an organ may be more important than its somatic age in determining radiosensitivity.

III.5 Prenatal irradiation - The effects of irradiation at different periods during intrauterine life have been studied extensively in animals. Human data are scarce, scattered, sometimes controversial, and, except for the material from the Atomic Bomb casualties, often poorly documented. It is fortunate that there have been no major disasters from prenatal irradiation of the human comparable to those resulting from exposure of substantial adult populations to Ra-226 or thorotrast, but the paucity of reliable material necessitates extrapolation from animal data. This can introduce uncertainties because human prenatal development differs considerably from that in mice, rats, or even dogs, the species in which most experimental work of this type has been done. Much of the experimental material is reviewed in the monograph by Brent & Gorson (Bre 72). Irradiation in the pre-implantation period, even with quite small doses, results in the death of many embryos but those that survive develop normally. Irradiation during the period of organogenesis causes defects in the development of whatever systems are differentiating most rapidly at that time. This selectivity is not specific to radiation but is similar to the teratogenesis seen after exposure during very narrow time ranges to thalidomide or rubella. Irradiation during the late fetal period corresponding to the third human trimester may produce general retardation of development but causes few specific abnormalities. Changes such as the above have been produced with some regularity by doses of 50 rads or more but there is little clear experimental evidence of effects from less than 10 rads. It must be remembered that experimental pre-natal irradiation always entails irradiation of the ovaries and adrenals of the mother and often, as in the mouse, of the entire body. Maternal doses less than 10 rads are not likely to have significant effects, but 50 rads or more can easily produce maternal injury that could cause secondary changes in the fetus. Unfortunately there have been few studies in which young animals irradiated in

utero have been kept for lifespan studies of the incidence of cancer. Thus, in this important field, we are dependent on such scanty observations in humans as are available.

III.6 Irradiation of juveniles - It is generally believed that juveniles are more susceptible to many types of irradiation injury than are the adults of the same species. The numerous regulations limiting radiation exposure of children which are in force in many places are partly a result of this belief. They are also the result of the knowledge that late effects will have time to manifest themselves during the lifetime of a person exposed in childhood while the long latent period of many changes prevents their appearance during the remaining lifespan of persons exposed as adults.

III.7 It is obvious that radiation injury resulting in defects in development can take place only before development is complete. Irradiation of open epiphyses readily causes stunting. Irradiation of the bones of adult men or dogs can not alter the stature because the epiphyses are closed, but it can depress the capacity to repair injury as much or more than in the juvenile. This is not true of rats and mice which continue to grow slowly throughout life and have no well-defined period of adulthood. Irradiation of the gonads of juveniles can prevent puberty; irradiation of the gonads of adults may cause sterility but rarely reverses secondary sexual characteristics which have already developed. These and other qualitative differences in the responses of the growing and mature animals are distinct from the possible quantitative differences in susceptibility to carcinogenesis.

III.8 Comparison of carcinogenesis in the juvenile human and in young experimental animals is even more uncertain than it is in the corresponding adults because of the relative slowness of human maturation. Human childhood can be said to last for 15 years or 20% of the average lifespan. Corresponding values for the dog are about 1/15 years or 7%, and for the mouse 6/100 weeks or 6%. Such differences in maturation rate could vary the susceptibility to radiogenic cancer in ways that are difficult to predict. Ratios in the higher primates are closer to those for man but large scale experiments on them are precluded by expense and other difficulties. Thus, while results suggestive of increased susceptibility to carcinogenesis in the juvenile period are

available from work with animals, especially dogs, we are largely dependent on results of accidents or ill-advised medical techniques for data on the carcinogenic effects of radiation exposure in the human child. At present the evidence of increased susceptibility of children to radiogenic cancer of bone, thyroid and breast seems fairly convincing. These will be considered in detail later.

III.9 Irradiation of adults - The majority of radiogenic cancers which are seen are in adults. They include cases which were induced by irradiation in childhood but did not become manifest until maturity as well as those which were induced by irradiation in adult life. They do not include those that were induced in aging adults who died of other diseases before the end of the latent period. In evaluating the risk of exposure of adults, the persons who developed cancer in adult life after irradiation in childhood can be excluded readily except when there is continuing exposure from internally deposited radionuclides acquired early in life. The category of those potential cases who die of other causes before the end of the latent period is always a cause of uncertainty especially in comparisons of populations of very different socio-economic backgrounds. The last 3 items in Table II.1, while important at all ages, are especially important in assessing the significance of cancers occurring after exposure in adult life.

III.10 Latent period - Latent periods of many years between the start of exposure to the inducing agent and the overt appearance of environmentally induced cancer are the rule rather than the exception. This is true for chemical as well as radiation carcinogenesis. In both the distinction must be made between cases in which the exposure takes place for only a few minutes to weeks and those in which it continues during a large fraction of the life span. Brief exposure is uncommon in chemical carcinogenesis where the toxic agent is often an integral part of an industrial process and exposure continues as long as employment does. Exposure for brief periods is important in many cases of radiation carcinogenesis, however. Some of these are the cancers which are induced by very short exposures, as in the Atomic Bomb casualties, or intermittent exposure for a few days or weeks, as in radiation therapy. In such cases the only uncertainties in measuring latent period are minor ones in the time of diagnosis of the cancers and usually total no more than a few months.

III.11 In contrast to the situation where the exposure is acute, cases of cancer resulting from chronic exposure to the inducing agent are the usual ones where the agent is an industrial chemical. Cancer can also occur as a result of chronic external exposure to ionizing radiation. Examples are the increased incidence of leukemia in radiologists and cancers of the skin of the hands of radiation technologists. Chronic exposure is also caused by internally deposited long lived radioactive isotopes such as Ra-226 and the Th-232 of Thorotrast. In these chronically exposed cases the concept of latent period loses its clarity. It is not possible to know when, within a range of many years, the initiating event, cluster of events, or sequence of events takes place that commits cells to malignant change.

III.12 It is evident from the above discussion that a long latent period is common to several types of environmental carcinogenesis and is not peculiar to that caused by ionizing radiation. For radiation exposures continuing for no longer than a few months most of the latent periods which have been reported lie between 4 and 25 years. Distribution tends to be skewed with a tail on the high side so that mean values are misleadingly high. Median values for solid tumors are usually between 10 and 20 years and are somewhat less for leukemia. No reason is known why there should be a lower limit at 4 years and somewhat shorter induction periods may be valid for the leukemia. Nevertheless, apparent very short induction periods always need careful scrutiny to assure that they do not merely represent the time needed for re-activation of some cell population in a pre-existing tumor that has received radiation therapy. For brief exposures latent periods are not clearly related to dose. For chronic exposures the latent period appears to be an inverse function of accumulated dose.

III.13 Death rate from other causes - It is not always realized how serious a confounding factor the death rate from causes other than cancer can be in population studies. It may act either to increase or to decrease the apparent incidence of radiation-induced cancer. It is obvious that persons who die of other causes before the end of the latent period will not be counted in studies of the probability of carcinogenesis. A factor which can act to cause a spurious increase in apparent hazard is the "healthy worker

effect". In this a population is selected by hiring practices, good working conditions, good medical care or a combination of all three in such a way that the death rate from all causes is less than the national or regional average. If the death rate from cancer is the same as the average, then the fraction of the total deaths which is due to cancer will be above average. If the healthy population is one which is exposed to radiation occupationally, then the increase in proportional cancer mortality may be wrongly attributed to radiation when in reality there are not more deaths from cancer but fewer deaths from other causes. A valid comparison between the risks of death from cancer in an exposed population and a control population can not be made on the basis of the proportion of total deaths that are due to cancer unless the mortality from other causes is the same in both groups. Otherwise the comparison must be made on the basis of cancer death rates per unit of living population at risk.

III. 14 Natural incidence of cancer - Ionizing radiation, like some chemical carcinogens, can induce malignant change in tissues in which spontaneous cancer is rare as well as in those in which it is common. Cases of the first type are likely to be noticed as soon as they begin to appear and the extent of the hazard can usually be estimated fairly easily. A striking example from the chemical field is the hemangiosarcoma of the liver which results from exposure to vinyl chloride monomer (Ber 76, Tho 75). This is a very rare tumor, being seen in only about 1 in 10^5 autopsies in the unexposed population in the U.S.A. In contrast, it was the cause of 3 out of 25 deaths in one exposed population of a few hundreds. Unfortunately the long latent period (median = 20 years) prevented recognition of the hazard until a considerable population had been exposed but the etiology of the disease was in no doubt once it was observed. There are few analagous examples in the field of radiation carcinogenesis. One may be the early observation by Martland of osteogenic sarcoma in the radium dial painters (Mart 31). Here the proportion of osteogenic sarcomas seen in autopsies of radium-burdened persons was about 400 times that in unexposed populations. This is the more striking because the patients were aged in the late 20's and early 30's, a period when the natural incidence of osteogenic sarcoma is low, and the report was made soon after the end of the latent period and before the majority of tumors had appeared.

III.15 In most cases a radiation etiology for malignant change is far from obvious. The importance or even the existence of supposed radiogenic cancer can seldom be evaluated without reliable information on the natural incidence of the same type of cancer in a population comparable in all other respects to the irradiated one. The typical situation is one in which the incidence of a common type of cancer such as that of the female breast is a few percent higher in an exposed population of no more than several hundred than it is in the national average. The natural incidence of breast cancer, i.e., the number of cases diagnosed per unit, usually 10^5, of population, is strongly age-dependent, increasing 10-fold between ages 30 and 50 years and more slowly thereafter (Sch 75). It is obvious that the incidence in a small exposed population can not be compared with the uncorrected national or state average. If the comparison is to be valid it must be with a subpopulation matching the exposed one in age distribution. It must also be of the same ethnic composition. Japanese women have a much lower incidence than North American Caucasians, and the latter vary somewhat according to socio-economic background. If exposure doses are low and suspected radiogenic cancers are few it may be impossible to find a control group which is matched well enough for differences due to radiation to be demonstrated.

III.16 Control and exposed groups must often be matched for date as well as for age. The most striking example of the need for this is in the study of cancer of the lung. With the advent of widespread cigaret smoking this cancer has increased from a rare disease to a major cause of death in males. At present it is exceedingly difficult to separate the carcinogenic effects of radon and concurrent cigaret smoking in uranium miners. This would not have been true 40 years ago before the carcinogenic effect of smoking began to be conspicuous. In a very different setting there was an increase in the incidence of childhood leukemia in the 1940's shortly after the introduction of antibiotics had reduced the deathrate from the respiratory infections to which pre-leukemic children are especially susceptible. Hence the incidence of leukemia in previously irradiated children who developed the disease in the latter part of that decade must be compared with incidence of non-irradiated children diagnosed in the same time span, not with the lower incidence at the time they were

irradiated. Other examples of changes in the incidences of malignant disease in the general U. S. population are the marked decline in stomach cancer over the past 50 years and a more recent increase in colon cancer.

III.17 The incidence of cancer is the parameter of major interest in evaluating radiation hazards and was emphasized above for that reason. In practice, however, it is often easier to obtain information on cancer death rates than on incidences. Confounding factors such as errors in diagnosis and the healthy worker effect have already been considered (Chapter II.1; Chapter III.13). An additional difficulty in the use of death rates is the variation in the curability of cancers of different types and at different times. At opposite ends of the scale, the death rates from the common types of skin cancer are so low that mortality tables can not be used at all in evaluating their prevalence, while the present death rates from cancers of the pancreas or lung are so high and the survival times are so short that little error is incurred in equating rates of death and incidence. Until 1970 this was also true of leukemia, but recent advances in chemotherapy now result in many 5 year survivals and a significant number of apparent cures so that mortality tables have ceased to be a reliable index of the prevalence of the disease. Other types of cancer have different patterns of incidence, survival rate and survival time and the last two obviously vary with the medical facilities available to the population concerned. All of these factors must be considered when the significance of an apparent increase in the incidence of cancer in an irradiated population is being evaluated.

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER IV -- GENERAL CONSIDERATIONS FOR CARCINOGENESIS IN DIFFERENT ORGANS AND SYSTEMS

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IV.1 Much of the literature of radiation carcinogenesis in the human is concerned primarily with the determination of how the cancer death rates in populations are related to the quantity of radiation to which the populations have been exposed and to the rate at which the exposure was received. The validity and usefulness of this approach is not in question but the method can give only part of the true picture of the extent of the risk. To cite a few examples -

1.2 It is known that basal cell and squamous carcinomas of the skin of the hands were common among careless workers 30 to 40 years ago and appear to be uncommon now but this apparent improvement can not be documented from mortality statistics because the death rate from these cancers is only 1% to 2%. The role of heavy exposure to radon daughters in the etiology of miners' lung cancer is well established but it seems useless to attempt to prove or disprove a carcinogenic effect of radon concentrations only a few times the average background at the present time when the incidence of lung cancer among tobacco smokers is so high and is changing so rapidly. There is concern over possible induction of osteogenic sarcoma by plutonium but (fortunately) no human data are available. Risk from plutonium can not be assumed from direct comparison with the well-documented human cases of bone sarcoma induced by radium-226 because of the differences in the metabolism of the two radionuclides. Both are well documented in the beagle dog. Comparison must therefore be made on the assumption that Pu/Ra-226 (dog) = Pu/Ra-226 (man), but this may not be true because of differences in the microscopic geometry in the bones of the two species.

IV.2 In view of such complexities it seems best to take up the different types of cancer separately and to explore the uncertainties associated with each type. They will be considered in approximately the chronological order in which the radiogenic etiology was recognized. This is partly as a matter of historical interest but partly because the lessons learned from the study of each cancer facilitated the investigation of the next. The diagnoses to be considered are as follows -

2.1 Basal cell and squamous carcinomas of the skin - These are so easily observed and so well localized to exposed areas that they seem to have been recognized within 15 years of the discovery of X-rays.

2.2 Osteogenic sarcoma - The role of Ra-226 and Ra-228 in causing this highly malignant bone tumor was established in a series of papers by Martland between 1925 and 1931. Evidence from the radium cases was an important factor leading to the studies of X-ray induced osteogenic sarcoma between 1940 and 1950. Unfortunately it did not prevent the disaster from injection of Ra-224 between 1944 and 1951. Work with this tumor has been aided greatly by the use of the reliable animal model afforded by the beagle dog.

2.3 Miner's lung cancer - This disease was described as early as 1500 A.D and was recognized as cancer in 1879 but the etiological role of radon decay products did not begin to be considered seriously until 1931. Information obtained in the earlier studies was not used to prevent the small epidemic which is now occurring in the U. S. A.

2.4 Leukemia - My personal recollection is that it was suspected as early as 1935 that the incidence of leukemia was higher among workers with radiation than the low natural incidence in the general population. The absolute incidence even among rather heavily exposed groups was low enough, however, so that an increased risk could not be demonstrated in persons exposed occupationally or therapeutically until 1950-1957. Radiogenic leukemia in the mouse has proved to be a useful model for interpretation of effects in humans.

2.5 Carcinoma of the thyroid - Interest in radiogenic thyroid cancer dates from the observation about 1957 that persons who had been irradiated in childhood for benign conditions of the head, neck and chest seemed to be unusually subject to benign and malignant tumors of the thyroid in adult life. Also, the increasing use of radioiodine for the treatment of hyperthyroidism aroused fears of late malignant change in the treated glands. Studies are continuing in these fields. The problems in epidemiology have proved to be unusually severe.

2.6 Carcinoma of the female breast - In this disease there is the confusing combination of a high and strongly age-dependent spontaneous incidence, a rather low relative risk from radiation, and the circumstance that there are few situations in which the breast is likely to be irradiated incidentally during the therapy of other organs. Hence it was not until about 1960 that radiologists who had been alerted to other types of radiogenic cancer discovered an unusually high prevalence of breast cancer in mature women who had been fluoroscoped frequently in youth because of pulmonary tuberculosis. This led to a systematic study of these and other groups where female breasts had been irradiated, and to the establishment of a definite correlation between irradiation and the subsequent incidence of cancer.

2.7 Liver cancer - Radiogenic liver cancer has not been a major problem to date but might become so under certain conditions of plutonium contamination. Hence a consideration of the cancers of the liver which are occurring many years after the acquisition of the long-lived alpha-emitting Thorotrast (particulate ThO_2) is pertinent.

IV.3 The above appear to constitute most of the types of human radiogenic cancer for which firm evidence exists at present. There are sporadic and anecdotal reports of other cancers of probable radiogenic origin which may prove to be valid in the future but which can not be quantitated at present because of inadequate evidence. Still other reports have so many of the defects discussed in Chapter II that they must be rejected. On the other hand, there is always the possibility that the use of a radionuclide of unfamiliar metabolic characteristics or administered by an unusual route will lead to an unexpectedly high exposure of some organ. There is also the possibility that there is a synergism between effects of radiation and of one or more of the anti-cancer drugs which are being used simultaneously or sequentially with radiation at present. Considerable in vitro work is being done in different centers on radiation sensitizers at present but there are not many studies in animals, results of which could be applicable to humans. It is to be hoped that these fields will be investigated in future clinical and epidemiological programs.

RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER V -- CANCER OF THE LUNG

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V.1 The great majority of radiogenic human lung cancers that have been recorded have occurred in workers in mines where uranium was a significant or predominant mineral. As discussed in the Introduction (Chapter I.1), a disease of the lungs which was probably cancer occurred among miners in Joachimstal and Schneeberg in central Europe and was described nearly 500 years ago. The mines were still being worked for various metals, particularly uranium, after 1900. The health of the miners was so poor that a commission to study conditions was financed by the League of Nations in 1922. Reports (Rost 26, Sik 30, Pir 32) showed that working conditions were very dusty and otherwise unhygienic, the death rate was high, and about 50% of all deaths were due to lung cancer. There were also many deaths from pulmonary tuberculosis and pneumoconiosis, the latter being especially prevalent in Schneeberg. The data are not presented in a form from which it is possible to calculate the incidence of lung cancer in the exposed population as a whole nor in any substantial control group. It is clear, however, that the incidence in the miners was extraordinarily high and that the development of cancer was usually preceded by inflammatory disease of the lungs of many years duration.

V.2 Earlier workers had attributed the lung cancers to arsenic and other known chemical carcinogens in the dust which the miners inhaled in large amounts and it is probable that these did account for some of the cancers. By 1932, however, it was suspected that radon was the major etiological factor. Measurements made at that time are difficult to interpret now but it is thought that the Rn-222 concentration in the atmosphere of the mines may have been as high as 10^4 pCi/ℓ and the concentration of Rn daughters about 1/2 of the equilibrium value (quoted by Holaday, Hol 69). Political changes and the subsequent outbreak of World War II hampered further research in these mines although stricter regulations regarding ventilation have apparently resulted in improved health among the miners.

V.3 The greatly increased demand for uranium which resulted from the development of nuclear fission led to the opening of a number of mines on the Colorado Plateau

in the U.S.A. These were mostly quite small operations with little or no artificial ventilation, but came to employ a total of several thousand men. In 1949 the Colorado State Department of Health, aware of the European experience, appointed a group from various Federal and State health agencies to study health problems among uranium miners. A prospective study of underground uranium miners was accordingly set up. Out of an estimated total of about 5000 men there were 3414 who were available for prolonged follow-up. The rates and causes of death of these men were compared with those for the general white male population of the Colorado Plateau, with open pit uranium miners, and with underground miners of ores not associated with the emission of radon. The radioactivity in the air of the mines where the men had worked was measured whenever possible. The methods used are described and evaluated in two reports by the Federal Radiation Council (FRC 67, FRC 68), and the results for miners with underground experience from 1950 through 1963 are given in references Wag 65 and Lun 68. There is a significant increase in the death rate from lung cancer. The Relative Risk (RR), as derived from the Standard Mortality Ratio (SMR) to the reference unexposed populations, was 3.9 in 1965 and had risen to 6.2 in 1969. The difference is due to the increasing proportion of cases who had been observed for times longer than the latent period. In this series the minimum latent period appears to be about 5 years; the maximum is not yet known. A correlation between lung cancer incidence and accumulated radiation dose was evident in 1965 and marked in 1969. The majority of miners smoked cigarettes but their smoking histories were known and a comparison of smokers and non-smokers indicated that at least 2/3 of their excess mortality from lung cancer was due to radiation. This was in harmony with the steep dose-response curve. The epidemiological methods used in these studies were good and the results are convincing. The only puzzling feature of the reports is that the small group of 761 Amerinds who worked in the uranium mines during the same period did not show an excess mortality from lung cancer. It is not clear what control population was used for these men nor what the radiation levels were where they worked.

V.4 The radiation dosimetry for lung cancer is difficult. Early workers assumed that Rn-222 in the mine air, which originated in the decay of Ra-226 in the uranium ore,

was the main source of the radiation. Radon-222 in a dust-free atmosphere is not, however, a very dangerous radionuclide because its time of retention in the human body is short compared to its physical half-life ($T_{\frac{1}{2}}$) of 3.8 days. It is absorbed readily through the lungs but most of what enters the plasma is cleared back to the expired air with a biological half-time ($T_{\frac{1}{2}}$) of only a few minutes. A small portion dissolves in various tissues but, since radon is inert chemically, the dissolved material is retained poorly. In an experiment in which a normal man remained for 8.5 hours in an atmosphere of 500 pCi/ℓ of Rn only about 1.3% of the activity inhaled was retained. Of this, about 67% was lost with $T_{\frac{1}{2}}$'s varying from 0.4 min. to 3.4 hours. Only the remaining one third, which was presumably in adipose tissue, was retained long enough ($T_{\frac{1}{2}}$ about 18 hrs) for a significant fraction of the radon to decay in situ (Har 58).

V.5 It was soon recognized, however, that Rn-222 in the air of uranium mines was in at least partial equilibrium with its decay products. These isotopes of polonium, lead, bismuth and thallium, are potentially solids but, since they are generated atom by atom, they are present in the air as single ions or as adsorbates on dust particles. If inhaled the dust particles will be held on the parenchymal surfaces for times which will be long enough to permit the short-lived radionuclides to decay. This situation led to the development of the Working Level (WL) as a unit of exposure. This is defined (FRC 67) as "any combination of radon daughters in one liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential alpha energy and is equivalent to the α energy released by the total decay of the short lived daughter products at radioactive equilibrium with 100 pCi of Rn-222 per liter of air". The problems of converting this exposure dose to absorbed dose in rads in the cells of the pulmonary epithelium is discussed in the 1972 BEIR Report (BEI 72). By making various estimates of the relation of the range of the α particles to the depth of the basal cells and of the residence time of the inhaled particles the author concludes that one working level month (WLM) is equivalent to a dose of 1/2 rad within a factor of 2 or 3. Even with this uncertainty it appears that nearly all of the miners who were discussed in V.3 had accumulated doses of more than 100 rads of alpha radiation and at least half of them had received more than 1000 rads.

V.6 There seems little doubt of the carcinogenic effect of exposures to radioactive atmospheres of the magnitudes of those described in V.1 and V.3. The dose-response curve of the USA cases, although full of uncertainties, suggests a linear no-threshold relationship which could properly be extrapolated back to much lower doses. Hence it is of interest to examine populations who have been exposed chronically to levels of atmospheric radon significantly higher than the world average but much lower than those in the uranium mines. Few such groups have been studied adequately but some data have been obtained in the town of Bad Gastein in Austria (Poh 72,75,78). This is a spa in a narrow valley in which there is a chain of hot springs. The waters as they come from the ground contain traces of uranium, thorium and radium-226 and about 40 nCi/ℓ of dissolved Rn-222. Evaporation of the radon leads to a concentration of 3 nCi/ℓ in the air of an old mine shaft which is used for heat treatment of patients and 11 pCi/ℓ in indoor air in some parts of the town. Doses to the attendants in the thermal gallery are estimated as 30 - 100 rem annually to the lungs and 4 - 12 rem/yr to the blood. The higher blood doses are associated with a significant increase in chromosome aberrations. It is not stated what Quality Factor is used in converting from rads to rems. It is stated that there is no increase in mortality from pulmonary or other cancer in the exposed population but no figures for death rates are given and the numbers of people at risk are not stated. Hence no definite conclusion can be drawn regarding the risk of cancer from inhaling radon at these concentrations. A piece of negative evidence of some interest is the fact that the radium dial painters have not shown an increased incidence of lung cancer. They do have a significant increase of carcinoma of the paranasal sinuses and mastoids where the Rn-222 which is generated in their body burdens of Ra-226 is trapped long enough to decay. Their expired air sometimes contains 10 to 100 times the average natural background concentration of radon, but exposure of the pulmonary epithelium to this for as much as 50 years does not seem to have been sufficient to produce a significant excess of lung cancer.

V.7 While most of the radiogenic cancers of the lung which have been reported have resulted from inhalation of radioactive materials, lung cancer can also be produced by external irradiation with photons and neutrons. A recent evaluation of the

A-bomb survivors (Lan 78) showed a relative risk from lung cancer of 1.5 to 3.0 in persons who had received 100 rads or more, the higher RR being in those who were over 50 years of age at exposure. On the other hand, no increase in lung cancer has been reported (Smi 78) in spondylitis cases although portions of the lungs of those treated over the dorsal spine must have received doses of several hundred rads. Unfortunately details of field sizes and exposure doses are not given and the mortality of the irradiated patients is compared with the age-corrected mortality for Great Britain as a whole rather than that for spondylitic cases who were treated in other ways. Hence the significance of the lack of reported excess of lung cancer in these patients is uncertain.

V.8 Enough information is now available to permit the formulation of safety regulations which should be adequate to protect uranium miners. Fortunately there have been no instances of induction of human lung cancer from inhalation of radionuclides other than those occurring in the air of mines where uranium and thorium are prominent. There is, however, considerable anxiety lest nuclear accidents or improper radwaste disposal may result in inhalation of dangerous amounts of other radioactive materials, especially plutonium. Hence several institutions maintain programs for the study of radiogenic lung cancer in animals. It seems appropriate to review some of these studies here for comparison with the human experience. As a caution in interpreting some of the results it should be pointed out that rats and mice of most laboratory strains develop nodules in the lungs spontaneously as they age. There is some question whether these are inflammatory lesions or true neoplasms (adenomas). They are not malignant but resemble cancers in gross appearance. Hence, in any report of an increase in the number of "tumors" in the lungs of rats or mice, the reader should be careful to note whether the tumors have been examined microscopically for malignancy. The following are a few of the more significant animal studies.

V.9 Many studies are under way of the effects on dogs of inhalation of several radionuclides, usually as particulates. These are lifespan studies in a long-lived species and can be expected to need many more years for completion. They have

already demonstrated that lung cancer can be induced readily by this method in an animal rather similar physiologically to man. In rats it has been shown (Yui 67) that a single exposure to inhalation of Po-210 aerosol would cause microscopically proved lung cancer after an accumulated dose of 200 to 500 rads. The experiment is interesting in that it isolates the effect of a single α-emitter in the radon decay series. Exposure of the lungs of mice to 750 - 3000 R of X-rays (Yuh 73) resulted in a great increase in the natural incidence of adenomas with a marked peak at 1500 R but no cancers. This is in contrast to the late carcinogenesis following photon exposure of humans (Lan 78) and illustrates the difficulty of extrapolating between species. An elaborate study of the effects of Pu-238, Pu-239 and Am-241 in rats (Mor 75) produced many microscopically proved lung cancers. The elements were inhaled either as the oxides (the particulate form to which accidental exposure would be likely) or as the soluble nitrates. Much less difference between the effects of the two forms was found than was anticipated, sufficient of the supposedly non-diffusible oxides being translocated to produce several osteogenic sarcomas.

V.10 A series of papers (Lit 75, 78, Des 78) on effects of Syrian hamster lung of instilled Po-210 either as solution or adsorbed on Fe_2O_3 particles is valuable because only small differences were found in the numbers of cancers produced by the two methods of administration when the dose was averaged over the whole lung. This may show that in this particular geometry the number of cells at risk happens to be in nearly exact inverse proportion to the dose per cell, or it may be due to some other cause. In another study in the Syrian hamster (And 79), promethium-147 incorporated in ZrO_2 microspheres was injected into the jugular vein and lodged permanently in the capillaries of the lung and gave a dose-dependent yield of proved cancers with a threshold at about 900 rad/yr. This study is interesting because Pm-147 emits β rays with a mean range of 0.35 mm rather than the very high LET α particles which have been used in most studies of lung cancer.

V.11 The evidence in the uranium miners cited above leaves little doubt that doses to the respiratory epithelium of several hundreds of rads resulting from Rn-222 and its decay products in the respired air will lead to a high incidence of pulmonary cancer.

Results of animal experiments make it reasonable to suppose that comparable exposure to other radionuclides, especially α-emitters, would have similar results. A credible dose-response curve exists for American miners but extrapolation of this curve down to low doses is extremely difficult because of the concurrent high and rising incidence of lung cancer due to tobacco smoking. Even when good vital statistics are available for large control populations there are formidable epidemiological problems in separating a small radiation effect from a large tobacco effect in an exposed group. As long as the incidence of tobacco-induced lung cancer remains high and variable it may prove to be impossible to obtain reliable observations of the effects in man of atmospheric exposures leading to accumulated doses of a few tens of rads in the pulmonary epithelium. We may remain dependent on the results of animal experiments with all the uncertainties of cross-species extrapolations.

V.12 Summary - Most of the radiogenic lung cancers that have been seen in man can be attributed to exposure to more than 100 rads of alpha radiation from radon decay products in the air of mines.

12.1 In this system the radiation dose can be calculated within a factor of 2 or 3, and credible dose-response curves have been constructed for accumulated doses in the hundreds of rads. It is not likely that reliable observations on the portion of this curve near ten rads can be obtained by epidemiological studies as long as the incidence of respiratory cancer resulting from tobacco smoking remains as high as it is at present.

12.2 In animals of several species lung cancers have been produced by exposure to several α-emitting radionuclides and at least one β-emitter. In the Atomic Bomb survivors a small excess of lung cancer has been seen 25 years after whole-body exposure to a mixture of photons and neutrons.

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER VI -- CANCER OF THE SKIN

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VI.1 Cancer of the skin was one of the first examples of radiation carcinogenesis to be recognized but it has had little reliable quantitative study. This is partly because no adequate distinction is made between the several very different malignant diseases which may originate in the integument. Basal cell carcinoma and squamous carcinoma are the two most common types of skin cancer. It is well established that both are associated with exposure to the ultraviolet photons of sunlight and can also be produced by ionizing radiation. Malignancy is low and mortality in countries with good medical facilities is near zero, especially for basal cell carcinoma. Hence these cancers seldom appear in death statistics. The malignant diseases originating in the integument which do appear in death statistics are of very different types. The best known is malignant melanoma, a highly lethal neoplasm originating in the melanocytes of skin and other tissues. It occurs spontaneously with some weak circumstantial evidence that it may be associated with exposure to ultraviolet light. I am not aware of any clear evidence linking it to ionizing radiation. Kaposi's sarcoma is fairly malignant and occurs in the skin but it is not really a skin cancer, being related to the lymphomas. Xeroderma pigmentosa is a lethal disease precipitated by exposure to U.V. light but caused by a genetic defect in the enzyme which normally repairs the damage to DNA which is caused by ultraviolet light. It is not known to be related to ionizing radiation. Thus, none of the diseases which are likely to be listed in death records as skin cancer are known to have any causal relation with ionizing radiation.

VI.2 Some of the basal cell or squamous carcinomas of the skin which have been accepted as having a radiation etiology are described here.

2.1 Cancers in the skin of the hands of persons exposed occupationally were the first to be reported. These include some of the early radium technicians and the medical and paramedical personnel who exposed their hands in the beam of diagnostic X-ray machines. Especially vulnerable were those who reduced fractures under fluoroscopic control, but all fluoroscopists were heavily at risk. It is impossible to compute the accumulated dose received by these people, but considering the primitive

instrumentation in the 1920's and 1930's, chronic skin doses in excess of 10 rads/wk for many years seems reasonable. Malignant change did not ordinarily appear until after decades of increasing fibrosis, keratosis and infection.

2.2 Cancer has been reported in chronic infected ulcers in skin which had been damaged by therapeutic X-irradiation directed at deep-seated tumors. In such cases the dose in air is often known to have been 3000 R - 4000 R in a few tens of days but the energy of the early therapy machines was so low that the absorbed dose equivalent 1 - 3 mm below the surface was much higher than this. Many studies have been made of skin changes at various times after such irradiation, and it is clear that late fibrosis and occlusion of blood vessels are common and lead to chronic hypoxia and poor nutrition of the surviving skin cells. It is in this milieu that malignant change takes place 20 or more years after the initial insult. Such cancers are also known to develop in old infected scars from heat burns or other injuries, and it might be questioned how specific the role of ionizing radiation is in such cases.

2.3 Basal cell and squamous carcinomas of the skin have also been reported after X-ray treatment of such benign conditions as acne and fungus infections. Many of these treatments were given in private offices with sketchy dosimetry and short follow-up, and are useless for assessing hazards. There are, however, two excellent follow-up studies of large series of patients irradiated during childhood for tinea capitis (ringworm of the scalp). In both the dosimetry is good, controls are well chosen, and the follow-up is from 13 to 25 years.

2.4 One series is from New York City (Sho 76, Alb 78). It includes 2213 children, mostly boys and mostly Caucasian, treated at ages of 5 to 10 years between 1940 and 1959, together with 1396 controls. Doses were 500 - 800 rads to each of several scalp fields at 100 kVp, inherent filtration only. The incidence of basal cell carcinoma in controls was 4/1396 = 0.29%; in irradiated non-whites it was 0/540; in irradiated whites, 64/1683 = 3.6%. Nearly half of the tumors were on the forehead and ears, although these had been partly shielded. The incidence was less in the more heavily irradiated skin of the scalp.

2.5 The other tinia capitis series is from Israel (Wer 68, Mod 74). It reports a follow-up through January 1, 1973 of 10,902 cases irradiated between 1949 and 1960 together with 10,902 population controls and 5496 untreated siblings. Patients were 1-15 years old at treatment. Administered doses were 350 R to each of 5 scalp fields at 75 - 100 kVp. Absorbed doses are given in detail. The incidence of malignant tumors of the scalp was only 0.01%, or very much lower than in the New York series, but still significantly above the zero values in the controls.

VI.3 It is evident that basal cell carcinoma of the skin is an infrequent but definite late effect of exposure to ionizing radiation, even with doses of not more than 500 rads, as used in the tinea capitis cases. It is recognized that the spontaneous incidence of basal cell carcinoma of the skin in Caucasians has been shown to be strongly correlated with exposure to the ultraviolet component of sunlight and with skin color, being a serious problem among people with very fair skins living in the tropics (Per 62). Incidence ordinarily increases rapidly with age, but it is not clear whether this is an inherent part of the aging process or is due to the long latent period which is common after exposure to carcinogens. The absence of cancers in the non-whites in the New York series, and the low incidence in the Israelis, who were nearly all dark Caucasians from North Africa, suggest that there may be common factors in susceptibility to induction of skin cancer by ionizing radiation and ultraviolet light. Further evidence on this would be valuable.

VI.4 Occupational radiation carcinogenesis in the skin is fully preventable and observance of present regulations can be expected to virtually eliminate it in the future. The late development of skin cancer after therapeutic irradiation can also be expected to become less common because of the skin-sparing physics of present therapy machines. A few cases can still be anticipated but, in view of their curability, they probably constitute an acceptable risk.

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER VII -- OSTEOGENIC SARCOMA

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VII.1 Osteogenic sarcoma has probably been studied more thoroughly than any other radiogenic cancer. In several ways it is easier to evaluate than most other types of malignant disease. Its natural incidence is low, being estimated as about 1 in 10^5/year, although the likelihood of errors in diagnosis which were discussed in Chapter II.1, make the exact figure uncertain. Until recently its cure rate was only about 20% so that mortality statistics gave a reliable indication of incidence. It has an unusual age distribution with a very pronounced peak at adolescence, a low rate in early adult life, and a slow rise in middle and old age when it is often associated with other types of bone disease. These characteristics make it likely that a cluster of cases occurring in a group with special occupational or other characteristics will be noticed and its significance will be susceptible to statistical analysis. Hence when, in the 1920's such a cluster began to appear in young adult women who had been employed painting watch dials with self-luminous preparations containing Ra-226 or Ra-228, it at once attracted the attention of Dr. Harrison Martland, the Chief Medical Examiner in Essex County, New Jersey, USA, who already was interested in other unusual disorders in these women.

VII.2 Martland correctly attributed these sarcomas to radiation from radium which had been ingested by the women in the course of their work and deposited in their skeletons. Several radiologists recognized the importance of obtaining the maximum of information from this inadvertent experiment in humans and organized prospective studies at the Massachusetts Institute of Technology, the New Jersey State Board of Health and the Argonne National Laboratory. In related fields the University of Utah has long maintained a life-span study of the carcinogenic effects of bone-seeking radionuclides in dogs and has also sponsored a joint study with West German physicians of effects of Ra-224 in humans. Studies of X-ray induced osteogenic sarcoma have been made in the Memorial Cancer Center in New York and elsewhere. A group in the United Kingdom has made major contributions to the difficult dosimetry of ionizing radiation in bone. The literature of the subject is

voluminous. I shall not attempt to review it fully, but shall cite only the most significant and comprehensive papers.

VII.3 Belief that solutions of radium taken orally or by injection were effective in the treatment of rheumatism or as a general tonic developed early. An advertisement in 1915 showed that this was a well-established pharmaceutical which had been accepted by the American Medical Association for inclusion in New and Non-official Remedies. Solutions offered for drinking contained 2 μg Ra/60 cc; 2 cc ampoules containing from 5 to 100 μg Ra were available for intravenous injection. The doses from the intravenous injections were substantial, as were those received by the people who drank the radium waters frequently. It was impossible to know the size of the population who received treatments of this sort from private physicians, but such patients as could be located were included in the study group. Also included was a stable group of known size and approximately known dosage in a hospital for the mentally retarded.

VII.4 The technique of preparing self-luminous paint was developed just before World War I, and by 1917 there were numerous plants in the New England States and New Jersey in which considerable numbers of young women were employed painting figures on the dials of watches, clocks and military instruments. At least one concern was fairly large and employed, besides painters, several chemists, physicists and engineers occupied in separating the salts of Ra-226, Ra-228 and Th-228 and in preparing the doped zinc sulfide crystals that were combined with binders in the paint. Other plants were small, bought their materials from other suppliers, employed only a few painters and moved frequently leaving behind contaminated premises and tangled finances but no records of employees. The plants were regulated poorly or not at all and subsequent investigation showed some that were unventilated and so dusty that the walls and the employees' clothing glowed in the dark. For the finer work the painters pointed their brushes with their lips and so ingested microgram amounts of radium and/or thorium daily, in addition to inhaling considerable radon and accumulated significant gamma ray doses from the stocks of radioactive materials which were kept unshielded about the premises.

VII.5 In the early 1920's the attention of several physicians and health authorities in northern New Jersey was drawn to the unusual number of deaths from ill-defined causes that were occurring among employees of the luminizing industry. Several reports were published, of which the most significant were by Martland and co-workers (Mart 25, 29, 29a, 31; StG 29). This led to a survey by the U. S. Department of Labor (DL 29) and the promulgation of strict safety standards for the luminizing industry which, with a few unfortunate exceptions, have been effective in preventing severe exposure since then. It also led to the organization of the study groups mentioned in Chapter VII.2. The only instruments available to the early investigators were electroscopes, zinc sulfide screens, and qualitative techniques for autoradiography. Despite this Martland was able to conclude (Mart 31, p. 2513) that radium body burdens of less than 0.5 μg are dangerous and that burdens too small to be detectable by techniques available at the time might prove at some future date to be carcinogenic.

VII.6 The situation among the radium dial painters was very confused at first, but can be reconstructed from the evidence obtained by the early investigators and in light of subsequent knowledge. The most heavily exposed workers died of bone marrow depression in a year or two, and thus before they had had time to develop clinical disease of the more resistant bone tissue. Those somewhat less heavily exposed survived long enough to begin to have arthritis-like symptoms 3 to 5 years after the start of exposure. Visible bone lesions were shown in those patients who had diagnostic X-rays. The most prominent lesions were in the jaws, and in some cases these were accompanied by intractable infections that caused death. The prominence of jaw lesions was probably due to a combination of severe radiation damage from radium lodged about the teeth and infection by the readily available mouth bacteria. Immune mechanisms were probably impaired in these women, some of whom were reported to be anemic and pancytopenic. This may have contributed to the severity of the jaw infections. In the 41 cases of radium poisoning described in reference DL 29 there were two probable cases of leukemia. They are not well documented and the size of the population at risk is not given. Hence it is not possible to

say whether they represent an increase in the natural incidence of this disease. Two skin cancers occurred in the hands of chemists engaged in refining radium.

VII.7 The first reported case of osteogenic sarcoma in a dial painter occurred in 1927, ten years after the start and eight years after the end of exposure (DL 29, Case #14). This latent period is in harmony with other cases of radiogenic osteogenic sarcoma and illustrates why the disease was not seen in the persons who were so heavily exposed that they died of bone marrow damage in shorter times. By 1931 Martland had reported 5 cases of osteogenic sarcoma that occurred in 1924-1931 among about 800 persons employed in one plant that manufactured watch dials. While the series is not susceptible to firm statistical analysis, the annual incidence was 5 in 7 years per 800 persons, or about 1×10^{-3}. This is sufficiently different from the estimated annual incidence of 1×10^{-5} for the country as a whole to leave little doubt of the etiological role of the internally deposited radium in the observed cases. No new cases of severe anemia or jaw necrosis were appearing at this time. The absence of evidence of continuing marrow damage may reasonably be attributed to the burying of many of the superficial radium deposits by new bone mineral so that none of the alpha and little of the beta radiation can reach the marrow cells. This is confirmed by a recent report (Pol 78) on the peripheral blood counts of 393 selected dial painters about 40 years after low to moderate intakes. Little evidence of residual bone marrow damage was found. The survival times of 1235 workers exposed before 1930 were the same as for the U. S. white population as a whole if those who died of radium-related cancers were excluded (Ste 78). This is additional evidence that late signs of injury from radium are confined to the skeleton.

VII.8 During the 48 years since (Mart 31), osteogenic sarcomas have continued to appear in persons carrying burdens of Ra-226 or residual Ra-228. During this time a comprehensive effort has been made to locate as many as possible of the people who were exposed. The known population now totals 2072 whose radium burdens have been measured and nearly 1300 others whose body burdens were unknown or uncertain (ANL 78). This series is probably skewed somewhat toward the high side because cases with crippling benign bone lesions or malignant tumors are much more likely

to be located than those with minimum symptoms. Nevertheless it permits a fair estimate of radiation risk. At the same time that additional cases were being located great advances were made in the theory and practice of the radiation dosimetry of bone. This permitted an analysis of the dose-response relationship for cancer induction. Some of the more important reports on these cases will be considered here. Dosimetry will be discussed later.

VII.9 In 1952 Aub et al. reported (Aub 52) on 30 cases, (14 dial painters, 5 chemists and physicists, 11 therapy patients) for whom radium burdens had been determined. Of these, 5 had died of osteogenic sarcoma and 3 of carcinoma of the paranasal sinuses or mastoids, 19 to 25 years after initial exposure. This is a selected sample and does not show the true incidence of malignant change. It does, however, suggest a threshold value at a terminal body burden of 0.5 μg Ra-226 and/or its equivalent for Ra-228 below which cancer induction is unlikely.

9.1 In 1969 Evans et al. (Eva 69) gave the results of studies of 496 cases out of a total of 1064 known to the Massachusetts Institute of Technology. The existence of a threshold is supported by the fact that no cancers were seen in persons whose average cumulative skeletal dose was less than 1200 rads. Above this the tumor incidence was 40%, but if self-selected cases were excluded it was 29%. These results were shown for the first time to be incompatible with a linear no threshold dose-response. They have been confirmed more recently (Eva 74, 79). The latent period was longer for the lower doses. This is to be expected since it takes longer for the accumulated threshold to be reached at a lower dose than at a higher one.

9.2 In 1978 Rowland (Row 78) reported on the status of 1474 female dial painters who entered the industry before 1930 and had been followed to death or to December 1976. These included the Argonne National Laboratory series and some cases studied by other participating institutions. Since nearly 50 years have passed since these people were first exposed in early adult life, the death rate of the survivors from causes unrelated to radium is now high. Thus they will soon constitute a closed series of great value for epidemiological studies. In the entire group there

had been 61 bone sarcomas and 21 head cancers at the close of 1976. In the 759 cases with a known Ra body burden the incidence of bone sarcomas was 5.0%, of head cancers, 2.2%. Calculations of the accumulated radiation doses were corrected for the fraction of the total exposure which was due to Ra-226 or to Ra-228. For bone sarcoma the observations could not be fitted to any linear dose-response curve. The best fit was with a complex function of the quantity of radium which entered the blood stream during the period of exposure, and there was a threshold at an accumulated dose of about 1000 rads. The best fit for the dose-response curve for head cancer was linear, with a threshold at about 500 rads.

9.3 The most recent summary of malignancies induced by Ra-226,228 (ANL 78) covers 3327 exposed persons and gives a 50 year incidence for osteogenic sarcoma of 2.5% and of head carcinomas, 1.0%.

VII.10 By 1931 the study of the dial painters had made it clear that the long-lived isotopes of radium were dangerous substances when taken internally. Despite this an extensive clinical trial of a short-lived isotope of radium (Ra-224, $T_{\frac{1}{2}}$ = 3.64d) was made in Germany between 1944 and 1957. Radium-224 is a radionuclide in the thorium series. It has no long-lived daughters and the gaseous first product, Rn-220, has a half life of only 55 sec., and so has little opportunity to escape from the body. In the metabolism of bone, radium, like other alkaline earths, is taken up from the blood stream first onto the surfaces of pre-formed bone mineral. There it may be incorporated into new bone crystals if they are being laid down on the surfaces, or it may be translocated and deposited diffusely in the volume of bone mineral. The latter processes are slow, with time scales of days to weeks, so that most of a pulse of Ra-224 when taken up from the blood will decay on the surface before it has time to diffuse. The osteoprogenitor cells, which are thought to be those which give rise to sarcoma, lie in sheets on the bone surfaces within the range of the alpha particles from radium deposited there. These cells are thought to accumulate about a 10-fold greater radiation dose than they would if the same number of microcuries were distributed diffusely. The daughters of the Ra-224 which is deposited on bone, with the possible exception of Pb-212 ($T_{\frac{1}{2}}$ = 10.6 hrs), probably do not have time to diffuse

into the circulation but decay in situ. The solution which was injected, however, contained Ra-224 in equilibrium with its decay products. These pre-formed products, in contrast to those generated in bone, reached targets in the body which were determined by their biochemical properties. In particular, a number of late cases of renal disease may have been related to injury from Bi-212 ($T_{\frac{1}{2}}$ = 60 min) which was taken up selectively by the kidney.

VII. 11 A total of about 2000 patients were treated by intravenous injection of Ra-224 solution. Of these nearly 900 have been studied by Spiess and by Mays (Spies 69, 70; May 78). Thirty-seven percent of the patients had tuberculosis of bone and 14% had tuberculosis of soft parts. Most of the remainder had ankylosing spondylitis. They ranged in age from one to 70 years at injection, about 2/3 being adults. Total administered doses of Ra-224 were 40 to 5000 μCi in injections of 8 to 70 μCi each, repeated at varying intervals for total times up to 20 months. As of the Mays, 1978 report, 54 of 897 cases (6%) had developed osteogenic sarcoma. This is close to the total incidence to be anticipated, since this type of treatment was discontinued in 1957 and the latent period for radiation-induced osteogenic sarcoma seldom exceeds 20 years after exposure ceases. In these cases exposure ceased a few weeks after the last injection in contrast to the Ra-226, 228 cases where exposure continued for life. The incidence in fully documented juveniles was 35 of 204 = 17%; in adults, 13 of 612 = 2.1%. The incidence increased greatly as the span of injection increased, being about 50% higher when injections were protracted over a year or more than when they were completed in 6 months. This is unusual but is confirmed by experiments with Ra-224 in mice (Mül 78). In most of the systems that have been studied experimentally protraction allows time for repair of some of the radiation damage and reduces the over-all effect. For equal injection spans the incidence of sarcoma was not very much greater in juveniles than in adults. The latent periods between the first Ra-224 injection and the diagnosis of sarcoma ranged from 4 to 18 years, with means near 10 years, less for higher doses. No sarcomas were seen in cases where the average dose to whole bones was less than 90 rads. This would be equivalent to a dose to bone cells of 800 to 900 rads

and is in reasonable agreement with the threshold for accumulated dose which was seen in the Ra-226,228 cases.

VII.12 In the radium dial painters the bones which subsequently underwent malignant change were normal at the start of exposure and effects of radiation could not be confused with possible effects of pre-existing bone disease. This is not true of the Ra-224 cases, the majority of whom had bone lesions due either to tuberculosis or to ankylosing spondylitis. Neither of these diseases is known to lead to osteogenic sarcoma and there is some positive evidence that spondylitic patients do not have an increased spontaneous incidence of malignant disease (Smi 77). Nevertheless it would be desirable if a comparison can be made of the epidemiology of the group that was treated with Ra-224 and of comparable groups that were treated in other ways. In the case of the osteogenic sarcomas the question of possible effects of confounding factors is academic since the significance of a crude RR factor of $54 / 0.2 = 270$ (May 78) can hardly be in doubt. The stunting which is reported in persons treated in childhood is to be expected but it would be useful if it could be correlated with dose and with control values from other tuberculous children. The high incidence of exostoses is also to be expected although it can not be quantitated readily because of the absence of reliable information on the natural incidence of the condition. It is a frequent result of irradiation of open epiphyses in both humans and animals and is probably caused by the pinching off of nests of viable cells during the irregular recovery of the epiphysis from radiation injury. The lesions are usually benign although late malignant changes are seen occasionally.

VII. 13 Further comparison with control groups might also help to clarify the effects on various soft tissues. In particular, it would be desirable if the role of Bi-212 in the high death rate from renal disease could be investigated further. The deaths due to pancytopenia can safely be attributed to radiation but it would be useful to know the statistical significance of the cases of leukemia. Such comparison with control groups would not be expected to alter the very clear-cut demonstration of the relation of Ra-224 to the high incidence of bone sarcoma. This is the most important and convincing result of this careful investigation.

VII. 14 Osteogenic sarcoma induced by X-rays - Osteogenic sarcoma following X-ray therapy was reported as early as 1922 (Von 22), but it was not until the papers by Hatcher (Hat 45) and by Cahan et al. (Cah 47) that this cancer was recognized as a possible late effect of external irradiation of bone. Since then there have been scattered reports of perhaps 250 cases. The recent paper by Kim et al. (Kim 78) puts special emphasis on dosimetry. With the exception of rare cases in the hands of radiologists nearly all of these sarcomas originated in bones that had been exposed to therapeutic radiation. Here it is important to make a distinction between sarcoma arising in bones that were normal but were in a field of radiation directed at disease of underlying or overlying soft parts and sarcomas that arose later in bones that had been irradiated for bone disease. This distinction is not made in many of the published reports including some of the earlier ones from the Memorial Hospital group. The mechanisms of carcinogenesis may be quite different in the two cases. When sarcoma arises in a previously normal bone that has been irradiated, the malignant change can safely be attributed to the radiation, subject to the usual epidemiological caveats. When sarcoma arises in a previously diseased bone that has been treated with radiation, there is always the possibility that the treatment may merely have uncovered a pre-existing malignant potentiality. This is especially true when the primary bone disease is enchondroma, fibrous dysplasia or giant cell tumor, all of which are known to be capable of sponteneous transformation into tumors which may be difficult to distinguish from de novo osteogenic sarcoma. The problems associated with this situation are important but they are primarily clinical and I shall not consider them here. I shall consider only sarcomas which appear to have been induced by X-rays or other external sources of ionizing radiation in bones in which there is no evidence of prior disease.

VII. 15 In the most recent report from the Memorial Hospital group (Kim 78), 51 cases were accepted as osteogenic sarcoma induced in previously normal bone by external irradiation. Of these 24 were from the literature and 27 were known personally to the authors. A large number from the literature and some of those previously reported from Memorial were rejected because of the presence of known or probable disease in the bone in which sarcoma subsequently developed. A few were

excluded because radiation therapy had been given for sarcoma of soft parts adjacent to bone and it was not possible on histological or anatomical grounds to be sure that the tumor which subsequently appeared in bone actually originated there or was an invasion by a recurrence of the initial soft part sarcoma. Acceptable radiation dose calculations were available in 9 cases from the literature and 20 from Memorial. Fourteen or 30% of the adult patients were male and 33 or 70% were female; in 4 infants the sex was unknown. In spontaneous osteogenic sarcoma the M/F ratio is about 55 to 45. The female predominance in this series is due to the large proportion of the adults who were treated for carcinoma of the breast or uterus. The latent period from start of exposure to diagnosis of sarcoma was 4 to 27 years, median 11 years.

VII.16 Eighteen, or 35% of the patients were irradiated at ages from one month to 4 years. This series is drawn from a population of unknown size who were treated in many institutions in the U.S.A. and Canada between 1935 and 1974. It is not possible to know what proportion of them were under 5 years old when treated. In Memorial Hospital only 2.5% of about 38,000 cases treated between 1956 and 1968 were less than 5 years old, but it is not known how many of them survived longer than the latent period for osteogenic sarcoma development. Despite this uncertainty the figures suggest strongly that the very young child is more susceptible than the older child or the adult to radiogenic osteogenic sarcoma. This seems to have been true to a much less extent in the Ra-224 cases (Chapter VII. 11).

VII.17 This series suggests strongly that there is a threshold dose for osteogenic sarcoma induction. The radiation doses in the published paper are given in rets (rad equivalent therapy) in order to compare the results of treatments given at different protraction schedules. The doses in rads ranged from 2000 to 30,000 rads, with a median of 5300 rads. This indicates a threshold at about 2000 rads, or considerably higher than in the radium cases. Except for 3 patients who were treated twice, all of the patients in this series received all of their radiation in a few weeks or months. In this respect they were more similar to the Ra-224 cases than to the Ra-226 dial painters in whom a number of years was needed to accumulate a threshold dose.

The difference in protraction thus does not explain the apparent difference in threshold. Another reported series which overlaps this gives a threshold for induction of osteogenic sarcoma by therapeutic irradiation as 1800 rads (Yos 77). There is always the possibility that the appearance of a threshold is spurious, being simply due to the fact that there are few cases at risk from lower doses. Palliative treatments which may be less than 2500 rads are given only to patients with disseminated cancer who seldom survive as long as the latent period. Curative treatments which may permit prolonged survival usually deliver much higher doses to the primary tumor. When multiple convergent fields are used to attain a high tumor dose, however, the dose to bones underlying each field may be comparatively low. So far we have not found reports of sarcoma in such cases.

17.1 There are other clinical observations which give evidence of a threshold dose. No increase in osteogenic sarcoma was seen in the atomic bomb survivors (Yam 69, Bee 78). These people received instantaneous whole-body doses of photons and some neutrons. Doses varied considerably but seldom exceeded 300 rads since few who received higher doses survived. These doses thus lie much below the apparent threshold of 1000 to 2000 rads. Another pertinent group is the considerable number (14,554) of patients who received X-ray treatments to the spine for ankylosing spondylitis between 1935 and 1954 (Cou 65). These patients showed significant increases in the incidence of leukemia and of various cancers of soft parts but only a questionable rise in bone sarcoma from one case expected to 3 cases observed. Unfortunately nothing is said in this important paper about the X-ray doses used, but the usual practice was to give 800 to 1500 rads in not more than 5 fractions. This is close to the apparent threshold and the insignificant increase in bone sarcoma incidence in these cases is in harmony with this. The evidence for a threshold dose for osteogenic sarcoma induction in humans appears to be substantial.

VII.18 Radiation dosimetry in bone - The unique problems of photon dosimetry in bone stem from the presence of large amounts of hydroxyapatite containing calcium and phosphorus with atomic numbers of 20 and 15 in various geometrical relationships with living bone cells composed of elements with Z values of one to 8. At the time

when the X-rays used in therapy had half-value layers of 0.5 to 0.75 mm Cu it was believed that bone tissue was very radiosensitive because pathological fractures and other evidences of necrosis were seen so often in bones that had been in therapy fields. However, Spiers (Spier 46, 49, 51) and Wilson (Wil 50) showed that bone cells situated within a few tens of micrometers from mineral surfaces in an X-ray field received heavy irradiation from secondary electrons generated by photoelectric absorption in bone mineral in addition to energy from the direct beam. Working with Spiers (Woo 53) and with Laughlin (Woo 57), I was able to obtain biological confirmation of the physical calculations by quantitative measurement of the alkaline phosphatase produced in known locations in mouse bone. Alkaline phosphatase in bone is produced by mature osteoblasts. These are not necessarily the cells that give rise to osteogenic sarcoma but are in close proximity to them, so these findings can be used in computing doses for carcinogenesis. Errors from this source could amount to factors as high as 2 or 3 in computing bone doses from the early X-ray machines but are only about 10% with the present megavoltage sources. The only serious problems that remain at present in calculating X-ray doses that have led to osteogenic sarcoma are due to uncertainties as to the exact location at which a large tumor arose and to lack of information as to the siting of the therapy fields.

18.1 The dosimetry of radiation from bone-seeking radionuclides is much more complex. For convenience, elements which are concentrated selectively in or on bone are divided into "volume seekers" or "surface seekers". Volume seekers are substances which can be incorporated into bone mineral. They include the isotopes of the alkaline earths calcium, strontium and radium as well as fluorine and phosphate. All are taken up initially on bone surfaces and become distributed into the volume of the bone and ultimately recycled back into the circulation with time constants that range from minutes to years. Heaney (Hea 63) gives a good discussion of the kinetics of these processes. Although fluorine is a normal constituent of the apatite in bone mineral, fluorine-18 is effectively a surface seeker because of its short $T_{\frac{1}{2}}$ of 110 min. The importance of the short half-life of Ra-224 has already been discussed (Chapter VII.10).

18.2 Of the true surface seekers plutonium is the most important at present, but the other actinides may become significant as they are produced in larger amounts. All of them bind promptly and permanently to various constituents of bone surfaces (Chi 72) where their alpha emissions irradiate overlying bone cells selectively. They remain there until the surfaces themselves are removed by resorption or are buried by subsequent deposition of mineral. Many other elements, radioactive or stable, if they are present in the blood stream as ions can be adsorbed on bone surfaces, but the process usually reverses too rapidly to be of physiological significance.

18.3 There is an extensive literature on the dosimetry of bone-seeking radionuclides. It includes in vivo kinetic studies in humans and animals; in vitro studies of the microscopic geometry of bones of various species; experimental carcinogenesis especially in dogs; development of mathematical models to explain observed results. Some of the more recent and significant reports are the following.

18.4 Results of extensive studies of mean path lengths and surface areas in trabecular bone are summarized in (Bed 76) and (Spier 78). These supply data essential for calculation of the energy absorbed from alpha and beta particles by cells on bone surfaces and in marrow cavities.

18.5 Calculations have been made of the dose to cells on bone surfaces and bronchial epithelium from plutonium and several other actinides (Har 76, 79).

18.6 A comprehensive theory has been formulated for the induction of bone cancer by alpha radiation (Mars 77, 78). Although this was developed specifically for α-emitters it can be adapted for electrons by suitable alteration of mathematical constants. It is reviewed constructively in (UNS 79) and it has been found to give a good fit for observed data for the radium dial painters (Row 78).

18.7 Taken together these advances constitute a fairly reliable basis for computation of the quantity of absorbed radiation which is associated with malignant or other pathological changes in bone.

VII.19 Animal work - Many research workers have been engaged actively for a number of years in the study of the effects of radiation on animal bone. Rats and mice

are useful for screening because they are inexpensive and their short lives expedite the accumulation of data. Unfortunately the data so obtained are not easily extrapolated to humans because most rodents continue to grow throughout life and this results in kinetics different from those of animals with well-defined periods of adulthood. Dogs are much more satisfactory in that their period of growth is well defined although it is a shorter fraction of the life span than in man (Chapter III.8). The microscopic structure of their bones is similar to man but allowance must be made for differences in dimensions especially in small dogs such as beagles. Some important findings in animals are the following.

19.1 Plutonium-239 has been shown to be about 16 times more effective than Ra-226 in the production of osteogenic sarcoma in beagles (Jee 75) owing to its surface-seeking properties. The presence of a threshold dose is probable.

19.2 The carcinogenicity of the beta-emitting Sr-90/Y-90 system has been demonstrated in six species of animals (Edi 69). There is some evidence of a threshold at about 1000 rads.

19.3 Paralleling the comparison of Ra-226 and Pu-239 is a comparison of the carcinogenicity of Ra-224 and Th-227 in mice, but the comparison is not clear-cut because of the Ra-223 daughter of Th-227 (Mül 78).

19.4 Beta-emitters other than Sr-90/Y-90 have also been shown to produce bone sarcomas in animals. Blackett observed sarcomas in a high proportion of rats injected with P-32 orthophosphate (Bla 62), but was not able to resolve the problem of dosimetry in the rapidly growing animals that he used.

19.5 The vulnerability of bone cells to radiation originating in the marrow was illustrated by the finding of a few bone sarcomas in mice that had been treated with Fe-55 (Lai 77).

19.6 There have been few reports of carcinogenic effects of X-rays on animal bones. Blackett (Bla 62) reported osteogenic sarcoma in a high proportion of rats that had received exposure doses of 3000 R to the hind legs. He published no experimental details but apparently used X-rays with a half-value layer of 1.0 mm Cu, so the doses absorbed by the bone cells may have been as high as 3800 rads. I saw no

tumors in 47 mice that I kept for other reasons for one year after 1900 to 2600 rads to one hind leg (Woo 79a). Negative values are not very meaningful in series as small as this but they do suggest that, in these two closely related species, X-rays induce bone sarcoma readily at doses higher than 2500 rads, but not often at lower doses.

VII.20 Summary - It seems clear from the preceeding evidence that malignant tumors of bone can be induced by ionizing radiation in all mammalian species that have been studied. This is true whether the radiation is in the form of α or β particles or photons and, in absence of strong contrary evidence, it must be assumed that it is also true of neutrons, mesons, etc. It also appears that there is a practical threshold in the neighborhood of 1000 rads below which cancer induction is unlikely. What are the dimensions of this risk in human populations?

20.1 In the radium cases the risk was obviously totally unacceptable, but it is now well understood, is preventable by adequate controls, and need not recur. This does not end the problems of bone-seeking radionuclides however. The extreme toxicity of the bone-surface seeking plutonium has been demonstrated clearly, and some other transuranium elements behave in the same way. If the likelihood of exposure to these radionuclides should become general as a result of the development of a plutonium economy it could constitute a major hazard. It is to be hoped that the ongoing studies in animals directed at improved quantitation of the cancer hazard from these elements will continue vigorously.

20.2 Except for a few preventable cases in persons exposed occupationally, practically all of the bone sarcomas that have resulted from external irradiation have been due to radiation therapy. The size of the population that has received curative radiation therapy and lived for 5 to 25 years thereafter is not known but must have totaled tens or even hundreds of thousands in the area of North America and the United Kingdom from which the 51 cases in (Kim 78) were drawn. This would suggest that the risk is small, except that it is probable that the majority of the actual cases are unreported or even unrecognized. For example, since (Kim 78) went to press the authors have seen an additional 10 probable cases (Woo 79b). Even if the risk is considerably

larger than appears at present, it can be considered acceptable in comparison with the benefits of curative radiation therapy. The risk from paliative therapy is small both because the doses are lower and because few patients survive the latent period. The risk of bone sarcoma induction by diagnostic X-rays appears negligible in view of the strong evidence for a threshold dose.

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER VIII -- LEUKEMIA

CHAPTER VIII -- LEUKEMIA

VIII. 1 For several reasons leukemia has probably caused more concern among radiobiologists than any other radiogenic cancer. It appears to be induced more readily than other malignancies, especially at low doses. This results in a high figure for relative risk (RR). It does not necessarily mean that the total number of cases resulting from a particular dose level will be higher than the number of other cancers which have a lower RR but higher natural incidence. The spontaneous incidence of leukemia in most populations is less than $5/10^5$/yr, so that even an RR of 10 does not imply a large number of cases. The extreme malignancy of leukemia causes concern about any increase of incidence, however. Until recently the mortality rate was close to 100% and times of survival after diagnosis were only from a few weeks to one or two years (Scho 71). There has now been a slight improvement in survival but the high mortality still makes it possible to equate the death rate as given in vital statistics with the incidence rate with only minor adjustments. The disease is easy to study in animal models, there being numerous strains of mice with widely varying incidences.

VIII. 2 Leukemia is a disease manifested by abnormalities in the numbers and forms of the leukocytes which are generally produced in the hematopoetic marrow and released into the blood stream. Two broad types are recognized, the lymphatic and the granulocytic, as well as various sub-groups. The acute forms are more common in childhood; the chronic forms are more likely to occur in older age groups. The reported incidence more than doubled between 1930 and 1955 in England and the U.S.A. (Cou 57) for reasons which are not entirely clear. Some of the rise may have been due to better diagnosis and some to the effectiveness of antibiotics in preventing deaths from the respiratory infections to which persons in the pre-leukemic stage are very susceptible. Incidence in Japan is reported to be lower and less variable than in the U.S.A. (Hey 60). These variations in the spontaneous incidence make it necessary to choose controls from cohorts of the same location, age and calendar date as any series of supposed radiogenic leukemia which is being evaluated.

VIII.3 Radiation dosimetry - Bone-seeking radionuclides have been shown to cause leukemia in animals of several species when the marrow is irradiated by isotopes concentrated on the adjacent mineral bone. As discussed above (Chapter VII.7) this was not a major problem in the human radium cases although some of the early deaths reported as having been due to anemia may actually have been due to leukemia. The situation is different when the bone seeker emits an energetic β particle as with the Sr-90 - Y-90 pair. Here the marrow is irradiated by up to 50% of the β's until such a time as the parent Sr-90 is too deeply buried for its electrons and those of its daughter Y-90 to reach the endosteal surface. Some β-emitters, as ^{35}S inorganic sulfate, are incorporated selectively into the marrow cells and irradiate them directly. Others, as ^{32}P inorganic phosphate, are taken up selectively in both tissues. In addition to those elements which metabolize as single ions or molecules there are other radionuclides such as polymeric plutonium which gain entrance to the circulation as micelles and are trapped in the bone marrow and other parts of the reticuloendothelial system. The microscopic geometry of the marrow spaces, knowledge of which was developed in the study of bone sarcomas, can be used in computation of the doses to bone marrow (Bed 79). Data are scanty on the distribution of radionuclides in the lymphatic system but enough observations have been made on, for example, the transfer of particulates from the lungs to the mediastinal lymph nodes to permit approximate calculations of doses to the nodes.

3.1 Doses to the bone marrow and the lymphatic system from externally incident photons can be computed by standard radiological techniques and present no problems in physics. They do present a problem in physiology, however. It is well known that hematopoietic progenitor cells are present in the circulating blood, can colonize marrow spaces that have been depopulated and can exchange into and out of the lymphatics. It is possible that these progenitors are the cells that undergo the changes that result in leukemia. In the case of radiogenic solid tumors the dose to the site of origin is the one of interest and doses to other parts of the body may be disregarded. In the case of leukemia the site of origin is not known and may be anywhere in the reticuloendothelial system. To complicate the situation further,

there would seem to be no reason why progenitor cells should not undergo malignant change as readily while in the circulating blood as when they are in the marrow or lymph glands. If the whole body has been irradiated, as in the atomic bomb casualties and most experiments with small animals, the dose to different tissues will vary by a few percent owing to shadowing, etc., but special calculations at sensitive sites are seldom needed. If, however, leukemia has followed therapeutic irradiation of a single limited region of the body, the most reasonable procedure would seem to be to calculate the dose to whatever bone marrow or lymphoid tissue is known to be in the field. The distribution of marrow in the adult (Woo 60) and in the neonate (Hud 65) are well known. There is little information on marrow in the child, and quantitative data on lymphoid tissue are scanty. The fraction of the circulating blood which is exposed during the few minutes of the average treatment can probably be disregarded except when the heart or large parts of the aorta are in the field. The situation is much more complex when multiple non-converging fields have been used, and it is not known how much migration of critical cells takes place into and out of these and non-irradiated sites. Court-Brown and Doll discuss this problem (Cou 57) and present doses calculated by several methods. One, the use of megagram roentgens to the whole body, seems untenable because it is equivalent to summing the doses to cells that can give rise to leukemia and those that are unexposed. It might be possible, however, to use the sum of the gram-rads absorbed by the reticuloendothelial tissue in all of the exposed fields as an index of leukemiogenic potential. If leukemiogenesis is directly proportional to dose, as some dose-response curves suggest (Bee 78), this method should be appropriate. This would give the average number of ergs absorbed per gram of exposed cells, but ignores the important factor of the total mass of cells at risk.

VIII.4 The possibility that leukemia could be induced by external exposure to ionizing radiation was suspected soon after the use of X-rays and radium became common although the early reports were only anecdotal and suggestive (DeL 28). It was not until March compared the proportion of the total deaths of radiologists and other physicians that were due to leukemia that any quantitative assessment of risk could be made (Marc 44,50). Combining the two series which he reported, we find

that, of 65,806 deaths of non-radiologists reported by the American Medical Association between 1929 and 1950, 334 or 0.51%, were due to leukemia. During the same period radiological societies reported deaths of 297 members. Of these 14, or 4.7%, were due to leukemia. The crude relative risk is thus about 9. The actual radiation doses accumulated by these men were not known but the "tolerance dose" of 0.2 R/day or 50 - 60 R/yr. was accepted for much of this period. Part of this exposure was to soft scattered X-rays from diagnostic machines, only a portion of which would reach the blood forming organs, but part was to penetrating gammas from radium and radon. An active radiologist could accumulate doses of several hundred rads in 20 years of practice. There are various confounding factors which can influence the results of a study of proportional mortality such as this. Nevertheless there seems little doubt that exposures in the range which is probable in these radiologists did entail a greatly enhanced risk of leukemia. A similar study of British radiologists failed to indicate the same correlation but it was shown (Buc 59) that the British population at risk was too small to demonstrate an increase in leukemia at reasonable dose levels.

VIII.5 Data on radiogenic leukemia in the atomic bomb survivors are the most extensive and reliable that are available in humans. The exposed populations investigated are very large, about 62,000 in Hiroshima and 20,000 in Nagasaki. The dosimetry has been studied exhaustively, account being taken not only of the geometric distribution of the primary radiation but of its spectrum and the magnitude of shielding by different types of structures. The population was unselected except for urban living, and included both sexes, all ages and a wide variety of social and economic conditions. Japanese vital statistics are very well maintained and reliable so that it has been possible to follow up the survivors and suitable control groups very completely. Subsets have been constructed according to sex, age at time of bomb (ATB) and date of death. Numerous reports have been published on carcinogenesis and other effects in this population, first by the Atomic Bomb Casualty Commission (ABCC) and later by the Radiation Effects Research Foundation (RERF). The recent one by Beebe et al (Bee 78) is a comprehensive review of mortality from 1950 through 1974. As this covers times up to 30 years after the bombs it is possible to see the pattern of late effects as well as early ones.

5.1 Excess deaths from leukemia were observed early and became highly significant in 1950-1954. They then began a slow decline. Differences from controls became insignificant in 1971-1974 in Hiroshima and in 1963-1966 in the smaller sample from Nagasaki. This behavior is different from that of solid cancers where the increased incidence began later and was still increasing in 1974. For leukemia both absolute and relative risks were much greater in the cohort which was less than 10 years old at the time of the Bomb (ATB) than at later ages, and the average latent period was shorter. This accounts for much of the wave of deaths which occurred between 1950 and 1958.

5.2 The curve for dose vs relative risk for the 323 deaths from leukemia in Hiroshima, 1946-1974 (Figure 11 in Bee 78) has not been analyzed strictly but it appears to be linear, and there is a suggestion (Ibid. Tab XVIII) that a threshold, if any, is not above 10 rads. Data for the 231 leukemia deaths in Nagasaki are similar but more variable, the rate being much lower in Nagasaki. The higher death rate in Hiroshima has been attributed to the higher proportion of the total exposure in Hiroshima which was due to neutrons (19 to 27% vs 1-2% in Nagasaki). Attempts have been made to derive an RBE for neutrons from this difference but Beebe et al doubt the reliability of such determinations. It has been suggested that the higher leukemia rate in Hiroshima is due to irradiation of bone marrow by energetic betas from P-32 generated by action of neutrons on the P-31 in bone mineral (Mye 80). The absolute risk of leukemia as excess cases per million person years per rad (10^6 PYR) is 2.3 for Hiroshima and 1.5 for Nagasaki for all dose levels. The corresponding relative risks for those who received an average dose of about 400 rads were 18 and 11 for the two cities.

5.3 With few exceptions the atomic bomb casualties received whole-body radiation. It is probably that a whole-body dose of 50 rads or more, which includes the entire endocrine system, will cause at least transitory hormonal imbalance. This needs to be taken into account in evaluating the carcinogenic effect of whole body exposure on such hormone-dependent tissues as the mammary and thyroid glands. Leukemia is not known to be hormone-dependent, however. From the above evidence

there can be no doubt that whole-body exposure in the mid-lethal range entails a very substantially increased risk of leukemia in the survivors. Evidence of risk from doses below 10 rads is still uncertain but is sufficiently suggestive to justify the continuation of efforts to keep diagnostic and occupational exposures substantially below the lowest observed toxic level.

VIII.6 The only other extensive and well documented study of the incidence of leukemia in humans after exposure to photons is the one on patients with ankylosing spondylitis who were treated with X-rays. Ankylosing spondylitis is a disease which causes intractable bone pain, especially in the spine. It is not neoplastic and is not lethal in itself, but persons suffering from it have an above-average death rate from diseases such as those of the respiratory and digestive systems which are associated with immunological disturbances. Alkylosing spondylitis cases were treated with X-rays extensively in the 1930's and 1940's in Great Britain, and the suspicion that they were later showing an unusually high incidence of leukemia prompted the (British) Medical Research Council to sponsor a study of the subject. Results of this study are given in a special report (Cou 57). It covers 13,352 patients, mostly male, treated from 1935 through 1954, and is detailed and meticulous particularly in X-ray dosimetry and in the establishment of the diagnosis of leukemia. Unfortunately later reports (Cou 65, Smi 78) are lacking in detail. A report (Smi 77) on causes of deaths in spondylitis cases not treated with radiation is useful in establishing that there is not a close inherent association with leukemia. No leukemias were seen in this sample, although only 0.44 were expected.

6.1 In Table 19 of (Cou 57) the 37 observed cases are tabulated for 12 different spinal marrow dose categories from < 250 rads to 2750 + rads. The age-adjusted incidence per 10^4 men per year is then computed for 5 condensed dose categories and compared with the corresponding standardized incidence of 0.49 in the whole British population. The incidence is plotted against dose in a curve drawn by eye and shown in (Cou 57) as Figure 1. The curve appears to me to be linear up to 1250 rads but rises very rapidly thereafter. I have computed the RR's from Table 19 and find that the values rise from 4.0 for doses up to 499 rads to 147 for 2250 to 2750 rads, with a mean for the whole series of 12.2. The mean period

from first X-ray treatment to death was 5.2 years (my calculations) with a range of 2 to 12 years. Of the 13,352 cases studied, 5210 or 39% were first treated in 1951-1954 and were therefore within the mean latent period at the time of the report. By 1960 (Cou 65) the number of cases of leukemia had risen to 60 where 7 were expected for an RR of 8.6 for all dose categories. Further details are not given. Another report (Smi 78) evaluates the causes of 1759 deaths that had occurred up to 1970 in patients of the original series who had received only a single course of radiation. In this smaller series there were 31 deaths from leukemia where 6.5 were expected for an RR of 4.9. Again, no relation with dose is recorded. The mean observation period was 16.2 years and this is long enough for evaluation of the time course of development of leukemia. The incidence peaks at 5 years after the single course of treatment at an RR of about 11, and then declines toward, but not to, a normal value at 20 years. This is similar to the behavior of the atomic bomb cases.

VIII.7 As was discussed in VIII.3.1, there is a question as to whether the volume of reticular tissue irradiated should be taken into account in computing the doses resulting in leukemia. In this context a comparison of the atomic bomb survivors and the spondylitis cases may be interesting. In the atomic bomb survivors the entire reticuloendothelial tissues were exposed. In the spondylitis cases most of the radiation was directed at the spine with less frequent treatments to the sacrum, hips and shoulders. The spine contains 14.7% of the total marrow, or about 30% of the functional marrow (Woo 60). The amount in the pelvis is similar, but only portions were treated, and there is little active marrow in the long bones of adults. A reasonable estimate might be that 40% of the active marrow was exposed. There are few quantitative data available on the distribution of lymphoid tissue. In these patients the para-aortic, cervical and mediastinal nodes would have been exposed, together with a small part of the liver. The spleen, most of the liver, and all of the lymphoid tissues in the limbs would have been spared, and the axiliary and inguinal nodes would have been exposed only occasionally. It thus is likely that less than half of the lymphoid tissue was irradiated.

7.1 The point of interest is whether there is evidence that the RR of leukemia is related to the volume of reticuloendothelial tissue exposed. The comparison is made in Table VIII.1 for the dose ranges which overlap. The difference between

the RR values at similar doses in Hiroshima and Nagasaki is so great that no strict comparison can be made. Nevertheless, the RR values at comparable doses are consistently lower for the spondylitis cases than for the atomic bomb survivors, and the differences are greater than would be expected from the longer observation period for the Japanese.

TABLE VIII.1

Comparison of rad Dose and Relative Risk of Leukemia in the Atomic Bomb Survivors and the Ankylosing Spondylitis Cases

Group	Dose, rads		RR	Reference
	Average	Range		
Hiroshima	136		9.6	Beeb 78
	388	237 - 600	18.2	Table XXIII
Nagasaki	404	275 - 600	11.3	
Spondylitis	298	144 - 471	4.0	Cou 57
		500 - 999	9.5	Table 19
		1000 - 1500	14.7	H.Q.W. calculations

VIII.8 Leukemiogenesis by alpha-emitters - As has been noted (Chapter VII.7) the induction of leukemia has not been a major problem either in the Ra-226 or the Ra-224 cases, although some of the most heavily exposed dial painters probably died of leukemia. The much-publicized deaths of Marie Curie and Irene Joliot-Curie were probably caused more by external γ-ray exposure than by internal contamination. There have been no significant human exposures to plutonium or other transuranic α-emitters. The action of plutonium when deposited on the trabecular surfaces of dog bone is strikingly illustrated in (Jee 61). A layer of adjacent bone marrow is totally destroyed and is not repopulated but is replaced later by fibrous tissue. It is to be expected that less heavily irradiated marrow areas could undergo malignant change. The same effects could be produced in man in the event of extensive contamination with plutonium.

VIII.9 Leukemiogenesis by beta-emitters -There have been few extensive exposures of humans to β-emitting radionuclides, but some of these isotopes have been studied thoroughly in animals. Strontium-90 was of concern during the period around 1960 when fallout from nuclear testing was at a maximum. It is a bone-volume seeker with a physical $T_{\frac{1}{2}}$ of 29 years. Its 0.55 MeV β can irradiate the bone marrow only when the isotope is on or near the bone surfaces. Its daughter yttrium-90, although not a bone-seeker, has a $T_{\frac{1}{2}}$ sufficiently short (64 hrs) so that much of it decays in or on the bone where it was generated. The 2.3 MeV β of Y-90 is sufficiently energetic to irradiate the marrow even when the parent Sr-90 is no longer on the surface. Strontium-90 has been studied extensively in the dog where it causes numerous bone sarcomas and occasional leukemias (Fin 71). Interestingly, pigs treated with Sr-90 die of blood dyscrasias before the end of the latent period for the development of osteogenic sarcoma (Cla 71). This may be a true species difference in susceptibility but the possibility is being investigated that the real difference is one in microscopic bone structure leading to differences in radiation dose in the marrow. Presumably heavy contamination of humans with Sr-90 could lead to leukemia. The difference between dogs and pigs suggests caution in extrapolation of results in animals to man.

9.1 Phosphorus-32 ($T_{\frac{1}{2}}$, 14.3 d.; 1.7 MeV β) administered as orthophosphate, is a bone-volume seeker although a considerable fraction can decay on bone surfaces before the slow transfer to the volume is complete. It is also taken up selectively by all replicating cells including those of the bone marrow which are thus irradiated by the energetic β's from both sources. Phosphorus-32 orthophosphate was used extensively in the treatment of leukemia from about 1940 until it was superseded by the more effective chemotherapeutic agents 25 years later. It has also been used in the treatment of polycythemia, a disease which sometimes transforms to leukemia spontaneously. There is a suggestion that this transformation is more frequent after treatment with P-32 than after other methods of control (Mays 73), but the evidence is not definite. There is no evidence of the induction of leukemia by P-32 in humans with previously normal bone marrow but the results of animal experiments make this seem possible.

9.2 The results of a trial of S-35 sodium sulfate in the treatment of chondrosarcoma and chordoma make it clear that this radionuclide is a potent leukemiogen. Sulfur-35 has a $T_{\frac{1}{2}}$ of 89 days and emits a single β ray of 0.17 MeV. When administered as inorganic sulfate it is concentrated by cartilage during the synthesis of sulfated polysaccharides. It is not a bone seeker but is taken up selectively by the cells of the myeloid series in the bone marrow. Because of its concentration by cartilage it has been tried occasionally in the treatment of chondrosarcoma with limited success. Of the few cases reported in the literature up to 1970 none survived their primary disease for more than several months, so that late effects could not be observed. At this time a more extensive trial was started at Memorial Hospital (Woo 76; Maye 78). Fourteen of the 21 patients in the series died in a few weeks or months of their primary disease or received only test doses of S-35. Of the 7 patients who lived for 18 months or more after the start of a full therapeutic course, 3 died of leukemia. The other 4 died of progressive chondrosarcoma but with varying degrees of pancytopenia. Dosimetry was unsatisfactory because of the small number of tissue specimens available but the cumulative marrow dose was between 700 and 1600 rads. On the basis of this scanty evidence, S-35 in the form of inorganic sulfate appears to be one of the most leukemiogenic radionuclides known. Its use in therapy is clearly contraindicated. Fortunately accidental contamination is not likely.

VIII.10 There are some reports of human exposure to photons with or without associated β rays that have not been followed by an increased incidence of leukemia although the doses were such that an increase might have been expected.

10.1 A survey (Hut 68) of 30,000 patients who had received radiation therapy for cancer of the cervix uteri showed no increase in the incidence of leukemia although doses to substantial volumes of active bone marrow were estimated to be 300 to 1500 rads. Comparison with the spondylitis cases would lead one to expect an RR of about 8. The epidemiological methods used in the study are questionable and might have missed both early and late cases.

10.2 At lower exposure levels there is a reassuring lack of evidence of significantly elevated incidence of leukemia in patients who have been treated with I-131

for hyperthyroidism (Poc 60, Gre 61, Hof 76). Blood doses were usually in the 8-20 rad range with occasional values above 100 rads. On the other hand, there is limited evidence (Sei 53) of induction of leukemia by doses to the blood of 600-700 rads from I-131. There are two well controlled studies (Mod 74, Sho 76) of follow-up of large groups (11,000 and 2,500) of persons 13 to 24 years after X-ray treatments of the scalp for tinia capitis. The marrow in the skull, which constitutes 6-7% of the total functional marrow, received about 500 rads. Minor differences in the incidence of leukemia between irradiated and control groups are not considered to be significant.

10.3 Various attempts have been made to correlate the incidence of leukemia with changes in background radiation such as those due to altitude (Eck 74) or to building materials (Cou 59). Results have been inconclusive. This is not surprising when the backgrounds differ by not more than a factor of two, since the shape of the dose-response curve for the atomic bomb survivors indicates that it would be nearly impossible to find exposed and control populations large enough to show a significant difference. In a few locations where the background is as high as one rad per year a significant increase in chromosome aberrations has been found (Gon 74). The incidence of leukemia has not yet been studied adequately in these places. Results of numerous epidemiological studies of persons exposed occupationally to up to 5 rads/yr will be considered elsewhere.

VIII.11 Summary - Leukemia is induced readily by ionizing radiation in many mammalian species including man.

The dose-response curve is consistent with a linear, no threshold relation, and the threshold, if any, is below 10 rads.

The minimum latent period following acute exposure may be as short as two years and the mean is only about 5 years. These times are shorter than those for most solid radiogenic tumors.

The risk of leukemia in exposed populations compared to that in appropriate unexposed groups (RR) is high. The value is at least 10 after whole-body doses of 400 rads or partial body doses of 1000 rads. Because of the low natural incidence of leukemia, however, the absolute risk is less than that of several solid tumors.

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER IX -- CANCER OF THE THYROID

CHAPTER IX -- CANCER OF THE THYROID

IX.1 Thyroid Carcinoma - Although there is no doubt that ionizing radiation in even modest doses can induce carcinoma in the human thyroid, the phenomenon is very difficult to quantitate. Thyroid carcinoma is an uncommon disease with estimated annual incidence rates and death rates in the USA of 4 in 10^5 and 0.5 in 10^5 respectively (DHEW 77). The high survival rate of 80% which is implied here and is confirmed for the large series of patients treated at Memorial Hospital, New York (Scho 71) makes it inappropriate to use death statistics in choosing control groups for comparison with an irradiated population. Further complication is introduced by the fact that nodules are common in the human thyroid and the apparent prevalence varies with many factors, including the skill and experience of the examiner (Son 78). Hence a series of persons selected for thorough thyroid examination because of known prior radiation exposure could appear to have a higher incidence of thyroid nodules than an otherwise matched population that has only had a general physical examination, even if there were no real difference between them. In individuals not exposed to radiation, most thyroid nodules that are excised prove to be benign. Over 5% of the thyroid glands that have been obtained at routine autopsy of persons who had no known thyroid disease contain occult cancers. In the present review I shall cite observations both of increased nodularity and of microscopically proved cancer, but shall make the distinction clear.

IX.2 Dosimetry - Calculation of the dose to the thyroid from external exposure to photons presents no problems if the radiation factors are known, but there are serious problems in obtaining pertinent clinical data. Most of the evidence that we have of radiogenic thyroid cancer is derived from persons who received X-ray therapy as children for enlarged thymus or tonsils, otitis media, acne and other benign conditions. Some were treated by private physicians whose records are not available. Even in cases where treatment was at hospitals whose records have been preserved the location of the fields often is not given precisely enough to permit a reliable estimate of the radiation to the thyroid. It is only in the two series of tinea capitis cases that the investigators were able to reconstruct the dosage patterns by meticulous measurements in phantoms (Wer 68, Har 76).

2.1 Several radioactive isotopes of iodine are abundant in fission products. They are volatile, enter the food chain readily when released into the atmosphere, and can be absorbed either from the food or by direct inhalation and then be deposited very selectively in the thyroid. There has already been an instance of contamination of substantial population groups downwind from the site of a nuclear accident and it is to be expected that there will be similar accidents in the future as nuclear power becomes more widespread. In addition to this low level exposure of substantial numbers of the general population there is the possibility of heavier exposure of small groups who are working with chemicals and pharmaceuticals labeled with radioiodine. At present there has been little clear evidence of injury from these sources but, because of the size of the population at possible risk, it would be highly desirable to have reliable estimates of the radiation dose to critical cells in the thyroid. There are serious difficulties in such calculations, however.

2.2 Techniques for quantitative external monitoring of the amount of radioiodine in the thyroid are well established, but the results do not necessarily bear a close relation to the absorbed dose in the follicular cells in which thyroid cancer is thought to originate. The thyroid gland consists of follicles that vary in shape but are roughly spherical and have diameters varying from 25 to 200 μm. They consist of a cell layer 5 to 10 μm thick surrounding colloid made up of thyroglobulin. These structures make up 50 to 75% of the volume of the gland, the remainder being connective tissue, etc. Iodine-containing thyroglobulin is synthesized in the cells and stored in the lumens of the follicles for periods which vary with the functional state of the gland. It is then further processed in the cells and released into the circulation as thyroid hormone. The radioactive isotopes of iodine, notably I-125, have complex decay schemes with an abundance of low energy photons and electrons. Hence much of the radiation originating in disintegration in the lumens will fail to reach the surrounding cells and no single relation exists between the concentration of radioiodine (indicated here as *I) in the gland as a whole and the biological effects to be expected. These problems are discussed by Atkins (Atk 76), and a very thorough analysis of the dose

rate to the follicular cells from a constant level of 1 μCi/g of I-125 is given in Gavron and Feige (Gav 72). I have not been able to locate comprehensive calculations of the integrated doses to the human follicular cells which might be expected from a pulse label of radioisotopes of iodine with different decay schemes and physical $T_{\frac{1}{2}}$'s such as could result from a nuclear accident.

2.3 There have been numerous studies of the comparative effects of different radioisotopes of iodine on animal thyroids. The most comprehensive is the study of I-125 and I-131 in rat thyroids by deRuiter et al (deR 75). In this paper it was shown that I-131 was 10 to 25 times as effective as I-125, on the basis of administered dose, in reducing thyroid function and shortening life. The *I uptake and biological $T_{\frac{1}{2}}$ in the thyroids were determined but the radiation doses to the functioning thyroid cells from the two isotopes were not calculated. Although the title of this paper suggests that the study was directed mainly at carcinogenesis, the radioiodine treatments caused only a small increase in the naturally high incidence of medullary carcinoma of the thyroid in rats of this strain. Life shortening was due largely to the high incidence of benign pituitary adenomas. In animals as small as rats the pituitary can receive considerable radiation from I-131 deposited in the thyroid. Radiation-induced absence of thyroid hormone in the circulation also prevents negative feed-back of pituitary activity in producing thyroid-stimulating hormone (TSH). Which factor predominated in causing the adenomas is not known. A recent report (Boo 80) compared the effects of I-131 and the short-lived I-132 ($T_{\frac{1}{2}}$ = 2.29 hrs) in impairing the response of rat thyroids to goitrogens. The biological effect of I-131 was found to be about 9 times as great as that of I-132 on the basis of calculated rad dose to the whole glands but, again, doses to functional thyroid cells and to the pituitary were not estimated.

2.4 In summary, additional work is needed on the dosimetry, at the cellular level, of radioactive isotopes of iodine in the thyroid. Application of results in animals to the human should take account of the different sizes of critical structures. Dose to the pituitary should be calculated if the animals are small enough so that the *I in the thyroid can irradiate the pituitary.

IX.3 Results in humans - Much of the information available on radiation carcinogenesis in the human thyroid is derived from evidence of late effects of external radiation administered for the treatment of benign conditions of the head, neck and chest. This use of radiation became popular around 1930, especially in the treatment of enlarged tonsils and adenoids where it was thought to be effective and free from the immediate complications which sometimes resulted from surgery. It continued to be used frequently until the availability of antibiotics led to better control of chronic respiratory infections. By about 1950, however, it began to be noticed that an increasingly large proportion of young adults attending clinics for the treatment of benign or malignant tumors of the thyroid gave histories of having received radiation therapy to the head, neck or chest in early life. This observation led several medical institutions with long term and reliable records to set up projects to recall for evaluation of their thyroid status all of their patients who had received such treatments. The studies encountered all the problems discussed in Chapter IX.1 and Chapter IX.2, and some were inconclusive. Results of the most conclusive investigations are summarized in Groups A, B, C and D in Table IX.1.

3.1 Not all of the information which would be desirable is available in every series and, in particular, it is only in Group D that adequate controls could be obtained. Nevertheless, the followup periods, when given, are comparable to the longer latent periods so it is not likely that a large fraction of radiogenic cancers have been missed. Estimates of radiation doses to the thyroid are variable and somewhat uncertain, but there is a strong suggestion that both nodules and cancer are more frequent after doses of 500 rads or above than after lower doses. It is particularly interesting that, in Group D, cancer was seen only in the small number of patients in whom both pituitary and thyroid had been exposed. The possible role of the pituitary was mentioned in the discussion of experiments on small animals (Chapter IX. 2.3) The incidences in Groups A and B are much greater than would be expected from a 20 year observation of the general population with an annual incidence of 4 in 10^5; the incidences in Groups C and D are not above expected values. The statistical significance of these differences can not be known without more age-matched controls.

IX.4 Another non-malignant condition which was often treated by X-rays during this period was ringworm of the scalp (tinea capitis). This is readily cured by agents which cause total epilation of the infected hair shafts but is difficult to treat in other ways. Early use of thallium compounds to produce epilation resulted in the deaths of a number of children so that X-ray therapy, which had no immediate general ill effects, became the preferred method of treatment. Two excellent studies of the long-term effects of this modality are summarized as Groups E and F in Table IX.1. In both groups the dosimetry is meticulous and controls are adequate and in one, Group E, the population is large. In Group E there was a significant increase in the incidence of thyroid cancer after doses of 4.3 to 16.8 rads. In the smaller Group F no thyroid cancer was seen after average doses of 6 rads, but there was a possible increase in the natural low incidence of thyroid nodules. In all cases the pituitary received doses somewhat larger than those to the thyroid. The folow-up periods are long enough so that not many additional cancers are to be expected. These series are valuable because they indicate that the threshold dose, if any, for the production of cancer of the thyroid is less than 10 rads when there is associated irradiation of the pituitary.

IX.5 The populations considered so far have been infants or children up to 10 years of age. Group G, the atomic bomb casualties in Japan, were of all ages but predominantly older than 10 years. The series is very large and has good controls, so that the effects of high and low radiation doses can be compared and their respective relative risks computed. These people received whole body photon and neutron irradiation which gave equal doses to thyroid and pituitary. The thyroids may have received small additional doses from radioiodine in fallout. Thyroid doses of 50 rads or more were associated with a definite increase in the incidence of thyroid cancer relative to that in matched controls. There was no increased incidence from doses below 50 rads.

IX.6 In all of the previous groups the exposure has been to external radiation with photons with the possible exception of a small amount of *I in Group G. In the very small Group H, the primary exposure was to radioiodine taken up from fallout with the addition of some whole-body gamma irradiation. The pituitaries were irradiated by

the external gammas and must have received some additional gamma dose from I-131 in the thyroids. This series is much too small for strict statistical treatment, but it is obvious that the incidence of thyroid cancer is much higher than is to be expected in an unexposed population and that the incidence of thyroid nodules is very high in those exposed as children. The incidence of thyroid cancer is not related to age at exposure.

IX.7 Large numbers of people who have been treated for hyperthyroidism with I-131 are available for study. Group K in Table IX.1 is made up of patients who were treated for hyperthyroidism in 26 medical centers. Controls are patients treated with antithyroid drugs in the same centers. I have omitted the thyroidectomy controls. I have also omitted data obtained less than one year after the start of treatment. These are listed separately by the authors and show that the incidence of thyroid cancer in essentially untreated patients with hyperthyroidism is about 0.17%. Treatment in the numerous centers involved was so variable that the authors do not attempt to summarize the radiation dose, but the usual dose is several thousand rads, or much higher than that in the other groups cited. The average follow-up period is only 8 years. In this short period there is a deficit, rather than an excess, of the expected amount of thyroid cancer. This may reasonably be attributed to the drastic reduction which has taken place in the cell population at risk, but proof of the absence of a carcinogenic effect of doses of this magnitude requires a longer period of observation.

IX.8 Various authors have attempted to analyze the dose-response curve for radiogenic thyroid cancer (Hem 68, Schm 78). Their results are consistent with, but do not prove, a linear no-threshold response for doses not above about 500 rads. It appears to me that no strict analysis of the dose-response relation is possible until the dosimetry of internally deposited radioisotopes is clarified and until there are more prolonged observations of effects of higher doses. Evidence from the tinea capitis cases is, however, strongly indicative that there is no effective threshold dose. Evidence both in Bee 78 and Schm 78 tends to disprove the commonly held opinion that juvenile thyroids are more susceptible to radiation carcinogenesis than adult ones.

IX.9 Summary - There is strong evidence that ionizing radiation in the dose range of 5 to 500 rads can induce both benign and malignant tumors of the human thyroid. This is true whether the radiation is from externally applied photons or from internally deposited radioisotopes of iodine.

Problems both in physical dosimetry and in epidemiology hamper satisfactory quantitation of the risk.

Table IX.1

CARCINOMA OF THE THYROID

Group	Dates of irradiation or years of follow-up	Type of radiation	Cause for irradiation	Dose to thyroid	# Cases with nodules	# Cases with carcinoma	References and remarks
A 1452 Children	1937 - 1957 Follow-up 12 - 35 yrs.	X-ray	Enlarged tonsils (84%) adenoids, etc.	~ 700 rads	27%	60 = 4.1%	Arn 75, Fav 76 - results of two reports are combined here
B 2878 Infants	1926 - 1957	X-ray	Enlarged thymus	≤ 500 rads	14%	19 = 6.7%	Dol 68 Mean latent period is 20 yrs.
C 786 Infants	1930 - 1951 Average follow-up 28 yrs.	X-ray	Enlarged thymus	< 300 R	0.9%	1 = 0.13%	Pif 68
D 971 Children	----	X-ray	Adenoids	Thyroid 10 - 670 R Pituitary 220-1000 R	---	3 = 0.3%	Haz 66 All of the thyroid cancers occurred in the 170 children in whom both thyroid and pituitary were irradiated Latent period, 5 - 17 yrs.
417 Children	----	Radium	Adenoids	Thyroid < 1 R Pituitary 18-36 R	---	0	
2746 Sib. controls	----	0		0	---	0	
E 10,902 4 - 10 yrs.	1948 - 1960	X-ray	Tinea capitis	4.3 - 16.8 rads	---	0.11%	Mod 77 Latent period, 4 - 21 yrs.
10,902 Pop. controls		0		0	---	0.02%	
5496 Sib. controls		0		0	---	0.02%	
F 2545 5 - 10 yrs.	Average follow-up = 20 yrs.	X-ray	Tinea capitis	Thyroid 6 rads Pituitary 49 rads	0.27%	0	Har 76, Sho 76
1809 Pop. controls		0		0	0.12%	0	
G 82,000 All ages	1945 Follow-up 30 yrs.	Gamma, some neutrons whole body	Atomic bomb, direct radiation	0 - 49 rads 50 - 400 rads	---	49 R.R.=0.84 38 R.R.=2.3	Bee 78 (Tab. XVII) R.R. values calculated by HQW
H 244 All ages < 10 yrs. old	1954	* I Some gamma	Atomic bomb fallout	50 - 556 rads from *I 14 - 175 rads Gamma Whole body	17% 67%	7 = 2.9%	Lar 78, Hem 68 Latent period for nodules = 9 yrs.
K 21,718 All ages	1946 - 1968 Average follow-up 8 yrs.	I-131	Hyperthyroidism	Variable	0.39%	19 = 0.09%	Dob 74 Dose range not given by authors. Other reports suggest 5000-10,000 rads. Data are for observations made more than 1 yr. after start of therapy.
1238 Drug controls		0	Hyperthyroidism	0		4 = 0.32%	
L 2650 Infants	1926 - 1957 Average follow-up = 23 yrs.	X-ray	Enlarged thymus	30 - 1200 R	2.0%	24 = 0.9%	Sho 80
4800 Sib. controls					0.12%	0	

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER X -- CANCER OF THE BREAST

CHAPTER X -- CANCER OF THE BREAST

X.1 Radiation-induced carcinoma of the female breast was identified later than most of the types of radiogenic cancer that have already been discussed here. One reason for the late recognition is that the natural incidence of breast cancer among European and North American women is quite high and strongly age-dependent while, as is now known, the relative risk of induction by radiation is rather low and the latent period long. Hence a small cluster of radiogenic cases occurring in a special category of middle-aged or elderly women might not be noticed. Another factor may be that there are not many situations in which the breasts are likely to be exposed heavily during therapeutic irradiation of underlying tumors. One case might be lung cancer but here the primary tumor is so lethal that few patients survive long enough to develop breast cancer. The first clear cut evidence of induction of human breast cancer by X-rays was the report by Mackensie in 1965 (Mack 65) of 50 cases of breast cancer in women who had previously been treated for pulmonary tuberculosis. In 40 of these there had been multiple fluoroscopies for the purpose of monitoring artificial pneumothorax, often to the extent of causing permanently visible skin changes. This led to further follow-up of several other studies of populations of a few hundred to 1000 women whose breasts had been irradiated for various reasons. At about the same time evidence began to appear that, after a long latent period, there was a significant increase in breast cancer amont the atomic bomb survivors above the low incidence which is normal in Japanese women. This led to well organized studies of all available groups of exposed women.

X.2 The groups available for quantitative study were:

2.1 Female survivors of the 1945 atomic bombings of Hiroshima and Nagasaki - The total number was 63,263 of whom 12,843 received more than 10 rads whole-body exposure. In individuals there is some uncertainty as to the degree of shielding but this is random and not likely to introduce any systematic error in estimate of the dose-response curve. Hence the dosimetry can be considered to be satisfactory. Most of the radiation was high energy photons but about 1/4 of the total dose in Hiroshima was due to neutrons. There was no selection as to age or other population factors among females

(many males were in the army) and adequate age-matched control groups are available. The exposure was instantaneous so that questions of effects of fractionation do not arise, and the follow-up period now exceeds 30 years. The group thus appears to be almost ideal for an epidemiological study. It must be remembered, however, that this was whole-body irradiation and that there may have been indirect effects on the breast from radiation-induced alterations in the pituitary, adrenals or ovaries. Such indirect actions can be quite important in the evaluation of effects of radiation on induction of a cancer as strongly hormone-dependent as that of the breast. This series has been the subject of numerous reports of which the most recent are Tok 77 and pp. 170 and Table XIV of Bee 78. The highly significant findings in this population are considered in detail here in X.3 below.

2.2 A series of women treated in Massachusetts for tuberculosis between 1930 and 1954 - Of the total 1047 received pneumothorax monitored by multiple fluoroscopies and 717 were not fluoroscoped (Boi 78). The follow-up period was as long as 44 years in some cases. Special efforts were made to determine the number of examinations and the dose per examination. The mean cumulative absorbed dose to the breast was estimated to be 150 rads but with occasional values up to 1000 rads over a period of 2 to 3 years. There was a significant excess incidence of breast cancer at doses of 100 rads or above. The dose-response curve was analyzed by the authors and considered to be most consistent with a linear relationship although other forms were not excluded. The ages of these women at exposure are not detailed in the paper, but can be presumed to be predominantly between 15 and 25 years, since this is the range in which pulmonary tuberculosis is most commonly diagnosed. This series thus defines the hazard of absorbed doses usually below 600 rads delivered over periods of one to 3 years to the breasts of adolescent and young adult women.

2.3 A series of 623 patients treated in Nova Scotia between 1940 and 1949 with pneumothorax and 958 without pneumothorax (Mack 65, Myr 69) - This group was followed for 15 to 25 years. About half of the patients were males and none of these, whether fluoroscoped or not, developed breast cancer during the observation period. The incidence of breast cancer among the 300 females who were fluoroscoped was 22 cases

or 7.3%; among the 483 who were not fluoroscoped it was 4, or 0.85%. Mean latent period was 17 years. The range was from 8 to 24 years or about the maximum period of observation. Results are consistent with those in Boice, et al. (Boi 78) and the series is similar to the Massachusetts one except that it is smaller, the follow-up period is shorter, and the dosimetry is not given in detail. It is useful in documenting the absence of cancer in the exposed male breast. This is in harmony with results of animal work demonstrating the potentiating effects of estrogen in the induction of mammary cancer by radiation (Seg 71).

2.4 A Series of 606 patients treated for acute post-partum mastitis in Rochester, N.Y. from 1940 to 1955 - Five hundred seventy one of these women were followed by mail survey for up to 34 years (Met 69, Sho 77). As is to be expected from the post-partum status, 86% of the patients were between 20 and 34 years of age. Radiation doses had been recorded as roentgens in air: the authors have computed the doses in rads at a depth of 2.5 cm in the breast. Thus the dosimetry is reliable. Doses ranged from 40 to 1500 rads but 85% were between 100 and 500 rads. There were 993 controls made up of the normal sisters of the irradiated cases and of mastitis cases not irradiated and their normal sisters. This interesting choice of controls tends to eliminate bias due to a possible familial tendency to breast cancer among the mastitis cases or to a possible precancerous effect of the mastitis itself, although the latter has never been documented. For the entire irradiated group the relative risk of breast cancer during the period of 10 to 34 years post exposure was 2.2, but for the period between 20 and 34 years it was 3.6. There was no significant excess incidence during the first 10 years but the rising value during the latter part of the follow-up time suggests that observation for the entire life span is needed for complete evaluation of risk. The existence of a significant risk is demonstrated clearly. There remains the possibility that the sensitivity of the breasts may have been increased by the increase in the proportion of cells in mitosis which is produced by hormone stimulation during pregnancy or by the rapid metabolism associated with the inflammatory reaction but this is at least partly compensated by the choice of the control groups.

2.5 A series of 1023 patients treated in Sweden between 1927 and 1957 for "non-neoplastic" diseases of the breast - These women were followed for 6 to 42 years, mean 31.5 years (Bar 77). The majority of the patients (855) had a clinical diagnosis of fibroadenoma; most of the remainder had mastitis. Dosimetry is good. Total doses ranged from less than 500 rads up to 4250 rads and were usually protracted for periods which were sometimes as long as 60 months. Cancers occurring within 5 years of the start of irradiation were excluded from the analysis as being likely to have been present when treatment was begun. There were 115 cases of breast cancer among these patients. The age-specific cancer rate for Stockholm in 1970 would give an expected 29 cases. The relative risk is thus 4.0. There was no excess incidence in the contralateral breasts of the patients. There was no clear-cut correlation of incidence with dose at least up to 1500 rads. There was a correlation with age at exposure, the risk being more than 3 times as great for the 10-29 year age group although the mean radiation dose was less than half as great. This series is carefully worked up. Beside the good dosimetry it has the advantages of being fairly large with a long follow-up period. It has the very serious defect that there is no information available on the late incidence of carcinoma in breasts which are the sites of supposed fibroadenomas which have not been irradiated. Many oncologists consider such lesions to be definitely neoplastic and pre-malignant. Supposedly benign tumors which are excised surgically often show microscopic foci of malignant cells and it is not known what proportion will become malignant clinically if they are left in situ as these lesions were.

X.3 Risk estimates - Despite the many uncertainties involved, the studies outlined above give convincing evidence that exposure to the female breast to low LET ionizing radiation can increase the risk of subsequent development of mammary cancer. Evaluation of the magnitude of the risk requires primarily reasonably reliable data on the magnitude of the absorbed radiation dose from which the shape of the dose-response curve can be computed. In addition it is important to have data on the protraction of the exposure and the latent period before the malignant change is evident, and such factors as the age, endocrine status, and spontaneous breast cancer incidence in the

exposed population. These factors are considered in a recent paper by Boice et al (Boi 79). The original of this excellent study should be consulted for details. I will summarize the findings here.

3.1 In Table I of Boice et al there is shown a fairly good correspondence between the mean absorbed dose and the relative risk (RR) of breast cancer for the 5 groups which I discussed in X.2 above. This is surprising in view of the varied characteristics of the populations concerned and the strongly skewed dose distributions in the atomic bomb survivors and the Swedish therapy cases. The absolute risk, i.e., the estimated number of additional cases of breast cancer per 10^6 WY-rad, ranges only from 6.2 to 8.4 for the Caucasian women. The number is lower for Japanese women in harmony with their lower spontaneous breast cancer incidence.

3.2 The authors have tested the data for the atomic bomb survivors, which are the most complete available, for fit with linear and quadratic dose-response equations, both with and without a cell-killing term. For both Hiroshima and Nagasaki the best fit was linear. There was no evidence of a differential due to the neutron component of the radiation at Hiroshima nor of a cell-killing factor. For the fluorocopy cases there was little difference between the fit of the linear and quadratic models. There appeared to be a cell-killing factor for the mastitis cases. It should be remembered that the Swedish therapy group was the only one considered here in which the cumulative dose was greater than 500 rads in a substantial fraction of the cases. Cell killing is not likely to be important at doses below 500 rads except in a few very sensitive tissues. The authors found no convincing evidence that the cancer incidence was influenced by the varying degrees of dose fractionation.

3.3 One relation which appears clear-cut is that between risk and age at exposure. The greatest risk was between the ages of 10 and 19 years, or the time at which the rate of development and maturation of the mammary gland is at its maximum. This was most definite in the atomic bomb survivors because of the larger numbers involved but was also consistent with the findings in the tuberculosis fluoroscopy cases. There is an interesting minimum of risk among the Japanese women irradiated between ages 40 and 49 years. This is perhaps related to the menopause and enhanced by effects of radiation on the ovaries. There were too few women over 40 in the other groups for satisfactory evaluation.

3.4 Age at exposure also influences the latent period. The minimum latent period is about 10 years for the younger women but is as short as 5 years for those who were in their middle or late years at irradiation. All groups are still showing an excess incidence of breast cancer up to the maximum follow-up periods of 30 to 45 years. It appears that radiogenic breast cancers do not begin to appear until the ages at which the natural incidence is rising rapidly. This raises the question of whether the absolute or the relative risk models are the more appropriate. The authors (Boi 78) believe that longer periods of observation will be necessary before the question can be decided, but incline toward the multiplicative model. All evidence indicates that the risk continues for the entire life span. When age at irradiation is corrected for there is not an inverse relationship between latency and dose. This is contrary to the widely held belief that the latent period at very low doses may be so long as to exceed the natural life span of the species and thus constitute the equivalent of a threshold dose. Latent period was not related to dose in a series of X-ray induced osteogenic sarcomas (Kim 78). It was related to the radium burden in the Ra-226 cases but there the burden determines the time required to accumulate an effective threshold dose. It may be that the concept of an inverse relationship between absorbed dose and latent period will have to be abandoned, at least for systems where the duration of irradiation is short compared to time to the appearance of radiogenic cancer.

X.4 There is little evidence among the atomic bomb survivors that irradiation of the breasts of pre-adolescent girls is followed by increased incidence of cancer later in life but Boice et al point out that these women have not yet reached the age of high natural risk. There is much evidence from animal work that exogenous estrogen can enhance the tumorogenic effect of radiation on the mature female breast. Little is known about the results of irradiation of the undeveloped juvenile human breast prior to the stimulation by endogenous estrogen which occurs at puberty but there is scattered evidence that radiogenic mammary cancers can arise even in breasts that were irradiated in infancy or early childhood so heavily that development was largely prevented (Rei 77, Woo 80). An incidence of 0.6% of breast tumors is reported (Col 77)

in a series of 5000 women who were irradiated for benign conditions during childhood, but it is not stated how many of the tumors were malignant nor how much breast development was impaired. A large cell-killing factor would be expected whenever development is impaired but it obviously was not large enough in some of these cases to prevent carcinogenesis.

X.5 In the beginning of the 1970's the demonstration of the usefulness of mammography in the early detection of breast cancer led to recommendations for its wide-spread use as a screening agent. Some of the early techniques used exposure doses as high as 15-25 R per film (Rot 75, Boa 76). This, especially if repeated annually, would soon result in absorbed doses in the superficial layers of the breast well above the 50 rads which have been shown to be definitely associated with radiogenic breast cancer. To date there has been no evidence that cancer has been induced by mammography, but concern lest it might induce the disease that it was designed to detect led the National Cancer Institute to appoint a broadly-based panel to study the subject (NCI 78). The Panel recommended that the procedure should not be used in routine screening programs but might be used sparingly in high risk patients (Per 78). Energy absorption from X-ray beams of less than 50 keV, such as are used in mammography, depends strongly on the mean atomic number (Z) of the tissue on which they impinge. Little has been known of the elemental composition of the glandular, adipose and dermal tissues of which breasts are composed and the use of so-called "tissue equivalent" phantoms for measurement of absorbed doses has sometimes led to misleading results. In a recent study (Ham 79) the elemental composition of breast tissue was determined experimentally and matched with appropriate phantoms for measurement of depth doses. Results indicate that the dose to the mammary gland from the best available equipment is low enough so that the risk is acceptable if the recommendations of the Panel are followed.

X.6 Summary - There is good evidence that the incidence of carcinoma of the female breast is increased by exposure to ionizing radiation. The relative risk from doses below 600 rads is not high but the absolute risk may be substantial in populations where the natural incidence is high. The risk to the male breast is negligible.

6.1 The best fit for the dose-response curve is linear. A cell-killing component has not been demonstrated but data are scanty for doses greater than 600 rads. No increase in incidence has been shown for doses below 50 rads but the shape of the dose-response curve is such that it is prudent to assume that this is not a true threshold and that the response is linear nearly down to zero dose.

6.2 The minimum latent period is about 5 years; the maximum is probably greater than the present follow-up time of about 35 years. The latent period is inversely related to age at exposure. When corrected for age it is not a function of dose.

6.3 Sensitivity to carcinogenesis is maximal at ages 10 to 19 years when the rate of development of the breast is most rapid. Data are too scanty for evaluation of risk from exposure in infancy and early childhood.

6.4 The radiation doses from the best current mammographic techniques are low enough to be acceptable for use in selected patients but not for general screening programs. Statistically the risk from doses of 1000 rads or more is substantial, so that radiologists should plan therapy fields directed at adjacent organs so as to spare the female breast as far as possible.

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER XI -- CANCER OF THE LIVER

CHAPTER XI -- CANCER OF THE LIVER

XI.1 The title of this chapter may be somewhat of a misnomer since most of the subject matter will be concerned with the late effects of colloidal $^{232}ThO_2$ (Thorotrast). The long series of radioactive decay products of ^{232}Th are damaging to many tissues but when it is administered intravascularly as the dioxide, the carcinogenic effect on the liver far exceeds that on any other organ. The only good evidence in humans for the induction of liver cancer by radioactive particulates comes from the Thorotrast cases and they may to some extent serve as prototypes for the hazards of plutonium and other alpha-emitting elements which might gain access to the blood stream in the event of a nuclear accident.

XI.2 Cancer of the liver is common in some parts of the world, especially central Africa and southeast Asia, where it is associated with a prior history of hepatitis. In North America and Western Europe, however, primary liver cancer is very uncommon. For example, it comprises only 0.45% of all the 27,000 cases of malignant disease in the Memorial Hospital admissions for 1949-1962 (Ber 69). Some statistics are unreliable owing to confusion between primary cancer of the liver and the much more common metastases to the liver from cancers of other origins. If these are excluded it is clear that, at least in the U.S.A., primary liver cancer is so uncommon that cases occurring in a cluster are very likely to have a common etiology.

XI.3 Thorotrast was developed in the late 1920's as a contrast medium in diagnostic radiology. It is a colloidal preparation of $^{232}ThO_2$ and was chosen because of the good contrast provided by its high atomic number. Thorium-232 was known to be radioactive but its low level of activity apparently was not considered dangerous. Rundo, in his excellent analysis of the biological behavior of the ^{232}Th decay series (Run 78), points out that the parent ^{232}Th is the only member of the series that can exist in macroscopic quantities in Thorotrast. With a $T_{\frac{1}{2}}$ of 1.4×10^{10} years, one μCi weighs 9.3 g. Mays states (Mays 78) that a typical Thorotrast dose was 25 ml in volume of the thorium oxide suspension and 0.6 μCi in activity. This would be equivalent to a total of 5.5 g of thorium at a concentration of about 0.22 g/ml, a massive burden of a foreign element

to impose on the circulatory system. The chemical toxicity of Thorotrast seems to have been low. Neither generalized toxic symptoms nor acute local inflammatory reactions around extravasated material are mentioned in reports that I have seen. Either thorium is biochemically inert or the dioxide is as insoluble in body fluids as it is in pure water.

XI.4 Thorotrast was used mainly in angiography, particularly of the brain, but was also used for imaging sinuses, fistulous tracts and the liver, and sometimes for retrograde pyelography. Its popularity decreased as more suitable contrast media were developed and it was seldom used after 1950 although it remained on the list of Approved New Drugs until at least 1972. It seems to have had much more widespread use in Europe than in the United States. Sporadic reports of late ill effects began to appear in the late 1950's and early 1960's (Rij 63, Fre 64) and it became clear that there was a substantial population at risk of radiogenic cancer. Thorotrast cases had been monitored in Denmark since 1949, and a survey of such cases was set up in Portugal in 1960 and in Germany in 1968. Various progress reports on these studies appeared at intervals and the most recent clinical results were combined with dosimetric analyses at a symposium held in Utah in 1974, Proceedings of which were published in the July, 1978 issue of Health Physics (Thor 78). Most of my discussion will be confined to papers in this symposium.

XI.5 Results of studies of the three groups are summarized in Table XI.1. The Groups are:

A. Causes of the deaths of 1162 out of about 6,000 patients injected with Thorotrast compared with the deaths of 883 of about 6,000 patients in the same hospitals not so treated. Reported by van Kaick et al from Germany (VanK 78).

B. Causes of deaths of 931 out of 1,237 patients injected with Thorotrast compared with the deaths of 571 of 829 similar patients who were examined with other media. Reported by daSilva Horta from Portugal (daS 78).

C. Cause of the deaths of 621 out of 1,012 patients injected with Thorotrast compared with deaths of age-matched controls in the general population. Reported by Faber from Denmark (Fab 78).

There was no series from North America reported at this Symposium. Through no fault of the authors the epidemiology of these studies is unsatisfactory. Most of the exposure to Thorotrast took place before, during and immediately after World War II. Problems due to destruction of records, displacement of populations and deaths due to war-related causes are discussed by vanKaick and were especially severe in Germany, but were present in other countries also. I have recalculated the data for Groups B and C to give a percent of the total deaths which were due to each of the three types of malignant disease that were probably radiation-induced. I did this in order to allow a better comparison between the different groups. Elsewhere in this review (Chapter III.13) I have pointed out that the use of relative mortality can cause serious confounding because the "healthy worker effect" can give a spuriously high cancer death rate owing to the lower than average death rate from other causes. In the present series an analagous "sick patient effect" may give falsely low cancer death rates because the high death rates from the primary disease or other causes eliminates many potential cancer cases before the end of the latent period. The relative mortality seems the best parameter to use here, however, because of the large fraction of the exposed Population A which could not be traced and the lack of sick controls in Group C.

XI.6 Despite the various problems in epidemiology, the figures in the Table leave little doubt that the percent of deaths due to liver cancer is much greater in the exposed population than in the specific controls or in the general population of western Europe. The incidence is fairly consistent between the three groups, varying only between 5% and 8% of the total deaths. Not all of the liver cancers were diagnosed microscopically, but, of those that were, from 1/4 to 1/2 were derived from the reticuloendothelial cells in the liver, whereas most liver cancers in non-exposed populations originate in hepatocytes. This is important because it indicates that the malignant change took place in cells that had phagocyted ThO_2 or that were adjacent to such cells. Evidence of increased incidence of leukemia is less clear-cut but is strongly suggestive. There is no significant evidence of increased incidence of primary malignant tumors of bone. Only one of the 4 cases listed in Group B was diagnosed microscopically. Confusion in the diagnosis of such tumors is common and has already been discussed (Chapter II.1) and three of these cases can not be accepted without confirmation. Not shown in the

Table is the incidence of cancer of the lung, which is not significantly different in the exposed and control groups. Also not shown is the incidence of benign granulomas of the connective tissue adjacent to extravasated deposits of ThO_2. They were numerous and sometimes large enough to be life-threatening and had no counterparts in the control populations. Benign blood dyscrasias were common and one, aplastic anemia, was an occasional cause of death. Data on latent periods are not given in detail but most of those recorded for solid tumors are 20 to 30 years and it is thought that additional ones may be found after longer periods of observation. There is a statement in the text of Faber's paper that the minimum latent period for leukemia is 8 years and for solid tumors, 17 years. Granulomas began to be apparent in 5 to 10 years and grew slowly but progressively thereafter. No cancers of the spleen were seen in these series nor are any reported elsewhere. As will be seen below, the uptake of Thorotrast in the spleen, and the consequent radiation dose, are higher than in any other organ, so that the lack of malignant change is surprising at first glance. Some cases that came to autopsy, however, were for all practical purposes splenectomized, the spleens having been reduced to nodules of fibrous tissue by heavy radiation before they could undergo carcinogenesis.

XI.7 Dosimetry - The dosimetry of Thorotrast is of two types. One concerns the radiation dose to cells adjacent to the primary particles themselves. After intravascular injection these are deposited mainly in the liver, spleen and bone marrow. Uptake is essentially complete in a few hours and translocation during the ensuing years is slight and largely confined to the regional lymph nodes. The other type of dosimetry concerns the radiation absorbed by cells at the sites of deposition of the decay products of the initial ^{232}Th. The decay scheme is complex but most of the energy transfer is via high LET alpha particles. The most important elements in the decay chain are:

^{228}Ra, a bone volume seeker with $T_{\frac{1}{2}}$ = 5.75 years.

^{228}Th, a bone surface seeker with $T_{\frac{1}{2}}$ = 1.91 years.

^{224}Ra, chemically a bone volume seeker but kinetically a bone surface seeker because its $T_{\frac{1}{2}}$ = 3.62 days.

^{220}Rn (Thoron), an inert gas much of which decays at its generation site because its $T_{\frac{1}{2}}$ = only 56 sec., but some of which reaches the lungs.

^{212}Pb, with $T_{\frac{1}{2}}$ = 10.6 hours, has time to migrate from its generation site but the kinetics of its partition between erythrocytes, kidney and bone are not well known.

7.1 Several authors have used the above parameters to estimate radiation doses to different tissues in the human Thorotrast cases. The dose estimates are based on concentrations actually found in autopsy material and on the properties of the elements in the decay chain. Results are summarized in Table XI.2. I have normalized the reported figures to a 30 year accumulated dose from 25 ml of Thorotrast injected intravascularly in a 70 kg man. This is approximately equivalent to 0.01 μCi/kg.

7.2 There is considerable variation between the different estimates. This is to be expected from the small amount of observational material available and the resulting large number of assumptions that were necessary. The estimated doses to spleen and liver are not inconsistent with the observed near destruction of the former and the frequent induction of cancer in the latter. The estimated doses do, however, seem rather too small to account for such severe damage as was seen, especially as the dose rate was low. It must be remembered that these doses are averaged over the entire organs. Since nearly all of the energy absorbed was from alpha particles originating in discrete aggregates, the cells in the immediate neighborhood would have received far more than the average dose. This is also true of the bone marrow although the magnitudes of the estimated doses are consistent with the small increase in the incidence of leukemia in these cases. Doses to lung are attributed to exhaled ^{220}Rn and are subject to numerous assumptions about the fraction of this short lived gas which can reach the lung. The lack of significant excess of lung cancer in the patients suggests that the dose estimates are too high.

7.3 Much of the dosimetric effort has been directed toward bone because of the possibility that the ^{224}Ra generated from the ^{232}Th might have the same carcinogenic effect as the ^{224}Ra administered as such and discussed in Chapter VII. The dose estimates vary greatly. The most reliable is probably the dose to cells on the endosteal surfaces proposed by Mays. This is also the highest of the estimates but even so is below the apparent threshold for radiogenic bone sarcoma induction which was reported in Chapter VII. This is in harmony with the very equivocal evidence for an excess of primary malignant tumors of bone shown in Table XI.1. Liver disease is by far the greatest hazard resulting from injection of ^{232}Th particulates into the blood stream.

XI.8 Thorotrast is no longer in use and there is no prospect of the introduction of other long-lived radioactive particulates into the blood stream for medical purposes. It should perhaps be noted that numerous particulates labeled with ^{99m}Tc ($T_{\frac{1}{2}}$ = 6 hrs) are in regular use in nuclear medicine at the present time. Doses to the liver from these preparations are usually in the range of one to 2 rads, or far below any level which has been shown to be carcinogenic. Hence it might seem that the late effects of Thorotrast are of little further interest except to those of the unfortunate victims who are still alive but for whom little can be done. It must be remembered, however, that long-lived radioactive particulates, especially of plutonium, can be dispersed by nuclear accidents and later inhaled. Their subsequent fate depends both on size and chemical form. Larger particles, if not ciliated out and swallowed, tend to remain in the lung permanently and to constitute a hazard of cancer. Smaller particles may be retained but they may also be translocated to the blood stream and behave as if they were injected there. This process is a proper subject for investigation in animals and several programs for such studies are presently under way. Two recent reports illustrate the complexity of the processes involved. In one experiment (LaB 80) calcined particles of PuO_2 inhaled by monkeys were retained in the lungs and peribronchial lymph nodes for several years with hardly any translocation to other organs. In the other (Met 80), substantial fractions of particulates of a Pu-Mg alloy inhaled by rats were translocated to the bone in a few days and small but significant amounts were trapped in the liver. It is evident that knowledge is needed of the size and chemical form of particulates as well as of the chemical behavior of the elements in the decay chain if the ultimate radiological effects are to be understood.

XI.9 Summary - Patients who were injected intravascularly with colloidal thorium dioxide (Thorotrast) show a high incidence of cancer of the liver and a moderately increased incidence of leukemia. A large fraction of the liver cancers are hemangioendotheliomas, an otherwise rare tumor originating in the reticuloendothelial system. The latent period for liver cancer which has been seen to date is 20 to 30 years; later cases are expected.

There has not been a significant increased incidence of cancers of lung or bone such as might be caused by radioactive decay products.

Dosimetry is complex and needs further study.

The Thorotrast cases may to some extent be considered as prototypes for the behavior in the human of other long-lived radioactive particulates, but details of the influence of the size and chemical form of the particles and of the chemistry of the decay chain on the biological outcome must be worked out in animals.

TABLE XI.1

Causes of Deaths of Thorotrast Injected Patients

Group	Mean age at injection	Mean years survival or latent period	Percent of deaths due to: Liver cancer	Leukemia	Bone cancer	Reference and remarks
A - 1162 deaths 3 yrs or more after ThO_2 injection of 6000 patients	40	17	(a) 88/1162 = 7.6%	18/1162 = 1.35%	2/1162 = 0.17%	vanK 78 Germany 1/4 of liver cancers were hemangiosarcomas No significant difference in lung cancer. Two myelomas in injected patients
A - 883 deaths of 6000 hospital controls			6/883 = (a) 0.68%	2/883 = 0.11%	0	
B - 931 deaths of 1237 traced patients injected with ThO_2 1930-1955		(a) 39	(a) 75/931 = 8.1%	(a) 12/931 = 1.3%	(a) 4/931 = 0.43%	daS 78 Portugal 1/2 of liver cancers were hemangioendotheliomas 1.7% of deaths were from local granulomas
B - 571 deaths of 829 patients injected with other drugs			1/571 = 0.17%	0	0	
C - 621 deaths of 1012 patients injected with ThO_2 1934-1946	(a) 32	(a) 26	(a)(F) 32 = 5.1%	(a)(F) 11 = 1.8%	0	Fab 78 Denmark 1/3 of liver cancers were hemangioendotheliomas 9 lung cancers and 2 mesotheliomas were found, 4 and 0 expected
C - Age-adjusted population controls			(E) 0.6	(E) 4.7	(E) 0.2	

a = calculated by Helen Q. Woodard
F = found
E = expected

TABLE XI.2

Tissue Doses Accumulated in 30 Years from an Intravascular Injection of 25 ml of Thorotrast

Tissue	Dose, rads	Source
Spleen	2100	Kau 78
Liver	750	"
Red marrow	270	"
Lung	60 - 620	"
Bone, calcified	18	"
Bone, endosteal cells	180	Kau 78/HQW
Kidney	13	
Bone without marrow and trabeculae	45	Dud 78/HQW
Endosteal cells	480	Mays 78/HQW
Spleen	3000-5100	Goldin 72/HQW
Liver	600-1500	Exact administered
Periportal lymph nodes	4500-6000	doses not known
Marrow	840	
Cortical bone	300	

Reported absorbed doses have been normalized for time and administered dose by HQW as indicated.

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RADIATION CARCINOGENESIS IN MAN

A CRITICAL REVIEW

CHAPTER XII -- FUTURE STUDIES NEEDED

CHAPTER XII -- FUTURE STUDIES NEEDED

XII.1 In Chapters I - IV of this review I discussed the problems of appraising the risk, or even of establishing the existence, of various types of radiogenic cancer. In Chapters V - XI, I examined the characteristics of seven of the best documented types of malignant disease which are associated with previous exposure to ionizing radiation from externally applied photons or internally deposited radionuclides. In each case involving radionuclides, I tried to bring out the metabolic behavior of the organ at risk and its relation to the chemical and physical properties of the agent. Finally I tried to assess the magnitude of the risk and the possible means of controlling it. The last ranged from the wholly preventable and inexcusable risk of the osteogenic sarcoma induced by Ra-224 to the calculated risk of infrequent skin cancers or leukemias which may develop many years after life-saving radiation therapy. I am well aware that many other cancers are suspected of being radiogenic but consider them to be too rare or too poorly documented to be discussed in a review which is intended to be critical rather than comprehensive. In this Chapter I shall discuss the types of additional studies which seem to me to be needed if the hazards which may occur in the future are to be foreseen and controlled.

1.1 I shall not consider radiogenic cancers which might result from nuclear war. In such an overwhelming catastrophe the few thousands of extra cancer deaths which might occur 20 years later among the survivors would be of minor importance compared to the tens of millions of acute deaths. The studies of the Japanese atomic bomb survivors that have already been published give excellent documentation of the type and magnitude of the effects that are likely to result from nuclear war.

1.2 In the absence of nuclear war I anticipate an economy in which there may be an increase in exposure of the population to ionizing radiation of various types and at a wide range of dose levels. The numbers of persons exposed occupationally can be expected to increase because of an increase in the number of nuclear facilities. Minor malfunctions in the operation of reactors or in the transport and processing of radwastes could result in low-level exposure of large numbers of persons in unrelated occupations. Despite the presently proposed tightening of regulations it is to be expected

that occasional major nuclear accidents may occur. These might result in exposure through fallout or in other ways of small populations to radionuclides at levels which are known to be dangerous. As discussed in Chapter II 12-14, the biological properties of some of these elements, especially those of the actinide series, are poorly understood. Also, new modalities in radiation therapy are being introduced continually. They may use particles or pulsed photons of high instantaneous dose rates whose biological properties have not been studied thoroughly. Various radionuclides are being used increasingly in nuclear medicine. Their usefulness depends on selective uptake in specific organs but the microdosimetry of the process is not always known. Even the mean doses may amount to several rads in some cases. If it should prove that there is a highly selective uptake in certain cell populations the dose might reach a level known to be carcinogenic especially if examinations are repeated often. There always is the possibility that a therapeutic trial will be made of an unusual radionuclide before its biological behavior has been studied adequately. All of these probable future developments require both theoretical and practical investigation if their potential for carcinogenesis is to be anticipated and controlled.

XII.2 Low dose considerations - Occupational exposures are supposed to be kept to a low level and few accidental exposures are large enough to cause acute signs and symptoms. Hence the great majority of persons for whom the risk of carcinogenesis needs to be assessed will have received rather small doses. The concept of "low dose" is often used but seldom defined. In this discussion I shall define it as "a dose between 0.2 and 5.0 rads accumulated in one year either acutely or chronically". It thus lies between twice the average natural background and the maximal permissible occupational exposure. Risks are often expressed as cases per million person years per rad (10^6 PY rad^{-1}). Ideally they should be derived from observations on populations who have received doses in the neighborhood of one rad, but practically they are usually obtained by extrapolation from effects of much larger doses by the assumption that the dose-response curve is linear and without threshold. I discussed the theoretical uncertainties of this method in Chapter II 5-8. Actual observations show that the best fit for the dose-response curve for radiogenic leukemia is linear without threshold; for breast cancer it is probably linear, at least below 600 rads; for osteogenic sarcoma

it is definitely non-linear and has a well-documented threshold. For some other types of cancer the data are too scanty or too poorly distributed for any plausible estimate of low dose effects. Since the results of extrapolation are so unreliable it is important to have good epidemiological studies of populations who have actually been exposed to low known doses.

2.1 Many such epidemiological studies have been made with variable results. Results of a highly controversial study are given in the so-called "Mancuso Report" (Man 77). This is an analysis of the cause of 3520 deaths among about 25,000 persons, mostly men, who were at some time employed at the Hanford reactor facility. Results purported to show that there was a significant excess of deaths from various types of cancer among exposed employees vs unexposed ones. The report has been criticized severely (And 78, San 78, Gil 79, Gof 79, Hut 79, Rei 79). I consider most of the criticisms to be fully justified. A major defect in the analysis is the use of proportional mortality instead of standard mortality ratio. The "healthy worker effect" is prominent at Hanford so that, while the death rate from cancer is about the same as for appropriate control groups in the general population, the death rate from other causes is lower with consequent increase in the proportion of cancer deaths. Another error results from failure to use age-matched controls. The men who had been employed longest had accumulated the largest radiation doses, but also had the highest natural expectation of cancer because of their age. Errors were also made because of the use of mean values for a strongly skewed dose distribution curve. One critic found the mean dose for one subset to be 4.8 rem while the median was only 1.5 rem. In the small high-dose subset with a mean dose of 23 rads there was a strong suggestion of an increased incidence of cancer. In the large majority of the population studied there was no evidence that mean accumulated doses of less than 5 rads were associated with an increased cancer incidence.

2.2 Prenatal irradiation - There have been several epidemiological studies of the incidence of cancer and other abnormalities in young people who were exposed in utero to small doses of radiation from diagnositic procedures. The most extensive is the Oxford survey which sought to correlate prenatal X-ray exposure with deaths from cancer during the first 10 post-natal years for children born between 1943 and 1965.

The results have been the subject of many publications of which one of the more comprehensive is by Stewart, the principle investigator (Ste 73). The study has been criticized as not making suitable allowance for disturbances in pregnancy which might have led to radiological examination and which also might have indicated the presence of spontaneous pre-cancerous disease in the fetus. The controversy has not been entirely resolved and not all of the findings are accepted. There have been other studies of the same type but there is only one (Opp 74) in which there was no selection of the cases by medical indications. Selection in this study was solely on the basis of whether the baby was or was not born during a 10 month period during which routine pelvimetry was performed in the third trimester of all primiparas admitted to a large maternity hospital. Controls were babies born immediately before or after this period. No cases were considered in which X-ray examinations were made for suspected abnormalities. Fetal doses averaged 700 millirads. No conclusive evidence of a radiation effect was found but the series of 1000 cases was too small to rule out the occurrence of rare types of radiogenic abnormalities. A study was made of 1292 persons exposed in utero in Hiroshima and Nagasaki and followed to 32 years of age. There was increased mortality up to one year of age but no significant increase in death rate or presence of abnormalities in these who lived for more than one year (Kat 78). The high early mortality may have been due to injury to the mother or to infections and other environmental factors. Among 53,000 people conceived after the parents were irradiated there have been 3510 deaths, but there has been no significant correlation between over all death rate or incidence of leukemia or other maligancies and preconception dose to either or both parents. These subjects and those irradiated in utero are, however, still too young to show whether there will be an increased incidence of late onset cancer.

2.3 Background radiation - Various studies have been made of effects of differences in background radiation. Two (Fri 75, Mas 74) were made on populations of several millions each living in parts of the USA where the background varied from 118 to 210 mrem per year. The variation in background was due largely to differences in cosmic ray flux at different altitudes. There was no increase in cancer death rates

in high background areas and even a slightly lower rate for some high altitude cities. In view of the many confounding factors which can be expected in such surveys one would not expect to find significant differences due to differences in background of a factor of only two, but it is reassuring to find this impression confirmed. It would be interesting to study the populations living at much higher altitudes such as those of the Andean Plateau and Tibet but this is not feasible since vital statistics in these regions are poor and there are no suitable ethnical and sociological control populations living at lower altitudes. At present the numbers of the crews of jet planes are too small and their times of service too short for significant carcinogenesis from cosmic ray exposure to be likely, but they will be suitable subjects for study. The healthy worker effect can be expected to be prominent in this highly selected group.

2.4 A study (Koc 76) was made of cytogenetic abnormalities in 12,918 persons in a district in Kerala, India where the population is exposed to 1500 to 3000 mR/yr. from thorium in the soil, and in a comparable group living on a similar diet and in similar sociological conditions in a nearby area where the background was only 100 mR/yr. There was a significant increase in chromosome aberrations in the heavily exposed populations, especially in the trisomy 21 which is associated with severe mental retardation (Down's syndrome). Cancer incidence was not studied in these populations but Down's syndrome is known to be associated with a greatly increased risk of acute myeloid leukemia. This may be a condition in which the primary cause of a radiogenic cancer is a genetic one rather than a somatic one.

2.5 It appears from the above examples that epidemiological studies of populations exposed to low levels of ionizing radiation have seldom yielded definitive information. Since such studies are often quite expensive both in money and in qualified personnel, their cost-effectiveness may be questioned. They may even be counterproductive, since minor variations which are known by the investigators to be trivial or unreliable may be inflated by the media to dimensions which can mislead the public. I am in general agreement with the conclusion of Land (Lan 79) that the study of populations exposed to higher doses is a more promising way of assessing risk, but that some sort of epidemiological monitoring of the increasingly large populations who are exposed occupationally will need to be continued. As examples, such a program

has just been inaugurated to study military participants in the Nevada Test Site maneuvers (MMWR 79). A program to study workers in a thorium refinery has been started by Rundo et al and a preliminary report has been made (Run 79). It is obvious that such studies should be designed so as to avoid the blunders of the sort that were made in the Mancuso report. I also suggest that, before any study is organized, there should be an analysis of the type made by Boice et al (p. 592 of Boi 79) on the size of the population which would have to be studied in order to obtain significant results in the dose range of interest.

XII.3 Life span studies - The studies of the atomic bomb casualties have made evident the need for long-term studies. This is important not only so that cancers with long latent periods may not be missed but also to show how the total number of radiogenic cancers is related to the change with age in the natural incidence of non-radiogenic ones. Continuity of the life span studies of both the atomic bomb survivors and the radium dial painters is assured by the stability of the organizations administering the programs. It is 50 to 60 years since the start of exposure of some of the dial painters and the series will be essentially closed in another 10 years. It should be noted that the concept of latent period is different in these two series. In the atomic bomb cases the latent period is the time from the single instantaneous exposure to the diagnosis of cancer, and the threshold dose, if any, is the initial dose. In the dial painters burdened with Ra-226 the latent period for bone sarcoma is the time of continuing exposure until the threshold dose is accumulated.

3.1 The continuity of some other programs of long term observations is not so well assured although the value of some of the studies is high. The Ra-224 program is up to date at present but will need to be continued for many more years if it is to provide a reliable comparison of the effects on bone of continued irradiation by Ra-226 and pulsed irradiation by Ra-224. Studies of late effects of Thorotrast seem to be progressing as well as their numerous methodological problems permit and it is hoped that they will continue to do so. It is greatly to be hoped that further follow -up studies of the spondylitis cases will be available. The report by Court-Brown and Doll in 1957 (Cou 57) was excellent, but the follow-up times then were too short for definitive results.

Subsequent reports have been fragmentary. The follow-up time is now approaching the natural life span of some of the older subjects and additional data should be very valuable.

3.2 Knowledge of effects of pre-natal irradiation in the human with doses above 5 rads is derived almost entirely from the atomic bomb casualties. As discussed above (Chapter XII 2.2), results of studies of effects of pre-natal doses of one rad or less have been so inconclusive as to discourage further epidemiological studies. Further information on effects of higher doses is needed, however. No other human groups suitable for study are known and it is to be hoped that none will be available in the future. Hence animal studies must be relied on. There is an extensive literature on effects of pre-natal irradiation in several animal species but results have usually been evaluated on the basis of the incidence of developmental abnormalities and pre-natal or neonatal deaths. Very few life span studies that might evaluate risks of carcinogenesis have been published. Mice are not very satisfactory for such work because of the difficulty of irradiating the fetuses in such small animals without exposing considerable volumes of the tissues of the mother. Monkeys are ideal subjects because of the similarity of their reproductive processes to those of humans but are too expensive for large scale experiments. Dogs are probably the most favorable choice, and it is encouraging that preliminary results are already available in a suitable study (FDA 77).

XII.4 Macrodosimetry - Problems in dosimetry have been pointed out in several places in this review. These very seldom involve determination of doses from low LET photons in macroscopic volumes of tissue at centimeter depths. Technology here is far advanced and usually nothing is needed to secure reliable results beyond reasonably detailed information on exposure factors. There are a few situations where detailed data on the elementary composition of the tissue at risk are needed for satisfactory dosimetry of X-rays of intermediate LET. One of these problems was discussed in Chapter X.5, where it was shown that uncertainties in dosimetry could reach a magnitude that was highly significant in evaluating the risk of carcinogenesis in the breast. There is also need to re-examine the composition of all so-called "tissue equivalent"

materials if they are to be used in the construction of phantoms for use in calibrations. Some of these materials have been shown by White (Whi 78) to be quite unsuitable for use with certain qualities of radiation. Special problems exist in the dosimetry of neutrons in both macroscopic and microscopic volumes of various tissues, but they are recognized and are under active study in various laboratories.

4.1 Microdosimetry - There is need for more dosimetry at the cellular level. The term "microdosimetry" is often used to distinguish measurements referred to volumes visible only under the microscope from those made in masses visible to the naked eye. I shall use it here to include dosimetry in volumes from those of intracellular structures of diameters of 1 to 2 μm up to masses of 50 μm diameter which may include 2 to 5 cell layers. The importance of microdosimetry has been recognized since the pioneer work of Spiers on bone (Spier 46,49,51) which has been discussed here in Chapter VII.18. The dosimetry of the low energy β-rays of tritium was well worked out by Bond in 1966 (Bon 66). Other important fields remain to be explored, however. Some are important for the understanding of present problems in radiogenic cancer; others are not part of any immediate practical need but are of theoretical interest.

4.2 Perhaps the field in which there is the most urgent need for microdosimetry is in evaluation of the lung cancer caused by inhalation of radioactive particles. The dosimetry of Rn-222 decay products adsorbed on dust and trapped in the lungs was discussed in Chapter V.4 and V.5. In this system, the dust itself is not radioactive although it is an irritant that can lead to non-malignant but lethal lung disease. The products of the complex decay chain of the radionuclides originally adsorbed may decay in situ or may de-sorb and migrate according to their chemical properties. The result is a system which is complex kinetically as well as geometrically but progress is being made in its dosimetry. This Rn-222 system is the only one of importance in human radiogenic lung cancer at the present time but there are several others which must be anticipated. The most conspicuous of these is based on the inhalation of plutonium particulates. As I pointed out in Chapter VII.18.2 and 19.2, plutonium, when injected into the blood stream in solution, is taken up selectively on bone surfaces

if it is in monomeric form and by the liver and bone marrow if it is polymeric. If plutonium or other heavy elements are inhaled accidentally they will probably be in the form of oxides. Some of these are listed as having vanishingly small solubilities in water and would be expected to remain in the lungs indefinitely, although their decay products might be translocated. Insolubility in body fluids can not be assumed without direct observation, however, as is shown by the ready absorption of supposedly insoluble $RaSO_4$ from the gastrointestinal tract. Several programs for the study in animals of the production of lung cancer by inhaled particulates of the transuranium elements are active at present. If they are so designed that microdosimetry can be correlated with cancer production there will be a firm basis for evaluating human risk. The results of studies with gamma- and beta-emitting particulates, such as the recently reported one (Lun 80, Hah 80) with $^{144}CeO_2$, should be useful for comparison with effects of the alpha-emitting heavy elements.

4.3 The dosimetry of beta- and gamma-emitting radionuclides can seldom be considered as microdosimetry since it commonly involves distances of millimeters or even centimeters. In some cases, however, such as the comparison of different radioisotopes of iodine in the thyroid gland which was referred to in Chapter IX.2.3, the dimensions range down to micrometers, and computations averaging doses over centimeters are misleading. The dosimetry of the radioisotopes of iodine is of some urgency in view of the probability that considerable amounts of these isotopes would be released during a nuclear accident. Further work on the dosimetry of ^{35}S inorganic sulfate might be considered redundant since the inadvertant demonstration of the extreme leukemogenic effect of this agent by my colleagues and myself (Woo 76, Maye 78) should preclude any further therapeutic use. In that work we reported mean values for doses to bone marrow and cartilage because lack of knowledge of the microscopic distribution of ^{35}S in the few tissue specimens available made microdosimetry impossible. The reported mean values are probably much lower than the doses to individual cells. Some dosimetric studies in animals might throw light on the reasons why this radionuclide proved so hazardous.

XII.5 Dosimetry in continuing exposure - No conceptual difficulties are involved in the often-accepted theory that two or more ionization events must be accumulated in a cell during a time span of a few hours or days in order to cause damage leading to malignant change. The existence of a threshold dose would thus depend on the statistical probability of such a change in the cell population at risk. Nor is there any inherent difficulty in the idea that a change might take place in the nuclear DNA that would not be manifest until the cell was stimulated to divide many years later. Other reasonable mechanisms such as slow failure of replacement of cytoplasmic elements by defective messenger RNA might be postulated to explain a latent period. The conceptual difficulty arises when the radiation exposure continues for times which are long compared to the life spans of the cells at risk. This is especially pertinent in the induction of bone sarcomas by Ra-226. As brought out in Chapter VIII, there is a threshold dose in this system which is not very different from that found for exposure to X-rays. The latent period for sarcoma development after acute X-ray exposure is independent of dose; that for chronic exposure to Ra-226 depends on the time required to accumulate a threshold dose. Bone cells are replaced slowly throughout human life. Although the cell cycle is much slower than that in, for example, bone marrow, it is fast enough so that the cells now being exposed to Ra-226 deposited 20 years earlier are not the same ones as those at risk immediately after the radionuclide was acquired. It is difficult to understand how the effects of ionization events could accumulate in successive generations of bone cells except by transmission of mutations. The statistical probability of the occurrence of a critical event will, of course, increase with time also. Marshall and his co-workers have made major contributions to kinetic theory and, in a recent paper (Mars 79), have included a factor for rate of replacement of lethally exposed cells by stem cells. They obtain good fits with actual observations on bone sarcomas in the radium dial painters. Analysis of this sort is pertinent to all types of chronic exposure from internally deposited radionuclides and I hope it will be applied to other systems as well as bone. Livers which are regenerating chronically because of injury from Thorotrast might be a suitable system.

XII.6 Dosimetry of migrating cells - Problems in the dosimetry of cells that migrate during exposure have some similarities to problems with cells that replicate during exposure. I discussed and referenced the dosimetry of leukemia briefly in Chapter VIII.3.1. To recapitulate, leukemia is believed to arise from defects in stem cells which are usually present in the bone marrow but which may circulate from time to time in the blood stream or implant in other hematopoeitic tissues from those in which they originated. The mobile characteristics of these cells are not important in computing doses from whole-body irradiation such as that from the atomic bomb, from most types of occupational exposure and from gamma-emitting internally deposited radioisotopes. In such situations the stem cells, wherever they are at the moment, will receive the same dose as the average for the body as a whole. The problem arises when only part of the body is irradiated as in most radiation therapy. This problem was pointed out by Court-Brown and Doll in 1957 (Cou 57) but without definite recommendations for a solution. Since then there has been much progress in the understanding of the kinetics of hematopoietic tissue and it would seem to be time to examine the kinetics of migrating cells in greater depth. I shall point out some of the factors which might be involved in such an analysis.

6.1 The basic problem is whether the controlling factor in evaluating the risk of radiogenic leukemia is the total ionizing energy absorbed in all the hematopoietic cells that are exposed or whether it is the concentration of energy absorbed in the tissue receiving the highest "dose". Is a dose of 5000 rads to 100 g of active marrow equal in leukemiogenic hazard to one of 1000 rads to 500 g of marrow even when the dose-response curve is linear? They obviously are not equivalent when the curve is not linear. When is it proper to use the mean of doses to several fields and when should the maximum be used? Court-Brown and Doll were undecided about this but they were dealing with dose ranges of about 800 to 1400 rads so the question does not seem very important for their case. At the other end of the range, it is obviously absurd to average the 15 rads of whole-body exposure that might result from a battery of diagnostic tests and the 3500 rads to 1/3 of the active marrow from subsequent mantel therapy. Between these extremes there is a wide range in which the method of expressing

the dose is important. Should some attempt be made to compute the dose to circulating stem cells? A radiation field directed at the mediastinal lymph nodes will include a considerable portion of the heart and aorta. The dose to the blood can be computed, but what fraction of the stem cells is in the circulation at any one time? All of these questions have both theoretical and practical importance and deserve further study.

XII.7 Summary - It seems likely that future populations will be exposed to increasing amounts and types of ionizing radiation. Efforts should be made to anticipate the carcinogenic risk of these developments.

7.1 None of the past epidemiological studies have produced unequivocal evidence that exposure of populations to less than 5 rads per year of ionizing radiation is associated with an increased incidence of cancer. Such studies should continue but should be so designed in advance as to avoid the faults which have made some past surveys inconclusive or misleading.

7.2 Evidence now appearing in heavily exposed groups makes it clear that in humans, as has long been evident in animals, nothing less than observation over the entire life span gives complete indication of the magnitude of radiation effects. Such studies should therefore be based on government or other institutions of sufficient stability to assure the necessary continuity.

7.3 There is need for more dosimetry at the cellular level. To some extent this is a new discipline which should be encouraged.

7.4 Innovative theoretical work is needed in systems in which several cell generations are affected during chronic exposure or in which exposed cells migrate during or after acute exposure. A beginning has already been made, especially in the first system, but much more work is needed.

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GLOSSARY

The following terms were defined when first used in the text, but are listed here for the reader's convenience.

ATB	At Time of Bomb
ABCC	Atomic Bomb Casualty Commission
HVL	Half Value Layer
LD-50 (30)	The dose which is lethal to 50% of a population in 30 days.
LET	Linear Energy Transfer
PM	Proportional Mortality. The fraction of the total number of deaths in a population which is due to a condition of interest. Compare SMR below.
PY-rad	Person Year per rad. Used as the denominator of a fraction to express number of cases per person per year per rad of exposure. The fraction then has the dimensions of a rate and is usually expressed as $N/10^6$ PY-rad.
Q-factor	A factor introduced to compensate for the change in biological effectiveness with radiation quality.
RBE	Relative Biological Effectiveness. The reciprocal of the ratio of the quantities of radiation of two different qualities which produce the same biological effect.
RERF	Radiation Effects Research Foundation. Successor to the ABCC.
SMR	Standard Mortality Ratio. Ratio of the death rate from a condition of interest in a population under study to the death rate from the same condition in a control population. Compare PM above.
$T_{\frac{1}{2}}$	The time required for a radionuclide to decay to half of its initial activity. Sometimes called HL = Half Life.
TSH	Thyroid Stimulating Hormone
WL	Working Level. A unit of radioactivity which depends on the concentration of the decay products of ^{222}Rn in air. Also WLM = Working Level Month, etc., which is effectively a unit of exposure.